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Review

Six Dehydrogenase Gatekeepers of Carbohydrate Metabolism: Metabolic Integration in Health and Disease

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Abstract

Dehydrogenases function as metabolic gatekeepers, regulating carbon flux, redox balance, and biosynthetic capacity at critical branch points in cellular metabolism. This narrative review examines six key dehydrogenases, namely glyceraldehyde-3-phosphate dehydrogenase (GAPDH), lactate dehydrogenase (LDH), pyruvate dehydrogenase complex (PDHC), malate dehydrogenase (MDH1/2), isocitrate dehydrogenase (IDH1/2/3), and glucose-6-phosphate dehydrogenase (G6PDH), that collectively orchestrate the partitioning of nutrients among energy production, biosynthesis, and redox homeostasis. These enzymes share common features, including cofactor-dependent catalysis (NAD^+/NADH or $NADP^+$/NADPH), strategic positioning at metabolic nodes, and integration of compartmentalized metabolism between the cytosol and mitochondria. Under physiologic conditions, these dehydrogenases enable metabolic flexibility, allowing cells to adapt nutrient utilization to changing energetic demands and biosynthetic requirements. However, their dysregulation drives pathogenesis across diverse human diseases. In cancer, altered dehydrogenase activity supports metabolic reprogramming, exemplified by the Warburg effect mediated by LDHA, oncometabolite production (mutant IDH1/2), and enhanced biosynthetic capacity associated with G6PDH activity. Metabolic syndrome and diabetes feature PDHC suppression via pyruvate dehydrogenase kinase (PDK) upregulation, contributing to metabolic inflexibility and impaired glucose oxidation. Inherited enzymopathies, including G6PDH and PDHC deficiencies, underscore the essential roles of these enzymes and their tissue-specific requirements. In neurodegenerative disorders, oxidative modification of GAPDH promotes protein aggregation, whereas age-related decline in NAD^+ compromises the activity of multiple NAD^+-dependent dehydrogenases in a tissue- and context-dependent manner. The central importance of these enzymes has generated substantial therapeutic interest. Successful clinical translation includes mutant IDH inhibitors that reverse oncometabolite-driven epigenetic reprogramming in cancer. However, targeting essential metabolic enzymes presents challenges, including narrow therapeutic windows, metabolic compensation, and tissue-specific toxicities. Future therapeutic strategies will likely focus on exploiting disease-specific vulnerabilities, developing isoform-selective inhibitors, and combining metabolic interventions with conventional therapies. Understanding these six dehydrogenase gatekeepers provides crucial insights into metabolic regulation and highlights opportunities for precision-medicine approaches targeting the metabolic dependencies of human disease.

Keywords: dehydrogenases; oxidoreductases; glyceraldehyde-3-phosphate dehydrogenase; lactate dehydrogenase; pyruvate dehydrogenase complex; malate dehydrogenase; isocitrate dehydrogenase; glucose-6-phosphate dehydrogenase

1. Introduction

Dehydrogenases are among the largest and most functionally diverse enzyme families in biology, acting as key regulators of redox homeostasis and metabolic flux [1]. Classified within the oxidoreductase family (EC 1.1), dehydrogenases couple substrate interconversion to electron transfer, thereby regulating cellular pools of reducing equivalents essential for energy generation, biosynthesis, and redox balance [2]. Unlike oxidases, which rely on molecular oxygen as the final electron acceptor, dehydrogenases facilitate reversible electron transfer through cofactors including NAD^+/NADH, $NADP^+$/NADPH, FAD/$FADH_2$, or FMN/$FMNH_2$ as redox carriers [3]. NAD(H) and NADP(H) form major cellular redox pools, and NAD(P)-dependent reactions proceed via hydride transfer to/from the nicotinamide ring, enabling reversible redox chemistry central to metabolism [4,5]. Depending on cellular conditions, electrons flow either from substrates to oxidized cofactors (oxidation) or from reduced cofactors to substrates (reduction). These bidirectional redox reactions exhibit remarkable specificity and catalytic efficiency, and these properties also make dehydrogenases robust biocatalysts in organic and synthetic chemistry [3]. Fig. 1 provides an overview of dehydrogenase classification, cofactor specificity, and their major metabolic roles.

Mechanistically, dehydrogenases can be broadly grouped into NAD(P)-dependent hydride-transfer enzymes, flavin-dependent redox enzymes, and multicomponent complexes (e.g., pyruvate dehydrogenase complex-PDHC) that couple oxidation to sequential cofactor cycling and intermediate channeling. Most soluble NAD(P)-dependent dehydrogenases share a conserved

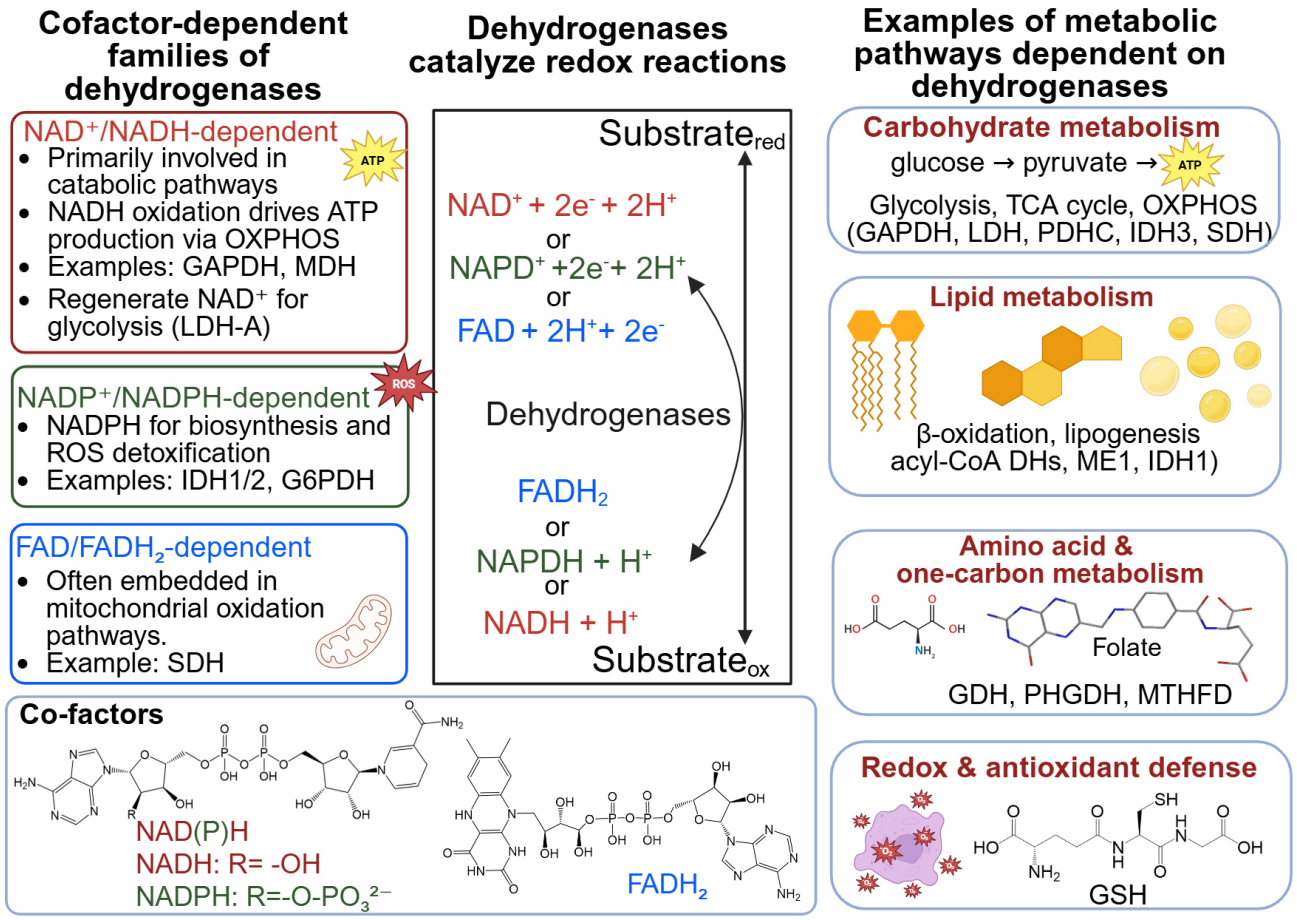


Fig. 1. Dehydrogenases act as metabolic gatekeepers that regulate cellular redox balance and pathway flux. Dehydrogenases catalyze reversible redox reactions using nicotinamide (NAD^+/NADH, $NADP^+$/NADPH) or flavin ($FAD/FADH_2$) cofactors as electron carriers. Left panel: Cofactor-defined enzyme families exhibit distinct functional roles: NAD^+/NADH-dependent dehydrogenases drive catabolic energy metabolism and regenerate NAD^+ for glycolysis; $NADP^+$/NADPH-dependent dehydrogenases supply reducing power for biosynthesis and antioxidant defense; $FAD/FADH_2$-dependent dehydrogenases participate primarily in mitochondrial oxidative pathways. Center panel: Generalized dehydrogenase reaction illustrating bidirectional electron transfer between substrates and redox cofactors. Right panel: Examples of metabolic pathways that rely on dehydrogenase activity, including carbohydrate metabolism (glycolysis, TCA cycle, OXPHOS), lipid metabolism (β-oxidation, lipogenesis), amino acid and one-carbon metabolism (serine synthesis, folate cycle), and redox homeostasis (glutathione regeneration). Bottom panel: Chemical structures of major nicotinamide and flavin cofactors. Abbreviations: GSH, Reduced glutathione; OXPHOS, Oxidative phosphorylation; ROS, Reactive oxygen species; TCA, Tricarboxylic acid cycle. Dehydrogenase abbreviations: Acyl-CoA DHs, Acyl-coenzyme A dehydrogenases; G6PDH, Glucose-6-phosphate dehydrogenase; GAPDH, Glyceraldehyde-3-phosphate dehydrogenase; GDH, Glutamate dehydrogenase; IDH, Isocitrate dehydrogenase; LDH, Lactate dehydrogenase; MDH, Malate dehydrogenase; ME1, Malic enzyme 1; MTHFD, Methylenetetrahydrofolate dehydrogenase; PDHC, Pyruvate dehydrogenase complex; PHGDH, Phosphoglycerate dehydrogenase; SDH, Succinate dehydrogenase. Created in BioRender. Papaneophytou, C. (2026). https://BioRender.com/r67qir1.

catalytic logic: substrate binding positions a reactive carbon adjacent to the C4 of the nicotinamide ring, enabling stereospecific hydride transfer coupled to proton transfer mediated by acid–base residues and/or ordered water networks. Many $NAD(P)^+$-dependent enzymes employ Rossmann-like dinucleotide-binding architectures that orient the cofactor and confer specificity for NAD^+ versus $NADP^+$ by recognizing the 2′-phosphate. In contrast, flavin-dependent dehydrogenases use stepwise electron transfer via FAD/FMN redox cycling and frequently interface with respiratory electron-transfer chains. Multicomponent assemblies such as PDHC constitute a distinct mechanistic class in which oxidation is distributed across coordinated catalytic modules (TPP-, lipoyl-, FAD-, and NAD^+-dependent steps), thereby enabling intermediate channeling and tight coupling among decarboxylation, acyl transfer, and NADH generation. Across these mechanistic classes, differences in oligomeric organization, reg-

ulatory interfaces, and compartmentalization shape state-dependent control of carbon flux and redox balance [6].

Biochemically, dehydrogenases catalyze a broad spectrum of oxidation–reduction reactions, including the oxidation of alcohols, aldehydes, amino acids, and organic acids, as well as the reduction of ketones and other carbonyl compounds, transformations fundamental to intermediary metabolism across glycolysis, the tricarboxylic acid (TCA) cycle, fatty acid oxidation, and amino acid catabolism [7,8]. A defining property of these enzymes is their strict cofactor specificity: NAD^+-dependent dehydrogenases primarily support catabolic, ATP-generating pathways, whereas $NADP^+$-dependent dehydrogenases generate reducing power for anabolic biosynthesis, detoxification reactions, and antioxidant defense [9,10]. The existence of distinct, compartmentalized NAD(H) and NADP(H) pools in the cytosol, mitochondria, and other organelles creates a highly regulated redox landscape that dehydrogenases help maintain through dynamic modulation in response to metabolic demand [10]. Through their central role in redox chemistry, dehydrogenases act as metabolic rheostats that regulate electron flow, sustain cellular redox balance, and coordinate energy production with biosynthetic and antioxidant pathways [11]. Their activities are therefore indispensable for maintaining cellular homeostasis and supporting diverse physiological processes ranging from ATP generation to redox buffering [12].

Structurally, dehydrogenases show great diversity, from small monomeric enzymes to large multimeric complexes. They are broadly classified into short-chain, medium-chain, and long-chain dehydrogenase/reductase families based on sequence motifs, chain length, mechanistic features, and structural organization [13,14]. Short-chain dehydrogenases/reductases (SDRs), such as Drosophila alcohol dehydrogenase, represent one of the largest enzyme superfamilies, with more than 46,000 members characterized by substantial sequence divergence but highly conserved catalytic motifs [15]. Long-chain dehydrogenase/reductases (LDRs) include enzymes such as glucose-6-phosphate dehydrogenase (G6PDH) and UDP-glucose dehydrogenase, which participate in carbohydrate and nucleotide metabolism [14,16]. Across families, the Rossmann-fold dinucleotide-binding motif, first described in lactate, alcohol, malate, and glyceraldehyde-3-phosphate dehydrogenases, remains a conserved structural signature and one of the most abundant protein folds in nature [16,17,18]. Larger multimeric complexes, such as the mammalian NAD^+-dependent isocitrate dehydrogenase 3 (IDH3), exemplify the intricate allosteric regulation possible within these enzyme families [8]. IDH3, an $\alpha\beta\gamma$ heterooctamer, is modulated by metabolites such as ADP, ATP, NADH, and NADPH, thereby enabling rapid adaptation to cellular energy charge and redox state [19]. Structural analyses across dehydrogenase classes have elucidated conserved principles of substrate recognition, cofactor specificity, and allosteric control, providing a foundation for rational drug design [19,20,21,22].

Alterations in dehydrogenase function, caused by genetic mutations, metabolic stress, epigenetic changes, or post-translational modifications, disrupt these interconnected pathways and can lead to various diseases. Reduced dehydrogenase activity has been associated with metabolic disorders, neurodegeneration, cardiomyopathies, immune problems, and cancer [23]. In tumor biology, dehydrogenases are often reprogrammed to support increased glycolysis, enhance redox buffering, and drive anabolic growth, hallmarks of malignant transformation [24]. In microbial pathogens, dehydrogenases aid in virulence, antibiotic tolerance, and adaptation to host-imposed stress [25]. Considering their central role in biochemistry and relevance to disease, dehydrogenases have become attractive therapeutic targets. Several inhibitors are already used in clinical practice or are under study for cancer, metabolic and cardiovascular diseases, infectious diseases, and inflammatory conditions. Progress in structural biology, metabolomics, and computational drug design continues to uncover new regulatory mechanisms and metabolic weaknesses, underscoring the therapeutic potential of targeting dehydrogenase activity for precise metabolic treatments. In this review, we focus on six dehydrogenases: GAPDH, lactate dehydrogenase (LDH), pyruvate dehydrogenase complex (PDHC), glucose-6-phosphate dehydrogenase (G6PDH), malate dehydrogenase (MDH1/MDH2), and isocitrate dehydrogenase (IDH1/IDH2/IDH3). These enzymes act as key metabolic "gatekeepers" within carbohydrate metabolism. They operate at critical branchpoints that link glycolysis, the pentose phosphate pathway (PPP), and the TCA cycle, determining whether glucose carbons are directed toward energy production, biosynthesis, or redox balance. By examining their structural features, catalytic functions, regulatory mechanisms, and metabolic crosstalk, we clarify how these enzymes serve as control points for metabolic flux. We also explore how their dysregulation contributes to human disease and assess emerging therapeutic strategies that target these enzymes. This system-level view provides a foundation for understanding metabolic integration and highlights opportunities for precise metabolic intervention. In this review, we define "carbohydrate metabolism" operationally as the network of processes that govern the routing of glucose-derived carbon and associated redox equivalents (NAD(H)/NADP(H)) into energy production, biosynthesis, and signaling pathways, rather than limiting the discussion to enzymes that directly act on carbohydrate substrates.

Before proceeding, we clarify that throughout this review, we consistently use the abbreviation "DH" rather than "D" for all dehydrogenases discussed. Although both conventions appear in the literature (e.g., GAPD vs. GAPDH), we adopt the "DH" nomenclature for clarity and consistency.

2. Methodology

This narrative review was conducted through a structured qualitative analysis of the literature addressing the roles of key dehydrogenases in carbohydrate metabolism, redox regulation, metabolic flux control, and disease-associated metabolic reprogramming. The review was developed in accordance with SANRA guidelines to ensure transparency, balanced synthesis, and critical interpretation of the literature [26]. A comprehensive search of PubMed, Scopus, and Web of Science was performed for peer-reviewed articles published through November 2025, using combinations of enzyme-specific terms (GAPDH, LDH, PDHC, G6PDH, MDH1/MDH2, IDH1/IDH2/IDH3) together with broader keywords related to carbohydrate metabolism, glycolysis, the pentose phosphate pathway, mitochondrial metabolism, redox homeostasis, NAD(H)/NADP(H) balance, metabolic flux, and nutrient partitioning. Disease-related terms, including cancer metabolism, metabolic syndrome, diabetes, cardiovascular disease, neurodegeneration, and inherited enzymopathies, were incorporated to capture pathophysiological relevance. Seminal primary studies and high-impact reviews were selectively included when they provided foundational mechanistic or conceptual insights. Rather than applying formal quantitative quality-scoring systems, studies were evaluated qualitatively based on clarity of experimental design, mechanistic depth, relevance to metabolic regulation, and consistency with established biochemical principles. Data were synthesized thematically into an integrative framework that positions six dehydrogenases as metabolic gatekeepers coordinating glucose-derived carbon routing, redox balance, and biosynthetic capacity across physiological and disease contexts.

3. Dehydrogenases as Central Nodes in Carbohydrate Metabolism

Carbohydrates are the most abundant biomolecules on Earth, mainly because plant polysaccharides such as cellulose and starch, both composed of glucose polymers, are produced in massive quantities [27]. This widespread availability makes glucose a dominant environmental carbon source and one of the most evolutionarily conserved metabolic fuels [28]. Its chemical properties, including high solubility, a stable cyclic structure, and controlled reactivity, make glucose well-suited for energy production, biosynthesis, and redox regulation across all domains of life.

Glycolysis serves as the central pathway for glucose catabolism and a key metabolic hub connecting carbohydrate metabolism to multiple downstream pathways [29]. This conserved ten-step sequence converts glucose into two molecules of pyruvate while generating ATP via substrate-level phosphorylation and reducing NAD^+ to NADH. Although historically associated with anaerobic conditions, glycolysis remains indispensable in aerobic cells by supplying pyruvate for mitochondrial oxidation and producing intermediates used in biosynthetic pathways. In cells lacking mitochondria, such as erythrocytes, or under hypoxic stress, glycolysis becomes the primary source of ATP [30]. For decades, glycolysis has been classified as "anaerobic" or "aerobic". In classical anaerobic glycolysis (the Embden-Meyerhof-Parnas pathway), pyruvate remains in the cytosol and is reduced by LDH-A to lactate, regenerating NAD^+ to sustain glycolytic flux [31,32]. The so-called "aerobic" glycolysis, better known as the Warburg effect, refers to the preference of many cancer cells for glycolysis despite abundant oxygen and functional mitochondria [33]. Although traditionally viewed as a hallmark of malignant transformation, recent evidence indicates that the Warburg effect also contributes to physiological adaptations in non-cancerous cells, challenging the idea that it is strictly pathological [34]. Emerging perspectives from recent reviews by our group [35] and Schurr [36], argue against classifying glycolysis as either anaerobic or aerobic. Instead, glycolysis should be viewed as a single pathway in which lactate, rather than pyruvate, is often the final product, regardless of oxygen availability. This perspective is supported by growing evidence that lactate production occurs even in well-oxygenated tissues and plays a key role in metabolic communication and redox balance [34,37].

Beyond ATP production, glycolytic intermediates feed into several anabolic pathways, including nucleotide synthesis via the pentose phosphate pathway, serine and one-carbon metabolism, glycerolipid biosynthesis, and amino acid synthesis. Depending on cellular demands, glucose may be directed toward structural polymer synthesis, storage as glycogen, oxidation in the pentose phosphate pathway, or full catabolism through glycolysis [38].

The liver plays a central role in systemic glucose regulation by coordinating glycogenesis, glycogenolysis, glycolysis, and gluconeogenesis [39]. After dietary carbohydrates are digested, the resulting glucose enters tissues as the primary substrate for ATP generation. In most mammalian cells, pyruvate enters mitochondria and is irreversibly converted to acetyl-CoA by the pyruvate dehydrogenase complex. Acetyl-CoA then condenses with oxaloacetate to initiate the TCA cycle, which produces GTP and the reduced cofactors NADH and $FADH_2$. These cofactors fuel oxidative phosphorylation, driving ATP production [40]. Together, these interconnected pathways form the backbone of cellular energy metabolism. Within this network, specific regulatory enzymes, particularly dehydrogenases, govern metabolic flux at key branch points. By controlling the distribution of carbon, energy, and reducing equivalents, these dehydrogenases act as metabolic gatekeepers, shaping the balance between energy production, biosynthesis, and redox homeostasis.

Although cells express hundreds of dehydrogenases across different compartments, only a small subset exerts dominant control over carbon routing and redox balance at

the most influential biochemical branch points. This review focuses on six dehydrogenases that consistently emerge as master regulators of nutrient fate and redox balance in both physiological and pathological contexts (Fig. 2). These enzymes, including GAPDH, LDH, PDHC, MDH (MDH1/MDH2), IDH (mainly IDH1/IDH2 and, to a lesser extent, IDH3), and G6PDH, were selected based on four criteria:

i. Strategic positioning at metabolic branches where their activity determines carbon flow toward energy production, biosynthesis, or storage;

ii. Tight coupling to redox cofactors ($NAD(P)^+$/NAD(P)H, $FAD/FADH_2$) that control reaction direction and flux;

iii. Integration of compartmentalized metabolism, enabling communication between cytosolic and mitochondrial processes;

iv. Established relevance to human diseases, including cancer, diabetes, cardiovascular conditions, neurodegeneration, and inherited metabolic disorders.

Each dehydrogenase controls a specific metabolic decision: GAPDH regulates glycolytic flux and cytosolic NAD^+/NADH balance; LDH determines whether pyruvate undergoes fermentation or mitochondrial oxidation; G6PDH controls glucose entry into the pentose phosphate pathway for NADPH generation; PDHC commits pyruvate to mitochondrial acetyl-CoA production; MDH isoforms coordinate cytosolic-mitochondrial redox transfer; and IDH enzymes link TCA cycle flux to NADPH production and biosynthesis. Together, these six enzymes form an integrated network governing metabolic flexibility in mammalian cells (Fig. 2).

3.1 Redox Cofactors and Metabolic Flux Control in Carbohydrate Metabolism

The six dehydrogenase gatekeepers examined in this review rely fundamentally on cellular redox pairs, NAD^+/NADH and $NADP^+$/NADPH, that serve as universal metabolic currencies. These cofactors connect oxidation–reduction reactions throughout metabolism while playing specific roles: NAD^+/NADH primarily support energy extraction through glycolysis, the TCA cycle, and fatty acid oxidation, whereas $NADP^+$/NADPH promote reductive biosynthesis and antioxidant defenses [4]. Glycolysis illustrates this dependency. The GAPDH-catalyzed oxidation of glyceraldehyde-3-phosphate depends on a continuous supply of NAD^+. Importantly, when NAD^+ levels drop, glycolytic flux halts at this step [41].

Cells regenerate NAD^+ through mechanistically distinct pathways with markedly different energetic consequences. One route involves LDH-A (Warburg-like glycolysis), which rapidly regenerates cytosolic NAD^+ by reducing pyruvate to lactate, thereby sustaining glycolytic flux but limiting ATP yield to 2 ATP per glucose molecule [42]. In contrast, the malate–aspartate shuttle (MAS) transports cytosolic reducing equivalents into mitochondria, enabling NADH oxidation at Complex I and supporting complete glucose oxidation via the TCA cycle and oxidative phosphorylation, yielding ~30–32 ATP per glucose [43]. This order-of-magnitude difference in ATP output underscores how routes for NAD^+ regeneration fundamentally shape metabolic efficiency.

Beyond energy production, redox cofactors directly regulate biosynthetic pathways. For example, the glycolytic intermediate 3-phosphoglycerate is diverted into serine biosynthesis through the NAD^+-dependent enzyme phosphoglycerate dehydrogenase, linking redox state to one-carbon metabolism [44]. Similarly, the oxidative pentose phosphate pathway (oxPPP) uses $NADP^+$ to generate NADPH and ribose-5-phosphate, coupling redox balance to nucleotide synthesis and anabolic capacity. Together, these examples illustrate how cofactor availability integrates energy production, biosynthesis, and redox homeostasis, positioning redox balance as a central determinant of cellular metabolic state.

3.2 Integration of Cytosolic and Mitochondrial Metabolism by Dehydrogenase Gatekeepers

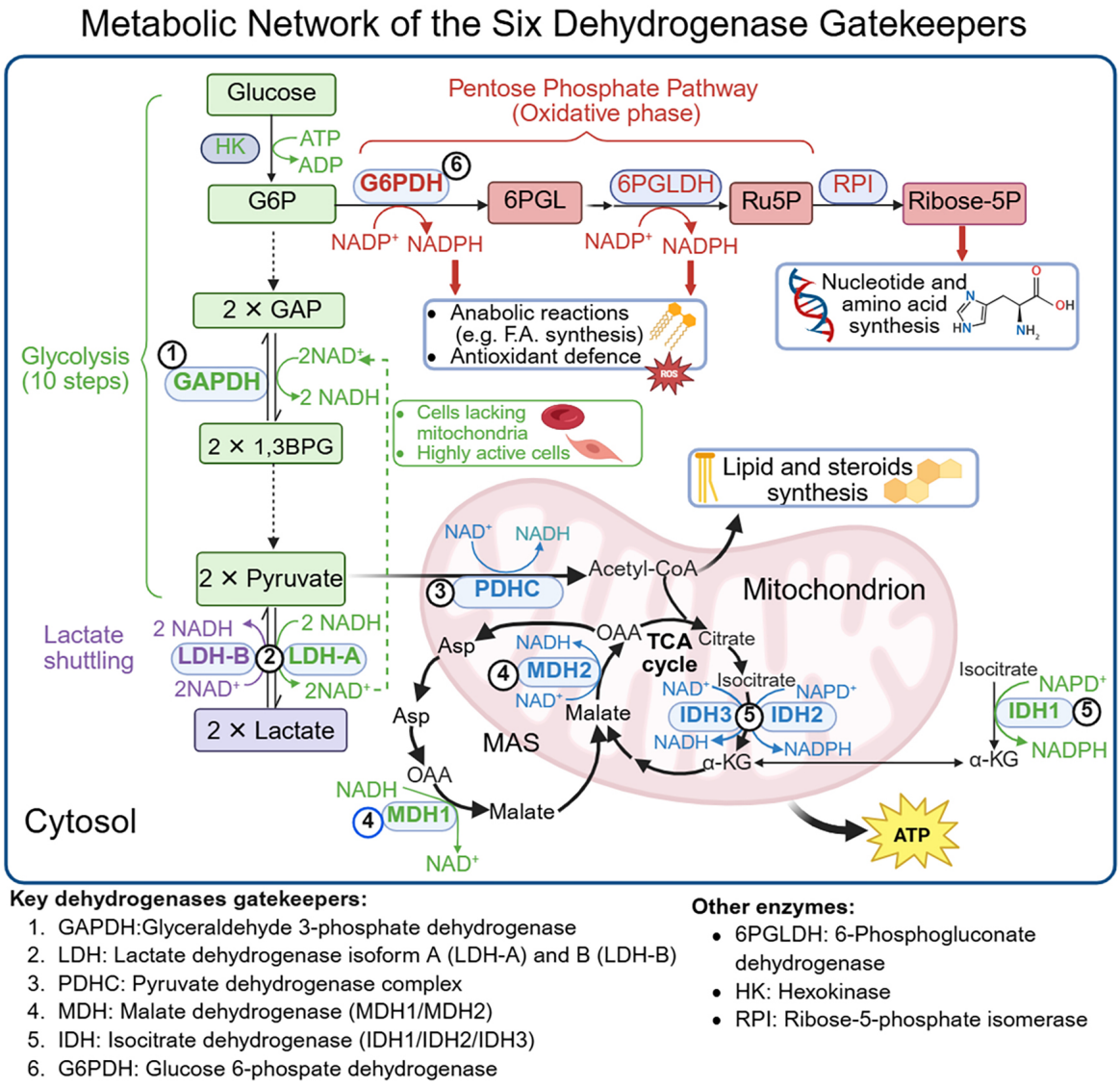
The six dehydrogenases coordinate metabolism across pathways and cellular compartments, enabling dynamic redistribution of carbon flux and reducing equivalents in response to energetic demand, biosynthetic requirements, and environmental conditions.

i. GAPDH functions as a central glycolytic redox checkpoint by coupling glyceraldehyde-3-phosphate (G3P) oxidation to NAD^+ reduction, thereby linking glycolytic flux directly to the cytosolic redox state. Because its activity is acutely sensitive to NAD^+ availability and oxidative modification, GAPDH serves as a metabolic sensor that integrates energy production with stress signaling and metabolic rerouting [45].

ii. LDH governs the terminal fate of pyruvate and cytosolic NADH, balancing lactate production with mitochondrial oxidation. LDH-A–mediated reduction of pyruvate to lactate rapidly regenerates NAD^+ to sustain glycolysis under high flux or hypoxia, whereas LDH-B favors lactate oxidation in oxidative tissues, supporting inter-tissue lactate shuttling and metabolic symbiosis [46].

iii. PDHC exemplifies mitochondrial commitment control by converting pyruvate to acetyl-CoA, thereby linking glycolysis to oxidative metabolism. Its activity is tightly regulated by cellular energy charge and metabolite ratios (acetyl-CoA/CoA, NADH/NAD^+), supporting the Randle cycle and enabling adaptive switching between carbohydrate and lipid utilization [47,48].

iv. MDH isoforms connect cytosolic and mitochondrial metabolism through the malate–aspartate shuttle: cytosolic MDH1 oxidizes NADH generated by glycolysis to support continued glycolytic flux. In contrast, mitochon-



Key dehydrogenases gatekeepers:

1. GAPDH:Glyceraldehyde 3-phosphate dehydrogenase
2. LDH: Lactate dehydrogenase isoform A (LDH-A) and B (LDH-B)
3. PDHC: Pyruvate dehydrogenase complex
4. MDH: Malate dehydrogenase (MDH1/MDH2)
5. IDH: Isocitrate dehydrogenase (IDH1/IDH2/IDH3)
6. G6PDH: Glucose 6-phospate dehydrogenase

Other enzymes:

- 6PGLDH: 6-Phosphogluconate dehydrogenase
- HK: Hexokinase
- RPI: Ribose-5-phosphate isomerase

Fig. 2. Metabolic integration of six dehydrogenase gatekeepers in carbohydrate metabolism. Glucose-derived carbon enters glycolysis (green, left) and can either proceed to pyruvate or be diverted into the oxidative pentose phosphate pathway (PPP; red, top). Six key dehydrogenases regulate flux at critical branch points: ① GAPDH catalyzes NAD^+-dependent oxidation of glyceraldehyde-3-phosphate (GAP) to 1,3-bisphosphoglycerate (1,3-BPG), linking glycolysis to NADH production; ② LDH controls pyruvate fate, LDH-A reduces pyruvate to lactate, regenerating cytosolic NAD^+ to sustain glycolysis, whereas LDH-B oxidizes lactate to pyruvate for mitochondrial oxidation; ③ PDHC irreversibly converts pyruvate to acetyl-CoA for TCA cycle entry or citrate export for lipid and steroid synthesis; ④ MDH isoforms drive the malate-aspartate shuttle (MAS), with cytosolic MDH1 reducing oxaloacetate (OAA) to malate using glycolytic NADH, and mitochondrial MDH2 oxidizing malate to OAA to regenerate mitochondrial NADH for oxidative phosphorylation; ⑤ IDH catalyzes oxidative decarboxylation of isocitrate to α-ketoglutarate (α-KG) within the TCA cycle, producing NADH; ⑥ G6PDH initiates the PPP, generating NADPH for biosynthesis and antioxidant defense. The complete oxidative phase (via G6PDH and 6PGLDH) yields two NADPH per glucose-6-phosphate and ribulose-5-phosphate (Ru5P) for nucleotide synthesis. Color coding: green = glycolysis and cytosolic NAD^+/NADH cycling; red = PPP and NADPH generation; purple = lactate metabolism and inter-tissue shuttling; blue = mitochondrial metabolism and electron transfer (PDHC, TCA cycle, MAS). Abbreviations: Asp, aspartate; 6PGL, 6-phosphogluconolactone; Ru5P, ribulose-5-phosphate; TCA, tricarboxylic acid cycle. Created in BioRender. Papaneophytou, C. (2026). https://BioRender.com/zh8f7kl.

drial MDH2 regenerates NADH within the matrix, coupling cytosolic redox balance to mitochondrial ATP production [49].

v. The IDH family further partitions redox and biosynthetic control, with $NADP^+$-dependent IDH1 and IDH2 supplying NADPH for reductive biosynthesis and antioxi-

Table 1. The six dehydrogenase gatekeepers of carbohydrate metabolism are examined in this review.

Enzyme and localization[1]	Primary reaction and cofactor	Metabolic gatekeeping function	Ref.
GAPDH Cytosol	Oxidation of GAP to 1,3-BPG $NAD^+ \rightarrow NADH$	• Controls glycolytic flux; • Redox-sensitive metabolic switch; moonlighting functions	[54,55]
LDH (LDHA/LDHB) Cytosol	Reversible Pyruvate ↔ Lactate $NADH \leftrightarrow NAD^+$	• Determines pyruvate fate • Lactate shuttling • NAD^+ regeneration	[46]
PDHC Mitochondrial matrix	Pyruvate → Acetyl-CoA $NAD^+ \rightarrow NADH$ $FAD \rightarrow FADH_2$	• Commits glucose carbon to mitochondrial oxidation • Regulates TCA cycle rate	[47]
MDH • MDH1: Cytosol • MDH2: Mitochondrial matrix	OAA ↔ Malate $NADH \leftrightarrow NAD^+$	• MAS shuttle • Redox balance • Replenishes TCA cycle intermediates	[49]
IDH • IDH1: Cytosol • IDH2/3: Mitochondrial matrix	IDH1/2: Isocitrate → α-KG $NADP^+ \rightarrow$ NADPH IDH3: Isocitrate → α-KG $NAD^+ \rightarrow NADH$	• NADPH production • Redox control • TCA flux regulation	[50]
G6PDH Cytosol	Oxidation of G6P to 6PGL $NADP^+ \rightarrow$ NADPH	• Gatekeeper of PPP • Generates NADPH • Regulates G6P fate	[51,52,53]

[1] Primary subcellular localization of each enzyme in the context of glucose metabolism.

Abbreviations: 1,3-BPG, 1,3-bisphosphoglycerate; 6PGL, 6-phosphogluconolactone; α-KG, α-ketoglutarate; G6P, glucose-6-phosphate; MAS, malate–aspartate shuttle; OAA, oxaloacetate; PPP, pentose phosphate pathway; TCA, tricarboxylic acid cycle. Note: Arrows indicate reaction directionality: (↔) reversible reactions; (→) predominantly unidirectional under physiological conditions.

dant defense, and NAD^+-dependent IDH3 driving TCA cycle flux and mitochondrial NADH production for oxidative phosphorylation [50].

vi. G6PDH controls entry into the oxidative pentose phosphate pathway, determining whether glucose-6-phosphate is directed toward glycolysis or toward NADPH and ribose-5-phosphate production. Cells upregulate G6PDH during proliferation or oxidative stress to meet increased demands for nucleotide synthesis, lipid biosynthesis, and antioxidant defense, thereby balancing energy metabolism with biosynthetic and redox needs [51,52,53].

Together, these enzymes enable semi-independent yet coordinated regulation of energy production, biosynthesis, and redox homeostasis across cellular compartments. As a distributed metabolic control network, the six dehydrogenase gatekeepers provide the flexibility needed to adapt to physiological stress and pathological states, underscoring their central importance in metabolic disease and therapeutic targeting. A summary of their catalytic activities, cofactor dependencies, subcellular localization, regulatory features, and disease relevance is presented in Table 1 (Ref. [46,47,49,50,51,52,53,54,55]).

3.3 Post-Translational Modifications as Dynamic Regulators of Dehydrogenase Gatekeeping

Beyond transcriptional regulation and metabolite levels, post-translational modifications (PTMs) provide rapid, reversible mechanisms by which dehydrogenases adapt to shifts in the cell's metabolic state. PTMs allow cells to precisely adjust enzyme activity, localization within the cell, interactions with other proteins, and affinity for cofactors on timescales too rapid for changes in gene expression alone. Consequently, PTMs function as dynamic molecular switches that connect nutrient supply, redox balance, energy levels, and stress responses to cellular functions and metabolic flux control [56].

Several classes of PTMs are particularly relevant to dehydrogenase regulation, including phosphorylation, acetylation, redox-dependent cysteine modifications, and lysine acylations, each of which is tightly linked to cellular metabolic conditions. For example, phosphorylation often reflects signaling inputs from growth-factor, hormonal, or stress-responsive kinase pathways, whereas acetylation and deacetylation are directly coupled to acetyl-CoA availability and NAD^+-dependent sirtuin activity. Redox-sensitive PTMs such as S-nitrosylation, sulfenylation, and S-glutathionylation directly sense intracellular reactive oxygen and nitrogen species, providing a biochemical link between oxidative stress and enzyme function [57].

Of the six dehydrogenase "gatekeepers" discussed here, their regulation via PTMs differs significantly in both scope and mechanistic understanding, highlighting biological diversity and the current state of knowledge in the literature. For some enzymes, PTMs are well established as

dominant regulatory mechanisms: the PDHC is a canonical example, in which reversible phosphorylation of the E1α subunit by pyruvate dehydrogenase kinases and phosphatases determines the commitment of pyruvate to mitochondrial oxidation, thereby integrating nutrient availability, hormonal signals, and cellular energy status [58]. Similarly, GAPDH is highly sensitive to redox-dependent PTMs targeting its catalytic cysteine; oxidative modifications inhibit glycolytic activity and promote non-glycolytic regulatory functions that help redirect glucose flux toward antioxidant and stress-response pathways [59].

IDH isoforms also exhibit PTM-dependent regulation, linking mitochondrial and cytosolic metabolism to cellular energy and redox balance. In mitochondria, acetylation of IDH2 suppresses enzymatic activity, whereas deacetylation by SIRT3 restores NADPH production, coupling IDH2 function to NAD^+ availability and mitochondrial metabolic state [60]. Cytosolic IDH1 is also subject to nutrient- and redox-linked regulation, and these inputs shape its role in cellular metabolic flexibility. When oxidative TCA flux is limited, e.g., under hypoxia, mitochondrial dysfunction, or rapid cell division, cells rely more on IDH1-mediated reductive carboxylation of glutamine-derived α-ketoglutarate to produce citrate for lipid synthesis and to maintain NADPH levels [61,62]. This reductive pathway also supports redox homeostasis under stress [63], positioning IDH1 as a metabolically responsive dehydrogenase whose activity integrates nutrient state, redox balance, and biosynthetic demand.

MDH isoforms remain strongly influenced by substrate availability, cofactor ratios, and compartmentalized flux within the malate–aspartate shuttle; however, growing evidence indicates that PTMs can tune these shuttle functions. For example, SIRT3-sensitive acetylation of mitochondrial GOT2 enhances its association with MDH2 and alters NADH redox transfer [64]. Unlike regulation mainly through metabolite levels, LDHA in many mammalian systems is heavily influenced by PTMs: phosphorylation at Tyr10 (by kinases such as HER2, Src, and FGFR1) boosts activity, promotes tetramer formation, and enhances metastatic properties, while acetylation at Lys5 reduces activity and stability [65].

For G6PDH, PTMs such as acetylation and O-GlcNAcylation modulate enzyme stability and activity, thereby linking pentose phosphate pathway flux to nutrient status, oxidative stress, and growth signaling. Notably, site-specific acetylation can either inhibit or activate G6PDH, underscoring the nuanced roles of acetylation in metabolic control [66,67].

Importantly, PTM-mediated regulation should be viewed as part of a broader regulatory network that also includes cofactor availability, compartmentalization, substrate competition, and transcriptional control. The varied PTM regulation observed among dehydrogenases reflects their distinct biochemical functions and constraints rather than inconsistent regulatory strategies. Together, these PTMs allow dehydrogenase gatekeepers to act as dynamic metabolic sensors, quickly adjusting carbon flow and redox balance in response to changing physiological needs and stress conditions. This multilayered regulatory system supports metabolic flexibility in health and promotes metabolic rewiring during disease.

4. Enzyme-Specific Roles of Dehydrogenase Gatekeepers in Carbohydrate Metabolism

As discussed above, carbohydrate metabolism proceeds through a network of carefully positioned dehydrogenase-catalyzed branch points that determine how glucose-derived carbon and reducing equivalents are partitioned among different metabolic pathways. Six dehydrogenases, namely GAPDH, LDH, PDHC, MDH1/2, IDH1/2/3, and G6PDH, operate either in cytosolic and/or mitochondrial compartments to regulate metabolic flow by controlling NAD^+/NADH and $NADP^+$/NADPH ratios, irreversibly directing carbon into specific pathways, and coordinating energy production with redox balance and biosynthesis. These enzymes collectively decide whether pyruvate undergoes fermentation or mitochondrial oxidation, whether glucose-6-phosphate proceeds through glycolysis or the pentose phosphate pathway, whether cytosolic NADH leads to lactate production or ATP synthesis via the malate-aspartate shuttle (MAS), and whether TCA cycle intermediates are used for complete oxidation or biosynthetic extraction. Through localized cofactor regulation, allosteric sensing, and PTMs, these six dehydrogenases form an interconnected network linking carbohydrate breakdown to redox defense, mitochondrial energy generation, lipid and nucleotide production, and stress response.

The following sections analyze each gatekeeper enzyme, examining its catalytic mechanisms, structural features, regulatory controls, metabolic roles, and disease significance.

4.1 Glyceraldehyde-3-Phosphate Dehydrogenase: Regulator of Glycolytic Flux and Redox Balance

GAPDH (EC 1.2.1.12) is a homo-tetrameric enzyme that catalyzes the sixth step of glycolysis, the oxidation and phosphorylation of G3P to 1,3-bisphosphoglycerate (1,3-BPG), thereby coupling carbon oxidation to NAD^+ reduction [41]. It is widely considered a "housekeeping" protein, expressed at stable levels across most tissues and contributing to essential cellular functions linked to survival [68]. As one of the most abundant cytosolic proteins (~2,000,000 molecules per cell) [69], reaching concentrations of ~70 μM in muscle cells [68], GAPDH supports high glycolytic throughput through its tetrameric architecture and catalytic efficiency.

A defining regulatory feature of GAPDH is its reliance on a reactive catalytic cysteine residue (Cys152 in humans),

which is essential for catalysis and renders the enzyme highly sensitive to the intracellular redox environment [70]. Oxidative and nitrosative modifications, including sulfenylation, nitrosylation, and S-thiolation, impair catalytic activity and promote functional reprogramming by altering protein interactions, redistributing subcellular components, and engaging stress-responsive signaling pathways [59]. Because GAPDH activity depends strictly on NAD^+ availability, it is also responsive to shifts in the NADH/NAD^+ ratio. Conditions that elevate NADH/NAD^+, including hypoxia, mitochondrial dysfunction, or excessive NADH production, slow GAPDH catalysis and constrain glycolytic flux. In this setting, inhibition of GAPDH (via oxidative modification or pharmacological blockade) increases upstream metabolite accumulation and favors glucose diversion into the pentose phosphate pathway, thereby enhancing NADPH production and antioxidant capacity [52,71]. This establishes GAPDH as a redox-sensitive control point that couples glycolytic flux to cellular redox buffering.

Importantly, the consequences of GAPDH regulation are strongly state- and disease-dependent. In proliferating cells and tumors, increased GAPDH expression and activity can support high glycolytic flux and sustain biosynthetic demands, while redox-dependent modulation of GAPDH can facilitate adaptive rerouting of glucose metabolism toward NADPH generation to improve oxidative stress tolerance [72]. In contrast, in aging and neurodegeneration, where chronic oxidative and nitrosative stress is prominent, persistent GAPDH modification and dysfunction can contribute to impaired energy metabolism and activation of maladaptive stress pathways, consistent with its involvement in neuronal vulnerability and degenerative processes [73]. Recent work by Talwar et al. [74] further supports this view by demonstrating that GAPDH operates as a redox-responsive metabolic switch that redistributes glucose between ATP production and antioxidant defense, providing mechanistic and *in vivo* evidence that GAPDH oxidation can promote oxidative tolerance and tumor survival.

4.2 Lactate Dehydrogenase: Partitioning Pyruvate Between Fermentation and Oxidation

LDH catalyzes the reversible interconversion of pyruvate and lactate coupled to NADH/NAD^+ cycling [75]. This reaction allows NAD^+ regeneration, which is crucial for maintaining glycolytic flow, especially under anaerobic conditions. The enzyme exists as tetramers composed of LDHA (muscle-type) and LDHB (heart-type) subunits in five isoenzyme forms, each with distinct kinetic properties and tissue distributions [76]. Beyond regulation by substrate availability and the NADH/NAD^+ balance, LDH activity is increasingly recognized as modulated by PMTs in a context-dependent manner. Phosphorylation and lysine acetylation of LDH isoforms have been shown to influence enzymatic activity, protein–protein interactions, and subcellular localization, thereby fine-tuning lactate–pyruvate interconversion under metabolic stress and in proliferative states. Redox-dependent modifications further link LDH function to cellular oxidative state, supporting the view that PTMs serve as modulatory layers rather than primary determinants of LDH flux [65].

LDHA-rich isoforms dominate in glycolytic tissues and promote pyruvate-to-lactate conversion, whereas LDHB-rich forms in oxidative tissues mainly catalyze lactate-to-pyruvate conversion. This bidirectional capacity enables tissues to adapt flexibly to changes in oxygen availability and metabolic demand. The widespread presence and cytosolic abundance of LDH make serum LDH levels a valuable clinical biomarker for tissue damage, hemolysis, and cancer [77,78]. In cancer, LDHA drives the Warburg glycolysis (effect) by maintaining NAD^+ regeneration. Tumor cells frequently overexpress LDHA to sustain glycolytic ATP production even in the presence of adequate oxygen [79]. The resulting lactate production acidifies the tumor microenvironment, promoting invasion, angiogenesis, and immune evasion. Metabolic cooperation between glycolytic and oxidative cancer cells through lactate exchange reinforces intratumoral heterogeneity [80]. LDHA inhibition restricts glycolytic ATP production and alters redox balance, thereby inducing a metabolic crisis, particularly in hypoxic tumor regions [80]. In erythrocytes lacking mitochondria, LDH-mediated NAD^+ regeneration is essential for sustained glycolysis and survival [81]. Beyond pathology, tissue-specific LDH isoforms enable metabolic flexibility: LDHB in the heart and brain supports lactate utilization as an oxidative fuel, and as discussed above, positions lactate as a circulating metabolic substrate rather than a waste product [34,82].

4.3 Pyruvate Dehydrogenase Complex: The Irreversible Gateway to Mitochondrial Oxidation

PDHC catalyzes the irreversible oxidative decarboxylation of pyruvate to acetyl-CoA, establishing the metabolic commitment point between glycolysis and mitochondrial oxidation [83]. This multi-enzyme complex determines whether glucose-derived carbon enters the TCA cycle for complete oxidation or remains available for lactate production, gluconeogenesis, or biosynthesis. PDHC catalyzes the irreversible oxidative decarboxylation of pyruvate through a large multienzyme complex. This complex consists of multiple copies of three catalytic components: The E1 component (pyruvate dehydrogenase) uses thiamine pyrophosphate to decarboxylate pyruvate; the E2 (dihydrolipoamide acetyltransferase) transfers the resulting acetyl group to coenzyme A; and the E3 (dihydrolipoamide dehydrogenase) regenerates the oxidized lipoyl groups while producing NADH [84].

The activity of PDHC is regulated by associated regulatory enzymes, pyruvate dehydrogenase kinases (PDK1-4) and phosphatases (PDP1-2), which provide dynamic control through reversible phosphorylation of three ser-

ine residues (Ser232, Ser293, Ser300) on the E1α subunit [85,86,87]. PDHC regulation integrates multiple metabolic signals. PDKs are activated by NADH and acetyl-CoA (indicating mitochondrial energy sufficiency) and inhibited by pyruvate and ADP (signaling energy demand) [58]. Hormonal control further modulates activity: insulin activates PDHC to promote glucose oxidation in the fed state, while fasting induces PDK expression to spare glucose [88]. Hypoxia upregulates PDK1 via HIF-1α, redirecting pyruvate toward lactate and limiting mitochondrial ROS production. This regulatory complexity enables PDHC to orchestrate the Randle cycle, where increased fatty acid oxidation suppresses glucose oxidation through PDK activation [89]. Dysregulation contributes to metabolic disease: elevated PDK expression in diabetes impairs glucose oxidation, while PDHC suppression in cancer supports aerobic glycolysis [90]. Inherited PDHC deficiency causes severe lactic acidosis and neurodegeneration due to the brain's reliance on oxidative glucose metabolism [91]. Therapeutic PDHC activation remains an active area of research. Dichloroacetate (DCA) inhibits PDKs broadly but lacks isoform selectivity [92]. More selective inhibitors targeting specific PDK isoforms are under development for metabolic disorders and cancer, aiming to restore oxidative metabolism while minimizing toxicity [93].

4.4 Malate Dehydrogenase: A Regulated Decision Node Linking Redox Transfer, Anaplerosis, and Biosynthetic Coupling

MDH catalyzes the NAD^+-dependent interconversion of malate and oxaloacetate (OAA), functioning both within the TCA cycle and as a central coordinator of cytosolic–mitochondrial redox coupling [49]. Two isoforms, cytosolic MDH1 (cMDH) and mitochondrial MDH2 (mMDH), share ~60% sequence identity yet occupy distinct metabolic niches [94]. Under high glycolytic flux or mitochondrial constraint, MDH1/MDH2 activity helps determine key metabolic decisions, including whether cytosolic NADH is reoxidized via the MAS to support mitochondrial ATP production or diverted to lactate formation via LDH, and how carbon is partitioned among oxidative metabolism, anaplerosis, and biosynthetic demands [95].

MDH2 catalyzes the final step of the TCA cycle, generating NADH for oxidative phosphorylation [96]. MDH1, together with MDH2 and associated transporters, supports the MAS, the primary mechanism for transferring glycolytic NADH into mitochondria in oxidative tissues [97]. The MAS bypasses mitochondrial membrane impermeability to NADH: cytosolic MDH1 reduces OAA to malate using glycolytic NADH; malate enters mitochondria, where MDH2 regenerates NADH; OAA is trans-aminated to aspartate for export and cytosolic regeneration, completing the cycle [98]. In tissues such as the brain, heart, and liver, MAS activity enables complete glucose oxidation via the TCA cycle and oxidative phosphorylation, yielding ~30–32 ATP per glucose molecule, whereas reliance on LDHA-mediated cytosolic NAD^+ regeneration converts pyruvate to lactate and limits glycolytic yield to 2 ATP per glucose [99]. In this sense, MDH-dependent redox transfer constitutes a regulated branchpoint that influences the balance between fermentative NAD^+ regeneration and respiratory ATP production.

Although MDH isoforms are strongly influenced by substrate availability, cofactor ratios, and compartmentalized flux, additional regulatory layers further shape their function. MDH2 is regulated by a dimer–tetramer equilibrium and by allosteric inputs from ATP, NAD^+, and TCA intermediates, aligning matrix NADH production with respiratory capacity and overall TCA flux [100]. Accumulating evidence indicates that MDH1 and MDH2 engage in protein–protein interaction networks that influence their coupling to MAS components and to broader metabolic modules, with consequences for effective redox transfer and metabolite channeling in specific cellular states [101]. Proteomic and biochemical studies report extensive acetylation, ADP-ribosylation, and methylation of MDH1 and MDH2, and these modifications have been associated with changes in catalytic behavior, oligomeric assembly, and interaction networks, particularly under metabolic stress and in disease contexts [102]. For example, in pancreatic ductal adenocarcinoma, O-GlcNAcylation of MDH1 at Ser189 stabilizes the substrate-binding pocket and enhances catalytic activity, acting as a 'molecular glue' that promotes glutamine metabolism and tumor growth. MD simulations and functional assays suggest the modification's effects on oligomeric state and specific protein–protein interactions, but these effects warrant direct biochemical confirmation [103].

MAS capacity, driven by MDH1/MDH2 and mitochondrial carriers, is a state-dependent decision node that directs glycolysis-derived reducing equivalents toward mitochondrial respiration or lactate production; MAS impairment depletes NAD^+/NADH and reshapes respiratory coupling and biosynthetic output [104]. Although a unified mechanistic model has not yet been established, the available data support the view that PTMs provide a tunable layer of regulation that can fine-tune MAS efficiency and cytosolic–mitochondrial redox coupling in a state-dependent manner.

Beyond redox transfer, MDH2 supports TCA cycle flux and contributes to anaplerotic/cataplerotic balance by regulating malate and OAA availability in the mitochondrial matrix [100]. MDH1 supports gluconeogenesis and contributes to aspartate availability and redox balance during high biosynthetic demand [105]. Because aspartate is frequently growth-limiting in proliferating cells, MDH-dependent redox transfer and OAA–aspartate interconversion can indirectly support proliferative capacity by sustaining nucleotide and amino acid biosynthesis [105]. Thus,

MDH1/MDH2 sit at a functional intersection between energy metabolism, redox homeostasis, and biosynthetic output.

The relative importance of these regulatory layers differs across disease-specific metabolic states. In cancer, MDH1 overexpression has been linked to proliferative metabolism, supporting NAD^+ regeneration and precursor supply in contexts where high glycolytic flux and biosynthetic demand must be coordinated [106]. In neuroendocrine tumors, pathogenic MDH2 alterations have been linked to pseudohypoxic signaling, consistent with the broader principle that perturbing mitochondrial redox metabolism can trigger hypoxia-like transcriptional programs [107]. Inherited MAS defects cause severe neurological disorders with lactic acidosis, highlighting the dependence of brain energy metabolism on efficient MDH-mediated NADH transfer into mitochondria [107]. Collectively, MDH isoforms exemplify how compartmentalized versions of a single reaction can act as regulated metabolic decision points, coupling metabolism across cellular compartments [108].

4.5 Isocitrate Dehydrogenases: Gatekeepers at the Intersection of Energy Metabolism, Redox Control, and Oncogenesis

IDH isoforms connect the TCA cycle with redox metabolism, biosynthesis, and cellular signaling by catalyzing the oxidation of isocitrate to α-ketoglutarate (α-KG) [50]. Three mammalian isoforms, viz. IDH1, IDH2, and IDH3 differ in localization, cofactor specificity, and metabolic function [109,110].

IDH1 and IDH2 are $NADP^+$-dependent homodimeric enzymes that catalyze a reversible step, enabling flexible control of α-KG and NADPH availability in cytosolic and mitochondrial compartments, respectively [111]. IDH1 localizes to the cytosol and peroxisomes, generating NADPH for lipid synthesis and antioxidant defense [112]. IDH2 resides in mitochondria, contributing to the matrix NADPH pool and supporting both oxidative flux and reductive carboxylation [113]. Under normoxia, the reaction proceeds oxidatively; under hypoxia or metabolic stress, the reverse flux enables reductive carboxylation of glutamine-derived α-KG to generate citrate for lipogenesis [62,114]. IDH2 activity is regulated by lysine acetylation, with deacetylation by sirtuins restoring activity and linking function to NAD^+ availability [113]. Both enzymes supply α-KG for dioxygenases, including ten-eleven translocation (TET) DNA demethylases and histone demethylases, linking metabolism to epigenetic regulation [109].

IDH3 is an NAD^+-dependent dehydrogenase found only in the mitochondrial matrix and catalyzes an essentially irreversible oxidative decarboxylation reaction. The enzyme consists of three different subunits (α, β, and γ) and forms a functional heterooctamer with the stoichiometry $(\alpha_2\beta\gamma)_2$. Through this multimeric complex, IDH3 converts isocitrate into α-KG, producing NADH and CO_2 [115]. As a rate-limiting enzyme of the TCA cycle, IDH3 generates NADH to fuel oxidative phosphorylation [116]. Its activity is tightly coupled to cellular energy status through allosteric regulation: activation by ADP and Ca^{2+} increases TCA cycle flux during periods of high energy demand, whereas inhibition by ATP and NADH restrains flux when cellular energy charge is sufficient. In addition, metabolites such as citrate further modulate IDH3 activity, enabling fine-tuned control of mitochondrial respiration [115,117].

Recurrent neomorphic mutations in IDH1 (R132) and IDH2 (R140, R172) occur in gliomas, AML, and other malignancies [118]. Rather than simple inactivation, these mutations confer a new activity: reduction of α-KG to the oncometabolite D-2HG using NADPH. D-2HG accumulation competitively inhibits α-KG-dependent dioxygenases, causing DNA and histone hypermethylation, differentiation arrest, and transformation [109,119]. Mutant-selective inhibitors, such as ivosidenib (IDH1) [120] and enasidenib (IDH2) [121,122], reduce D-2HG levels and induce differentiation in IDH-mutant cancers. These therapies exemplify how targeting metabolic-epigenetic connections can restore regular cellular programs, though resistance through secondary mutations or metabolic adaptation remains challenging.

4.6 Glucose-6-Phosphate Dehydrogenase: Gatekeeper of the Oxidative Pentose Phosphate Pathway

The final dehydrogenase gatekeeper examined in this review, G6PDH, catalyzes the first and rate-limiting step of the oxPPP, oxidizing glucose-6-phosphate to 6-phosphogluconate while reducing $NADP^+$ to NADPH [55,123]. This reaction positions G6PDH at a critical metabolic branch point, determining whether glucose-derived carbon is directed toward glycolysis for ATP production under energy-demanding conditions or diverted into the PPP to support NADPH generation and ribose-5-phosphate synthesis during oxidative stress and proliferative states [55].

The PPP consists of two functionally distinct modules: an irreversible oxidative phase that produces NADPH and a reversible non-oxidative phase that generates R5P and interconverts pentose phosphates with glycolytic intermediates. This modular architecture enables cells to independently adjust NADPH production and nucleotide biosynthesis. Under conditions of high reductive or antioxidant demand, glucose carbon can be oxidized through the PPP while pentose carbons are recycled back into glycolysis; conversely, when nucleotide demand is high, R5P can be produced from glycolytic intermediates with minimal NADPH generation [123,124]. NADPH supports a wide range of anabolic and protective processes, including tetrahydrofolate metabolism, deoxyribonucleotide synthesis, fatty acid and cholesterol biosynthesis, proline synthesis, and detoxification reactions. Through these functions,

G6PDH operates as a central redox and biosynthetic gatekeeper, coordinating carbohydrate metabolism with cellular growth, stress resistance, and metabolic adaptation [124].

Structurally, G6PDH is a polypeptide of approximately 515 amino acids (~59 kDa). The enzyme exists in several structural forms: an inactive monomer and active dimers and tetramers. The equilibrium among these forms is influenced by factors such as pH and ionic strength, with higher pH and ionic strength favoring the conversion of tetramers to dimers. Human G6PDH maintains a dynamic dimer–tetramer balance and comprises two main domains: an N-terminal $NADP^+$-binding region and a C-terminal catalytic domain [125,126].

G6PDH activity is tightly regulated by substrate availability and, most importantly, by the intracellular $NADP^+$/NADPH ratio, allowing flux through the PPP to respond dynamically to cellular redox state [127]. Post-translational modifications provide additional layers of regulation: acetylation suppresses enzymatic activity, whereas SIRT2-mediated deacetylation activates G6PDH under conditions of metabolic or oxidative stress [51]. O-GlcNAcylation further stabilizes and activates G6PDH, particularly under hypoxic conditions and in cancer. At the transcriptional level, G6PD expression is induced by growth and stress-responsive pathways, including mTOR, HIF-1α, and NRF2, linking PPP activity to nutrient availability, hypoxic signaling, and antioxidant responses [51,67].

The essential physiological role of G6PDH is most clearly illustrated in erythrocytes, which lack mitochondria and therefore depend entirely on the PPP for NADPH production [128]. PPP-derived NADPH maintains reduced glutathione and protects red blood cells from oxidative damage. Genetic G6PDH deficiency, one of the most common human enzymopathies, compromises this defense, leading to oxidative injury and hemolytic anemia. In severe cases, impaired NADPH also disrupts leukocyte oxidative burst, increasing infection risk and highlighting the PPP's dual role in antioxidant defense and ROS/NOS production [129].

5. Pathophysiological Roles of the Six Key Dehydrogenases in Human Disease

Metabolic dysregulation, characterized by altered pathway flux, redox imbalance, and metabolite buildup, is a key feature of many diseases. The six crucial dehydrogenases, GAPDH, LDH, PDHC, MDH1/2, IDH1/2/3, and G6PDH, play vital roles in energy metabolism, redox regulation, and biosynthesis. Small changes in these enzymes' activity can destabilize cellular homeostasis, leading to conditions such as cancer, metabolic syndrome, cardiovascular disease, neurodegenerative disorders, immune disorders, and inherited disorders. Under normal conditions, they allow metabolic flexibility, adjusting in response to nutrient and energy needs. In disease, mutations, expression changes, or regulatory issues reprogram metabolism, leading to maladaptation and pathology (Table 2, Ref. [58,84,108,130,131,132,133,134]).

While Sections 3 and 4 examined each dehydrogenase individually to define its biochemical function and regulation, disease pathophysiology rarely arises from isolated enzyme defects. Instead, alterations propagate across interconnected metabolic networks, with multiple dehydrogenases contributing to energy production, biosynthesis, redox balance, and epigenetic regulation. Dysregulation from mutations, transcriptional changes, post-translational modifications, and flux redistribution leads to shared issues such as redox imbalance, cofactor misallocation, and loss of metabolic flexibility. The following sections focus on five pathological contexts, including cancer, metabolic syndrome and cardiovascular disease, inherited enzymopathies, neurodegeneration and aging, and immunometabolism and inflammation, in which dehydrogenase dysfunction is central. Despite clinical differences, these conditions share common metabolic gatekeepers, underscoring their importance to cellular homeostasis and their vulnerability. In cancer, these changes promote uncontrolled growth; in metabolic disease, they cause insulin resistance and substrate inflexibility; in neurodegeneration, they lead to energy failure and oxidative damage. Understanding these rewired circuits offers insights into disease mechanisms and potential therapies.

5.1 Dehydrogenase Dysregulation in Cancer Metabolism and Metabolic Reprogramming

Cancer cells undergo metabolic reprogramming as a hallmark adaptation to malignancy [135]. These metabolic changes arise from both cell-intrinsic oncogenic signals and cell-extrinsic environmental pressures. While some adaptations drive transformation, others support growth, promote survival under stress, and confer therapeutic resistance. Most cancer metabolism research has focused on clinically visible tumors or experimental models derived from them, leading to the identification of stereotyped metabolic phenotypes in highly proliferative cancer [136]. The Warburg effect illustrates this phenomenon: cancer cells tend to convert glucose into lactate even when oxygen and fully functional mitochondria are present, a metabolic shift regulated by oncogenes and tumor suppressors [137]. This reprogramming of central carbon metabolism enables cancer cells to meet their needs for ATP, biosynthetic precursors, and redox buffering while maintaining an undifferentiated state [138]. In addition to LDH-mediated NAD^+ regeneration, the capacity of the MAS, driven by MDH1/MDH2, is a key decision node that determines whether glycolysis-derived reducing equivalents are directed toward mitochondrial respiration or lactate production [96]. In proliferating cells, this routing has direct biosynthetic consequences because MAS activity supports mitochondrial redox balance and sustains cytosolic aspartate availability, which is often

Table 2. Key dehydrogenases across major human diseases.

Dehydrogenase and primary disease contexts	Dominant mechanisms	Pathophysiological roles	Ref.
GAPDH • Cancer • Neurodegeneration • Aging • Immune activation	• Glycolytic flux control and NAD^+ regeneration • Redox-sensitive post-translational modifications • Moonlighting functions	• Supports Warburg glycolysis in cancer • Promotes stress-induced apoptosis or survival signaling • Aggregation in neurodegeneration	[130,131]
LDH (LDHA/LDHB) • Cancer • CVDs	• Pyruvate–lactate interconversion • Cytosolic NAD^+ regeneration • Lactate-mediated microenvironmental remodeling	• Warburg phenotype and metabolic symbiosis in tumors • Acidic, immunosuppressive tumor microenvironment	[131]
PDHC • Cancer • Metabolic syndrome • Diabetes • CVDs	• Control of pyruvate entry into mitochondria • PDK-mediated inhibition of mitochondrial glucose oxidation • Regulates glycolysis/OXPHOS	• Sustained Warburg glycolysis in cancer • Insulin resistance and substrate inflexibility • Mitochondrial underutilization	[58,84]
MDH1/MDH2 • Cancer • Neurodegeneration • Mitochondrial disorders	• MAS function • Cytosol–mitochondria NADH transfer • TCA cycle anaplerosis and redox coupling	• Impaired ATP production when the shuttle is compromised • Vulnerability to redox imbalance	[108]
IDH1/IDH2 • Cancer (glioma, AML) • Metabolic disorders	• NADPH production and redox buffering • Reductive carboxylation under hypoxia	• Epigenetic reprogramming • Oncometabolite-driven tumorigenesis • Altered lipid metabolism	[132]
G6PDH • Inherited enzymopathies • Cancer • Immune dysfunction	• NADPH production via oxPPP • Antioxidant defenses • Support of nucleotide and lipid biosynthesis	• Oxidative vulnerability of erythrocytes • Tumor resistance to oxidative stress • Impaired immune oxidative burst	[133,134]

Abbreviations: AML, Acute Myeloid Leukemia; CVDs, Cardiovascular disorders; OXPHOS, oxidative phosphorylation; oxPPP, oxidative pentose phosphate pathway.

growth-limiting for nucleotide synthesis. Consistent with this principle, ETC impairment that lowers the mitochondrial NAD^+/NADH ratio can deplete aspartate and arrest proliferation, whereas restoring redox balance or supplying aspartate rescues growth [138]. In parallel, $NADP^+$-dependent IDH1/2 influences the same proliferative state by supplying NADPH for antioxidant defense and lipid biosynthesis and, in IDH-mutant settings, by diverting α-KG to D-2HG with downstream epigenetic effects. Together, LDH, MDH/MAS, and IDH coordinate a state-dependent balance between NAD^+ regeneration, mitochondrial coupling, and redox/biosynthetic capacity (see Sections 4.2 and 4.4).

Dehydrogenases function as critical control points within cancer-associated metabolic circuits. Positioned at redox and carbon branch points, they regulate the NAD(H)/NADP(H) balance, biosynthetic capacity, and epigenetic states [4,139]. Altered activity or mutations in IDH1/2, G6PDH, LDHA, and pyruvate dehydrogenase kinase (PDKs) modify metabolic flux through glycolysis, the pentose phosphate pathway, the TCA cycle, and one-carbon metabolism.

Recent work by Chen et al. [140] demonstrated the essential role of cytosolic dehydrogenases in cancer metabolism. In colon cancer cells, G6PDH, IDH1, and malic enzyme 1 (ME1, an $NADP^+$-dependent dehydrogenase beyond the scope of this review) collectively maintain NADPH homeostasis, which is required for redox balance and biosynthesis. CRISPR-mediated deletion studies revealed that while IDH1 and ME1 show partial redundancy, G6PD loss uniquely disrupts the NADPH/$NADP^+$ ratio. This alteration impairs oxidative defense and profoundly impairs folate metabolism. Elevated $NADP^+$ levels inhibit dihydrofolate reductase (DHFR), causing accumulation of dihydrofolate and dUMP, which compromises nucleotide biosynthesis. These findings demonstrate how perturbations in dehydrogenase activity propagate from redox imbalance to biosynthetic and epigenetic dysfunction,

confirming that cancer metabolic reprogramming depends critically on dehydrogenase activity [140].

5.1.1 Glycolytic Endpoint Control: LDH and Lactate-Driven Microenvironmental Remodeling

As discussed above, cancer cells exhibit a unique metabolic phenotype, the Warburg effect (glycolysis), in which they preferentially convert glucose to lactate even when oxygen is abundant. Warburg glycolysis meets the energetic and biosynthetic needs of rapid cell growth, making it a hallmark of cancer metabolism [141,142]. LDHA catalyzes the central reaction enabling this metabolic reprogramming. By reducing pyruvate to lactate while regenerating NAD^+ (Fig. 2), LDHA maintains the high glycolytic flux essential for tumor growth. LDHA overexpression performs several roles: it maintains cytosolic redox balance by regenerating NAD^+, diverts pyruvate away from mitochondrial oxidation, and provides a steady supply of glycolytic intermediates for biosynthesis. The enzyme's position at the NADH/NAD^+ junction makes it indispensable for sustaining the Warburg phenotype [143]. Consequently, LDHA inhibition modulates this metabolic program, reduces ATP production, induces oxidative stress, and impairs tumor growth *in vivo*, establishing LDHA as an attractive therapeutic target for glycolysis-dependent cancers [143,144].

As noted earlier, recent discoveries have revolutionized our understanding of lactate, revealing functions far beyond its traditional designation as a metabolic waste product. Lactate now emerges as both a significant fuel source and a signaling molecule with diverse biological activities [145]. Metabolic tracing studies demonstrate that lactate contributes substantially to the TCA cycle carbon in lung cancer [146] and serves as a primary circulating substrate for tumor metabolism [147]. Through MCT1-mediated uptake, lactate fuels the oxidative pentose phosphate pathway, enhances antioxidant capacity by reducing ROS levels, and promotes metastatic efficiency [147]. The multifaceted roles of lactate extend to microenvironmental remodeling [148]. Tumor-derived lactate acidifies the extracellular space, creating an immunosuppressive niche that protects cancer cells from immune surveillance [149]. This acidification also facilitates metabolic symbiosis, in which glycolytic tumor cells export lactate, which neighboring oxidative cells import as a fuel. Additionally, lactate provides carbon for membrane lipid biosynthesis, supporting the structural demands of proliferating cells. Through these mechanisms, LDHA-driven lactate production shapes the tumor microenvironment, reinforces metabolic heterogeneity among cancer cell populations, and promotes disease progression. Challenging the conventional view of lactate as merely a glycolytic byproduct, Cai et al. [141] recently demonstrated that lactate functions as a direct mitochondrial regulator. Both L- and D-lactate stimulate oxidative phosphorylation independently of their metabolism, suppressing glycolysis while enhancing pyruvate entry into the TCA cycle by activating pyruvate dehydrogenase. Lactate enters mitochondria without the pyruvate carrier, shifting energy production to respiration. This supports cell growth under respiratory stress and enhances T cell function, making lactate a key player in bioenergetics and immunity. These findings highlight LDHA and lactate metabolism as central to cancer reprogramming, influencing cellular energy, the tumor microenvironment, and immune responses.

5.1.2 IDH1/2 Mutations: Oncometabolite-Driven Epigenetic Reprogramming

IDH1/2 normally catalyze the oxidative decarboxylation of isocitrate to α-KG while reducing $NADP^+$ to NADPH [150]. However, recurrent mutations at specific active-site residues fundamentally alter this catalytic function, transforming IDH enzymes from metabolic workhorses into oncogenic drivers [151]. IDH1/2 mutations occur almost exclusively as heterozygous alterations at conserved arginine residues within the active site: R132 in IDH1, and R140 or R172 in IDH2 [152,153]. Rather than simply inactivating the enzyme, these mutations confer neomorphic activity, in which mutant IDH1/2 catalyzes the NADPH-dependent reduction of α-KG to D-2-HG. This reversal of normal catalytic function transforms a metabolic substrate into an oncogenic product. Under physiological conditions, cellular D-2HG levels remain low due to the activity of D-2-hydroxyglutarate dehydrogenase (D2HGDH), which efficiently converts D-2HG back to α-KG [154]. Consequently, D-2HG accumulates to millimolar intracellular concentration levels 100-fold higher than normal. This massive accumulation can be detected systemically in the serum of patients with IDH-mutant acute myeloid leukemia (AML) and locally within IDH-mutant glioma tissue, serving as both a biomarker and pathogenic driver [151].

D-2HG functions as an oncometabolite by competitively inhibiting α-KG-dependent dioxygenases, a large enzyme family crucial for epigenetic regulation [124]. The structural similarity between D-2HG and α-KG allows D-2HG to occupy the active sites of these enzymes without supporting catalysis. Primary targets include Ten-Eleven Translocation (TET) DNA hydroxylases, which initiate DNA demethylation, and Jumonji-domain histone demethylases, which remove repressive histone marks [155]. This competitive inhibition produces profound epigenetic consequences. TET enzyme blockade prevents DNA demethylation, while histone demethylase inhibition maintains repressive chromatin states. Together, these effects establish a CpG island methylator phenotype (CIMP), characterized by widespread hypermethylation of gene promoters [109,156]. The resulting epigenetic landscape silences differentiation programs, locking cells into an immature, proliferative state that is conducive to malignant transformation.

It is important to note that several well-characterized oncometabolites arise from deficiencies in other TCA enzymes, including succinate and fumarate from SDH and fumarase loss [157]. However, in this section, we limit our discussion to oncometabolite pathways most directly linked to the six dehydrogenase gatekeepers covered in this review, with the IDH1/2–driven D-2HG axis as the canonical example. Beyond mutant IDH itself, the metabolic state that permits or amplifies oncometabolite-associated programs is strongly shaped by redox routing and α-KG availability. In particular, LDH activity influences cytosolic NAD^+ regeneration and lactate accumulation, while MDH1/MDH2 via MAS regulates cytosolic–mitochondrial NADH transfer and TCA intermediate routing. Because MAS capacity determines how efficiently glycolysis-derived reducing equivalents are transferred into mitochondria, it can shift the NADH/NAD^+ balance and modulate flux through α-ketoglutarate–linked nodes that feed into IDH-dependent reactions [106]. We therefore discuss MDH primarily as a regulator of redox and flux states that can permissively shape oncometabolite phenotypes, rather than as a direct oncometabolite-generating enzyme (see Section 4.4).

Targeting IDH mutations exhibits distinct patterns across cancer types. In AML, IDH1 R132 mutations occur in 5-–10% of newly diagnosed cases, while IDH2 mutations, predominantly R140Q and R172K, affect approximately 12% of patients [118]. Beyond hematologic malignancies, IDH mutations define molecular subtypes in gliomas, cholangio-carcinomas, and chondrosarcomas, underscoring the broad applicability of this oncogenic mechanism [158]. Notably, the reliance of IDH-mutant cancers on continuous D-2HG production has facilitated the creation of mutant-selective IDH inhibitors. Pharmacologically blocking mutant IDH1 or IDH2 decreases D-2HG synthesis, partially restores α-KG–dependent dioxygenase activity, and encourages differentiation of malignant cells, especially in AML. These drugs demonstrate that oncometabolite-driven epigenetic reprogramming is reversible and can be targeted therapeutically. However, they carry risks such as differentiation syndrome that require careful clinical management.

5.1.3 Pyruvate Dehydrogenase Control: PDK-Mediated Switching Between Mitochondrial Oxidation and Glycolysis

PDHC catalyzes the irreversible conversion of pyruvate to acetyl-CoA, committing glucose carbon to mitochondrial oxidation. This critical step decides if pyruvate enters the TCA cycle or is diverted to lactate, alanine, or other metabolites [85]. PDKs phosphorylate and inactivate the E1α subunit of PDHC, effectively blocking pyruvate oxidation and promoting non-oxidative pyruvate utilization [159].

In cancer, PDK1 and PDK3 are frequently upregulated downstream of hypoxia-inducible factor-1α (HIF-1α), c-Myc, and PI3K/Akt signaling pathways. PDK-mediated inhibition of PDHC reduces mitochondrial oxygen consumption, lowers reactive oxygen species (ROS) production, and sustains high glycolytic flux, adaptations that support tumor cell survival and proliferation under metabolic stress [160]. Suppression of PDHC activity also facilitates citrate export for lipid biosynthesis and enables IDH1-dependent reductive carboxylation, highlighting how dehydrogenase regulation coordinates carbon routing between cytosolic and mitochondrial compartments [161].

Pharmacologic inhibition of PDKs can reverse this metabolic state [58]. Agents such as DCA activate PDHC, enhance mitochondrial oxidation, increase ROS production, and induce apoptosis in select tumor types [162]. These effects position the PDHC–PDK axis as a central metabolic switch governing the balance between glycolytic and oxidative metabolism [163].

Clinical evidence further supports the pathological relevance of PDHC suppression in cancer progression. In hepatocellular carcinoma (HCC), reduced PDHA1 (the E1α subunit of PDHC) expression correlates with poor patient survival. Restoration of PDHA1 expression in HCC cell lines decreases glycolytic flux, reduces lactate production, enhances oxidative phosphorylation, increases ATP levels, and promotes apoptosis, identifying PDHA1 loss as a driver of glycolytic reprogramming and tumor progression [163].

Beyond cancer, PDK-mediated PDHC inhibition represents a common mechanism across multiple disease contexts, including metabolic syndrome and ischemic disorders [164]. Elevated PDK expression induces a characteristic “glycolytic shift”, marked by reduced oxidative phosphorylation, increased lactate production, and metabolic remodeling that favors pathological cell survival and growth [165]. Collectively, these findings underscore the PDHC–PDK axis as a conserved dehydrogenase-based regulatory node linking mitochondrial dysfunction to disease-associated metabolic reprogramming.

5.1.4 NADPH-Generating Dehydrogenases: Redox Control, Biosynthesis, and One-Carbon Metabolism

Tumor cells require substantial NADPH to support fatty acid and nucleotide biosynthesis, maintain glutathione and thioredoxin antioxidant systems, and counter reactive oxygen species [166]. Three major cytosolic dehydrogenases generate NADPH: G6PDH in the oxPPP pathway, IDH1 via isocitrate oxidation, and ME1 via malate decarboxylation [116]. These enzymes form an interconnected network enabling tumors to maintain anabolic growth and redox homeostasis under variable conditions. Recently, Talwar et al. [74] demonstrated that although compensatory fluxes from alternative NADPH-generating pathways can sustain redox balance, the loss of G6PDH imposes distinct metabolic liabilities, revealing its indispensable role in oxidative stress tolerance. G6PDH deficiency specifically alters the NADPH/$NADP^+$ ratio, creating re-

dox stress and impairing folate metabolism. PPP-derived NADPH sustains dihydrofolate reductase (DHFR) activity; when NADPH becomes limiting, dihydrofolate accumulates, dUMP increases, and nucleotide synthesis fails. This leads to replication stress and genomic instability, establishing G6PDH as a non-redundant metabolic requirement despite the presence of alternative NADPH pathways [140].

Furthermore, IDH1 connects cytosolic NADPH production to mitochondrial metabolism by converting isocitrate to α-KG [167]. During hypoxia or mitochondrial dysfunction, IDH1 operates in reverse through reductive carboxylation, maintaining citrate production and lipogenesis when oxidative metabolism is compromised [114]. ME1 provides parallel NADPH generation by converting malate to pyruvate, linking mitochondrial malate export to cytosolic redox support [168]. The G6PDH-IDH1-ME1 network collectively buffers oxidative stress, fuels biosynthesis, and supports proliferation [169]. Targeting these enzymes offers therapeutic opportunities through oxPPP inhibition, IDH1 or ME1 blockade, and combinations that simultaneously limit NADPH production while increasing oxidative stress.

Beyond their direct roles in redox buffering and anabolic biosynthesis, NADPH-generating dehydrogenases are tightly coupled to one-carbon metabolism, linking cellular redox state to nucleotide synthesis and epigenetic regulation [170]. Dehydrogenases regulate flux through both mitochondrial and cytosolic one-carbon pathways, making redox balance central to DNA synthesis and chromatin regulation. Insufficient NADPH availability increases oxidative stress and stalls folate-dependent reactions, amplifying replicative and epigenetic instability [4]. Conversely, robust NADPH production supports reductive biosynthesis and antioxidant defenses. Additional glycolytic connections influence this network. Glucose-6-phosphate isomerase activity determines PPP flux and NADPH generation. Although GAPDH is not an NADPH-producing enzyme, its control of glycolytic flux in proliferating cancer cells influences 3-phosphoglycerate availability for serine biosynthesis, thereby linking glycolysis to serine–glycine metabolism and nucleotide production [171]. *De novo* serine synthesis, which is strongly upregulated in proliferating cancer cells, further channels glucose-derived carbon and reducing equivalents into glycine production and one-carbon metabolism [172]. These findings establish NADPH-generating dehydrogenases as master regulators integrating redox biology, anabolic metabolism, and epigenetic stability in cancer, providing a mechanistic rationale for therapeutic strategies targeting the redox-one-carbon axis.

5.1.5 Integrated Dehydrogenase Network: Systems-Level Control of Cancer Metabolic Phenotypes

Taken together, the above indicates that cancer metabolic reprogramming results from coordinated changes across an interconnected dehydrogenase network rather than from isolated enzyme dysfunction. The six examined dehydrogenases, namely, GAPDH, LDH, PDHC, G6PDH, MDH1/2, and IDH1/2, operate as an integrated system, controlling aspects of carbon metabolism essential for proliferation, stress response, and microenvironment remodeling. GAPDH influences glycolytic flux via NAD^+ dependence, while LDH regenerates NAD^+ under hypoxia by converting pyruvate to lactate. PDK inhibits PDHC, reinforcing glycolytic and hypoxic adaptations. NADPH-generating enzymes such as G6PDH, IDH1, ME1, and IDH2 provide reductive power for biosynthesis and redox balance, especially under metabolic stress. They enable reductive carboxylation under hypoxia, diverting carbon flow to support lipogenesis. Oncogenic mutations, such as those in IDH1/2, generate metabolites, including D-2-hydroxyglutarate, that affect epigenetic regulation and metabolic homeostasis. These interconnected pathways highlight that cancer metabolism relies on a distributed circuitry that regulates flux, redox, and epigenetic processes, underscoring the importance of targeting networks rather than individual enzymes.

5.2 Dehydrogenases in Metabolic Syndrome, Obesity, and Type 2 Diabetes

Metabolic syndrome encompasses a cluster of interconnected disorders, central obesity, insulin resistance, dyslipidemia, and hypertension, that collectively increase the risk of type 2 diabetes (T2D) and cardiovascular disease (CVDs) [173]. At the molecular level, these conditions share a key characteristic: impaired metabolic flexibility, which is the inability to effectively switch between glucose and fatty acid oxidation depending on nutritional status [174]. The six dehydrogenase gatekeepers play pivotal roles in this metabolic inflexibility, with their dysregulation both contributing to and resulting from the pathophysiology of metabolic syndrome.

5.2.1 Pyruvate Dehydrogenase Complex Suppression and the Randle Cycle in Insulin Resistance

PDHC represents a critical control point at which metabolic inflexibility emerges in insulin-resistant states [162,164]. Under physiological conditions, PDHC activity rises in the fed state to promote glucose oxidation and falls during fasting to conserve glucose for obligate glucose-utilizing tissues. In obesity and type 2 diabetes (T2D), this adaptive switching is altered, leading to chronic suppression of PDHC activity, driven primarily by sustained upregulation of PDK4 [162,175]. While PDHC–PDK control governs pyruvate entry into mitochondrial oxidation, MDH1/MDH2-mediated MAS capacity provides a complementary layer of control by determining how efficiently glycolysis-derived NADH is reoxidized via mitochondrial respiration [176]. Mitochondrial dysfunction and altered regulation of mitochondrial enzymes and dy-

namics in insulin-resistant states reduce the capacity to oxidize NADH, thereby promoting metabolic inflexibility. Although these changes make compensatory reliance on cytosolic NAD^+-regenerating pathways plausible, direct evidence implicating impaired MAS flux as the primary driver requires MAS-focused studies [177].

PDK4 levels are significantly increased in the skeletal muscle tissue of genetically obese, diet-induced obese, and insulin-resistant mice, as well as in diabetic rats, while the expression of other PDKs remains stable [178,179,180]. This abnormal increase in PDK4 is driven by various factors linked to metabolic syndrome: higher free fatty acids activate PPARα/δ transcription factors that boost PDK4 expression; persistent high blood sugar and excess lipids raise acetyl-CoA and NADH levels, thereby allosterically activating PDKs; and inflammatory cytokines, especially TNF-α and IL-6, increase PDK4 through NF-κB signaling [90]. Sustained inhibition of PDHC triggers a self-reinforcing cycle of metabolic inflexibility. Reduced glucose oxidation worsens hyperglycemia, further impairing insulin signaling and increasing dependence on fatty acid oxidation [181]. This process reflects the pathological activation of the Randle cycle, where elevated fatty acid oxidation suppresses glucose utilization, locking tissues into a substrate-inflexible state [182]. The effects of PDHC suppression go beyond skeletal muscle. In hepatocytes, increased PDK4 activity prevents pyruvate from entering the TCA cycle, redirecting carbon toward gluconeogenesis and maintaining excessive hepatic glucose output despite systemic hyperglycemia [183]. In the heart, cardiac-specific overexpression of PDK4 in mice mimics the metabolic profile of diabetic cardiomyopathy, characterized by an inability to increase glucose oxidation in response to insulin or increased workload [184]. This energetic inflexibility contributes to diastolic dysfunction and increases vulnerability to ischemic injury in diabetic myocardium.

Pharmacological inhibition of PDK has provided important mechanistic validation of PDHC suppression in insulin resistance. DCA, a pan-PDK inhibitor, restores PDHC activity and partially reverses metabolic inflexibility in animal models of T2D, improving glucose tolerance and insulin sensitivity. However, its lack of isoform selectivity and dose-limiting peripheral neuropathy have constrained clinical translation [184]. These limitations underscore the pathological relevance of PDHC suppression while highlighting the need for more selective PDK-targeted strategies.

5.2.2 GAPDH Glycation and Oxidative Modification in Diabetic Complications

While PDHC suppression drives systemic metabolic inflexibility in insulin resistance, chronic hyperglycemia in established diabetes creates a glucotoxic environment that directly modifies dehydrogenase function through non-enzymatic glycation and oxidative damage [185]. GAPDH, with its reactive catalytic cysteine (Cys152) and high cellular abundance, is particularly vulnerable to these modifications and serves as both a target and a mediator of diabetic complications [186]. Advanced glycation end products (AGEs) form when reducing sugars react with protein amino groups through the Maillard reaction [187]. Sofronova et al. [188] demonstrate that GAPDH undergoes lysine glycation, altering its structural properties and impairing interactions with protein and RNA partners, thereby demonstrating its susceptibility to glycation-induced functional modulation. Inhibition of GAPDH under hyperglycemic conditions reduces glycolytic flux, leading to accumulation of upstream intermediates that are diverted into pathogenic pathways, including the polyol and hexosamine pathways, and to enhanced methylglyoxal formation, thereby promoting AGE production and inflammatory signaling [185]. Beyond glycation, oxidative stress promotes GAPDH S-nitrosylation, sulfenylation, and carbonylation, inhibiting its glycolytic activity and driving nuclear translocation, where GAPDH participates in apoptotic and stress-responsive transcriptional programs [59].

Notably, GAPDH inhibition promotes diversion of upstream glycolytic intermediates into pathogenic pathways associated with diabetic complications. A central feature of this process is the methylglyoxal–GAPDH axis. When GAPDH activity is reduced, glyceraldehyde-3-phosphate accumulates and spontaneously degrades into methylglyoxal, a highly reactive dicarbonyl. Methylglyoxal modifies proteins, lipids, and nucleic acids, including GAPDH itself, reinforcing glycolytic inhibition and amplifying cellular stress. In parallel, methylglyoxal-mediated modification of mitochondrial proteins impairs oxidative phosphorylation, further exacerbating energetic dysfunction and redox imbalance in diabetic tissues [189,190].

5.2.3 Revisiting the G6PDH "Deficiency Paradox" in Metabolic and Cardiovascular Disease

G6PDH plays a complex and highly context-dependent role in metabolic disease. Although G6PDH deficiency is the most prevalent human enzymopathy worldwide [191], early epidemiological observations suggested that it might confer cardiovascular protection, mainly based on reports of reduced serum cholesterol levels and a putative "statin-like" effect [54,192]. This hypothesis, sometimes referred to as the "G6PDH deficiency paradox", has been fundamentally revised by more recent large-scale epidemiological and mechanistic studies, which demonstrate that G6PDH deficiency is associated with increased cardiovascular risk, particularly in metabolically stressed or genetically high-risk populations such as patients with familial hypercholesterolemia [123,193,194,195]. In a recent cohort study, Errigo et al. [192] showed that hereditary G6PDH deficiency markedly increases cardiovascular risk in familial hypercholesterolemia, underscoring the importance of intact

redox homeostasis for atheroprotection. Mechanistically, reduced NADPH availability in G6PDH deficiency compromises antioxidant defenses in endothelial cells, vascular smooth muscle cells, and macrophages. This redox imbalance promotes oxidative stress, nitric oxide dysregulation, endothelial dysfunction, and accelerated atherosclerotic plaque development, establishing a causal link between impaired PPP flux and vascular pathology.

In contrast, in obesity and metabolic syndrome, G6PDH expression and activity are frequently upregulated in adipose tissue, where increased NADPH production supports *de novo* lipogenesis and redox-dependent signaling pathways [196]. Adipocyte G6PDH activity correlates positively with body mass index, insulin resistance, and inflammatory cytokine production, and elevated pentose phosphate pathway flux promotes adipocyte hypertrophy, ectopic lipid accumulation, and inflammatory activation, in part through enhanced NADPH oxidase–derived reactive oxygen species [191]. Consistent with this, G6PDH, the rate-limiting enzyme of the PPP and a major source of cytosolic NADPH, is upregulated in adipose tissue of obese animal models [197]. Notably, moderate G6PDH deficiency has been reported to attenuate certain obesity-associated metabolic abnormalities. Experimental and epidemiological studies suggest that partial G6PDH deficiency may confer protection against obesity, insulin resistance, and T2D [191,198,199]. Proposed mechanisms include constrained lipogenesis due to limited NADPH availability, reduced oxidative stress secondary to lower NADPH oxidase activity, and restricted metabolic plasticity that may paradoxically limit the deleterious consequences of chronic nutrient excess.

The apparent contradiction between these observations reflects critical tissue-specific trade-offs. While reduced G6PDH activity may limit adipose tissue expansion under conditions of nutrient surplus, the same NADPH deficiency impairs vascular redox homeostasis, particularly in the setting of hyperlipidemia or chronic inflammation. In liver and skeletal muscle, G6PDH contributes to maintaining redox balance during metabolic stress, whereas in the vasculature its deficiency amplifies oxidative injury and atherogenesis [67]. Consequently, any potential metabolic benefit of reduced G6PDH activity in adipose tissue is outweighed by its pro-atherogenic effects at the vascular level.

Collectively, these findings establish G6PDH as a double-edged metabolic regulator. Excessive activity promotes lipogenesis and inflammation in obesity, whereas deficiency exacerbates oxidative stress and cardiovascular risk. This nuanced, context-dependent behavior underscores the importance of tissue specificity, disease stage, and metabolic background when considering G6PDH as a modifier of metabolic disease or as a potential therapeutic target in metabolic syndrome and diabetes

5.2.4 LDH Isoform Switching and Lactate Metabolism

As noted earlier, lactate, once regarded solely as a metabolic waste product, is now recognized as a significant metabolic substrate and signaling molecule. In metabolic syndrome and T2D, altered lactate production and utilization, driven in part by changes in LDH isoform expression, contribute to systemic metabolic dysfunction [200]. Feng et al. [201] demonstrated that, in diet-induced obesity, adipocyte-restricted upregulation of LDHA drives excessive lactate production, which in turn potentiates macrophage inflammation through direct inhibition of prolyl hydroxylase domain protein 2 (PHD2) and stabilization of HIF-1α. Consistent with these findings, additional studies have shown that obesity and T2D are associated with a broader shift toward LDHA predominance across multiple tissues, including skeletal muscle, liver, and adipose depots, reinforcing lactate-driven metabolic inflexibility and redox imbalance at the systemic level [202,203,204,205].

LDHA preferentially catalyzes the reduction of pyruvate to lactate rather than its mitochondrial oxidation, contributing to the chronically elevated circulating lactate levels commonly observed in insulin-resistant states [206]. Sustained hyperlactatemia is not metabolically neutral; instead, it exerts multiple deleterious effects. Lee et al. [207] recently demonstrated that lactate homeostasis is maintained through reciprocal regulation of glycolysis and lipolysis, whereby lactate impairs insulin signaling in skeletal muscle, activates the adipocyte G-protein–coupled receptor GPR81 to suppress lipolysis, and promotes its own clearance through mitochondrial oxidation. These findings position lactate as both a metabolic substrate and a signaling molecule, directly linking hyperlactatemia to impaired insulin action and systemic metabolic dysfunction. In addition, lactate accumulation contributes to local and systemic acidosis, further compromising insulin sensitivity and metabolic flexibility.

In adipose tissue, LDHA upregulation supports a Warburg-like metabolic phenotype in hypertrophic adipocytes. Despite adequate oxygen availability, these cells exhibit increased glucose uptake and preferential lactate production, resembling the metabolic behavior of proliferating cells [208]. This shift facilitates lipid synthesis and inflammatory cytokine production while creating a pseudo-hypoxic microenvironment that promotes fibrosis, immune cell infiltration, and adipose tissue dysfunction. Collectively, LDH isoform switching and altered lactate metabolism reinforce insulin resistance and metabolic inflexibility, positioning LDHA as a key mediator linking carbohydrate metabolism, redox balance, and inflammatory signaling in metabolic disease.

5.2.5 Integrated Dehydrogenase Dysfunction in Metabolic Syndrome

Metabolic syndrome arises from dysfunction across multiple dehydrogenases, creating a self-reinforcing

metabolic disorder. Suppressed PDHC limits glucose oxidation, while modified GAPDH impairs glycolysis, leading to hyperglycemia. Increased G6PDH activity in adipose tissue elevates NADPH levels, supporting lipogenesis and inflammation. Higher LDH activity and LDHA promote lactate accumulation, reinforcing redox imbalance and metabolic signaling. These changes cause metabolic inflexibility, impairing hepatic glucose suppression, skeletal muscle glucose uptake, and oxidation despite hyperglycemia. The syndrome arises not from isolated enzyme defects but from coordinated rewiring of metabolic circuits that control carbon flow, cofactor availability, and redox balance. Recognizing dehydrogenase dysfunction as central to metabolic comorbidity underscores how altering these key regulators destabilizes energy homeostasis, thereby maintaining insulin resistance.

5.3 Inherited Enzymopathies: Single-Gene Defects Revealing Dehydrogenase Essentiality

Enzymopathies, also known as enzyme disorders, are a group of genetic diseases characterized by dysfunctional enzymes, which are crucial players in biochemical pathways [209]. These disorders arise from mutations in genes encoding enzymes, leading to alterations in enzyme structure or function. The most common enzymopathies involve red blood cells, affecting intraerythrocytic metabolism [210]. The most common enzymopathies have been linked to red blood cells [211]; however, in this section, we will explore two enzymopathies, namely G6PDH deficiency, the most common human enzymopathy, and PDHC deficiency, a rare genetic metabolic disorder primarily affecting the brain.

To the best of our knowledge, no cases of inherited GAPDH deficiency have been reported in humans, consistent with the enzyme's indispensable role in glycolysis and its extensive regulatory functions in transcriptional regulation, apoptosis, and the cytoskeleton dynamics. Complete loss of GAPDH activity would abolish glycolytic ATP production, thereby compromising cellular survival and, by extension, embryonic development, rendering it untenable. Similarly, inherited deficiencies that affect the normal catalytic activity of IDHs have not been described. While IDH1 and IDH2 are well known for oncogenic gain-of-function mutations that produce D-2-HG, loss-of-function mutations that impair physiological IDH activity appear to be absent [109]. The presence of multiple isoforms (IDH1, IDH2, and IDH3) may provide partial metabolic redundancy; however, complete loss of IDH function would likely compromise both energy metabolism and NADPH regeneration, suggesting embryonic lethality. LDH deficiencies are exceptionally rare and typically involve single isoforms (LDHA or LDHB), with affected individuals often remaining asymptomatic or presenting with mild, tissue-specific phenotypes [212].

Together, these observations underscore how the clinical visibility of inherited enzymopathies reflects not only mutation frequency but also the tolerance of metabolic networks to enzyme loss. Enzymes that occupy essential or poorly buffered nodes of metabolism may never be manifested as viable inherited disorders, highlighting the fundamental importance of dehydrogenases in sustaining life

5.3.1 G6PDH Deficiency: The Most Common Enzymopathy

G6PDH deficiency affects approximately 500 million people worldwide, making it the most prevalent enzymopathy and one of the most common inherited metabolic disorders [53]. This X-linked condition arises from mutations in the *G6PDH* gene that impair enzyme stability, catalytic activity, or both [213]. To date, over 230 G6PDH variants have been identified. Most of these variants mainly arise from single-point mutations, but there is a growing recognition of the role of double mutations, synonymous mutations, and intronic mutations in causing G6PDH deficiency [214].

The central biochemical defect in G6PDH deficiency is impaired NADPH generation via the oxidative pentose phosphate pathway, leading to heightened susceptibility to oxidative stress [215]. Erythrocytes are uniquely vulnerable because they rely exclusively on this pathway for NADPH production, lack nuclei and ribosomes for enzyme replacement, and are continuously exposed to high oxygen tension and iron-mediated redox reactions [216]. Under physiological conditions, NADPH maintains glutathione in its reduced form (GSH) via glutathione reductase, thereby protecting red blood cells from peroxide-induced damage [217]. In G6PDH-deficient erythrocytes, oxidative challenges overwhelm the limited NADPH reserve, leading to GSH depletion, hemoglobin oxidation, Heinz body formation, membrane instability, and ultimately hemolytic anemia [218].

Clinical severity in G6PDH deficiency strongly correlates with residual enzymatic activity [219]. Variants classified as Class I (<10% activity) are associated with chronic nonspherocytic hemolytic anemia (CNSHA), reflecting severe, persistent impairment. Class II variants (10–60% activity) typically present with episodic hemolysis, often precipitated by oxidative stress, but do not cause chronic anemia. Class III variants (60–90% activity) are generally asymptomatic under basal conditions, though hemolysis may occur during intense oxidative challenges. Acute hemolytic episodes are commonly triggered by oxidant drugs (e.g., primaquine, rasburicase, sulfonamides), systemic infections, or ingestion of fava beans (*Vicia faba*), which contain the redox-active glycosides vicine and convicine. Clinically, episodes manifest with jaundice, dark urine, pallor, fatigue, and, in severe cases, life-threatening anemia. Management centers on avoiding oxidative trig-

gers, providing supportive care during crises, and educating patients about the risks of oxidant exposure [219].

The global distribution of G6PDH deficiency closely mirrors regions historically endemic for malaria, reflecting a classic example of balanced polymorphism. Heterozygous females and hemizygous males exhibit partial protection against severe *Plasmodium falciparum* infection, conferring a selective evolutionary advantage despite the risk of hemolysis. This evolutionary trade-off explains the high prevalence of G6PDH deficiency in sub-Saharan Africa, the Mediterranean basin, the Middle East, and Southeast Asia, underscoring how variation in a single metabolic enzyme can shape both disease susceptibility and human population genetics [217].

5.3.2 Pyruvate Dehydrogenase Complex Deficiency: Energy Crisis From Birth

As discussed in Section 4.3, the PDHC catalyzes the irreversible conversion of pyruvate to acetyl-CoA, thereby committing glucose-derived carbon to mitochondrial oxidation. Inherited deficiency of this complex disrupts the essential metabolic link between glycolysis and the TCA cycle, leading to pyruvate accumulation and its diversion into lactate. As a result, PDHC deficiency produces a profound and persistent impairment of cellular energy metabolism from birth. It represents a leading cause of primary lactic acidosis and early-onset neurodegenerative disease [220,221].

The most common form of primary PDHC deficiency arises from mutations in PDHA1, which encodes the E1α subunit of the complex and is located on the X chromosome. Less frequently, autosomal recessive mutations affect other structural components of the complex, including PDHB (E1β), DLAT (E2), DLD (E3), and PDHX (E3-binding protein). In addition, defects in more than 20 genes involved in complex assembly or cofactor metabolism, particularly in thiamine and lipoic acid pathways, can cause secondary PDHC deficiency [222].

Clinically, PDHC deficiency shows considerable phenotypic variability. Affected males typically present with three main forms: (i) severe neonatal lactic acidosis and encephalopathy, often linked to congenital brain malformations; (ii) Leigh or Leigh-like syndrome beginning in infancy or childhood; and (iii) milder, relapsing neurological issues starting in childhood, with symptoms like ataxia, dystonia, and peripheral neuropathy. Heterozygous females often display distinct, sometimes more complex, phenotypes such as microcephaly, dysmorphic features, epilepsy, and spastic diplegia or quadriplegia, due to mosaic expression from X-chromosome inactivation. Neuroimaging frequently shows cortical and subcortical atrophy, ventricular dilation, cystic lesions, or agenesis of the corpus callosum, with variable lactic acidosis [222,223].

Impaired pyruvate oxidation shifts pyruvate to lactate due to increased NADH: NAD^+ ratio, raising the lactate-to-pyruvate ratio above ~10:1, indicating redox imbalance rather than lactate overproduction alone [224]. Tissues with high energy demand, including the brain, heart, and skeletal muscle, are particularly vulnerable. In contrast to adaptive PDHC suppression in cancer or metabolic stress, inherited deficiency confers no metabolic advantage and instead results in a chronic energy crisis. Disease severity ranges from fatal neonatal forms to milder phenotypes with intermittent metabolic decompensation, and atypical presentations, such as isolated exercise-induced dystonia, can complicate diagnosis [225].

Several studies have expanded the molecular and regulatory landscape of PDHC deficiency. Bruhn et al. [226] demonstrated that synonymous and deep intronic variants can disrupt splicing of PDHA1, leading to exon skipping or pseudoexon inclusion and variable residual enzyme activity. Horga et al. [223] showed that skewed X-chromosome inactivation patterns can profoundly influence disease severity in females, even among monozygotic twins carrying identical PDHA1 mutations, highlighting the role of epigenetic mosaicism. Complementing these findings, DeBrosse et al. [227] reported striking heterogeneity in neurological outcomes and survival across a large cohort of genetically confirmed cases, with limited correlation among genotype, measured enzyme activity, and clinical course. Together, these observations underscore that complex interactions among genetic lesions, epigenetic regulation, and metabolic context shape PDHC deficiency.

Treatment centers on enhancing residual PDHC activity and managing metabolic consequences. High-dose thiamine can dramatically improve some patients by increasing PDHC cofactor availability and stabilizing the enzyme complex [223]. The ketogenic diet provides an alternative fuel source, bypassing the PDHC blockade [228]. DCA, which inhibits PDKs and activates PDHC, shows variable efficacy but risks peripheral neuropathy with chronic use [229]. Despite interventions, outcomes remain guarded, with most patients experiencing significant neurological morbidity.

5.3.3 Lessons From Inherited Enzymopathies

Taken together, the above indicate that inherited enzymopathies validate and reveal principles of metabolic networks in human health and disease, highlighting key points:

i. Metabolic bottlenecks: Certain dehydrogenases are non-redundant control points; G6PDH ensures NADPH in erythrocytes, and PDHC is crucial for glucose entry into mitochondria.

ii. Tissue vulnerabilities: Phenotypes depend on tissue demands; hemolysis in G6PDH, neurological issues in PDHC deficiency, and neurodevelopmental deficits in AGC1 reflect tissue-specific dependencies.

iii. Limits of compensation: Unlike acquired diseases, inherited enzymopathies show their metabolic flexibility limits, with networks being highly optimized.

iv. Therapeutic insights: Treatments leverage residual capacity, such as thiamine for PDHC, ketogenic diets for PDH deficiency, and avoidance strategies in G6PDH deficiency.

v. Evolutionary aspects: Variants like G6PDH persistence suggest evolutionary trade-offs, where metabolic diversity offers population benefits.

These lessons explain how minor perturbations in enzyme activity can lead to significant disease and connect core metabolic control to broader disease systems.

5.4 Dehydrogenase Dysfunction in Neurodegeneration and Aging

The progressive decline of neuronal function during aging and in neurodegenerative diseases reflects fundamental disruptions in cellular metabolism, with dehydrogenases acting as both critical targets and active mediators of pathology [230]. Unlike the acute and adaptive metabolic reprogramming observed in cancer or the systemic metabolic inflexibility characteristic of metabolic syndrome, neurodegeneration results from the cumulative effects of oxidative damage, mitochondrial dysfunction, and impaired redox homeostasis over decades [231].

Neurons are uniquely vulnerable to dehydrogenase dysfunction due to their exceptional energetic demands: despite accounting for only ~2% of body mass, the brain consumes approximately 20% of total oxygen [232]. This high metabolic burden, coupled with limited regenerative capacity, renders neuronal metabolism particularly sensitive to disruptions in NAD^+/NADH balance, mitochondrial integrity, and redox control. Across aging and neurodegenerative disorders, dehydrogenase dysfunction manifests as oxidative stress–mediated enzyme impairment and mitochondrial dysfunction, compromising ATP production and metabolic flexibility [233]. Complementary evidence shows that age-associated decline in NAD^+ pools, driven by PARP activation, CD38 activity, and reduced biosynthesis, disrupts NAD^+-dependent pathways, including sirtuin signaling [234]. Together, these interconnected mechanisms converge to accelerate neuronal aging and vulnerability to degeneration.

5.4.1 Glyceraldehyde-3-Phosphate Dehydrogenase: From Glycolytic Enzyme to Pathological Aggregation Seed

While Section 4.1 established GAPDH as a redox-sensitive metabolic switch, its contribution to neurodegeneration extends well beyond impaired glycolysis [235]. As discussed above, the enzyme's catalytic cysteine (Cys152), essential for its dehydrogenase activity, is a critical target of chronic oxidative and nitrosative stress that characterizes aging and neurodegenerative brains. In Alzheimer's disease (AD), Parkinson's disease (PD), and related disorders, post-translationally modified GAPDH undergoes a pathological transition from a soluble metabolic enzyme into an aggregation-prone protein with direct neurotoxic properties [236].

Multiple oxidative modifications of GAPDH have been documented in neurodegenerative conditions. S-nitrosylation of Cys152, driven by excessive nitric oxide production during neuroinflammation, abolishes enzymatic activity and promotes GAPDH nuclear translocation, where it participates in pro-apoptotic transcriptional signaling cascades [237]. Progressive oxidation of Cys152 to sulfenic, sulfinic, or sulfonic acid forms destabilizes the protein's tertiary structure, exposing hydrophobic regions that favor oligomerization and aggregation. S-glutathionylation, which can transiently protect Cys152 from irreversible oxidation, becomes maladaptive when sustained, promoting aberrant protein–protein interactions and aggregation [238].

The pathological consequences of GAPDH oxidation extend far beyond loss of glycolytic flux. Oxidatively modified GAPDH assembles into amyloid-like aggregates that act as nucleation seeds, propagating protein misfolding in a prion-like manner. These aggregates exert intrinsic neurotoxicity by destabilizing membrane integrity, impairing mitochondrial function, and triggering apoptosis signaling. Importantly, GAPDH aggregates interact synergistically with disease-specific aggregation-prone proteins. In AD, GAPDH accelerates β-amyloid (Aβ) fibrillization and amplifies Aβ-mediated toxicity; in PD, GAPDH co-localizes with α-synuclein within Lewy bodies; and in Huntington's disease, oxidized GAPDH binds mutant huntingtin, facilitating aggregate formation [235,239].

Notably, Itakura et al. [239] demonstrated that incubation of GAPDH aggregates with Aβ40 markedly accelerates amyloid assembly, eliminating the lag phase of fibrillization and promoting β-sheet–rich structures through cross-seeding interactions. The resulting hybrid GAPDH/Aβ aggregates exhibited enhanced neurotoxicity compared with either species alone, inducing mitochondrial membrane depolarization, cytochrome c release, and nuclear translocation of apoptosis-inducing factor (AIF) in neuronal models. *In vivo*, co-administration of Aβ40 and GAPDH aggregates produced more severe pyramidal cell loss in the hippocampal CA3 region, accompanied by pronounced gliosis and mitochondrial dysfunction, than Aβ40 alone.

Genetic evidence further implicates GAPDH in neurodegenerative susceptibility. A study by Ping et al. [240] identified the rs1136666 polymorphism in the GAPDH gene as a genetic factor associated with increased risk of Parkinson's disease, with the CC genotype conferring particular susceptibility in older male patients. Functional assays in SH-SY5Y cells demonstrated that expression of the rs1136666 CC variant induced oxidative stress, disrupted the balance between pro- and anti-apoptotic signaling, and promoted neuronal apoptosis. Moreover, the CC genotype sensitized cells to mitochondrial toxins such as rotenone, with combined exposure producing greater oxidative injury and cell death than either insult alone. These findings suggest that even subtle genetic alterations in GAPDH

can heighten neuronal vulnerability to oxidative and mitochondrial stress, thereby influencing neurodegenerative risk across the aging trajectory.

5.4.2 Mitochondrial Dehydrogenase Impairment: Energy Crisis in Neurons

Neurons rely almost exclusively on oxidative phosphorylation for ATP production, making mitochondrial dehydrogenases, including the PDHC, IDH3, and MDH2, essential for neuronal survival [241]. A recent review by Steffan et al. [242] highlights that age-related decline and disease-associated impairment of mitochondrial dehydrogenases directly contribute to the bioenergetic failure underlying neurodegeneration. In the aging central nervous system, reduced activity of these enzymes compromises oxidative phosphorylation, diminishes ATP production, and impacts metabolic flexibility. These deficits are further exacerbated in neurodegenerative disorders, where impaired mitophagy, dysregulated mitochondrial dynamics, and enzyme dysfunction accelerate neuronal vulnerability.

PDHC activity is significantly reduced (~30%) in AD brains, particularly in regions most affected by pathology [243]. The decline in PDHC activity observed in aging and AD reflects convergent mechanisms. Oxidative stress particularly compromises the thiamine-dependent E1 subunit, while metabolic stress–induced activation of PDKs and reduced expression of mitochondrial enzymes further suppress PDHC function [244]. Impaired pyruvate oxidation limits acetyl-CoA entry into the TCA cycle, forcing neurons to rely more on glycolysis. The resulting accumulation of lactate and local acidosis further compromises neuronal function and exacerbates synaptic dysfunction. Thiamine deficiency, common in older adults, amplifies PDHC dysfunction and has been linked to accelerated cognitive decline, underscoring the vulnerability of this enzymatic node in aging brains [245,246].

IDH3, the rate-limiting enzyme of the oxidative TCA cycle, also exhibits progressive impairment with aging [247]. In the pathological progression of AD, IDH3 activity is reduced by 27% [248]. This deficit directly limits NADH generation by Complex I of the electron transport chain, resulting in an ATP shortfall that neurons cannot adequately compensate for through glycolysis. Beyond energy failure, IDH3 dysfunction reduces α-ketoglutarate availability, with downstream effects on neurotransmitter synthesis and α-KG-dependent epigenetic regulation, thereby further compromising neuronal homeostasis [249].

In neuronal and other oxidative tissues, impaired MDH1/MDH2 function or reduced MAS flux limits the transfer of cytosolic NADH into mitochondria, prompting a compensatory shift toward cytosolic NAD^+ regeneration via lactate formation and thereby reducing energetic efficiency. This vulnerability may help explain, at least in part, why alterations in MDH-dependent redox coupling are linked to lactic acidosis, energy failure, and heightened stress sensitivity in neurological disease states [250]. Alterations in MDH2 expression during aging and in late-onset AD reflect broader remodeling of mitochondrial redox metabolism rather than a uniform loss of MAS capacity. Normal aging is associated with reduced MDH2 expression, which may limit cytosolic NADH transfer into mitochondria and modestly increase reliance on lactate dehydrogenase–mediated NAD^+ regeneration [251]. In contrast, late-onset AD (LOAD) fibroblasts show increased MDH2 expression, indicating disease-specific rewiring of the TCA cycle and redox fluxes rather than a simple age-related decline [252]. These disruptions in NADH handling and mitochondrial oxidation are particularly consequential at synaptic terminals, where the high ATP demand for vesicle cycling, neurotransmitter release, and ion homeostasis cannot be met solely by glycolysis.

The convergence of PDHC, IDH3, and MDH2 dysfunction creates a profound and self-reinforcing energetic deficit in vulnerable neuronal populations. Dopaminergic neurons in Parkinson's disease, characterized by extensive axonal arborization and high basal oxidative stress, are particularly unable to sustain the ATP levels required for long-term survival [253]. Similarly, hippocampal neurons in AD, which are critical for learning and memory and are energetically demanding due to synaptic plasticity, undergo selective degeneration as mitochondrial bioenergetic capacity progressively declines [254]. Collectively, these observations position mitochondrial dehydrogenase impairment as a convergent and mechanistically unifying contributor to neuronal energy failure and selective vulnerability in neurodegenerative disease.

5.4.3 NAD^+ Decline: The Common Denominator of Aging

Age-related decline in NAD^+ is a unifying mechanism linking dehydrogenase dysfunction to neuronal aging and neurodegeneration [255]. Notably, NAD^+ levels decline progressively with age: cutaneous NAD^+ levels decrease by at least 50% across adulthood [256], and cerebrospinal fluid NAD(H) concentrations decline by approximately 14% in individuals over 45 years of age [257]. This systemic erosion of NAD^+ availability has far-reaching consequences for all NAD^+-dependent metabolic and regulatory processes.

Multiple convergent mechanisms drive NAD^+ depletion during aging. Increased consumption by poly(ADP-ribose) polymerases (PARPs), which are activated in response to cumulative DNA damage, accelerates NAD^+ turnover. In parallel, chronic low-grade inflammation induces upregulation of CD38, a major NADase, further depleting intracellular NAD^+ pools. Age-associated downregulation of enzymes in the NAD^+ salvage pathway, including nicotinamide phosphoribosyltransferase (NAMPT), limits NAD^+ resynthesis. Oxidative stress also perturbs redox balance by shifting the NAD^+/NADH ratio

toward the reduced state, thereby functionally restricting NAD^+ availability for dehydrogenase-catalyzed reactions [255,258,259].

The decline in NAD^+ affects interconnected pathways, limiting glycolysis, impairing mitochondrial enzymes, and reducing sirtuin activity, thereby impacting mitochondrial health, antioxidant defenses, and neuronal survival. NAD^+ precursors like nicotinamide riboside or mononucleotide can partially restore NAD^+, improving mitochondrial function and reducing neuroinflammation. However, the complexity of NAD^+ metabolism across various cell compartments makes therapy challenging, requiring targeted strategies to restore balance.

5.4.4 Oxidative Stress: The Vicious Cycle of Dehydrogenase Damage

Oxidative stress in neurodegeneration establishes a self-amplifying cycle centered on dehydrogenase dysfunction [260]. Initial oxidative damage to key enzymes, including GAPDH, the pyruvate dehydrogenase complex, and mitochondrial dehydrogenases, impairs catalytic activity, thereby reducing ATP production and weakening cellular antioxidant capacity [261]. The resulting energy deficit compromises ATP-dependent ion pumps, disrupts calcium homeostasis, and increases mitochondrial ROS generation, further intensifying oxidative stress [262].

Oxidatively modified dehydrogenases tend to misfold and aggregate, activating microglia and astrocytes, which promote neuroinflammation and ROS production [263]. Damage impairs metabolism and fosters a pro-oxidant environment. In aging neurons, impaired PPP activity and reduced NADP(H) pools, together with oxidative modifications of G6PDH, weaken NADPH-dependent redox support. GAPDH oxidation normally diverts glucose into the PPP to sustain NADPH generation, but this adaptive mechanism becomes insufficient when the oxidative stress peaks [264]. These processes trap neurons in a cycle where they can't produce enough reducing power to combat damage, leading to mitochondrial dysfunction, redox imbalance, neuroinflammation, and vulnerability in neurodegenerative disease.

5.4.5 Therapeutic Implications of Dehydrogenase Dysfunction in Neurodegeneration

Elucidating the role of dehydrogenase dysfunction in neurodegeneration highlights multiple therapeutic targets. One emerging strategy is to prevent the pathological conversion of GAPDH into an aggregation-prone, neurotoxic species. Small molecules that stabilize GAPDH or impair its interactions with β-amyloid or α-synuclein may limit aggregation and toxicity. Preserving mitochondrial dehydrogenase function is another approach. Cofactor supplements such as thiamine or NAD^+ precursors support oxidative metabolism and ATP production. Enhancing residual glucose-6-phosphate dehydrogenase activity or NADPH could strengthen antioxidant defenses in vulnerable neurons. Given the interconnected nature of dehydrogenase dysfunction, single-target strategies are insufficient. Combination therapies that support energy, redox, and proteostasis are likely more effective. Early intervention guided by metabolic biomarkers may be crucial for preventing progression from metabolic dysfunction to neurodegeneration. These insights position dehydrogenases as active drivers of disease, making their preservation a promising strategy to mitigate cognitive decline and neurodegenerative diseases.

5.5 Immunometabolism and Inflammation: Dehydrogenases as Metabolic Switches in Immune Responses

The immune system's ability to mount rapid, coordinated responses against pathogens requires dramatic metabolic reprogramming. Upon activation, immune cells shift from quiescent metabolism to a highly active state that demands increased energy production, biosynthetic capacity, and redox control. The six dehydrogenase gatekeepers orchestrate these metabolic transitions, with G6PDH and LDH emerging as particularly critical nodes. Their dysregulation contributes to immunodeficiency, autoimmunity, and pathological hyperinflammation observed in severe infections. Unlike the chronic metabolic alterations in neurodegeneration or metabolic syndrome, immunometabolic changes occur rapidly, within minutes to hours, and must be precisely reversible to prevent tissue damage from sustained activation.

5.5.1 G6PDH: Master Regulator of the Neutrophil Oxidative Burst

Neutrophils critically depend on G6PDH to perform their antimicrobial functions. Upon pathogen encounter, glucose uptake increases dramatically, and most carbon flux is diverted through the pentose phosphate pathway to generate NADPH. This reducing power fuels the NADPH oxidase complex (NOX2), which produces superoxide during the respiratory burst, and supports inducible nitric oxide synthase (iNOS)–mediated nitric oxide production. Together, these pathways generate reactive oxygen and nitrogen species essential for pathogen killing [265].

G6PDH activity is also required for neutrophil extracellular trap (NET) formation, a ROS-dependent process that immobilizes and neutralizes extracellular pathogens. In G6PDH deficiency, NADPH availability becomes limiting, impairing maximal oxidative burst capacity. Nevertheless, G6PDH-deficient neutrophils exhibit partial functional compensation through upregulation of NAD^+ kinase and enhanced nicotinamide nucleotide biosynthesis, allowing residual NETosis under certain stimuli [51,266,267]. Clinically, this results in selective vulnerability to catalase-positive organisms while preserving defense against less oxidative-stress–resistant pathogens, illustrating that immune competence depends on metabolic reserve rather than on a binary enzyme function.

5.5.2 Metabolic Reprogramming in T Cell Activation: The G6PDH-LDH Axis

T cell activation induces one of the most profound metabolic transitions in mammalian biology [268]. Naive T cells primarily rely on oxidative phosphorylation, but antigen recognition triggers a rapid shift toward aerobic glycolysis and increased flux through the pentose phosphate pathway [269]. Upregulation of G6PDH expands the NADPH pool to support lipid biosynthesis and redox homeostasis, while increased R5P availability fuels nucleotide biosynthesis during clonal expansion, thereby coupling antioxidant defense with proliferative capacity [270].

Beyond biosynthesis, G6PDH influences effector function through epigenetic mechanisms. NADPH availability supports acetyl-CoA generation and histone acetylation, enhancing expression of cytotoxic genes such as granzyme B in $CD8^+$ T cells [271]. Notably, metabolic reprogramming to Warburg glycolysis is an essential component of T-cell activation [272]. LDHA upregulation sustains glycolytic flux by regenerating NAD^+ and supports rapid ATP generation during proliferation. LDHA expression peaks during cell-cycle phases with maximal biosynthetic demand.

Tumors exploit this metabolic wiring to suppress immunity. Lactate produced by cancer cell LDHA activity acidifies the tumor microenvironment, inhibiting T cell glycolysis and IFN-γ production while creating metabolic competition for glucose [273]. This lactate-mediated immunosuppression highlights the importance of dehydrogenase-controlled metabolism in shaping immune outcomes.

Furthermore, recent evidence refines this model by revealing a direct regulatory interaction between LDHB and the pentose phosphate pathway in exhausted $CD8^+$ T cells. Wan et al. [274] demonstrated that LDHB binds glucose-G6PDH, restricting its dimerization and catalytic activity, thereby depleting NADPH and triggering disulfidptosis, a redox-driven cell death program tightly linked to T-cell exhaustion. Genetic deletion of LDHB restores G6PDH activity, enhances PPP flux, preserves redox homeostasis, and reinvigorates antitumor $CD8^+$ T-cell function. Mechanistically, STAT3-dependent induction of LDHB couples chronic antigen stimulation to metabolic and epigenetic exhaustion programs, positioning the LDHB–G6PDH axis as a critical metabolic checkpoint in T-cell immunity.

5.5.3 Macrophage Polarization: Metabolic Switches Between M1 and M2 States

Macrophage functional polarization is tightly coupled to metabolic state. Pro-inflammatory (M1) macrophages adopt a glycolytic phenotype, characterized by increased GAPDH and LDHA activity, supporting rapid ATP production and the synthesis of inflammatory mediators. In this context, G6PDH-derived NADPH fuels both NADPH oxidase–dependent ROS generation and nitric oxide production [275].

In contrast, anti-inflammatory (M2) macrophages maintain intact PDHC activity and rely on mitochondrial oxidative metabolism to support tissue repair and resolution of inflammation. Transition between these states is mediated by coordinated regulation of dehydrogenases: inflammatory signals induce PDK expression, suppressing PDHC and reinforcing glycolysis, whereas anti-inflammatory cues restore mitochondrial oxidation [276]. This metabolic plasticity enables macrophages to adapt rapidly to changing tissue demands.

5.5.4 COVID-19 and Metabolic Exhaustion: When Dehydrogenases Fail

Severe infections illustrate how extreme immunometabolic demand can overwhelm redox capacity controlled by dehydrogenases. In COVID-19, sustained neutrophil activation and excessive NETosis impose extraordinary NADPH requirements. Post-mortem analyses reveal evidence of relative G6PD insufficiency, characterized by NADPH depletion and accumulation of oxidized glutathione [277,278].

This metabolic exhaustion creates a vicious cycle: impaired antioxidant capacity amplifies oxidative damage to metabolic enzymes, further compromising energy and redox homeostasis. Uncontrolled NET formation contributes to microvascular thrombosis, tissue injury, and acute respiratory distress. In parallel, prolonged T cell activation leads to metabolic collapse, with impaired glycolysis and mitochondrial dysfunction contributing to immune exhaustion and viral persistence [279]. COVID-19 thus exemplifies how failure of dehydrogenase-centered metabolic control converts protective immunity into pathological inflammation.

5.5.5 Therapeutic Implications

Collectively, these findings establish dehydrogenases as central regulators of immune cell fate and inflammatory intensity. Partial modulation of G6PDH activity may attenuate excessive NET formation without abolishing antimicrobial defense. Supporting T cell metabolic capacity while limiting tumor-derived lactate may enhance antitumor immunity. In macrophages, targeting the PDHC–PDK axis may shift the inflammatory balance toward resolution. The narrow margin between protective and pathological immune metabolism underscores the need for precise, context-specific modulation of these metabolic gatekeepers.

6. Therapeutic Targeting of the Six Dehydrogenase Gatekeepers

The strategic positioning of dehydrogenases at critical metabolic branch points presents both compelling opportunities and formidable challenges for therapeutic intervention. Throughout this review, we have shown how six dehydrogenase gatekeepers, GAPDH, LDH, PDHC, MDH1/2,

IDH1/2/3, and G6PDH, orchestrate fundamental cellular processes by controlling carbon flux, maintaining cofactor balance, and regulating redox homeostasis across cellular compartments. Dysregulation of these enzymes drives pathogenesis across a broad spectrum of conditions, including cancer, metabolic syndrome, neurodegeneration, immune disorders, and inherited enzymopathies, establishing dehydrogenases as high-priority therapeutic targets.

The therapeutic appeal of dehydrogenases lies in their ability to exert system-level control over metabolic networks. Modulation of a single dehydrogenase can propagate amplified effects across interconnected pathways, enabling large-scale metabolic rewiring to restore homeostasis or selectively eliminate diseased cells. This network-level leverage distinguishes metabolic therapies from conventional approaches that target isolated signaling molecules. However, the same centrality that makes dehydrogenases attractive targets also introduces substantial challenges, including their essential roles in normal physiology, extensive metabolic redundancy that enables compensatory adaptation, and the requirement for exquisite spatial, temporal, and isoform selectivity to avoid unacceptable toxicity.

This section reviews the current landscape of dehydrogenase-targeted therapeutics, ranging from U.S. Food and Drug Administration (FDA)–approved agents to advanced pipeline compounds and emerging experimental strategies. Although several of these agents have also received approval from other regulatory authorities, such as the European Medicines Agency (EMA), the focus here is not on regulatory comparison but on mechanistic insight. We emphasize representative examples to illustrate key principles, analyze successes in overcoming the intrinsic challenges of targeting central metabolism, and critically examine limitations that have hindered clinical translation.

Finally, we discuss emerging directions in the field, including combination strategies, context-specific targeting, drug repurposing, and artificial intelligence–assisted discovery, which together offer new opportunities to overcome historical barriers. A clear understanding of both the promise and the constraints of dehydrogenase modulation will be essential for advancing precision metabolic medicine and translating biochemical insight into durable clinical benefit.

6.1 Rationale for Therapeutic Targeting of Dehydrogenases

A central question is why targeting dehydrogenases may offer therapeutic benefit. Dehydrogenases are exceptional therapeutic targets because they control metabolic nodes where disease states create exploitable vulnerabilities. Their positioning at critical flux-control points, together with their regulation of essential cofactor systems, enables therapeutic interventions that can reshape entire metabolic networks rather than merely inhibit single reactions. Based on the preceding sections, the following points summarize why the six dehydrogenases discussed in this review represent compelling therapeutic targets:

i. Pathological states often create dependencies on specific dehydrogenase activities that exceed those in normal tissues. The Warburg effect exemplifies this: cancer cells that rely solely on glycolysis depend on LDHA for NAD^+ regeneration, creating a window in which LDHA inhibition targets tumors while sparing normal tissues with greater metabolic flexibility. Similarly, metabolic syndrome promotes PDK-mediated suppression of PDHC, thereby providing a reversible target for restoring glucose oxidation. A prime example is IDH1/2-mutant cancers, which produce the oncometabolite D-2-HG, a gain-of-function present only in tumor cells. This enables targeted therapy with FDA- and EMA-approved inhibitors, demonstrating that disease-specific enzyme states can be selectively targeted without compromising normal metabolism.

ii. Dehydrogenases regulate NAD^+/NADH and $NADP^+$/NADPH, key to cellular redox reactions. Modulating one can significantly affect metabolism. For example, G6PDH inhibition blocks PPP- and NADPH-dependent processes, including antioxidant defense, lipid, and nucleotide synthesis. This network effect makes metabolic therapies distinct from single-target treatments. The cofactor dependence of dehydrogenases also supports indirect strategies. Altering NAD^+ biosynthesis, salvage pathways, or cofactor-consuming processes can affect multiple dehydrogenases, suggesting potential in aging and neurodegeneration, where NAD^+ boosting may restore function across NAD^+-dependent processes.

iii. The spatial organization of metabolism allows targeted intervention. Cytosolic and mitochondrial NAD(H) pools remain separate, enabling compartment-specific modulation. DCA activates mitochondrial PDHC, shifting from glycolysis to oxidative phosphorylation without affecting cytosolic dehydrogenases. Isoform differences confer selectivity; LDHA is expressed in glycolytic tissues and tumors, while LDHB is expressed in the heart and brain. Developing LDHA-specific inhibitors could target tumors while protecting the heart and brain. Tissue-specific PDK isoforms also allow organ-specific modulation of glucose oxidation.

v. Dehydrogenases impact cellular processes like differentiation, proliferation, and death. IDH mutations block differentiation via epigenetic mechanisms; inhibitors promote maturation rather than death. G6PDH affects T cell activation and neutrophil function, making it a target for immune modulation. GAPDH links metabolism to transcription, apoptosis, and protein aggregation. Modulating dehydrogenases can have therapeutic effects beyond metabolism, including restoring differentiation in IDH-mutant cancers, boosting immunity, preventing neurodegeneration, and correcting metabolic issues in diabetes.

Table 3. Examples of inhibitors targeting key metabolic dehydrogenases.

Target enzyme	Representative inhibitors	Mechanism of action	Clinical status	Ref.
Mutant IDH1	Ivosidenib (AG-120)	Selective inhibition of IDH1-mutant neomorphic activity; blocks D-2HG production; induces differentiation	FDA-approved (AML, cholangiocarcinoma)	[280,281]
Mutant IDH1	Olutasidenib (FT-2102)	Selective, oral, small-molecule inhibitor of mutant IDH1	FDA-approved (AML)	[282]
Mutant IDH2	Enasidenib (AG-221)	Selective inhibition of IDH2-mutant neomorphic activity; lowers D-2HG	FDA-approved (AML)	[122]
Mutant IDH1/2	Vorasidenib (AG-881)	Dual IDH1/2 inhibitor; brain-penetrant; inhibits mutant D-2HG synthesis	FDA-approved for Grade 2 astrocytoma	[283,284]
PDHC via PDKs (all isoforms)	Dichloroacetate (DCA)	Inhibits PDK; activates PDHC; shifts metabolism toward mitochondrial oxidation	Investigational; approved only for rare disorders	[229]
LDHA	GNE-140, FX11	Competitive or allosteric LDHA inhibition; suppresses lactate production	Preclinical	[285,286]
G6PDH	6-Aminonicotinamide	Inhibits the PPP oxidative phase, reduces NADPH production	Preclinical	[287,288]
GAPDH	Koningic acid	Covalent inhibition via catalytic Cys122; alters glycolysis	Research use only	[289]

Abbreviations: AML, Acute myeloid leukemia; D-2HG, D-2-hydroxyglutarate; FDA, The Food and Drug Administration.

The therapeutic rationale for targeting dehydrogenases ultimately rests on their systems-level control of cellular metabolism. Unlike inhibiting a single biosynthetic enzyme, modulating a dehydrogenase gatekeeper can fundamentally rewire metabolic networks, alter cell fate, and exploit disease-specific vulnerabilities. The challenge lies in achieving sufficient selectivity to harness these effects therapeutically while avoiding toxicity, a challenge that has been met successfully with mutant IDH inhibitors and continues to drive innovation in metabolic drug development.

6.2 Examples of Dehydrogenase Inhibitors and Modulators

The translation of dehydrogenase biology into therapeutic agents has yielded compounds ranging from regulatory-approved drugs (FDA/EMA) to advanced investigational candidates. These agents employ diverse strategies, including catalytic inhibition, allosteric modulation, and interference with regulatory pathways, thereby reflecting the multiple levels at which dehydrogenase activity can be therapeutically controlled. Examples of inhibitors are summarized in Table 3 (Ref. [122,229,280,281,282,283,284,285,286,287,288,289]), illustrating their mechanisms of action, clinical status, and translational implications.

6.2.1 IDH Inhibitors: Clinical Validation of Precision Metabolic Therapy

Mutant IDH inhibitors represent the most successful translation of dehydrogenase targeting to date. Vorasidenib (AG-881) is an orally available pan-inhibitor of mutant IDH1/IDH2 and was the first pan-inhibitor developed through the Celgene and Agios Pharmaceuticals collaboration [290]. FDA approvals of ivosidenib in 2018 and of the EMA in 2023 [280,281], and olutasidenib [282] for IDH1-mutant cancers, especially AML, along with enasidenib [122] for IDH2-mutant malignancies, validate the strategy of exploiting neomorphic enzyme activities. These agents achieve remarkable selectivity by targeting the altered active site present only in mutant enzymes, suppressing oncometabolite D-2-HG production while sparing normal α-ketoglutarate metabolism. The clinical impact extends beyond simple metabolic normalization. By reducing D-2HG levels, these inhibitors partially reverse epigenetic silencing, restore α-KG-dependent dioxygenase function, and induce differentiation of malignant cells. Response rates of 40–60% in relapsed/refractory AML, with durable remissions in a subset of patients, demonstrate that metabolic reprogramming can achieve meaningful clinical outcomes. The brain-penetrant compound vorasidenib further extends this success to gliomas, addressing tissue-specific delivery challenges through optimized pharmaceutical properties [283,284].

6.2.2 PDK Inhibitors: Indirect Dehydrogenase Activation

Instead of targeting PDHC directly, PDK inhibitors modulate the complex through its regulatory kinases. AS discussed above, DCA, the prototypical PDK inhibitor, prevents phosphorylation-mediated inactivation of PDHC, thereby promoting glucose oxidation over lactate production. This indirect approach circumvents the challenges of targeting a multi-subunit mitochondrial complex while

achieving the desired metabolic shift. Despite decades of research, DCA's clinical utility remains limited to rare metabolic disorders because of dose-dependent peripheral neuropathy. However, the compound has proven invaluable in establishing proof-of-concept that forced mitochondrial oxidation can compromise glycolytic cancer cells [291]. Current efforts focus on developing isoform-selective PDK inhibitors that might preserve metabolic flexibility in neurons while targeting PDK isoforms upregulated in cancer and metabolic disease.

6.2.3 LDH Inhibition Strategies: Isoform Selectivity and Allosteric Targeting

Early LDH inhibitors, including oxamate, FX-11, and GNE-140, provided proof-of-concept that suppressing lactate production can impair tumor growth; however, these compounds had limited potency and poor selectivity [285,286]. A fundamental challenge in targeting LDH stems from the exceptionally high intracellular concentrations of its substrates, pyruvate and lactate, which severely limit the effectiveness of classical competitive inhibitors. This constraint has driven the field toward alternative strategies that move beyond direct competition at the catalytic site.

Contemporary LDH inhibitor development increasingly focuses on noncompetitive and network-informed approaches. Allosteric inhibitors that bind outside the active site offer improved selectivity and reduced susceptibility to substrate competition. Other strategies target LDH oligomerization, exploiting the requirement for tetramer assembly to achieve full catalytic activity. Isoform-selective inhibition represents another critical advance: preferential targeting of LDHA, which is frequently enriched in tumors, while sparing LDHB, which plays essential roles in oxidative tissues such as the heart and brain, addresses a primary toxicity concern [75,292]. In parallel, dual-targeting strategies combining LDH inhibition with blockade of monocarboxylate transporters (MCTs) limit lactate efflux and metabolic compensation, illustrating how pathway-level understanding enables rational combination design [293].

Importantly, recent work from our group demonstrated that, despite their high structural similarity, LDHA and LDHB differ substantially in their inhibitory mechanisms. Whereas most LDHA inhibitors act through competitive inhibition at the active site, LDHB is preferentially inhibited via allosteric mechanisms, revealing exploitable isoform-specific regulatory features [75]. Building on this insight, we identified two FDA-approved anticancer drugs, tucatinib and capmatinib, originally developed for breast and lung cancers, respectively, as uncompetitive inhibitors of LDHB. These agents bind to an allosteric site distinct from the catalytic domain, selectively impairing LDHB activity without competing with substrate binding [292]. Notably, although LDHB is predominantly expressed in cardiac muscle, genetic LDHB deficiency is not associated with overt clinical pathology, suggesting that pharmacological inhibition of LDHB may be tolerated and carry a lower risk of cardiovascular toxicity [292].

Together, these findings highlight a paradigm shift in LDH targeting, from broad, competitive inhibition to isoform-specific, allosteric, and network-aware strategies, and underscore the potential of drug repurposing to rapidly expand the therapeutic landscape of metabolic enzyme inhibition.

6.2.4 G6PDH Modulators: Navigating Safety in NADPH Alteration

As noted above, the therapeutic targeting of G6PDH poses exceptional safety challenges due to the enzyme's essential role in erythrocyte antioxidant defense and the high global prevalence of G6PDH deficiency. These constraints have limited clinical development despite a strong preclinical rationale for disrupting NADPH production in cancer.

The classical G6PDH inhibitor 6-aminonicotinamide (6-AN) illustrates both the potential and perils of this approach. While 6-AN showed anti-cancer activity in preclinical models and entered limited clinical trials in the 1960s–1970s for advanced malignancies, severe toxicities halted its development. Patients experienced profound neurotoxicity, hemolytic anemia, and metabolic acidosis, consequences of systemic NADPH depletion affecting all tissues. These early experiences established that systemic G6PDH inhibition causes unacceptable toxicity, necessitating more selective strategies. Contemporary approaches aim to exploit context-specific vulnerabilities while avoiding systemic NADPH depletion. Tumor-activated prodrugs represent one strategy, designed to release active G6PDH inhibitors selectively within the tumor microenvironment through pH-, enzyme-, or hypoxia-mediated activation. This approach could achieve local target engagement while sparing systemic exposure [287,288,294].

Synthetic lethality screens have identified genetic contexts that confer selective sensitivity to G6PDH inhibition. Tumors harboring KEAP1/NRF2 mutations show heightened dependence on G6PDH-generated NADPH due to constitutive oxidative stress and impaired alternative NADPH sources [295]. Similarly, cancers driven by oncogenes such as MYC, which elevate Nrf2 and upregulate both ox- and non-oxPPP enzymes, may be particularly dependent on PPP activity for NADPH generation and nucleotide synthesis [296].

Combination strategies offer another potential means of widening the therapeutic window but also highlight the risks of perturbing NADPH metabolism. Pro-oxidant agents, such as high-dose vitamin C, have been proposed as alternatives to methylene blue for treating methemoglobinemia in this setting, given their ability to reduce methemoglobin independently of NADPH-dependent pathways. However, clinical case reports show that supraphysiological vitamin C administration can paradoxically precip-

itate severe oxidative injury in G6PDH-deficient individuals, leading to methemoglobinemia, intravascular hemolysis, and acute kidney injury. These adverse outcomes reflect the limited capacity of G6PDH-deficient cells to regenerate NADPH and detoxify peroxide intermediates, underscoring the narrow therapeutic margin of prooxidant approaches when pentose phosphate pathway function is compromised [297,298].

Despite these innovative strategies, G6PDH remains a challenging target. Any clinical development must address the risk to G6PDH-deficient individuals through mandatory genetic screening, the need for tissue-selective delivery systems, and careful dose optimization to prevent hemolysis while achieving anti-tumor effects. The path forward likely requires accepting G6PDH as a sensitizing target rather than a standalone therapy, leveraging partial inhibition within carefully selected combination regimens.

6.2.5 GAPDH and MDH: Challenges in Essential Enzyme Targeting

Therapeutic development across the six dehydrogenase gatekeepers is currently uneven, reflecting differences in clinical tractability, opportunities for patient stratification (e.g., mutant IDH), and essentiality-driven toxicity constraints (e.g., GAPDH, MDH). More broadly, the clinical success of metabolic therapies (e.g., mutant IDH inhibitors and PDK-directed strategies) supports the principle that disease-selective metabolic dependencies can be therapeutically exploited, even when the targeted enzymes are embedded in essential networks.

The ubiquitous expression and indispensable metabolic roles of GAPDH and MDH have largely precluded their development as conventional therapeutic targets. Direct catalytic inhibition of either enzyme would be incompatible with normal cellular function, necessitating alternative, more selective strategies.

For GAPDH, therapeutic interest has shifted away from enzymatic inhibition toward modulation of its pathological, non-glycolytic activities. In neurodegenerative disorders, oxidatively modified GAPDH undergoes aggregation and participates in toxic protein–protein interactions. Small molecules that stabilize GAPDH's native conformation or prevent pathological aggregation may mitigate neurotoxicity while preserving essential glycolytic flux. Similarly, altering specific GAPDH protein–protein interactions could selectively block non-glycolytic functions, such as apoptosis, transcriptional regulation, or protein aggregation, without impairing energy metabolism.

Targeting MDH presents analogous challenges. Both cytosolic and mitochondrial MDH isoforms are integral to the malate–aspartate shuttle and the tricarboxylic acid cycle, making direct inhibition untenable. Although several small-molecule MDH modulators have been reported in preclinical studies and chemical biology resources, translation has been limited by isoform/compartment selectivity and narrow therapeutic windows. Instead, therapeutic strategies may focus on modulating shuttle activity indirectly, for example, by targeting associated transporters, regulatory proteins, or upstream signaling pathways that influence redox coupling between cytosol and mitochondria. An emerging possibility is the identification of disease-specific post-translational modifications of MDH that selectively alter its activity or interaction networks in pathological contexts, such as cancer or metabolic disease. Exploiting such context-dependent modifications could enable selective intervention while preserving essential mitochondrial and redox functions in healthy tissues.

Representative MDH-directed small molecules include LW6 (reported to target MDH2 and suppress HIF-1α signaling) [299], LW1497 (reported to suppress HIF-1α expression via MDH inhibition; $IC_{50} \approx 10$ μM, indicating modest potency) [300], and MDH1/2-IN-1 [301], which have shown potential for reducing tumor proliferation. Recent reviews discuss the potential of MDH as a therapeutic target across diverse disease contexts, including metabolic and neurological disorders, cancer, and infectious diseases [100,302].

6.3 Challenges and Opportunities in Therapeutic Targeting of the Six Dehydrogenase Gatekeepers: A SWOT Analysis

Building on the mechanistic rationale and therapeutic examples outlined in Sections 6.1 and 6.2, a systems-level assessment is required to guide future dehydrogenase-targeted drug development. Fig. 3 summarizes this landscape using a SWOT (Strengths, Weaknesses, Opportunities, Threats) analysis, integrating intrinsic enzyme properties, clinical experience, and emerging technological opportunities. This framework highlights both the constraints imposed by central metabolism and the avenues to overcome them.

6.3.1 Core Challenges in Therapeutic Targeting of the Six Dehydrogenase Gatekeepers

During the preparation of this review, several fundamental challenges emerged that constrain therapeutic targeting of dehydrogenases. A central issue is selectivity. Most dehydrogenases are indispensable for normal cellular metabolism. Complete inhibition of enzymes such as GAPDH, PDHC, MDH, or G6PDH is incompatible with life, and even partial suppression can be toxic in metabolically active tissues. Inherited enzymopathies provide compelling evidence of these constraints (Section 5). For example, G6PDH deficiency, affecting more than 400 million individuals worldwide, illustrates the erythrocytes' extreme sensitivity to impaired NADPH production, where even modest redox imbalance can precipitate hemolysis [53]. GAPDH poses a comparable challenge due to its high cellular abundance and extensive moonlighting functions, which complicate predictions of inhibition outcomes.

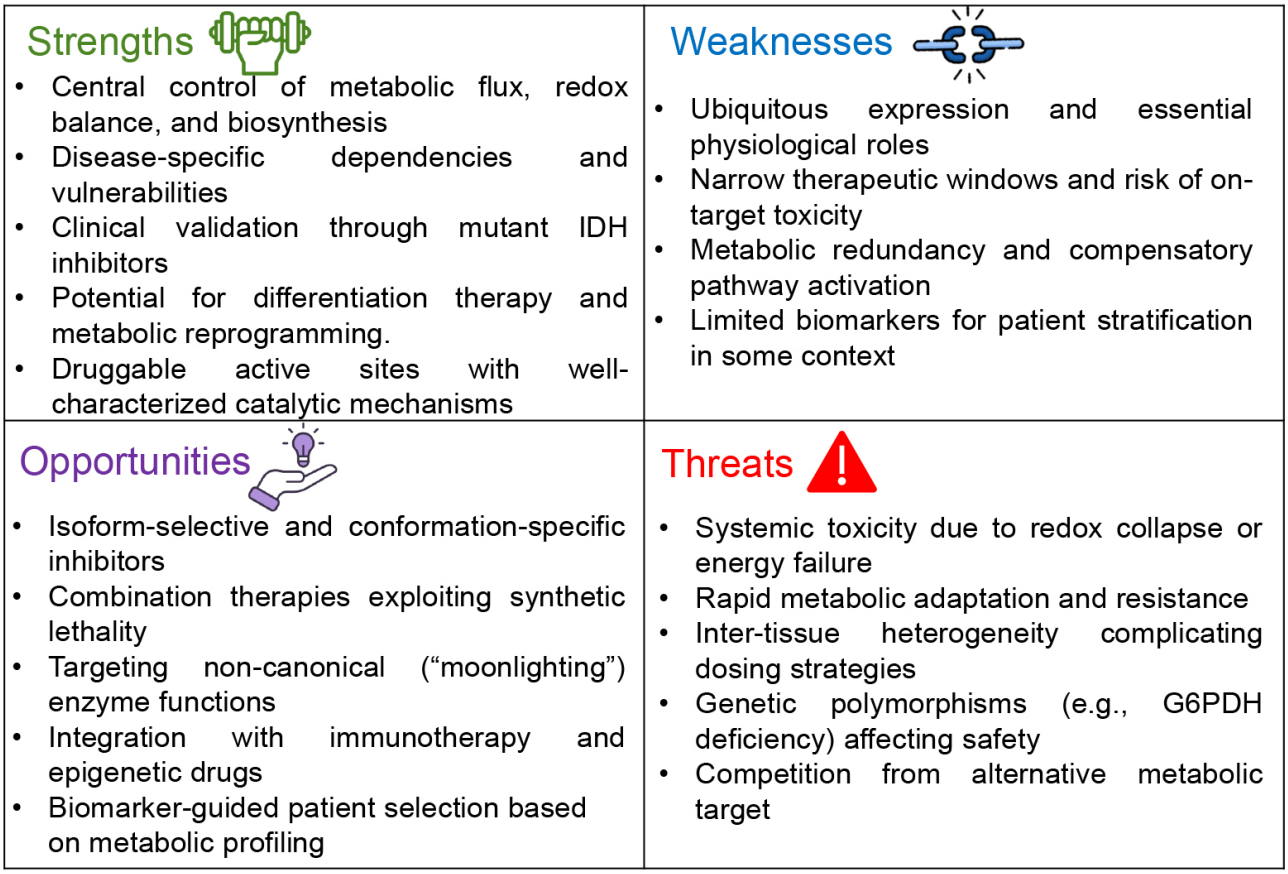


Fig. 3. SWOT analysis of therapeutic targeting of the six dehydrogenase gatekeepers. Strengths include their central positioning at metabolic and redox branch points and their strong relevance across multiple disease states. Weaknesses reflect challenges associated with ubiquitous expression, essential physiological functions, and extensive metabolic redundancy. Opportunities arise from advances in structure-based drug design, isoform- and context-specific targeting, drug repurposing strategies, and artificial intelligence–driven discovery pipelines. Threats include on-target toxicity, compensatory metabolic rewiring, tissue-specific vulnerabilities, and the intrinsically narrow therapeutic window associated with targeting core metabolic enzymes.

On-target toxicity represents a second major obstacle. Even when biochemical selectivity is achieved, physiological consequences may be severe. Mutant-selective IDH1/2 inhibitors exemplify this paradox: although they effectively lower D-2-HG levels and restore differentiation, they can also trigger differentiation syndrome, a potentially life-threatening inflammatory response associated with rapid leukemic maturation. Similarly, pharmacologic inhibition of PDKs with dichloroacetate promotes mitochondrial oxidation but is clinically limited by peripheral neuropathy and other toxicities arising from chronic metabolic forcing. These examples highlight how tissue-specific metabolic demands, particularly in the brain, heart, and peripheral nerves, narrow the therapeutic window.

A third challenge is metabolic redundancy and compensation. Cellular metabolism is highly plastic, allowing both normal and malignant cells to bypass single-enzyme inhibition by rerouting flux through parallel pathways. Redox metabolism is exceptionally robust: NADPH can be generated by the oxidative pentose phosphate pathway (G6PDH), IDH1, ME1, and one-carbon metabolism. Cancer cells exploit this flexibility by switching between glycolysis, oxidative phosphorylation, glutaminolysis, and fatty acid oxidation, contributing to both intrinsic and acquired resistance to metabolic therapies. Even in the context of mutant IDH inhibition, resistance frequently emerges through second-site mutations, alternative α-ketoglutarate production, or broader metabolic rewiring.

Finally, isoform-, tissue-, and context-specificity are essential but difficult to achieve. Many dehydrogenases exist as isoform families with divergent physiological roles. While LDHA is enriched in glycolytic tumors and LDHB predominates in oxidative tissues, emerging human genetic data indicate that LDHB activity is not strictly essential for cardiac or neuronal homeostasis. These observations challenge the assumption that LDHB inhibition is inherently cardiotoxic and support the feasibility of isoform- and context-selective LDH inhibition strategies. More broadly, the clinical success of mutant-specific IDH inhibitors demonstrates the power of exploiting disease-

restricted conformational states, but achieving comparable selectivity for wild-type enzymes remains substantially more challenging. Temporal considerations further complicate therapy, as intermittent or partial modulation may be beneficial in some contexts (e.g., immunometabolism), whereas chronic inhibition may prove deleterious.

6.3.2 Opportunities and Future Directions

Despite the substantial challenges outlined above, several converging advances are reshaping the therapeutic landscape for targeting the six dehydrogenase gatekeepers. A key implication of the framework developed in this review is that future success will depend less on indiscriminate catalytic inhibition and more on state-aligned control of flux routing and redox balance. Across the six enzymes, disease phenotypes repeatedly converge on a limited set of actionable state variables: cytosolic NADH reoxidation capacity (LDH versus MDH/MAS), NADPH dependency (G6PDH and IDH1/2), mitochondrial entry of glucose-derived carbon (PDHC), and redox/PTM-driven functional switching (GAPDH and, increasingly, MDH). Accordingly, "opportunities" in this space are best defined as strategies that selectively engage these nodes within disease-restricted metabolic states.

Artificial intelligence (AI) and machine learning are particularly valuable for dehydrogenase-specific tractability problems, including isoform selectivity (e.g., LDHA versus LDHB; MDH1 versus MDH2; IDH1/2 versus IDH3), compartment-linked conformational differences (cytosolic versus mitochondrial enzymes), and identification of allosteric or non-catalytic pockets that can modulate activity without collapsing essential flux. For the gatekeeper enzymes, AI-guided structural interrogation can prioritize binding sites that report on metabolic state (e.g., PTM-sensitive conformations or oligomerization interfaces) and accelerate discovery of modulators that shift flux rather than abolish catalysis.

Drug repurposing is a complementary strategy that aligns naturally with a state-based framework, because many approved drugs already perturb redox balance, mitochondrial function, or metabolite handling. Repurposing becomes especially informative when used to test explicit gatekeeper-state hypotheses, such as whether perturbing oxidative lactate utilization (LDHB) compromises defined tumor states, whether forcing pyruvate oxidation through PDHC alters a glycolysis-locked phenotype, or whether limiting NADPH supply unmasks redox fragility in high-stress proliferative contexts. Recent work from our group exemplifies this approach: by combining AI-assisted screening with experimental validation, we identified FDA-approved anticancer agents as previously unrecognized inhibitors of LDHB, supporting the idea that vulnerabilities in lactate routing can be uncovered when LDH biology is interpreted in the context of metabolic state rather than pathway labels alone.

Looking forward, several principles follow directly from the six-enzyme gatekeeper model and provide a more specific roadmap than generic "AI-driven discovery" statements:

i. State-based patient stratification: therapeutic benefit is expected when patients are selected by measurable metabolic states (e.g., lactate routing signatures, NADPH stress, PPP dependence, PDHC suppression, MAS limitation), rather than by tissue of origin alone.

ii. Network-aware combinations: because compensation is predictable within redox networks, combination strategies should be designed around gatekeeper coupling (e.g., NADPH limitation plus ROS-inducing therapy; LDH/MAS routing interference plus mitochondrial constraints; PDHC reactivation plus redox stress).

iii. Isoform- and compartment-selective modulation: the most defensible therapeutic windows arise from disease-enriched isoforms (LDHA), neomorphic activities (mutant IDH1/2), or compartment-dependent liabilities (MDH/MAS capacity and mitochondrial NADH handling), rather than from pan-enzyme blockade.

iv. Regulation- and interaction-targeted approaches for essential enzymes: for GAPDH and MDH, opportunities are most plausible through modulation of PTM-dependent switching, interaction networks, or shuttle-associated components rather than direct catalytic inhibition.

Beyond conventional small-molecule inhibitors, emerging modalities expand options for gatekeeper enzymes whose catalytic sites are difficult to exploit safely. Targeted protein degradation may enable context-restricted depletion when a therapeutic window exists, whereas covalent strategies may be appropriate only when a disease-enriched reactive microenvironment or isoform selectivity is achievable. Metabolite-based interventions, such as cell-permeable α-ketoglutarate analogs, represent an additional route to modulate dehydrogenase-linked signaling outputs, particularly for oncometabolite- and epigenetic-relevant states, without directly suppressing essential catalytic reactions.

Collectively, the forward direction for dehydrogenase therapeutics is best summarized by a central closing statement of this review: these enzymes are druggable when targeted as state-dependent routing nodes rather than as static pathway steps. Direct inhibition is most feasible for neomorphic activities (mutant IDH) or disease-enriched isoforms (LDHA), whereas essential enzymes (GAPDH, MDH, and often G6PDH and PDHC) will require strategies that modulate regulation, compartmentalization, and network coupling. This state-aligned approach provides a coherent rationale for the unevenness of therapeutic development today and a specific roadmap for how it can become more precise across the six gatekeepers.

7. Conclusions and Perspectives

Dehydrogenases play crucial roles in cellular metabolism, linking carbon flow, redox balance, energy generation, and biosynthesis across cellular compartments. This review focuses on six key metabolic gatekeepers, GAPDH, LDH, PDHC, MDH1/2, IDH1/2/3, and G6PDH, as central to metabolic flexibility in health and as vulnerability points in disease. Rather than acting independently, these dehydrogenases form an interconnected network that regulates glycolysis, mitochondrial oxidation, the pentose phosphate pathway, one-carbon metabolism, and redox stability. Disruption at any of these points can trigger a cascade of metabolic changes with significant pathophysiological effects.

In diseases such as cancer, metabolic syndrome, inherited enzymopathies, neurodegeneration, and immune disorders, common mechanistic themes emerge. These include imbalances in NAD^+/NADH and $NADP^+$/NADPH, loss of compartmental redox control, weakened coupling between glycolysis and mitochondrial function, and reduced metabolic flexibility. In cancer, these changes are exploited to support growth, redox balance, and epigenetic modifications. In metabolic diseases, they contribute to insulin resistance and substrate inflexibility. In neurodegeneration and aging, impaired dehydrogenase function accumulates, leading to energy failure and oxidative damage. In immune cells, rapid, reversible shifts driven by dehydrogenases determine the balance between host defense and harmful inflammation.

Therapeutic targeting of dehydrogenases shows promise but also faces obstacles. The success of mutant-specific IDH inhibitors demonstrates that dehydrogenases are druggable when disease-related mutations are present. However, targeting wild-type dehydrogenases poses challenges, including toxicity, metabolic adaptation, tissue-specific vulnerabilities, and narrow treatment windows. These experiences highlight that effective intervention likely depends on modulating dehydrogenase activity in specific contexts rather than on complete inhibition of the enzyme.

Looking ahead, advances in structural biology, chemical proteomics, and system-wide metabolism are helping identify allosteric sites, isoform-specific forms, and disease-restricted enzyme states. Artificial intelligence-based drug discovery and network modeling can predict metabolic compensation, identify synthetic-lethal interactions, and guide combination approaches. Repurposing existing drugs offers practical opportunities, especially for targeting shared redox and metabolic vulnerabilities across diseases. Research from our group and others on LDH isoforms and LDHB-targeted therapies demonstrates how combining computational methods with mechanistic insights can uncover unexpected therapeutic avenues.

Ultimately, this review emphasizes that dehydrogenases are not just metabolic enzymes but dynamic regulators at the crossroads of metabolism, signaling, and epigenetics. Maintaining or selectively reprogramming their networks may be key to restoring cellular balance and correcting metabolic disturbances underlying many diseases. As knowledge expands, targeted modulation of these six gatekeepers, using systems-level and precision strategies, holds great potential for advancing next-generation metabolic and personalized therapies.

Author Contributions

CPa and CPe designed, reviewed, and edited the paper. CPa wrote the paper and prepared the figures and tables. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agree to be accountable for all aspects of it.

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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this manuscript, the authors used ChatGPT (version 5.2) solely for assistance with language editing, including grammar and clarity. The authors subsequently reviewed, revised, and validated all content and take full responsibility for the accuracy, originality, and integrity of the work.

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