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Opinion

Navigating the Redox Precipice: Metabolic Gatekeeping as a Therapeutic Window in Pancreatic Precancer

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) remains a lethal malignancy largely because its early stages evade detection. Two recent studies by Hennequart et al. and Radyk et al. (2026, Nature Metabolism) agree on the following concept: pancreatic acinar cells must maintain a narrow "redox precipice" during acinar-to-ductal metaplasia (ADM), the initial reversible precursor of PDAC. Redundant nicotinamide adenine dinucleotide phosphate-generating systems-mitochondrial aldehyde dehydrogenase 1 family member L2 and cytosolic glucose-6-phosphate dehydrogenase/malic enzyme 1-generally regulate reactive oxygen species within a range that facilitates pro-survival signaling without inducing cell death. Disruption of these systems promotes ADM formation and pancreatic intraepithelial neoplasia, whereas antioxidant treatment inhibits progression. This Opinion integrates these findings within a broader framework of metabolic gatekeeping, discusses how the redox precipice interacts with epigenetic reprogramming and immune evasion, and proposes that the transition from redox balance to addiction results in stage-specific vulnerabilities. Circulating formate emerges as a promising biomarker for early detection, and we highlight key unanswered questions, including whether similar principles apply to other metaplasia-driven malignancies.

Keywords: pancreatic cancer; redox homeostasis; acinar-to-ductal metaplasia; NADPH metabolism; ALDH1L2; NRF2; formate

1. Early Detection Deadlock and a Metabolic Indicator

Despite major advancements, the majority of patients with pancreatic ductal adenocarcinoma (PDAC) are diagnosed at an incurable stage. The initial pre-neoplastic transformation, acinar-to-ductal metaplasia (ADM), is reversible, offering a potential window for intervention [1,2]. However, the metabolic mechanisms that determine whether an acinar cell successfully undergoes ADM or is eliminated remain poorly understood. Two independent studies in Nature Metabolism by Hennequart et al. [3] and Radyk et al. [4] address this gap by showing that the ability to produce nicotinamide adenine dinucleotide phosphate (NADPH) and precisely regulate reactive oxygen species (ROS) serves as a critical barrier. Their work collectively establishes a "redox precipice" model: acinar cells must navigate a narrow ROS threshold that is sufficiently elevated to promote pro-adaptive signaling but low enough to avoid ferroptosis, apoptosis, or senescence. In this Opinion, we argue that this model elucidates the onset of early lesions and reveals stage-specific metabolic deficiencies that might be exploited for early detection and prevention. Moreover, we offer our own perspective on future research priorities.

2. Redundant NADPH Systems as Protectors of Acinar Identity

In healthy pancreatic acini, ROS are maintained at a low homeostatic level by many, seemingly redundant NADPH-generating enzymes. Hennequart et al. [3] identified aldehyde dehydrogenase 1 family member L2 (ALDH1L2), a mitochondrial enzyme that oxidizes one-carbon intermediates (e.g., 10-formyltetrahydrofolate) to reduce $NADP^+$ (oxidized nicotinamide adenine dinucleotide phosphate) to NADPH, as a critical redox protector that is selectively expressed in acinar cells and progressively diminished during ADM. *Aldh1l2* deletion elevates mitochondrial ROS, accelerates ADM *ex vivo* and in cerulein-induced pancreatitis, and promotes the progression of pancreatic intraepithelial neoplasia (PanIN) in Kirsten rat sarcoma viral oncogene homolog (KRAS)-driven mouse models. Remarkably, the antioxidant N-acetylcysteine (NAC) completely reverses this accelerated phenotype, demonstrating that ROS are the underlying mechanism. Moreover, formate, a metabolite typically regulated by ALDH1L2, increases in the plasma of tumor-bearing mice and patients with PDAC, suggesting its potential as a circulating biomarker for early detection [3].

Concurrently, Radyk et al. [4] examined two cytosolic NADPH producers, namely, glucose-6-phosphate dehydrogenase (G6PD) and malic enzyme 1 (ME1), which are upregulated during ADM as components of a nuclear fac-

tor erythroid 2-related factor 2 (NRF2)-mediated antioxidant program. The genetic deficiency of G6PD or ME1 significantly promotes ADM and PanIN formation in KC mice, indicating that these enzymes normally function as a barrier to precancerous transformation. Notably, ME1 deletion promotes the progression to PDAC, whereas G6PD deficiency does not, revealing non-redundant, stage-specific roles: G6PD primarily inhibits early metaplasia, whereas ME1 is critical for progression to invasive disease. Antioxidant treatment mitigates the accelerated ADM phenotype, and buthionine sulfoximine (BSO)-mediated glutathione (GSH) depletion alone is sufficient to induce ADM, highlighting that shifting the redox balance toward oxidation actively promotes lesion formation [4]. Mechanistically, NADPH serves as the essential electron donor for two major intracellular antioxidant systems: the GSH pathway, which reduces H_2O_2 and lipid peroxides via glutathione peroxidases, and the thioredoxin (TXN) pathway, which reduces peroxiredoxins and maintains the redox state of protein thiols. The diminished levels of GSH and TXN, along with the redundant NADPH producers (mitochondrial ALDH1L2 and cytosolic G6PD/ME1), collectively protect acinar cells from oxidative damage. The absence of any single enzyme diminishes this protective function, increasing steady-state ROS and accelerating ADM—a result that is fully reversed by the thiol antioxidant NAC [5].

3. Redox Precipice: From Equilibrium to Dependency

Our perspective: Although the two studies effectively illustrate redundancy within NADPH systems, we argue that this redundancy is not a passive safety net but an active, evolved mechanism to protect acinar cell identity. The targeted depletion of ALDH1L2 during ADM, despite its protective role, suggests that the downregulation of this mitochondrial NADPH source may be necessary for facilitating an increase in ROS to pro-metaplastic levels. Thus, acinar cells must deliberately deactivate one of their redox defenses to reach the threshold. This raises a surprising hypothesis: partial, transient oxidative stress is not a side effect but a catalyst for ADM, and complete antioxidant blockade—though effective in mice—may inadvertently prevent beneficial tissue repair in humans. Therefore, we advise against the immediate clinical application of NAC or similar agents without biomarker-guided patient selection. On the basis of these findings, we propose a testable "redox precipice" model (Fig. 1).

Healthy acinar cells maintain a low basal ROS setpoint via redundant NADPH systems (ALDH1L2, G6PD, and ME1). In response to injury or oncogenic KRAS, the rise in ROS initiates ADM. Cells must navigate a narrow ROS window that activates NRF2-driven transcriptional reprogramming without inducing cell death. Cells that successfully upregulate antioxidant enzymes survive and proliferate; those that fail are eliminated. Surviving cells may then become "redox addicted", increasingly dependent on specific pathways such as NRF2 or glutathione peroxidase 4 (GPX4), creating novel therapeutic vulnerabilities [6,7,8]. This transition from equilibrium to reliance explains why antioxidants can prevent early lesions but promote late-stage disease, which is a paradox that has long puzzled researchers [7,9].

What else exists on the precipice? Recent evidence suggests that ROS also influences epigenetic reprogramming and immune evasion during early transformation. For instance, a self-amplifying NRF2-EZH2 loop converts KRAS-initiated progenitors into invasive PDAC [10], whereas an NAD(P)H quinone dehydrogenase 1 (NQO1)-activatable prodrug can selectively target NRF2-high PDAC cells [11]. Moreover, ROS can alter DNA methylation and histone changes, potentially stabilizing the ADM transcriptional state and influencing the tumor immune microenvironment from the early stages, affecting macrophage polarization and $CD8^+$ T cell infiltration [12,13]. Whether the redox precipice model extends to other metaplasia-driven cancers, such as Barrett's esophagus or gastric intestinal metaplasia, remains an intriguing and exciting question.

4. Translational Implications: A Stage-Specific Framework

The integration of these two studies has significant translational implications. During the precancerous phase, metabolic interventions that support redox balance, such as NAC or dietary antioxidants, may effectively hinder development. This aligns with the concept that nutraceutical antioxidants may exhibit neuroprotective or anti-cancer properties depending on context [7]. In advanced disease, targeting addiction pathways (e.g., GPX4 inhibitors and NRF2 inhibitors) may offer synthetic lethality, as persister cancer cells are susceptible to GPX4 inhibition [8] and NRF2-high PDAC can be selectively targeted by prodrugs [11].

Notably, circulating formate as a biomarker could address the critical unmet need for early PDAC detection [3]. Future studies should validate formate specificity in large cohorts, explore whether serial measurements can predict responses to antioxidant-based intervention trials, and determine its efficacy compared with other emerging metabolites.

5. Key Open Questions

Despite this progress, several questions remain. First, what factors affect the cell-type specificity of NADPH sources? ALDH1L2 is uniquely expressed in acinar cells, whereas G6PD and ME1 are broadly distributed; why is ALDH1L2 selectively lost during ADM [3,4]? Second, how does the redox precipice interact with epigenetic reprogramming [10] and immune evasion [12,13]? Third, can the balance-to-addiction trajectory be measured in human tissues to facilitate stage-specific intervention? Fourth,

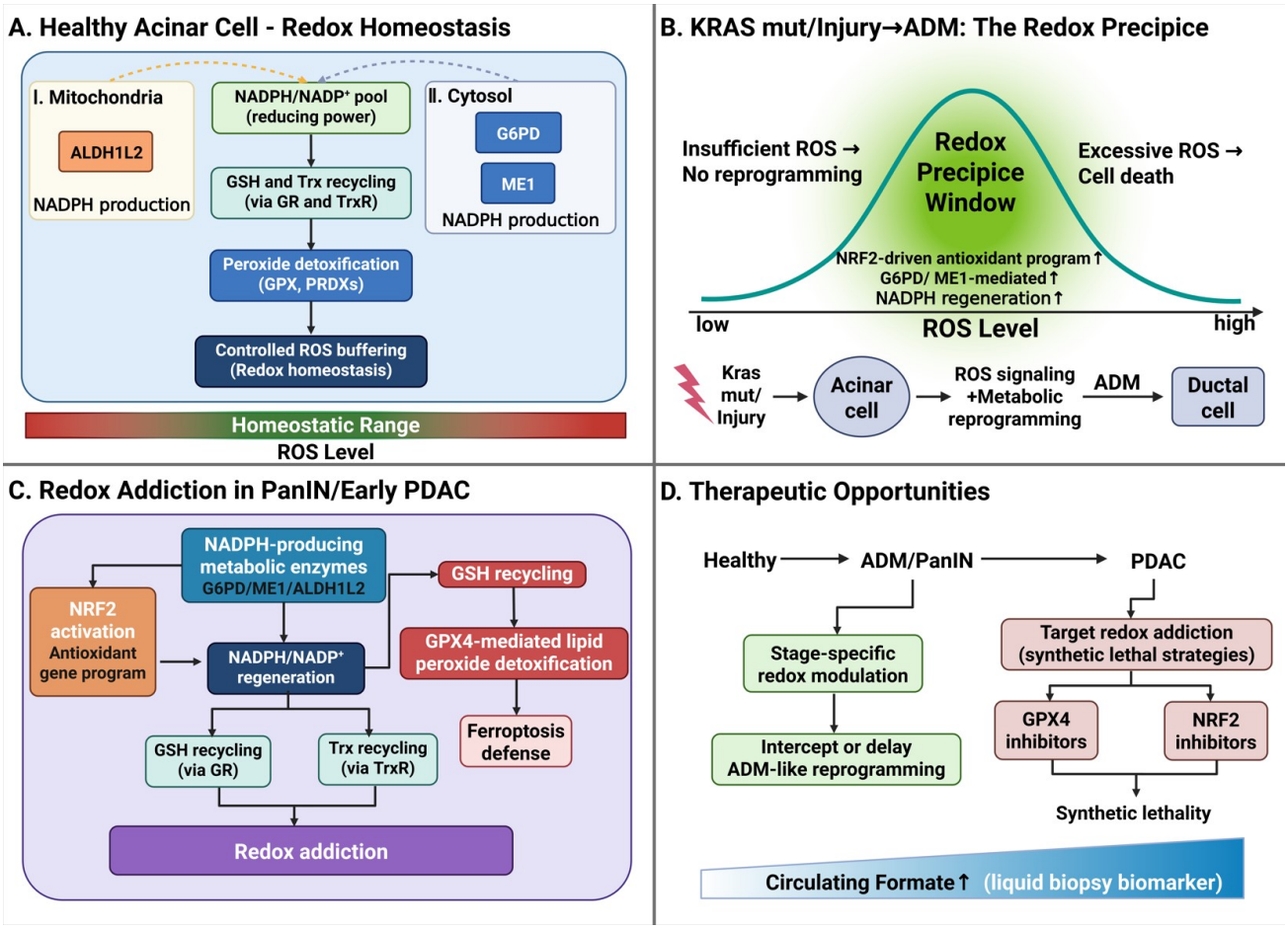

Fig. 1. The redox precipice model in early pancreatic carcinogenesis. (A) In healthy acinar cells, redundant NADPH-producing systems (mitochondrial ALDH1L2 and cytosolic G6PD/ME1) maintain ROS within a homeostatic range, supporting peroxide detoxification via GPX and PRDXs. (B) Upon oncogenic KRAS mutation or injury, ROS levels rise to initiate acinar-to-ductal metaplasia (ADM). Cells must navigate a narrow "redox precipice": insufficient ROS fails to drive reprogramming, while excessive ROS triggers cell death (ferroptosis/apoptosis). Only cells achieving an intermediate ROS level successfully undergo ADM and upregulate antioxidant programs. (C) Persistent adaptation leads to "redox addiction", rendering cells dependent on specific pathways (e.g., NRF2, GPX4). (D) This trajectory creates stage-specific therapeutic opportunities. In the precancer window, antioxidant intervention such as NAC can intercept ADM. In advanced disease, targeting addiction pathways (GPX4 inhibitors, NRF2 inhibitors) may offer synthetic lethality. Circulating formate (blue gradient) rises with disease progression, suggesting its potential as a liquid biopsy biomarker. Abbreviations: ALDH1L2, Aldehyde dehydrogenase 1 family member L2; NADPH, Nicotinamide adenine dinucleotide phosphate; GSH, Glutathione; Trx, Thioredoxin; ADM, acinar-to-ductal metaplasia; G6PD, glucose-6-phosphate dehydrogenase; ME1, malic enzyme 1; NAC, N-acetylcysteine; NRF2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; PDAC, pancreatic ductal adenocarcinoma; PanIN, pancreatic intraepithelial neoplasia; GPX, glutathione peroxidase; PRDXs, peroxiredoxins; GR, glutathione reductase; TrxR, thioredoxin reductase. Created in BioRender. Qi, D. (2026) https://BioRender.com/ufcesnt.

do these principles apply to other malignancies caused by metaplasia? Addressing these questions will require lineage-tracing studies, spatial metabolomics, and patient-derived organoid models.

6. Concluding Remarks

The studies by Hennequart et al. [3] and Radyk et al. [4] established a novel paradigm: early carcinogenesis is a redox-driven process. Our reasoning is not only descriptive but also logical. We propose that the redox precipice is not a "cliff to fall from", but it is a window of opportunity that disappears once addiction ensues. This implies that timing is crucial: the same intervention (e.g., NAC) that blocks ADM may accelerate progression if administered too late. Therefore, future clinical trials of metabolic interception in pancreatic cancer must incorporate dynamic biomarker monitoring (formate, GSH redox ratio, and NRF2 target genes) to ensure that treatment is delivered precisely during the reversible window. Without timely intervention, we risk the recurrence of errors from previous antioxidant trials that

failed because of a stage-agnostic design. Our Opinion calls for a redox-aware, stage-stratified approach for the prevention of pancreatic cancer, necessitating close collaboration between researchers engaged in basic metabolomics studies and clinical trials.

Author Contributions

DYQ: Conceptualization, Visualization, Writing-original draft. WLJ: Conceptualization, Funding acquisition, Supervision, Writing-review & editing. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no competing interests. Given his role as the Editorial Board member, Wei-Lin Jin was not involved in the peer-review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Claire Kuang.

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