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Review

Non-Enzymatic Lipid Peroxidation in Cancer Biology: An Overview

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Abstract

Cancer is characterized by a disrupted redox balance and impaired antioxidant defense, leading to the excessive production of reactive oxygen species (ROS) and oxidative stress. While moderate levels of ROS support tumor growth and adaptation, excessive oxidative stress induces lipid peroxidation (LPO), a self-catalyzed chain reaction that destroys cell membranes and generates reactive aldehydes. Among such reactive aldehydes, 4-hydroxynonenal (HNE) is considered a second messenger of ROS, exerting concentration- and context-dependent effects on cell proliferation, differentiation, apoptosis, immune modulation, and cell death. Since cancer cells are typically more sensitive to the cytotoxicity of HNE, it may also be considered not only a cofactor in carcinogenesis but also a natural factor in the organism's defense against cancer. This paper provides a comprehensive overview of non-enzymatic LPO in cancer, highlighting its dual role in tumor promotion and suppression. We discuss how persistent oxidative stress, metabolic reprogramming, and remodeling of the tumor lipidome shape LPO dynamics and ferroptosis susceptibility within the tumor microenvironment, as well as the emerging therapeutic strategies that exploit LPO. Therefore, exploring the advantage of LPO's dualistic nature may help to develop more individualized and efficient integrative biomedicine anticancer treatments.

Keywords: reactive oxygen species (ROS); oxidative stress; lipid peroxidation; 4-hydroxynonenal (HNE); carcinogenesis; tumor lipidome; apoptosis; ferroptosis

1. Introduction

Cancer remains one of the leading causes of death worldwide and a significant obstacle to increasing life expectancy. In 2022, there were an estimated 20 million new cancer cases and 9.7 million deaths globally. Approximately one in five people develops cancer during their lifetime, and about one in nine men and one in twelve women die from this malignant disease (https://gco.iarc.who.int/en). Despite decades of research and advances in cancer biology and therapy, cancer continues to pose a significant public health burden.

Cancer cells exhibit several traits that enable their survival and growth, all of which are linked to altered signaling pathways. These include sustained proliferation, evasion of growth suppressors and cell death, metabolic reprogramming, genomic instability, angiogenesis, inflammation, immune evasion, and the ability to invade and metastasize [1]. Additionally, cancer is characterized by a disrupted redox balance and impaired antioxidant defenses, leading to excessive accumulation of reactive oxygen species (ROS) and oxidative stress [2]. Oxidative stress plays a complex and dual role in cancer. Namely, ROS, traditionally viewed as damaging agents, also function as signaling molecules that modulate various physiological and pathological processes in both normal and malignant cells. At low to moderate levels, ROS may promote the proliferation, differentiation, migration, invasion, angiogenesis, and resistance to therapy of cancer cells [3–5]. These functions are essential for maintaining tumor cell homeostasis. In addition to their tumor-promoting role, ROS may also play an important role in tumor suppression, depending on their type and concentration, which is of high importance in anticancer therapies [6–12]. Hence, when ROS levels become excessive, they surpass the buffering capacity of cellular antioxidant systems, inducing oxidative damage and ultimately triggering various forms of cell death, including apoptosis and ferroptosis [3,13,14]. This is especially important in the case of radiotherapy and several cytostatic drugs targeting tumors with sufficient oxygenation. Still, it is also valid for hypoxic tissues, particularly when exposed to hypoxia-reoxygenation, which itself is considered a cytotoxic oxidative stress injury.

Complementary to oxidative stress itself, the resulting lipid peroxidation (LPO) may be a crucial process, especially when free radicals attack polyunsaturated fatty acids (PUFAs), where LPO acts as a non-enzymatic chain reaction. Such LPO can generate reactive aldehydes that act as second messengers of ROS. Due to its bioactivity and biomedical relevance, 4-hydroxynonenal (HNE) is the major bioactive LPO product of PUFAs, which typically binds to proteins, changing their structure and function. Consequently, HNE can regulate cell proliferation,

differentiation, and apoptosis in a concentration- and cell type-dependent manner, acting as an important signaling molecule with differential effects on both normal and malignant cells. Eventually, HNE can restart LPO even in the absence of oxidative stress and can work as a cytotoxic factor of LPO, causing cancer necrosis, notably ferroptosis.

The complexity of the LPO-cancer relationship is further underscored by the fact that various endogenous and exogenous pro- and antioxidants, as well as changes in lipid metabolism and immune/inflammatory processes, may modulate it.

2. Lipid Peroxidation (LPO)

The composition of the subcellular lipidome is closely associated with physiological and pathological conditions, including metabolic disorders, inflammatory diseases, aging, neurodegenerative disorders, and cancer [15]. PUFAs are key constituents of membrane phospholipids and are particularly sensitive to ROS, which trigger a chain reaction of LPO [16,17]. LPO occurs through different processes, generally divided into two pathways: the enzymatic and the non-enzymatic ROS-mediated pathway. These pathways differ significantly in their regulation and in the types of products they produce. This paper focuses on non-enzymatic LPO, which is primarily initiated and propagated under oxidative stress and contributes significantly to cellular damage and redox imbalance [18]. Non-enzymatic LPO is initiated by the attack of free radicals on the bis-allylic hydrogen atoms of PUFAs. Among the early markers of LPO are lipid hydroperoxides (LOOH), while in the later stages, the specific products generated depend on the type of PUFA involved. For example, oxidation of omega-6 PUFAs, such as linoleic acid and arachidonic acid, may yield hydroperoxy-octadecadienoates (HPODEs), F2-isoprostanes, and isofurans, while oxidation of omega-3 PUFAs, such as docosahexaenoic acid, may give rise to neuroprostanes [18].

The final products of LPO are reactive aldehydes, which include 4-hydroxyalkenals, 2-alkenals, ketoaldehydes, and other α,β-unsaturated species. Among these, 4-hydroxynonenal (HNE), malondialdehyde (MDA), and acrolein have been the most extensively studied. Due to its three reactive functional groups, HNE exhibits high reactivity with macromolecules, including proteins, nucleic acids, and lipids [19–21]. These interactions modulate macromolecular function and impact a wide array of cellular processes, including redox signaling, transcriptional regulation, and stress response pathways, underscoring their prominent role in cellular regulation and pathophysiology [22]. HNE, known for its high reactivity and signaling functions, is widely considered to be one of the most important LPO-derived signaling molecules. Similar to ROS, at physiological levels, HNE regulates metabolism, whereas at higher concentrations it induces cytostatic or cytotoxic effects, depending on dose and exposure time (Table 1, Ref. [23–36]).

As summarized in Table 1, HNE exerts highly concentration-dependent effects on multiple molecular targets and signaling pathways, ranging from adaptive and pro-survival responses at low concentrations to apoptosis, necroptosis, or metabolic dysfunction at higher levels. These data highlight HNE as a pleiotropic signaling mediator whose biological outcomes are dictated by dose, cellular context, and target specificity, thereby providing a mechanistic framework for its dual roles in inflammation, cell fate regulation, and tumor-associated pathology. It readily forms covalent adducts with proteins and nucleic acids, thereby modifying their structure and function. These interactions can regulate cell proliferation, differentiation, and apoptosis in a concentration- and cell-type-dependent manner [23,37–40].

The biological significance of LPO lies in its role in both health and disease, mainly through its impact on signaling pathways that regulate a wide array of physiological and pathological processes. While LPO is essentially a natural process, its excessive or uncontrolled progression may lead to widespread oxidative damage, disrupt biological homeostasis, and often result in cellular dysfunction, various diseases, or even cell death. Many pathological conditions, such as inflammation, neurodegenerative diseases, and cancer, are frequently linked to uncontrolled LPO [22]. On the other hand, at physiological or sublethal concentrations, LPO products act as important redox signaling mediators, initiating numerous cellular adaptive responses. These responses enhance cellular tolerance to subsequent oxidative stress by upregulating antioxidant compounds and enzymes. Therefore, while controlled levels of LPO are beneficial for essential cell signaling, deviations towards uncontrolled or excessive levels lead to various pathological consequences, including tumorigenesis.

3. Persistent Oxidative Stress in Cancer

Persistent oxidative stress in cancer promotes DNA damage, genomic instability, tumor progression, immune evasion, and metastasis (Fig. 1). To survive under these conditions, cancer cells upregulate their antioxidant defense mechanisms [2], which can lead to drug resistance and reduce the effect of redox-targeted therapies. Mitochondrial dysfunction, chronic inflammation, and endoplasmic reticulum stress are among the major sources of ROS that contribute to redox imbalance in the tumor microenvironment (TME) [41]. ROS overproduction is largely caused by dysfunctional mitochondria, which promote angiogenesis, invasion, and cell proliferation [42]. Elevated NADPH oxidases in tumor cells and tumor-associated macrophages further increase ROS levels, while hypoxic regions within tumors stabilize HIF-1α, which not only affects oxidative stress but also promotes a more aggressive tumor phenotype [42].

Table 1. Concentration-dependent effects of HNE on molecular targets and signaling pathways.

Molecular target specificity	Signaling pathway activation	Dose-response dynamics	Ref
The JNK-c-Jun/AP-1 pathway is activated by HNE adduction	Early JNK and p38 activation; ERK was downregulated	Apoptosis correlated with higher HNE concentrations	[24]
Protein adducts in vascular smooth muscle cells were detected	NF-κB activated at low HNE concentration; apoptosis at high	Concentration-dependent switch from proliferation to death	[25]
Mitochondrial and autophagy proteins adducted by HNE	Autophagy was activated at low, inhibited at high HNE concentrations	Biphasic autophagy response to HNE concentration	[26]
Src kinase is activated by HNE at Cys248	Src mediates p38 and ERK phosphorylation, AP-1 activation	Concentration-dependent Src activation and inflammation	[27]
5-LO expression is regulated by HNE via EGFR-mediated pathways	p38 MAPK/Sp1 and ERK/NF-κB pathways were activated	Dose-dependent transcriptional regulation of 5-LO	[28]
MKP-1 degradation leads to ERK1/2 activation by HNE	ERK1/2 phosphorylation mediates apoptosis in epithelial cells	Concentration-dependent ERK activation and apoptosis	[29]
RIP1 stabilized by HNE adduction, preventing degradation	Necroptosis was enhanced via RIP1 accumulation	Dose- and time-dependent necroptosis induction	[30]
NLRP3 inflammasome is inhibited by HNE binding	Inflammasome activation and pyroptosis were suppressed	Low concentration HNE inhibits inflammatory cell death	[31]
Endothelial and astrocyte proteins modified by HNE	Nrf2 and antioxidant defenses were variably activated	Concentration-dependent BBB functional changes	[32]
Mitochondrial complexes	Mitochondrial respiration and biogenesis	High concentrations impact mitochondrial bioenergetics	[23]
Fas and p53 apoptotic pathways activated by HNE	ASK1, JNK, and caspase-3 signaling engaged	Concentration-dependent activation of apoptotic cascades	[33]
Fas and Daxx proteins are adducted by HNE, regulating apoptosis	ASK1, JNK, and caspase-3 pathways modulated	Concentration-dependent regulation of apoptosis	[34]
Caspase-dependent AP-1 activation by HNE	JNK phosphorylation and calcium signaling are involved	Dose-dependent apoptotic signaling in neurons	[35]
Cyclins and CDK inhibitors modulated by HNE	Cell cycle arrest via p21 and hypophosphorylated pRb	Concentration-dependent cell cycle regulation	[36]

HNE, 4-hydroxynonenal; JNK, c-Jun N-terminal kinase; ERK, extracellular signal-regulated kinase; NLRP3, NLR Family Pyrin Domain Containing Protein 3; ASK1, apoptosis signal-regulating kinase 1; CDK, cyclin-dependent kinase; BBB, blood–brain barrier; Nrf2, nuclear factor erythroid 2-related factor 2.

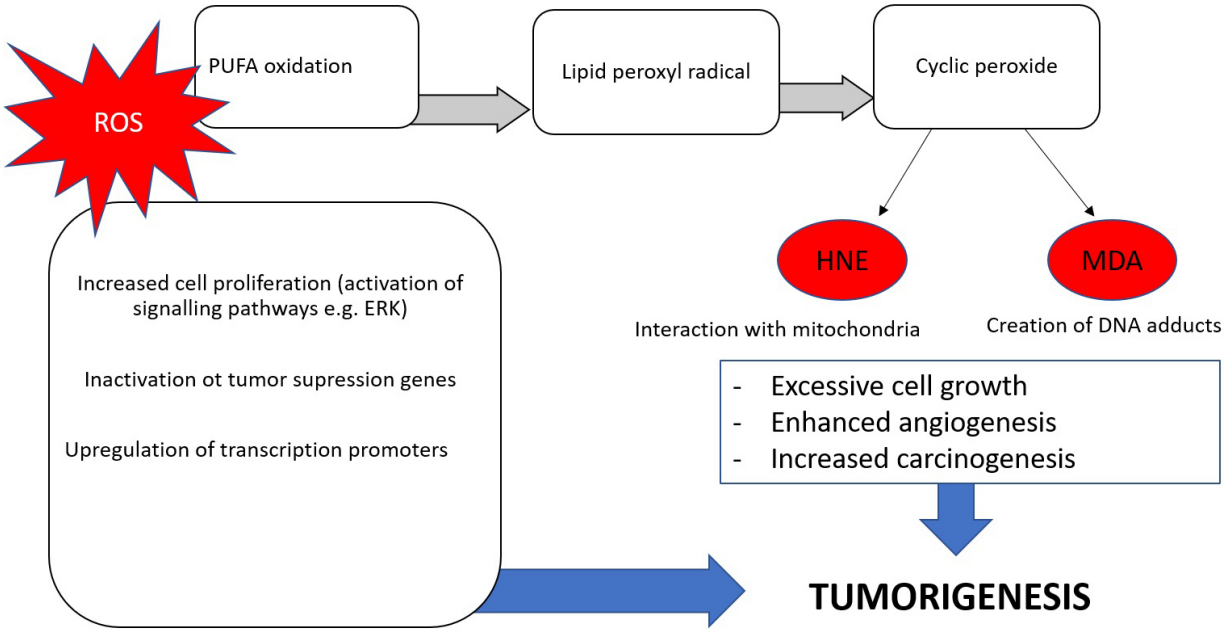

Fig. 1. Oxidative stress-driven mechanisms in cancer progression. ROS overproduction inside a cell leads to several mechanisms potentiating increased cell proliferation (activation of signaling pathways, e.g., ERK), inactivation of tumor suppression genes, and an upregulation of transcription promoters, which promote tumorigenesis. In addition, ROS lead to the oxidation of PUFA, the generation of lipid peroxyl radicals, and the formation of reactive aldehydes. The most prominent are HNE and MDA, involved in upregulated proliferation, invasion, and angiogenesis. PUFA, polyunsaturated fatty acid; MDA, malondialdehyde.

Changes in lipid metabolism, including LPO, have been recognized as hallmarks of cancer, impacting energy supply, membrane composition, and signaling [15,22,23]. Cancer cells frequently reprogram metabolism to support their high energy demands. Some of the alterations include increased *de novo* fatty acid synthesis, enhanced uptake of exogenous fatty acids, and greater lipid peroxidation [43]. In addition, the membrane lipidome is remodeled, including increased production of monounsaturated fatty acids, catalyzed by stearoyl-CoA desaturase 1, which are incorporated into membranes and help protect against elevated LPO and ferroptosis [44,45]. On the other hand, acyl-coenzyme A synthetase long-chain family member 4 (ACSL4) promotes the incorporation of PUFAs into the cell membrane, and inactivation of ACSL4 may also block ferroptosis (Fig. 2).

LPO and its byproducts, such as HNE, play ambivalent roles in cancer. For example, LPO products are involved in the modulation of signaling pathways such as nuclear factor erythroid 2-related factor 2 (Nrf2), mitogen-activated protein kinase (MAPK), and PI3K/Akt, which are pivotal for tumor proliferation, survival, and adaptation [2,46], while excessive LPO results in irreversible cellular damage and has the potential to inhibit tumor growth or induce cell death under specific conditions [11]. Cancer cells frequently upregulate enzymes that detoxify LPO products, including aldehyde dehydrogenases, glutathione-S-transferases, and glutathione peroxidase 4 (GPX4), which can play a critical role in regulating LPO levels in cancer [47]. As the biological activities of HNE are highly target- and concentration-dependent, it can alter several signaling pathways involved in tumor development, promotion, and progression. Notably, when it modulates specific pathways, HNE may also have a tumor-suppressive role, which we recently reviewed in more detail [11]. LPO-derived reactive aldehydes significantly influence the TME by promoting epithelial-mesenchymal transition (EMT), immune evasion, and interactions between tumor cells and their surroundings, thereby supporting cancer progression and metastasis. LPO activates multiple signaling cascades, including MAPK, PI3K/Akt, NF-κB, and TGF-β, which are crucial in the induction and progression of EMT, a process closely linked to cancer metastasis and drug resistance [46,48,49]. LPO further shapes the tumor immune landscape by influencing macrophage polarization, T-cell function, and immune evasion, thereby promoting immunosuppression and cancer metastases [50–52]. In tumor-associated macrophages (TAMs), LPO intersects with metabolic, cytokine, and transcriptional signaling pathways to shape functional phenotypes. Tumor-associated metabolic changes, such as enhanced glycolysis and lactate accumulation, favor polarization of macrophages toward an M2-like, immunosuppressive phenotype, characterized by reduced MHC-II expres-

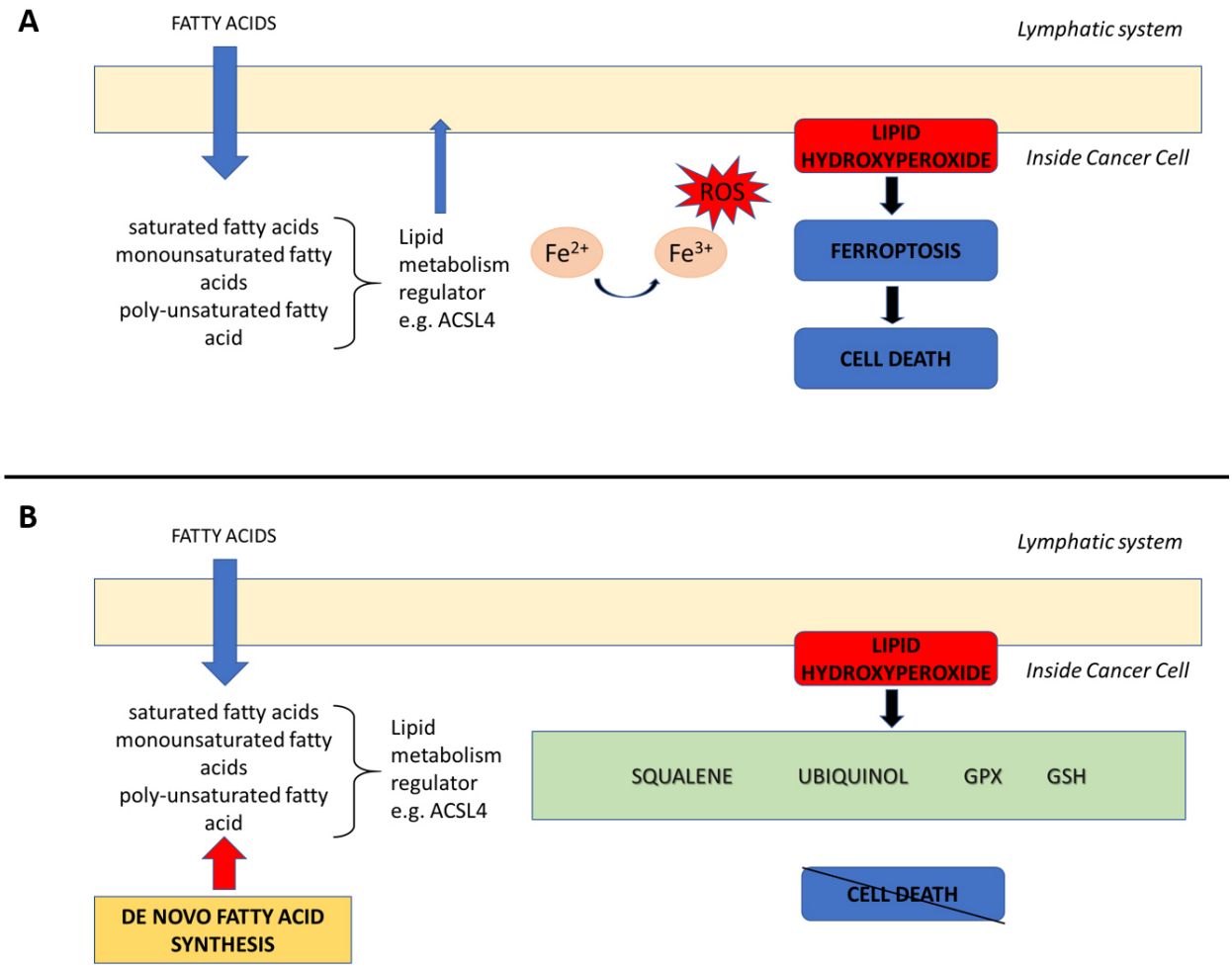

Fig. 2. Lipid metabolism and antioxidant defense mechanisms regulating ferroptosis sensitivity and resistance in cancer cells. Ferroptosis, as a form of cell death connected to the peroxidation of polyunsaturated membrane phospholipids, relies on the fatty acid uptake into cancer cells that can promote ferroptosis (A). Enzymes such as ACSL4 facilitate the incorporation of PUFA into the cell membrane, increasing cancer cells' sensitivity to ferroptosis. On the other hand, if the level of fatty acids is boosted by increased levels of lipids in lymph or *de novo* synthesis of fatty acids within the cell, it produces more lipids than necessary (primarily monounsaturated fatty acids), which in turn incorporate into the membrane and make the malignant cell more resistant to ferroptosis via the ACSL3-dependent pathway. At the same time, several glutathione (GSH)-dependent (upregulated GSH synthesis and the excessive GSH-dependent membrane phospholipid hydroperoxidase) and independent (generation of the potent antioxidant ubiquinol and radical-scavenging hydrocarbon squalene) antioxidant mechanisms are underlying resistance of cancer cells against ferroptosis (B). ACSL4, acyl-coenzyme A synthetase long-chain family member 4; GPX, glutathione peroxidase.

sion and pro-angiogenic signaling [53,54]. Altered lipid and cholesterol metabolism, controlled by pathways involving PPARs and SREBPs, further stabilizes this M2-like state, while cytokines such as IL-4, IL-10, and IL-13, together with lipid mediators like prostaglandin E2, reinforce immunosuppressive TAM functions [55,56]. These effects are coordinated by transcriptional and epigenetic regulators, which fine-tune macrophage phenotypes within the TME. In parallel, LPO negatively affects adaptive immune responses. Reactive LPO products, such as HNE, impair T-cell and NK-cell signaling and reduce cytotoxic activity, thereby facilitating tumor progression [50,57]. These findings highlight LPO as both a driver of immune dysfunction and a promising therapeutic target. Moreover, LPO-derived aldehydes may modify the extracellular matrix by altering its components and facilitating the detachment and migration of cancer cells [58]; however, these mechanisms remain to be elucidated.

Elevated LPO may render tumor cells more susceptible to ferroptosis (Fig. 2). Thus, the balance between cancer cell survival and ferroptosis is of highest importance in tumorigenesis, as LPO-induced ferroptosis can suppress tumor growth, whereas its inhibition may enhance cancer cell survival and promote EMT [59]. This balance may be regulated by enzymatic control of LPO via GPX4, lipoxygenases, and glutathione peroxidase [48,59,60]. Fur-

thermore, HNE and oxidized phospholipids act as signaling molecules that regulate EMT transcription factors and autophagy, thereby contributing to tumor progression and metastasis [61,62]. Cholesterol metabolism and lipid droplet accumulation, linked with altered LPO, further influence malignant cell phenotype and promote chemoresistance [15,63]. Therapeutically, targeting LPO enzymes and pathways shows promise for overcoming drug resistance and metastasis by inducing ferroptosis or disrupting protumorigenic lipid signaling [59,64,65].

4. Some Examples of LPO Across Different Types of Human Cancer

Reactive aldehydes, such as MDA and HNE, have been studied as potential biomarkers for diagnosis, prognosis, and therapeutic monitoring. These molecules are often measured in biological samples by liquid chromatography, mass spectrometry, or immunodetection of protein adducts, providing insights into systemic oxidative stress and local redox homeostasis [19,66–71]. MDA and HNE levels are consistently elevated in various primary and metastatic tumors, including those of the brain, lung, colon, and breast. Recent evidence demonstrates an association between HNE and alterations in lipid metabolism across different diseases [68,72] and that remodeling of the lipidome in tumor cells influences their sensitivity to HNE [69]. It is increasingly recognized that biomarker signatures indicative of altered lipid metabolism can predict resistance to immunotherapy and chemotherapy, particularly in tumors with high oxidative stress [73–76]. Different tumor subtypes display heterogeneous responses to LPO, exhibiting varying susceptibilities to ferroptosis and antioxidant defenses [77,78]. Molecular profiling of gliomas, breast cancers, and melanoma also reveals distinct lipidomic signatures that can help predict treatment outcomes. Studies employing lipidomics, immunohistochemistry, and RNA sequencing have mapped immunomodulatory roles of LPO across cancers, including melanoma and lung cancers [74, 75]. This review provides an overview of studies published over the past decade that investigate the role of LPO in the tumors of the lungs, gastrointestinal system, and central nervous system (CNS).

4.1 LPO in Gastrointestinal Cancer

Carcinogenesis of gastrointestinal (GI) tumors, such as colorectal cancer (CRC) and gastric cancer (GC), is significantly influenced by LPO. Numerous studies have characterized the involvement of lipid-derived electrophiles such as HNE, MDA, and epoxy-keto-octadecenoic acid (EKODE), demonstrating their capacity to drive inflammatory responses, epithelial damage, and tumorigenesis in the GI tract [63,79]. These peroxidation products activate stress signaling pathways, disrupt cellular homeostasis, and modulate lipid metabolism, contributing to a tumor-promoting environment [22,80]. Additionally, abnormal phospholipid and fatty acid metabolism has been identified as a hallmark of GI cancers by multi-omics analyses, which have also revealed metabolic signatures associated with altered LPO [81].

Profiling studies have revealed that markers of LPO, including oxidized lipids, ceramides, and sphingolipids, are significantly elevated in GI tumors and often correlate with disease stage, prognosis, and treatment outcomes [82,83]. Lipidomic data from CRC and GC patients indicate that LPO profiles can stratify tumors by molecular subtypes and predict patients' response to therapy [84,85].

The TME in GI cancers is greatly influenced by LPO, which modulates immune cell functions, including macrophage polarization and T-cell exhaustion, thereby fostering immune escape and supporting tumor progression [50]. LPO products affect autophagy, redox homeostasis, and immune checkpoint expression, contributing to immunosuppression in CRC and GC [51,86]. The reprogramming of lipid metabolism in immune subsets such as dendritic cells and myeloid-derived suppressor cells further exacerbates immunoevasive mechanisms and limits immunotherapeutic efficacy [87].

Mechanistically, LPO-derived aldehydes and electrophiles, such as EKODE and HNE, activate oncogenic signaling pathways, including JNK, PI3K/AKT, MAPK, and NF-κB, thereby promoting inflammation, survival signaling, and EMT in GI tumors [79,88]. Enzymes such as aldehyde dehydrogenases (ALDHs) and lipid metabolism regulators such as ACSL1 have been shown to modulate intracellular effects, linking lipid detoxification capacity to tumor aggressiveness and resistance to therapy.

The integration of LPO with oncogenic and metabolic signaling underscores its therapeutic potential. In preclinical models of GC and CRC, for example, induction of ferroptosis via LPO threshold manipulation has shown promising results [89]. Furthermore, combination therapies targeting lipid-associated reprogramming pathways, such as those involving PI3K/AKT or ACSL1, offer opportunities to interfere with metabolic adaptations that promote tumor growth [90]. However, the development of standardized therapeutic approaches remains hindered by heterogeneity across tumor types and by a lack of clarity regarding the mechanistic basis of LPO-mediated resistance in cancer cells.

4.2 LPO in Lung Cancer

Oxidative stress and LPO became the key players in the regulation of tumor biology, the immune system, and treatment response in respiratory system tumors, especially non-small cell lung cancer (NSCLC) and lung adenocarcinoma. This highlights how important lipid remodeling and peroxidation are in forming the TME, affecting immune evasion, and in the effectiveness of anticancer treatments against lung cancer [89,91]. For example, lipidomic profiling of NSCLC patients has revealed substantial changes

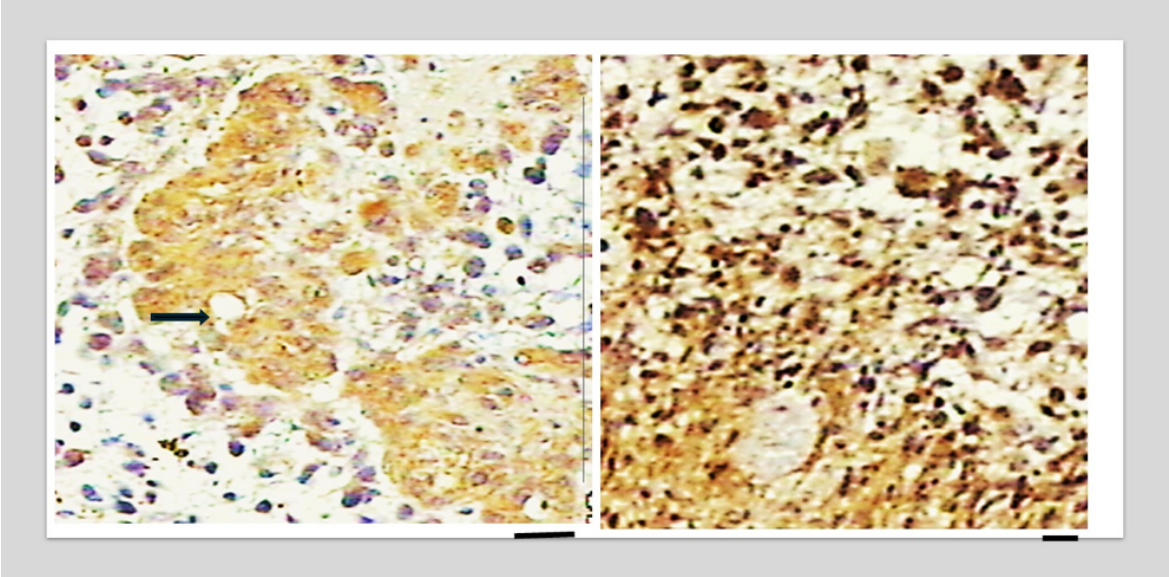

Fig. 3. The appearance of HNE in human glioblastoma. Tumor stromal cells (left), including the wall of blood vessels (arrow, left photo), are often HNE-positive (brown). HNE is more pronounced in tumor cells and less pronounced in necrosis (right photo, upper part: tumor tissue; lower part: necrotic tumor). The presence of the aldehyde was detected by immunohistochemistry specific for the HNE-histidine adducts in proteins (monoclonal antibody courtesy of Dr. Georg Waeg, University of Graz, Austria). The bars represent 50 µm.

in lipid composition after radiation, with specific associations to immune-related responses and ferroptotic pathways [92]. Importantly, studies have emphasized that lipid-derived ROS modulate not only tumor survival but also immune suppression via redox-sensitive transcription factors and cytokine signaling. Several reports have identified oxidative phospholipid derivatives, especially short-chain species, as biomarkers and therapeutic targets in NSCLC, reflecting redox imbalance and altered lipid metabolism in tumor tissues [93]. Redox imbalance is at least in part attributed to altered iron metabolism in NSCLC [94]. Serum-based studies further revealed that lipid metabolism parameters correlate with systemic oxidative stress parameters [73]. LPO exhibits spatial and temporal variation between primary and metastatic tumors, suggesting its diagnostic value in assessing tumor aggressiveness [95].

Radiation and chemotherapy alter glycerophospholipid unsaturation and cholesterol content in tumors, modulating ferroptosis, immune evasion, and therapeutic sensitivity [63,92]. LPO has been shown to impair antigen presentation and polarize macrophages towards immunosuppressive phenotypes, especially under the influence of genes such as CYP1B1 and ALDH1/3 [96,97]. Oxidative stress further impacts T cell infiltration and immune checkpoint expression, as evidenced by redox-related gene signatures and lncRNA profiles that correlate with tumor immune landscapes and therapeutic outcomes [98–100]. Therapeutically, combining ROS-inducing agents or targeting redox-sensitive pathways such as the H1.2-NRF2 axis or NADPH oxidases can enhance immune responses and sensitize tumors to chemo/radiotherapy [101,102], while salivary lipidomics offers a promising non-invasive tool for patient stratification and early detection in these tumors, which are difficult to access [103].

Overall, integrating lipid metabolism, oxidative stress, and immune regulation represents a promising avenue for novel therapeutic interventions in lung cancer. To translate these discoveries into precision oncology treatments, further research integrating immune modulation techniques, molecular targeting, and clinical profiling is necessary. Utilizing metabolic-immune crosstalk to improve treatment responsiveness and overcome resistance mechanisms may be key to the future of lung cancer therapy.

4.3 LPO in Central Nervous System (CNS) Tumors

Lipid peroxidation has been associated with the grade and aggressiveness of brain tumors, especially astrocytic tumors (Fig. 3) [18,104,105]. The prognostic value of redox-related gene signatures is further supported by transcriptomic studies associating them with patient survival [106]. Notably, integrated profiling of LPO markers with antioxidant capacity offers promising stratification of tumor phenotypes [104]. Oxidative stress and its byproducts influence immune evasion and susceptibility to ferroptosis, and cholesterol metabolism helps protect tumor cells from LPO-induced cell death [63,107,108].

LPO-derived reactive carbonyl species modulate key oncogenic signaling pathways, including NF-κB and Nrf2, and alter the expression of enzymes such as apurinic/apyrimidinic endonuclease 1 (APE1) and pyruvate

kinase M2 (PKM2), which are implicated in glioma progression and resistance [46,108]. Oxidative damage that affects mitochondrial function increases tumor aggressiveness and exacerbates metabolic rewiring [109]. Subtype-specific variations in redox regulation have been identified through comparative studies among CNS tumor subtypes. Higher-grade tumors tend to exhibit elevated oxidative stress and mitochondrial dysfunction compared to low-grade tumors, suggesting a redox-based vulnerability that may be exploited therapeutically [105,106,109].

Despite these promising insights, the field faces notable limitations. Many studies rely on *in vitro* or animal models with limited clinical validation, and the standardization of analytical methods remains insufficient. The translational impact of LPO research in CNS oncology remains challenged by tumor heterogeneity, the complexity of redox signaling, and the lack of clinical studies involving large, prospective cohorts [107,110,111].

4.4 Comparative Insights on LPO Across Cancer Types

A cross-cancer comparison reveals both shared and distinct roles of LPO in GI, lung, and CNS tumors, highlighting context-dependent mechanisms and therapeutic implications. Across tumor types, elevated reactive aldehydes, such as MDA and HNE, reflect oxidative stress and lipid metabolism remodeling, contributing to tumor progression, immune modulation, and therapy resistance. In GI cancers, LPO predominantly drives chronic inflammation, epithelial damage, and metabolic reprogramming that promote tumor growth and immune escape, with phospholipid and fatty acid remodeling directly linked to ferroptosis susceptibility and treatment outcomes. Lung tumors exhibit a stronger interplay among LPO, iron metabolism, and ROS signaling, which affects immune suppression, antigen presentation, and treatment response. CNS tumors, in contrast, exhibit subtype-specific redox regulation, in which elevated oxidative stress and mitochondrial dysfunction in high-grade tumors correlate with altered cholesterol metabolism, ferroptosis vulnerability, and immune evasion, highlighting a complex interplay between LPO and the neuronal microenvironment.

Although LPO affects oncogenic signaling, ferroptosis susceptibility, and immune responses in all these cancers, the extent of its impact varies due to differences in metabolism, antioxidant defenses, and the tumor microenvironment. Understanding these differences is essential for designing cancer-specific therapeutic strategies.

5. Selective Induction of Lipid Peroxidation in Tumor Cells as a Therapeutic Strategy Option

Although radiotherapy, various cytostatic drugs, and even surgery rely on oxidative stress and LPO to achieve anticancer efficacy, partially due to the ischemia/reperfusion injury, these conventional therapies are associated with side effects that limit their use [22]. Therefore, selective induction of LPO in tumor cells represents a promising strategy for targeted cancer therapy, exploiting the distinct metabolic and redox vulnerabilities of malignant cells. Namely, unlike normal cells, tumor cells often exist in a state of chronic oxidative stress and display altered lipid metabolism, making them more susceptible to oxidative damage. Harnessing this susceptibility through the controlled enhancement of lipid peroxidation offers new options for killing cancer cells while selectively sparing healthy tissue.

Many tumors exhibit resistance to therapies that target apoptosis. Ferroptosis circumvents this limitation by engaging an entirely different cell death pathway and has thus emerged as a central mechanism for selectively targeting cancer cells. Compounds such as RAS-selective lethal 3 (RSL3) or erastin induce lipid peroxide accumulation, leading to cancer cell death [112,113]. Similarly, increasing intracellular iron levels amplifies ROS formation through the iron-based Fenton reaction, further accelerating LPO [114]. High-dose ascorbate, in the presence of iron, can enhance hydrogen peroxide production selectively in tumor tissues, synergistically promoting LPO [112]. PUFAs are another critical component in promoting LPO. Targeted delivery of PUFAs via nanoparticles or liposomes enables selective accumulation in tumor tissue, increasing the specificity and efficacy of LPO-based treatments [115]. Furthermore, radical chain transfer agents, such as CTA-Fe nanoparticles, can catalyze the conversion of low-activity peroxyl radicals into highly reactive alkoxyl radicals, thereby intensifying lipid oxidation [116]. In addition, modulating cholesterol metabolism can increase membrane susceptibility to peroxidation, further promoting ferroptotic death in cancer cells [63].

Complementary to that, it should be noted that normal cells in the vicinity of cancer, as well as the entire tumor-bearing organism, are under persistent oxidative stress, which can be harmful but can also result in the production of HNE-protein adducts that could kill cancer cells [11,22,69,72,95,117]. That seems to be an important, often neglected aspect of the inflammatory response to cancer [6–11,118]. A crucial aspect of the anti-cancer effects of HNE is the higher-than-normal sensitivity of cancer cells to its cytotoxicity, which is associated with HNE targeting specific defense mechanisms of cancer cells [118–121].

Recent advances in ferroptosis research highlight a decisive shift toward mechanism-guided cancer therapies that leverage precise control of LPO through rationally designed inducers and smart nanotechnological platforms. Class IV ferroptosis inducers, including iron nitroprusside and superparamagnetic iron oxide nanoparticles, exemplify this approach by selectively disrupting iron homeostasis and amplifying oxidative stress in chemoresistant ovarian cancer subpopulations, thereby addressing a major limitation of conventional therapies [122,123]. Small-molecule fer-

roptosis inducers with enhanced structural diversity and metabolic stability have been shown to selectively trigger LPO–driven cell death without activating apoptotic pathways. For example, nanoparticle-based ferroptosis inducers, such as iron-chelated polydopamine nanoparticles, exploit the acidic tumor microenvironment to enable localized iron release, thereby facilitating ferroptosis and iron-dependent LPO in tumors [124]. Building on these principles, transferrin-targeted nanoplatforms that co-deliver ferroptosis inducers and Nrf2 inhibitors enable controlled ferroptosis through tumor-responsive release and external activation, effectively overcoming antioxidant defenses and improving therapeutic specificity [125]. These approaches are further strengthened by stimuli-responsive and multifunctional nanocarriers that enhance LPO, inhibit GPX4, or combine ferroptosis with chemotherapy and nanocatalytic therapies to address tumor heterogeneity and treatment resistance [115,126,127]. Importantly, emerging evidence suggests that coupling ferroptosis induction with immunotherapy may reprogram the tumor microenvironment, enhance immune infiltration, and restore antitumor immunosurveillance, thereby extending the therapeutic impact beyond tumor cell–intrinsic death pathways [128]. While ferroptosis-based strategies hold significant promise, further research is needed to address challenges related to microenvironmental complexity, adaptive resistance, and safety, reinforcing the need for combination approaches and biomarker-guided optimization to fully integrate ferroptosis into multimodal cancer therapy paradigms of integrative biomedicine.

However, significant challenges limit clinical translation of novel therapeutic strategies. Off-target effects, including oxidative damage to healthy tissues, modulation of immune cells, and the generation of a pro-tumorigenic microenvironment, may undermine therapeutic benefits [57,129]. Furthermore, LPO products, including HNE, can, depending on the concentration and cell type, have immunosuppressive or even tumor-promoting effects. This dual role of LPO in cancer challenges the balance between efficacy and safety [11,57,130]. Dose-limiting systemic toxicity and tumor heterogeneity further challenge the uniform application of these therapies, as subpopulations within tumors may exhibit distinct sensitivities to LPO-based interventions and adaptive resistance via antioxidant pathways [59,131]. To overcome these limitations, recent research has focused on improving selectivity and delivery of LPO-inducing agents. Advanced nanotechnology-based platforms, including activatable liposomes and targeted nanoparticles, allow spatially controlled delivery of PUFAs or ferroptosis inducers directly to tumor cells, thereby minimizing systemic toxicity and collateral damage [130,132]. Additionally, combination therapies integrating LPO induction with immunotherapy, ROS-generating agents, or metabolic modulators offer the potential to counteract tumor heterogeneity and resistance mechanisms [133–135]. Moreover, cancer cells can adapt to oxidative stress by upregulating antioxidant systems or altering lipid composition. Therefore, precise modulation of LPO levels is crucial, and integrating LPO-based therapies with precision oncology approaches and immune modulation strategies may create new opportunities to advance biomedicine for treating resistant or aggressive cancers.

6. Conclusions

LPO is recognized as a crucial mediator in cancer biology, regulating tumor growth, immune modulation, and therapeutic response in addition to serving as a marker of oxidative stress. LPO-derived reactive aldehydes, notably HNE, exert profound effects on cellular signaling, macromolecular integrity, and the tumor microenvironment. These bioactive molecules can both promote and suppress tumorigenesis in a dose-, context-, and cell-type-dependent manner. Importantly, LPO shapes the tumor immune landscape and contributes to resistance to conventional therapies. Clinical data indicate that increased LPO markers are associated with tumor aggressiveness, disease progression, and worse outcomes for cancer patients. On the other hand, oxidative stress and LPO are crucial for the efficacy of conventional anti-cancer therapies, while HNE, acting as a second messenger of ROS, can be utilized by normal cells and the organism as a whole to defend against cancer due to its cytotoxicity towards cancer cells. However, much of the existing evidence in the field is limited to *in vitro* and animal models, and there is also a lack of longitudinal clinical validation and inconsistencies in lipidomic methodologies. Standardization of analytical techniques and implementation of integrative and interdisciplinary approaches are essential for uncovering the complex, context-specific roles of LPO across tumor types. Several high-impact directions hold promises for advancing the field, including the development of non-invasive liquid biopsies based on LPO-derived markers, therapeutic strategies combining LPO modulation with immunotherapy, and the application of artificial intelligence to integrate complex lipidomic and redox datasets for predictive modeling and patient stratification. Together, these efforts support the development of precision redox oncology by positioning LPO as both a therapeutic target and a diagnostic tool for personalized cancer treatment.

Author Contributions

Conceptualization, NŽ; writing-original draft preparation, MJ, ASM, MH, SBŠ, PJ, KŽ, and NŽ; writing-review and editing, MJ, ASM, MH, JV, SBŠ, KŽ, and NŽ; visualization, JV, MJ, PJ, KŽ, and NŽ; supervision, KŽ, NŽ, and MJ. MJ, ASM, MH, SBŠ, and PJ performed literature search. All authors have read and agreed to the final version of the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The human tissues mentioned in the article have been approved by the Clinical Hospital Centre Zagreb Ethics Committee (Klasa: 8.1-17/53-2, Broj: 02/21 AG, Zagreb, 23. ozujka 2017) in accordance with the Declaration of Helsinki.

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Conflicts of Interest

The authors declare that they have no conflicts of interest. Neven Žarković is serving as the editorial board member of FBL and the guest editor for this Special Issue. We declare that Neven Žarković 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 Guohui Sun.

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