Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2026**; 31(11): 54371
https://doi.org/10.31083/FBL54371

Review

Photosensitized Lipid Peroxidation Products Navigate Intra- and Intercellular Death Communications in Cancer Cells

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Academic Editor: Sung Eun Kim
Submitted: 31 May 2026 Revised: 31 July 2026 Accepted: 7 August 2026 Published: 10 November 2026

Abstract

The lipid peroxidation cascade is recognized as a pivotal cellular signaling chain controlling the fate of cells through programmed cell death pathways and orchestrating organism defense by influencing inflammatory and immune responses. Its impact is enacted not only locally at the intercellular site of initiating events in membrane lipids but also expands to the level of intercellular communications. This is achieved by the capacity of non-radical lipid hydroperoxide (LOOH) species produced anew at every round of autocatalytic peroxidation step to translocate with remarkable speed and sustained intensity to distances reaching beyond several layers of neighboring cells. Engaged trafficking mechanisms, relying on active transfer/motor proteins (that also contribute by preventing LOOH degradation) and traveling chemical waves, ensure remarkable propagation characteristics of peroxidized lipid wavefronts. Lipid peroxidation cascades have emerged as a controlling executor in the interplay between various types of programmed cell death pathways. They have close relationship with ferroptosis, whose disseminative attributes are executed by propagative LOOH spatial trigger waves. Lipid peroxidation activity can be significantly promoted by oxidative treatments used for cancer therapy, a notable example being photodynamic therapy (PDT). Consequently, ferroptosis was found to play a significant role in the death of tumor cells following PDT treatment. Given the current considerable interest in ferroptosis as a highly promising anti-tumor tool and its exceptional potential for expanding cell-killing range pervasively to other tumor regions through propagative lipid peroxidation, further efforts for clinically exploiting the underlying potentials seem warranted.

Keywords: reactive oxygen species; intracellular and intercellular communication; lipid peroxidation cascade; lipid hydroperoxides; lipid transfer proteins; spatial trigger waves; ferroptosis

1. Introduction

All living cells produce reactive oxygen species (ROS) in the course of their normal metabolism (either in mitochondria, endoplasmic reticulum, plasma membrane, or peroxisomes) involving enzymatic or non-enzymatic routes [1]. The ROS (including highly interactive nitrogen, sulfur, carbon, selenium, and halogen species) can contain one or more unpaired electrons, and this unstable electron configuration drives them to react avidly with other molecules [2]. Acting as signaling molecules, ROS are vital for maintenance of numerous physiological functions including cell proliferation and death, as well as immune responses and inflammatory cascades [1,2]. Their levels are kept in check by the presence of antioxidant defenses developed for preventing damage from oxidative stress induction if ROS overproduction is excessive [3]. The latter can be provoked by metabolic changes in certain pathologic conditions such as malignant transformation or by a variety of environmental challenges including exposure to heavy metals, ionizing and UV radiation, or photodynamic therapy (PDT) treatment [2,4].

One of the key biological impacts of ROS is their interaction with cellular lipids (considered an integral process of lipid metabolism), causing their oxidative degradation with formation of primarily lipid hydroperoxides (LOOH) and their derivatives [5]. Such lipid injury is extremely damaging to cells because it disrupts the thickness, permeability, and structure of membrane bilayers [6]. The two types of ROS most prevalently involved in inflicting this type of lipid damage are hydroxyl radical (HO•) and hydroperoxyl (HOO•) [5]. Polyunsaturated fatty acids (PUFAs), which tend to be present at high levels in cellular membranes as essential for maintaining membrane fluidity, are particularly prone to sustaining radical attacks [7]. PUFAs contain multiple carbon-carbon double bonds that are sites of the radical-mediated abstraction of allylic hydrogen atoms at methylene carbons and formation of carbon-centered lipid radicals (L•) [5]. This free radical intermediate triggers the propagation process called the lipid peroxidation cascade, recognized as the most important instigator of free radical oxidative damage in biological systems and a potent inter- and intracellular communication system [8]. Importantly, monounsaturated fatty acids (MUFAs) are not only resis-

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tant to ROS-mediated oxidative attack, but their exogenous treatment promotes displacement of PUFAs from plasma membrane phospholipids, reduces the sensitivity of membrane lipids to oxidation, and inhibits lipid peroxidation-induced ferroptosis [9].

2. Lipid Peroxidation Cascade

The non-enzymatic cascade process of lipid peroxidation is a radical chain reaction that unfolds in three canonical stages of initiation, propagation, and termination [5]. The initiation step for the autocatalytic lipid peroxidation process is the formation of a free radical intermediate L• on PUFAs. Its presence triggers the propagation stage in which it rapidly reacts with oxygen to form a lipid peroxy radical (LOO•). In the next step, LOO• abstracts a hydrogen atom from another lipid molecule to produce a non-radical intermediate lipid hydroperoxide (LOOH) and generates a new L• that continues the chain reaction. The pivotal feature of the lipid peroxidation cascade is that it will persist to unfold until the available oxidizing lipid substrate is consumed or the termination stage is reached by LOO• encountering a proximal radical-trapping antioxidant. The resultant transfer of an H atom forms a non-radical species (LOOH) that is normally unable to propagate the chain [7,8]. However, the migrated LOOH can trigger new peroxidation cascade cycles if found in the cellular microenvironment presenting high levels of reactive ROS (see below). The chain-breaking lipophilic antioxidants that can suppress/terminate the primary cascade process include α-tocopherol (biologically active form of vitamin E), butylated hydroxytoluene, and low-level nitric oxide [10]. Thus, the major primary products of the lipid peroxidation cascade are LOOH.

Because of being more polar than parent lipids, the presence of LOOH could be deleterious to cells by perturbing membrane structure and function [11]. To prevent such damage, cellular defense relies primarily on an enzymatic antioxidant system based on glutathione (GSH)-glutathione peroxidase GPX4 that reduces hydroperoxides to nontoxic alcohols in biological membranes, or the CoQ10/FSP1 axis for improving cellular antioxidant capacity and suppressing ferroptosis [7,12]. Nonetheless, lipid peroxides have biologically important roles serving as active mediators of critical signal transduction pathways, making them key players in modulating cell death pathways, inflammation, and disease pathogenesis (as will be elaborated below). However, since the primary lipid peroxidation products are inherently unstable, they tend to break down by undergoing further oxidation followed by other reactions to yield a multitude of secondary lipid peroxidation products [8]. Predominant among them are highly electrophilic short-chain aldehydes and ketones formed from fragmentation of the hydrocarbon chain of oxidized lipids, as exemplified by malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) [8]. The former is widely used as a lipid peroxidation marker [5]. Other prominent secondary products include electrophilic truncated fragments of platelet-activating factor-like phospholipids (PAF-LPLs) [13]. These secondary and late derivatives and their end-products tend to be more harmful and cytotoxic than LOOHs by forming adducts with various biomolecules [5].

The basal activity of the lipid peroxidation cascade depends on the cell's inherent metabolic ROS production rate. Hence, cells with elevated metabolic states experience intensified lipid peroxidation activity [14]. Notable examples are malignant cells that harbor constitutionally upraised labile iron pools, rendering them predisposed for Fenton-catalyzed redox reactions producing high levels of hydroxyl radical [15]. Further intensification of lipid peroxidation activity in tumor cells can be instigated by their treatment with therapies like radiotherapy and PDT [2,16]. In fact, PDT, a clinically established treatment for destruction of tumors by oxidative cytotoxic species produced by light-activated photosensitizing drugs [17], is one of the most effective producers of LOOHs [16]. Photodynamic effect can occur via either of two basic mechanisms: Type-I and Type-II [18]. The Type-I mechanism involves electron transfer from the photoexcited triplet state sensitizer to ground state O_2, resulting in formation of cytotoxic oxyradical species, e.g., superoxide or hydroxyl radical. The Type-II mechanism involves energy transfer from the photoexcited triplet state sensitizer to ground state O_2 to give singlet molecular oxygen ($^1O_2$), a cytotoxic non-radical species [18]. Oxyradicals and $^1O_2$ can kill tumor cells by oxidizing vital proteins, nucleic acids, or lipids if they lie in proximity to the generation sites of these ROS. With respect to LOOH generation, Type-I photochemical mechanism produces L• directly, while Type-II features the engagement of singlet oxygen without the involvement of lipid radical intermediates [19]. Consequently, generated LOOH isomer profiles and downstream signaling could significantly differ between the two types of photochemical reactions.

3. Propagation/Trafficking Mechanisms of Peroxidized Lipids

Non-radical LOOH species, produced anew at every round of autocatalytic lipid peroxidation chain propagation, are extremely powerful signaling molecules capable of transmitting with remarkable speed critical impulses either to locations proximal to their generation site or spreading across larger distances and discharging intercellular communications (>5 mm) [20]. They are prone to become involved in intense intercellular trafficking and, upon reaching malignant cell microenvironments abundant in highly interactive ROS generated by the Fenton reaction, they could trigger new cycles of lipid peroxidation cascades [20]. These hydroperoxides have by far longer lifetimes than average radicals, which allows them to migrate from locations of their generation to distant sites, remaining engaged in peroxidation reactions presumed to last for hours or even days [14,16]. Depending mainly on distances in-

volved, there are three major types of transmission mechanisms by which such molecules can spread and be coordinated in space: (i) diffusion, (ii) active transport, and (iii) spatial trigger waves/traveling chemical waves [21,22].

3.1 Signal Trafficking by Spontaneous Diffusion

Diffusion is the basic mechanism for spreading molecules through space with random propelling motion caused by their thermal energy. It homogenizes differences in molecule concentrations very quickly on small spatial scales; for average-sized proteins, it takes ~2 seconds to diffuse 10 µm [22]. However, the diffusion slows dramatically at increased distances and becomes too slow to have a biological impact for ranges over several hundred µm. Hence, the LOOH transfer by spontaneous diffusion is not an effective mechanism for reaching targets beyond a few layers of neighboring cells. The main deficiency of diffusion is not only that with distance it loses speed, but also that the intensity of its impulses is dampened, losing amplitude as they travel [22].

3.2 Signal Trafficking by Active Transport

Active translocation of LOOH to other intercellular sites has been studied in some detail [14]. The engagement of specific transfer proteins in this process via shuttles, bridges, and tubes has been demonstrated [23]. Their involvement helps LOOHs not only to extend their migration but also prolong the lifetimes of these unstable species by preventing their degradation [14]. Active transport of various signaling molecules along actin filaments or microtubules has been reported, highlighting the participation of motor proteins such as dyneins and kinesins capable of propagating signals without distortion and slowing down with increasing distances [24]. The activity of molecular motors was reported to generate fluid flows called cytoplasmic streaming for enhancing transport of signaling molecules [25]. In addition, thin, long subcellular structures named cytonemes or nanotubes have been proposed to secure direct motion of molecules and enable transport of signaling molecules between distant cells [26].

3.3 Signal Trafficking by Spatial Trigger Waves

The most effective biological mechanism for robust transmission of larger quantities of signaling molecules over long distances without losing speed or amplitude is spatial trigger waves. These traveling chemical waves are self-regenerating chemical fronts capable of propagating over long distances [21,27]. They are characterized by reliance on dynamic excitable or bistable media/switches for signal regeneration and transmission [22]. Tumor cells sustaining oxidative stress were postulated to be primed to have their redox systems become bistable (having two stable states) in terms of responding to environmental cues, which facilitates the emergence of robust high-amplitude oscillations and their timing that permits signal propagation via trigger waves [20]. A series of specially-coupled events mediated by wavefronts of peroxidized lipids was shown to be associated with trigger waves of propagating ROS and to be essential for dissemination of ferroptotic cell death [16,20]. The progression of lipid peroxidation trigger waves seems to be controlled and supported through positive and negative ROS feedback loops, including a positive Fenton reaction loop, a NADPH oxidase (NOX) signaling loop, and a negative glutathione synthesis loop [20].

4. Advances in Understanding Lipid Hydroperoxide Translocation Mechanisms

Several years ago, Vila et al. [28] predicted that initiation of chain lipid peroxidation is not necessarily limited to a LOOH's membrane of origin (e.g., in a cancer cell subjected to PDT), but could be disseminated to other membranes via spontaneous or protein-mediated LOOH translocation [28]. Early model studies in this regard were carried out with photogenerated cholesterol (Ch) hydroperoxides (ChOOHs), e.g., singlet oxygen-generated species (5α-OOH, 6α-OOH, 6β-OOH) and free radical-generated ones (7α-OOH, 7β-OOH). Photo-peroxidized erythrocyte membranes (RBC ghosts) were used as ChOOH donors, small unilamellar liposomes (SUVs) as non-contacting acceptors, and HPLC-EC(Hg) for analysis [28,29,30]. The initial rate of 5α-OOH transfer to SUVs was found to be ~4 times greater than that of 7α/β-OOH, largely due to the latter's much lower initial concentration in ghost membranes. The cytotoxic potential of ChOOH transfer was first investigated ca. 20 years ago using ChOOH-bearing SUVs as donors and COH-BR1 cells as acceptors; the latter are a breast tumor subline that lacks the LOOH-reducing/detoxifying selenoperoxidase GPX4, thus allowing translocated LOOHs to be determined as such, using HPLC-EC(Hg) for analysis [30]. The viability of acceptor cells was found to decrease progressively with ChOOH exposure, the order of initial rates correlating with that of ChOOH transfer, i.e., 7α-OOH = 7β-OOH > 5α-OOH > 6α-OOH > 6β-OOH. Importantly, cell killing was terminated when desferrioxamine, an iron chelator/redox inhibitor, was present during incubation, suggesting that cytotoxic iron-catalyzed free radical reactions were responsible [28,30]. This was the first known evidence for dissemination of LOOH cytotoxicity via intermembrane translocation.

The ChOOH translocations described above occurred spontaneously, i.e., without protein assistance. However, transfers mediated by lipid transfer (trafficking) proteins have also been described, particularly for systems under oxidative stress. Most of these proteins are better known to play essential roles in lipid metabolism, biogenesis, and membrane structure/function [31,32]. Sterol carrier protein-2 (SCP-2) is a small (13.2 kDa) intracellular protein that mediates translocation of Ch and other sterols as well as various phospholipids [33] (Fig. 1, Ref. [34]). A ground-

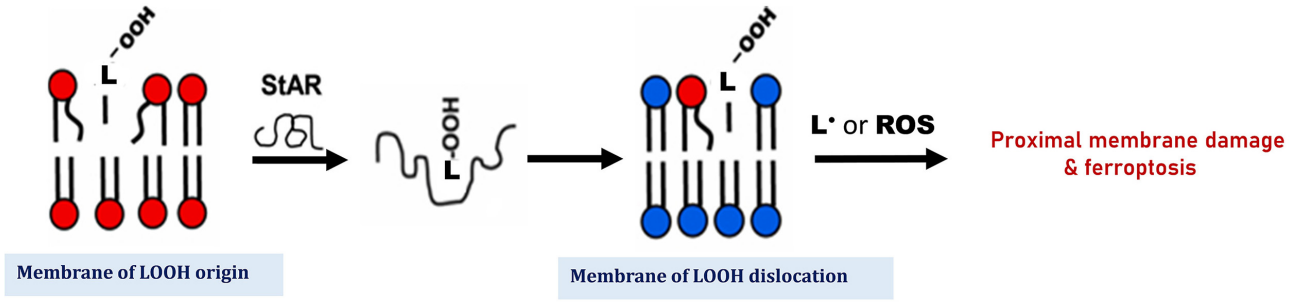


Fig. 1. Role of natural lipid trafficking proteins in intermembrane LOOH transfer. StAR family proteins, known to deliver cholesterol to mitochondria, mediate transfer of LOOH from a membrane of origin to membranes at other locations [34]. L•, carbon-centered lipid free radical; LOOH, lipid hydroperoxide; ROS, reactive oxygen species.

breaking study by Vila et al. [35] showed that SCP-2 not only stimulates Ch transfer between membranes, but also ChOOH transfer as well. It was found that ChOOH transfer from photo-peroxidized RBC ghosts to SUV acceptors could be substantially accelerated by either natural bovine SCP-2 or a recombinant human protein [35]. For various ChOOH isomers, the rate constants for SCP-2-accelerated transfer decreased in the same rank order as spontaneous transfer (see above) [28,30]. Thus, the most hydrophilic peroxides (7α/β-OOH) translocated fastest under both conditions. Steroidogenic cells, like vascular macrophages, require StAR family proteins for Ch delivery to mitochondria, with cytosolic StarD4 delivering it to the outer membrane and StarD1 (as part of a multiprotein complex) internalizing it for steroid hormone synthesis [34,35]. Persistent oxidative stress associated with disorders such as chronic inflammation, ischemia/reperfusion injury, and Type 2 diabetes can seriously impair steroid hormone biosynthesis [36,37]. This led to the hypothesis that 7α/β-OOH in donors like oxidized LDL can be StarD4/D1-transported to the mitochondria of steroidogenic cells and, after reaching the inner membrane, induce chain lipid peroxidation, which disables hormone synthesis [34]. Crucial data were obtained by exposing cyclic AMP stimulated testicular MA-10 Leydig cells to Ch-containing SUVs along with [^{14}C]7α-OOH [34]. Compared with non-stimulated controls, stimulated cells strongly upregulated StarD4 and D1, incorporated far more radioactivity into mitochondria, consistent with StarD4/D1-mediated delivery, and exhibited a greater loss of membrane potential. Also, progesterone output of stimulated cells was far lower than that of controls that had been exposed to SUVs containing Ch but lacking 7α-OOH. Cells remained attached after the incubation times used in these experiments [38], so the observed effects were not associated with any viability losses, although these began to be observed after prolonged incubation times.

The damage/dysfunction described for steroidogenic cells that can internalize peroxidized Ch (e.g., 7α/β-OOH) along with Ch itself needs to be better recognized by investigators seeking means of preventing or at least alleviating probable cytopathological effects. The capacity of phospholipid hydroperoxides (PLOOHs) to act as cytotoxic ligands for intracellular PL trafficking proteins that can also protect them from GPX4 [32] deserves attention (Fig. 1, Ref. [34]). One possibility for protecting target cells from damage/dysfunction by transfer protein-borne ChOOHs or PLOOHs would be to enrich their content of GSH and GSH-peroxidase-Type 4 (GPX4), which is the only enzyme known to catalyze reductive detoxification of membrane-bound LOOHs, e.g., after their release from transporter proteins. ChOOHs and PLOOHs appear to be resistant to GPX4 action when bound to transporters, but become sensitive upon internalization by cells and accumulation in mitochondrial membranes, for example [38]. Cytoprotection by administered free radical-quenching antioxidants is also feasible, e.g., vitamin E, β-carotene, and astaxanthin [39]. It is now clear that functional impairment of steroidogenic cells and Ch-regulating vascular macrophages can occur under conditions associated with oxidative stress, e.g., chronic obesity, diabetes, and ischemia/reperfusion. Although the toxic role of LOOH translocation to vulnerable sites has been amply demonstrated at the *in vitro* level [28,29,30], the importance of this mechanism at the *in vivo* level remains to be determined.

5. Kiss of Death: Lipid Peroxidation and Regulation of Cell Lethality

The lipid peroxidation cascade is becoming increasingly recognized as an active mediator in the complex interplay between various types of programmed cell death [7]. Due to the highly interconnected nature of cell death pathways, they are commonly engaged in cross-talk by sharing signaling molecules and the ability of mutual activation while featuring distinct morphological changes and molecular processes [40]. Excessive production of peroxidized lipids as well as ROS has been identified as critical initiators of programmed cell death pathways and determinants of preference in their engagement [7,38]. It was suggested that cellular contents from cell membranes ruptured by lipid peroxidation products generated by one type of reg-

ulated death pathways could include the released DAMPs (damage-associated molecular patterns) that may initiate other death pathways in neighboring cells [7]. By binding to pattern recognition receptors (PRRs) on immune and other cells, like Toll-like receptor 4 (TLR4), DAMPs trigger the activation of downstream transcription factors such as Nuclear factor kappa B (NF-κB) with the resultant production of critical immune mediators and navigators of immunogenic cell death (ICD) pathways [41].

Both intrinsic and extrinsic apoptosis pathways were shown to become activated by lipid peroxidation activity [7]. The peroxidation of phospholipid cardiolipin located on the inner mitochondrial membrane strongly promotes the permeabilization of this membrane and facilitates the release of cytochrome c, which results in downstream activation of caspases to execute apoptosis [42]. On the other hand, the presence of secondary peroxidation products such as 4-HNE causes an increase in the expression of death receptor Fas, whose binding triggers the extrinsic apoptosis pathway [43].

Lipid peroxidation was found to either promote or inhibit the pyroptotic death pathway under different conditions [7]. Intense peroxidation of cytoplasmic membrane lipids could promote pyroptosis via structural changes induced by gasdermin D pore formation, leading to cell swelling and increased expression of caspase-11 [44]. The inhibitory effect was reported with direct 4-HNE treatment, which binds this peroxidation product to critical domains of NOD-like receptor protein 3 (NLRP3), thereby disrupting the activation of this inflammasome [45].

By exacerbating oxidative stress, amassed lipid peroxides promote the activation of PARP1 (poly(ADP-ribose) polymerase 1), which can lead to DNA damage and trigger cell death by parthanatos. This is a distinct type of regulated cell death characterized by chromatin degradation [7,46]. The induction of parthanatos can reportedly be thwarted by cleaving excessive lipid peroxides with α-tocopherol [47]. It is of note that a reverse impact also exists, as inhibiting PARP1 can diminish lipid peroxidation activity [48].

Damaging lipid peroxidation has also been shown to be involved in the execution of autophagy and other programmed cell death pathways, including necroptosis, cuproptosis, lysosome-dependent cell death, and NETosis [7]. In the former case, secondary lipid peroxidation products such as 4-HNE were found to trigger autophagy by inflicting ER stress [49]. However, it was also shown that there is a feedback loop with activated autophagy promoting the degradation of damaged organelles and activation of antioxidant transcription factors in order to reduce the levels of ROS production and lipid peroxidation [7,50].

The activity of lipid peroxidation cascades has an especially close relationship with another important programmed cell death pathway (ferroptosis), which will be discussed in the following section.

6. Lipid Peroxidation and Ferroptosis

Ferroptosis is a form of caspase-independent necrotic programmed cell death pathway whose defining hallmark is lipid peroxidation activity [51]. It is a critical determinant in various pathological conditions including cancer, tissue ischemic injury, cardiovascular and neurodegenerative diseases [51]. Ferroptosis is initiated by the interaction of chelation-localized redox-active ferrous ions with lipid peroxides and driven by formed peroxyl radicals. All involved radical and non-radical lipid species interfere with cell membrane permeability and integrity, leading to its rupture and ultimately causing cell death [52]. The enzyme acyl-CoA synthase 4 (ACSL4), pivotal in shaping cellular lipid composition toward long-chain PUFAs, was identified as an essential pro-ferroptotic mediator [53]. Remarkably, the vulnerability to ferroptosis of individual tumors is apparently not set but mirrors their dynamic lipid remodeling programs [54].

The excessive accumulation of plasma, mitochondrial, or lysosomal membrane-localized peroxidized lipids will ultimately almost always trigger ferroptotic cell death [52,55,56]. Moreover, the intercellular trafficking of formed lipid peroxidation products creates a powerful tool for extending the areas of cells undergoing ferroptotic death and the extent of tissue damage [16,20]. In distinction to other forms of programmed cell death, ferroptosis tends to propagate, i.e., to affect previously unharmed cells in a non-autonomous mode spreading to functionally collocated cell formations in a manner called synchronized cell death [11,57]. Among the earliest observations of the propagative spreading nature of ferroptosis was the reporting of "exhibited synchronous death patterns that could spread and eliminate large groups of cells through domino-like effect" made in 2016 [58]. Since then, the propagative ferroptotic activity has been documented in various contexts with different types of cells and modes of ferroptosis induction, as summarized recently by Overholtzer's group [59]. These authors discerned two different modes of ferroptotic propagation, localized and long-range. The former features spreading from initiator cells directly to neighboring bystander cells requiring cell-cell adhesion, while the latter propagation is contact-independent, as featured by light-induced ferroptotic waves proficient in jumping over large gaps if distant cells are in a permissive state sensitized, for instance, by a lowered threshold of antioxidant capacity [59]. The massive, pervasive nature of large-scale cell death dissemination by ferroptosis was attributed to its evolutionary optimization for limb rearrangements in embryonic development [20]. The spatially and temporally extended character of ferroptosis expansion, featuring dynamic re-enforcing cycles of cell killing, could be explained by either the trafficking of generated LOOHs carried by transfer/motor proteins or to performance of lipid peroxidation wavefronts (spatial trigger waves) [16].

Once activated, e.g., in cancer cells, ferroptosis can lead to non-apoptotic cell killing [60,61]. Ferroptosis has been shown to play a significant role in the death of cancer cells after exposure to PDT. For example, photokilling of human SiHa cervical cancer cells pre-sensitized with 5-aminolevulinic acid (5-ALA)-induced protoporphyrin IX (PpIX) was stimulated by sorafenib, a ferroptosis inducer, but diminished by ferrostatin, a ferroptosis inhibitor [62]. These findings suggested that the onset of ferroptosis could promote cell killing during ALA-PDT, e.g., by acting synergistically with photosensitized killing. Satisfactory confirming evidence was obtained from *in vivo* model experiments using mice that carried SiHa cancer xenografts, and again, sorafenib stimulated cancer cell demise [62]. Ferroptosis features as the best candidate for the induction of anti-tumor PDT bystander effects (killing of tumor cells in therapeutically non-targeted areas) [16]. This is supported by findings of ferroptotic cells in deep-seated areas of PDT-treated mouse carcinomas, i.e., in regions located beyond the reach of therapy illumination [63]. Collectively, these studies revealed that anti-tumor photodynamic action depended not only on direct cell hits by photogenerated ROS, but on the synergy between this and ferroptotic stress arising alongside. Whether ferroptosis also accompanies other therapeutic modalities besides PDT, e.g., chemotherapies or radiotherapies, needs to be thoroughly assessed for a better understanding of underlying therapeutic mechanisms.

7. Conclusions: Summary and Perspectives

With its unique molecular mechanism and lipid peroxides in the focus as its pivotal executioner, ferroptosis has come to the forefront of cancer therapy research inspired by the prospects of extraordinary therapeutic potential. By exploiting the iron dependency of tumor cells, harnessing ferroptosis can be instrumental for enhancing tumor cell sensitivity to various therapeutic strategies. The outstanding issues and key translational barriers coming in the forefront are (i) whether ferroptosis can be made to last as long as needed to cover all areas in targeted tumors, and (ii) accurate and technologically convenient measuring of lipid peroxidation for patient stratification [7], (iii) tumor-selective delivery of pro-ferroptotic agent while omitting systemic toxicity, and (iv) which ferroptosis induction/amplification agents are clinically most potent? Another outstanding issue is the potential inhibitory effects of ferroptosis on the activity of immune cells in the tumor microenvironment, and such immunosuppressive aspects need to be prevented [64]. The lipid peroxidation cascade process deserves greater interest and further investigation, particularly its death signaling aspects in tumors.

This review focuses on PDT as a ferroptosis-inducing treatment. Photosensitizers used for PDT tend to localize in biomembranes and, when photoactivated, generate ROS that can oxidize membrane cholesterol and phospholipids, giving LOOH intermediates. In the presence of redox iron and reductants, LOOHs are converted to free radical species, which can expand membrane damage via free radical-mediated (chain) lipid peroxidation. When catalyzed by redox iron, this cytotoxic process, known as “ferroptosis”, can occur in many PDT-challenged tumors [62,63]. Primary ferroptosis in PDT-targeted tumor cells may give rise to ferroptosis in neighboring tumor bystander cells prompted by LOOH intermediates delivered via transfer-mediated mechanisms [16]. If tumor-contained, this would be a beneficial effect of LOOH translocation in contrast to possible deleterious effects of exogenous translocation described in Sect. 4. These direct and indirect effects, often described as bystander responses, can be instigated by other oxidative therapeutic treatments such as radiotherapies, cryotherapy and other thermal therapies, and certain chemotherapies [14,65]. More needs to be learned about each of these different possibilities.

Abbreviations

LOOH, lipid hydroperoxide; PDT, photodynamic therapy; ChOOH, cholesterol hydroperoxide; PLOOH, phospholipid hydroperoxide; DAMPs, damage-associated molecular patterns; SCP-2, sterol carrier protein-2; StAR, steroidogenic acute regulatory; 4-HNE, 4-hydroxynonenal; MDA, malondialdehyde; GPX4, glutathione peroxidase-type 4; NOX, NADPH oxidase; PAF-LPLs, platelet-activating factor-like phospholipids; PRR, pattern recognition receptor; ROS, reactive oxygen species; TLR4, Toll-like receptor 4.

Author Contributions

All authors meet the 4 criteria for authorship as outlined in the authorship. MK and AWG designed the research study and wrote the manuscript text. The author WK provided a substantial contribution to the design of the work as well as help and advice in manuscript finalization. All authors contributed to editorial changes in the manuscript. All authors read and approved the final 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

Not applicable.

Acknowledgment

Not applicable.

Funding

This research was funded by USPHS Grant CA70823 from the National Cancer Institute and by Grant 5520347 from the Advancing a Healthier Wisconsin Research and Education Foundation awarded to AWG.

Conflicts of Interest

The authors declare no conflicts of interest.

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