



The coming decade in ferroptosis research: Five riddles

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Abstract

Ferroptosis is, in many ways, the odd one out among cell death modalities. It does not, at least as far as we know, require an activating signal. Instead, it represents a default cellular fate that is continuously repressed by a multilayered network of surveillance systems. At its core, ferroptosis is driven by the unchecked peroxidation of polyunsaturated phospholipids (PUFA-PLs), a vulnerability shaped by lipid bilayer composition. Glutathione peroxidase 4 (GPX4) is a central defense enzyme that reduces lipid hydroperoxides to their corresponding alcohols using glutathione as a cofactor. This is complemented by ferroptosis suppressor protein-1 (FSP1)-mediated regeneration of coenzyme Q₁₀ or vitamin K at the plasma membrane and reinforced by dietary or endogenous radical-trapping antioxidants, such as vitamin E, squalene, and 7-dehydrocholesterol. Still, ferroptosis sensitivity is not just a function of antioxidant failure but also a direct consequence of the architecture of the membrane itself: the abundance of PUFA-PLs, shaped by acyl-CoA synthetases like ACSL4 and others; the relative scarcity or abundance of monounsaturated fatty acids, which confer resistance; the regulation of membrane repair and remodeling enzymes; and the delicate balance of redox-active iron within organelles such as lysosomes. Together, these elements converge to determine whether ferroptosis remains a manageable threat or becomes lethal. Despite growing mechanistic insights, fundamental riddles endure: Why does ferroptosis exist at all? What is the precise role of iron: catalyst, signal, or inherent peril? Where, within the cell or organism, does ferroptosis ignite? Can we safely harness this pathway for clinical benefit? And ultimately, is ferroptosis truly a form of regulated cell death, or the mere emergence of a primordial biochemical vulnerability? Inspired by Douglas Green's iconic riddle framework, this review distills five unresolved questions that may define the coming decade of ferroptosis research. Rather than solving them, we aim to refine their silhouettes at the intersection of lipid (bio)chemistry, evolutionary biology, and translational opportunity.

Keywords: Ferroptosis, iron metabolism, lipid peroxidation, evolutionary biology, immunogenic cell death

1. Introduction

What if ferroptosis was never meant to be a cell death pathway, but an ancient relic or an evolutionary trade-off? A molecular fossil of ancient Earth, shaped by the raw violence of iron and oxygen in a primordial soup. What if its function today is less about dying and more about remembering? About encoding evolutionary lessons in biochemical defense, and about guarding the cell's most vulnerable structures, its lipid membranes, from one of their oldest inherent enemies: oxidation.

But more importantly, what if this ghost of ancient biochemistry is not done with humanity? What if ferroptosis is the molecular switch that governs the balance between metabolism, immunity, and the trajectory of disease? We are starting to obtain an understanding of how to block it, induce it, and likely monitor it. But do we really know *why* it exists in the first place?

In this perspective, we follow five riddles, some of them old, some of them emerging, which we believe could shape the next decade of ferroptosis research. These questions are not only mechanistic; they may at times seem philosophical, because understanding ferroptosis is not merely about how cells die, but about asking whether this kind of death is, in fact, an ancient form of life's control.



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2. Riddle #1: Iron Gave Ferroptosis Its Name, but Does It Give It Purpose, or Only Permission?

2012 is to us what 1972 is to the apoptosis research community: the year when the term ferroptosis was first introduced, derived from the Latin word ferrum, meaning “iron”^[1] (Figure 1). For approximately two decades before then, evidence had been accumulating to show the existence of a distinct non-apoptotic form of cell death driven by unrestrained, iron-dependent lipid peroxidation^[2–6]. The importance of iron in ferroptosis was especially highlighted in 2008, when erastin and RSL3-induced cell death was found to depend on cellular iron levels and to be rescued not only by antioxidants^[7], but also by iron chelation or genetic inhibition of cellular iron uptake^[8]. In parallel, genetic perturbations of key cellular redox-related genes, especially glutathione peroxidase 4 (GPX4) and the cystine-glutamate antiporter system x_c^- , were found to lead to a similar form of non-apoptotic cell death marked by the accumulation of peroxidized lipids^[5,6]. Together, these findings connected iron-dependent lipid peroxidation to ferroptosis^[9].

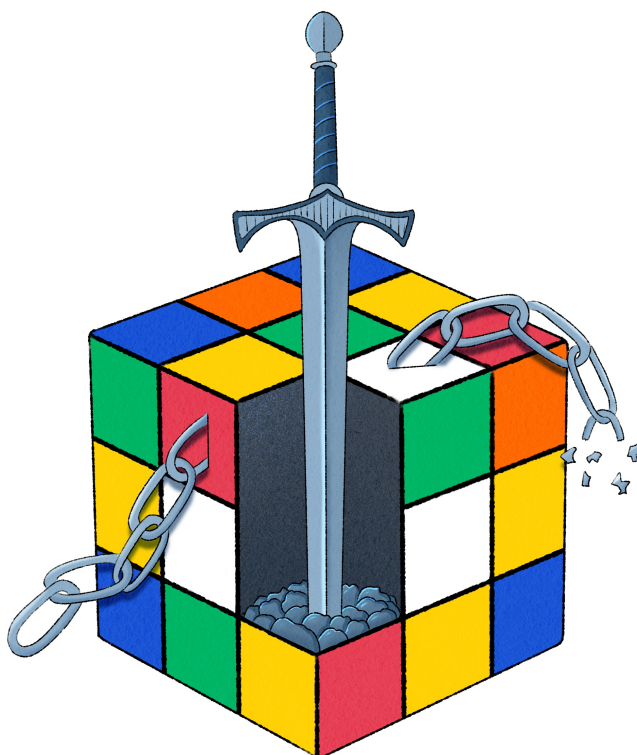


Figure 1. *In iron is forged my name. His blade made my fame. Yet my grounds it fails to explain.*

Evidently, the rescuing effect of iron chelators *in vitro* provides a solid link between ferroptosis and iron, along with its more or less well-recognized role in Fenton chemistry and ensuing lipid peroxidation^[10]. However, *in vivo*, the exact contribution of iron to ferroptosis remains poorly understood. Especially the precise nature of iron, which contributes to lipid peroxidation in ferroptosis—whether it be in its labile form or enzyme-bound form—remains debated. As such, the peroxidation of membrane-bound, PUFA-containing lipids, which leads to the formation of phospholipid hydroperoxides, can occur either through autoxidation or enzyme-catalyzed processes^[11]. In both cells and tissues, lipid peroxidation primarily occurs via autoxidation, where initiating radicals abstract bis-allylic hydrogens from PUFA chains followed by oxygenation, ultimately leading to the generation of lipid hydroperoxides. Upon initiation, this chain reaction can propagate through radical chemistry and Fenton-like processes, in which lipid hydroperoxides react with labile Fe^{2+} and Fe^{3+} ions to generate alkoxyl and peroxy radicals, respectively, initiating new chain reactions. Fenton chemistry also contributes to lipid peroxidation by generating new initiating radicals, particularly hydroxyl radicals from hydrogen peroxide^[11].

On the other hand, iron in non-heme iron-bound enzymes, such as lipoxygenases (LOXs), also catalyzes the production of lipid hydroperoxides^[12,13]. However, the extent to which enzymatic lipid peroxidation contributes to ferroptosis remains a matter of debate and appears to critically depend on the context, the LOX isoform, and the method of ferroptosis induction^[12,14–16]. For instance, 12S-LOX seems to be crucial for p53-driven ferroptosis^[17]. Although lipid peroxidation itself not only contributes to ferroptosis execution but also to other regulated cell death modalities, such as apoptosis, necroptosis, and pyroptosis, it is the unrestrained, excessive peroxidation of phospholipid species that distinguishes the lipid peroxidation process driving ferroptosis from other forms of cell death. In one way or another, iron thus contributes to lipid peroxidation, driving ferroptosis, but the more subtle cues through which it operates remain largely unknown.

Because iron is involved in Fenton chemistry, a large body of work has demonstrated how modulating key players of iron metabolism, thereby affecting the labile iron pool (LIP), can significantly influence a cell's sensitivity to ferroptosis. For example, the iron transporter transferrin receptor 1, which is primarily responsible for iron uptake in the form of Fe^{3+} -bound transferrin by most cells^[18], exhibits increased expression during ferroptosis and has been proposed as a potential biomarker of ferroptosis^[19], although these data require clinical scrutiny. The synthesis and autophagy-mediated degradation of the cellular iron storage protein ferritin, a protein complex that sequesters excess labile iron in the cytosol to prevent harmful Fenton reactions^[20], are also able to regulate intracellular labile iron levels^[21,22]. These processes thus exert opposing effects on cell sensitivity to ferroptosis^[23,24]. Moreover, some cancer cells can acquire resistance to ferroptosis by enhancing iron efflux through the iron export transporter ferroportin or through the prominin-2-dependent export of ferritin-containing multivesicular bodies^[25,26]. The destabilization of iron-sulfur clusters and heme degradation can also release iron, further contributing to the LIP^[27], although the contribution of these to overall ferroptosis sensitivity remains poorly mapped out. Despite acknowledging the importance of iron homeostasis in ferroptosis, the specific factors that may disrupt this balance and predispose cells or organs to ferroptosis under certain pathological conditions remain to be identified. One could stipulate that these factors likely extend beyond simple metabolic mistakes and could, in fact, represent strategic choices made by cells to thrive in their environments. Cells might, for instance, intentionally accumulate iron to transition toward a more “environmentally competitive” phenotype, as in the case of iron loading during cancer cell state transition^[28], or to mitigate specific stresses. Such hypothetical scenarios present cells with a dilemma: iron is crucially needed but entails a trade-off with increased vulnerability to ferroptosis.

While lipid peroxidation is known to spread to the plasma membrane in the final stages of ferroptosis^[29-32], the initial site of lipid peroxidation and its potential connection to iron levels have already led to much debate. Proposed locations include the endoplasmic reticulum (ER)^[31,33], mitochondria^[34], ER-mitochondrial contact sites^[35], and lysosomes^[36-38]. In particular, mitochondria and lysosomes play critical roles in iron homeostasis, as they are inherently rich in (labile) iron^[39]. It was thus intuitively believed that lipid peroxidation could first be initiated within or at the periphery of those organelles before propagating to others, such as the ER^[31]. However, the role of mitochondria, particularly of mitochondrial iron, in initiating ferroptosis is contentious. In some contexts, disrupting mitochondrial iron homeostasis, such as increasing mitoferrin-dependent mitochondrial iron uptake^[40] or disrupting iron-sulfur cluster biosynthesis^[41], increases cell sensitivity to ferroptosis. Notably, mitochondria may be required for cystine deficiency-induced ferroptosis^[34], due to the simultaneous depletion of cysteine-derived sulfur and glutathione (GSH), which are both necessary for iron-sulfur cluster biosynthesis^[42]. On the other hand, recent studies have highlighted the role of lysosomes, particularly lysosomal iron, in initiating ferroptosis, at least in the cancer context^[36-38]. Lipid peroxidation occurs early at endolysosomal membranes compared to other organelles^[38], and may induce lysosomal membrane permeabilization, facilitating lysosomal iron leakage to the cytosol and thus spreading lipid peroxidation to other organelles, such as the ER^[37]. Of note, as cellular labile iron may also stimulate reactive oxygen species (ROS) signaling pathways involved in pyroptosis^[43,44], triggering lysosomal membrane permeabilization and the subsequent release of lysosomal iron has been suggested as an effective dual strategy for promoting both ferroptosis and pyroptosis, thereby potentiating anti-cancer therapy^[45]. Excitingly, several small molecules that trap lysosomal iron and induce Fenton reactions in this organelle have been developed as potential novel therapies against iron-rich, drug-tolerant persister cancer cells^[38,45-47], which are particularly susceptible to ferroptosis^[47-49]. Overall, the exact site of ferroptosis initiation is likely context-dependent, requiring not only iron but also a membrane lipid composition prone to peroxidation and compromised antioxidant defenses. Only together can these factors ignite the spark necessary to trigger ferroptosis.

Iron is known for its essential role in a myriad of physiological processes critical to life^[50,51]. However, due to its high reactivity, iron overload can lead to cytotoxicity and has been implicated in disorders, such as liver fibrosis and hepatocellular carcinoma^[52,53], insulin-dependent diabetes^[54], and cardiomyopathy^[23,27]. Increased iron deposition is also characteristic of multiple neurodegenerative diseases, such as Alzheimer's^[55,56], Parkinson's^[57], and multiple sclerosis^[58]. An increasing number of studies have indeed suggested that ferroptosis is the underlying cell death mechanism in iron-overload tissues^[59-62]. However, the exact role of ferroptosis in iron overload keeps researchers on their toes as they explore this complex relationship *in vivo*. Indeed, iron accumulation *per se* does not necessarily result in ferroptosis. For instance, both the liver and pancreas of mice with systemic iron overload accumulate similarly excessive levels of iron; yet only the pancreas is extensively affected, resulting in exocrine pancreatic failure^[63]. Additionally, in aged mice, ferritin-driven iron deposition occurs in the hippocampus, which impairs cognitive function; yet, no ferroptotic cell death was detected in the neurons of this brain region^[64]. It is noteworthy that iron chelation therapies have been tested in phase II clinical trials in patients with Alzheimer's disease and Parkinson's disease, yet they markedly worsened clinical outcomes^[65,66]. Multiple elements, such as iron management and specific pathological conditions, can thus influence the induction of ferroptosis in contexts of iron overload. Therefore, the link between excessive iron and ferroptosis warrants careful interpretation and calls for further investigation to establish their cause-and-effect relationships.

3. Riddle #2: If Ferroptosis Is Older than Multicellularity, Was It Born to Kill, or to Protect?

“Ferroptosis” and the history of its development are inextricably linked to the origin of primordial forms of life. This has its roots in prokaryotic life approximately 3.8 billion years ago^[67] (Figure 2). In the anoxic oceans of the early Earth, soluble ferrous iron (Fe^{2+}) was a fundamental nutrient for primordial organisms. The Great Oxygen Event (GOE), also referred to as the “sulfur era”, led to changes in

geochemistry that made iron (Fe), oxygen (O), and sulfur (S) vital components of all forms of life^[68]. This resulted in the iron paradox and a crucial evolutionary problem for all living organisms. One could argue that iron played a double role, being an essential nutrient as well as a catalyst of oxidative reactions by Fenton chemistry, which exerted a selective pressure for the evolution of complex regulatory systems, such as dedicated iron-binding safeguarding and ROS eliminating systems^[69], and for the emergence of cell death pathways like ferroptosis as the ultimate key regulatory mechanism.

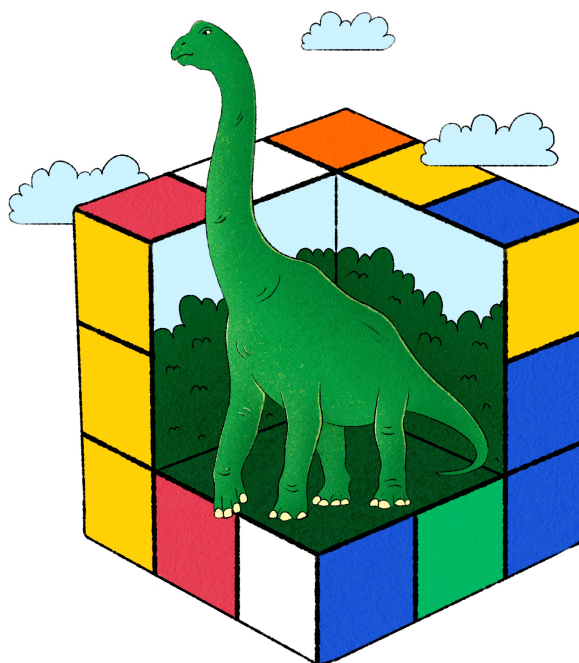


Figure 2. Through millennia and species, I thrive. From giant fossils to tiniest lives. Ever since iron and oxygen collision, I am the echo of life's adaptation.

The evolutionary lineage of ferroptosis is also intriguing, since its molecular determinants appear to be highly conserved across evolutionarily distant species, including protozoa, plants, fungi, and mammals^[70-72]. For instance, the presence of key surveillance proteins, such as GPX4 and ferroptosis suppressor protein-1 (FSP1), is preserved from yeast to mammals, revealing a fundamental evolutionary dependency^[73]. In mammals, the best-studied mechanism of the anti-ferroptotic defense centers around GPX4, which effectively counteracts ferroptosis by reducing highly reactive (phospho)lipids and cholesterol hydroperoxides to their respective alcohols^[74,75]. GPX4 belongs to the larger family of eight glutathione peroxidases in mammals, each with distinct substrate specificities and tissue distributions. Five of these glutathione peroxidases in humans belong to a unique family of selenoproteins, present in all three domains of life, which are characterized by carrying at least one selenocysteine (Sec), generally responsible for the oxidoreductase function of selenoproteins^[76]. Selenium itself is an essential trace element in the cell, present in significant amounts as an amino acid residue in selenoproteins. Sec is encoded by the opal codon UGA, requiring its own specific tRNA^[77]. Moreover, Sec-containing enzymes offer substantial advantages in catalytic efficiency, yet they bear some disadvantages: dependency on selenium availability, potential for side reactions, and an arduous insertion mechanism during co-translational protein synthesis^[78].

Current evidence suggests that selenoproteins are ancient evolutionary relics that have been progressively replaced by their common cysteine (Cys)-containing homologs across bacterial, archaeal, and eukaryotic domains^[79,80]. This suggests a clear evolutionary trajectory for antioxidant systems as they readily adapt to changing environmental and metabolic demands. For example, in aerobic organisms where oxygen is the prime electron acceptor, a process inevitably linked to the generation of ROS, bacteria like *Staphylococcus aureus* upregulate their Cys-based thioredoxin systems to counteract oxidative stress^[81]. Similarly, in *Bacillus subtilis*, the presence of redox-active “resolving” cysteines in peroxidase enzymes functions as elegant molecular switches, managing the cellular redox environment by cycling between thiol and disulfides, thereby protecting the “peroxidatic” cysteine from irreversible peroxide-induced overoxidation^[82]. This fateful event is prevented by thiols under the control of non-heme peroxidases throughout evolution, culminating in mammalian GPX4, which has become highly specialized for reducing lipid hydroperoxides, a task for which its cysteine-containing ancestors were less efficient^[83].

The vulnerability to oxygen and iron exposure, eventually causing lipid peroxidation, was present even in simpler organisms^[73]. The fundamental “lipid divide” as a result of divergent evolution, differentiated archaea and eubacteria, which triggered different defensive systems^[84]. Archaea use ether linkages - single bonds between an oxygen and two carbon atoms (R-O-R') - which are chemically stable and resistant to cleavage by oxidizing conditions^[85]. Eubacteria, on the other side, use ester linkages (R-CO-O-R'), which are more susceptible to chemical breakdown, particularly through oxidation^[85]. Due to this unique membrane chemistry,

archaea, as precursors of mammals, might naturally be protected from overoxidation and, in the case of well-studied vertebrates, from ferroptosis^[86]. Eubacteria, on the other hand, developed an alternative survival strategy, like sporulation to protect themselves from harsh environmental conditions^[87].

As the complexity of organisms increased, lipid profiles evolved into complex, highly specialized systems that play roles in intercellular communication (e.g., PUFAs as precursors of eicosanoids), homeostasis, temperature regulation, the nervous system, and vision ^[86]. The significant components of membranes in latest organisms are fatty acids (FA), which are activated by acyl-CoA synthetases (ACSLs) by ligating them to coenzyme A (CoA), creating water-soluble acyl-CoAs, which are either directed to metabolic pathways or are being used as building blocks for lipid membranes^[88]. ACSL homologs are found in all three domains of life^[89], undergoing countless rounds of diversification over billions of years, resulting in the large family of ACSL enzymes, each with specialized roles. For example, in humans, the different isoforms (ACSL1, ACSL3, ACSL4) have preferences for different types of fatty acids and are expressed in various tissues^[90]. It could be inferred that the ancient role of ACSLs in building membranes creates a vulnerability, and the specific adaptation enriches membranes susceptible to iron-catalyzed peroxidation and ferroptosis. It might seem that all these signatures illustrate an evolutionary “arms race” – as the threat of lipid peroxidation grew with the membrane compartment growing in complexity, a more specialized defense system developed.

The most recent evolutionary invention, primarily present in vertebrates and tracing back more than 550 million years ago, is the cystine-glutamate antiporter system x_c^- . This transporter is a support system fueling the GPX4 pathway, among others^[91]. It functions by importing cystine from the extracellular environment, which is subsequently reduced to cysteine inside cells, the rate-limiting substrate for GSH biosynthesis. GSH is the preferred cofactor of GPX4 function and is also important for numerous cellular processes, including Fe-S cluster biogenesis, drug metabolism, and likely Fe^{2+} chaperoning in the LIP. The gene encoding SLC7A11, the substrate specificity-conferring active subunit of the cystine transporter in system x_c^- , arose after the evolutionary split between protostomes (insects, mollusks, and worms) and deuterostomes^[92]. The appearance of system x_c^- in deuterostomes represents a significant adaptive turnover and an evolutionary advantage, most likely related to the complexity of antioxidant defenses and glutamatergic signaling^[93]. Therefore, ferroptosis, as we know it today, appears to be more than a mechanism of death; it may be an echo of life's adaptation to a changing environment, a memory written into the interplay among iron, lipids, and genes.

4. Riddle #3: Is Ferroptosis a Fire We Must Extinguish, or a Flame We Must Learn to Wield?

Ferroptosis is a fundamental process in cellular life and death, and consequently, systematically modulating it carries significant risks (Figure 3). A central challenge is achieving therapeutic control: how do we design highly potent drugs, that are harmless everywhere else? Recent research suggests that several compounds can selectively induce ferroptosis in cancer cells, providing a potential therapeutic target^[94]. But is it that easy? It is well known that only a few compounds working in the cell culture are directly translatable to the *in vivo* context. Such widely used drugs include erastin, RSL3, and FIN56, all of which have poor metabolic stability, low bioavailability, and toxicity, thereby restricting their use in any *in vivo* experiment^[10]. Ferrostatin-1, an archetypal ferroptosis inhibitor, is still commonly used in mouse experiments, but has already been shown to have inferior metabolic stability and is rapidly cleared from the bloodstream, which needs to be taken into consideration^[95]. Moreover, cell and tissue susceptibility to ferroptosis is highly context-dependent, influenced by numerous factors, such as, for example, fetal bovine serum, growth media supplements, cell density, as well as cell-to-cell metabolic crosstalk during *in vitro* handling^[96-99].

The selective induction of ferroptosis *in vivo* has been observed with compounds like APR-246, triggering ferroptosis through modulating cysteine metabolism and contributing to the therapeutic effect in acute myeloid leukemia^[100] and esophageal squamous cell carcinoma^[101]. Additionally, preclinical studies of JKE1674, which targets GPX4 directly, had high potential in lung cancer treatment, overcoming its resistance to ferroptosis induction^[102]. Nevertheless, neither the FDA nor the EMA approved either of these compounds for the treatment of cancer, as they were unable to demonstrate a statistically significant improvement over existing treatments. Some studies suggest that specific hormonal environments may modulate ferroptosis sensitivity, opening therapeutic possibilities in cancer therapy. In breast cancer, for instance, estrogen has been demonstrated to confer resistance to ferroptosis through the upregulation of SLC7A11 and GPX4^[103]. Conversely, membrane lipid-modifying enzymes, in particular membrane-bound O-acyltransferases (MBOAT), have been identified as key sensitizers of ferroptosis. By remodeling the phospholipid profile of cellular membranes to incorporate PUFAs, these enzymes create a ferroptosis-prone state. MBOAT1 was shown to sensitize estrogen receptor-positive (ER⁺) breast cancer cells to ferroptosis^[103,104], while MBOAT2 acts similarly in sensitizing androgen receptor-positive (AR⁺) prostate cancer cells^[105]. Lipid remodeling is one method of sensitizing cells, thereby further expanding the therapeutic landscape. For instance, recent studies have revealed that the cholesterol biosynthesis pathway, specifically the accumulation of 7-dehydrocholesterol (7-DHC), a direct cholesterol precursor, is an endogenous suppressor of ferroptosis^[32,106,107]. These discoveries led to the identification of emopamil-binding protein (EBP) as a potential therapeutic target^[108]. Inhibiting EBP with molecules like TASIN-30 blocks the conversion of lanosterol^[106] to 7-DHC and leads to the accumulation of metabolites that sensitize cells and effectively halt tumor growth. According to current knowledge, ferroptosis appears as a complex process involving numerous closely related metabolic determinants, including amino acid metabolism, carbohydrate metabolism, mevalonate pathway, and fatty acid metabolism. Beyond the aforementioned 7-DHC, like vitamin K, (phospholipid alcohols, acrolein, and many other metabolites have

demonstrated their ability to modulate susceptibility to ferroptosis^[9,109-111]. Notably, acrolein, a metabolic byproduct of polyamine oxidation, acts both as a ferroptosis inducer by fostering lipid peroxidation and as a necroptosis inhibitor by blocking oligomerization of the necroptotic effector mixed lineage kinase domain-like pseudokinase (MLKL), demonstrating that some metabolites may have opposing effects on different cell death modalities, thereby challenging targeted therapy development^[111]. In the same vein, there has been growing interest in the development of drugs capable of simultaneously targeting multiple modes of cell death, as is the case with sibiriline, which exhibits both anti-ferroptotic and anti-necroptotic activity in a rat model of Parkinson's disease^[112]. Nevertheless, these targets are not yet at the stage of clinical testing, requiring additional (pre)clinical developmental steps.

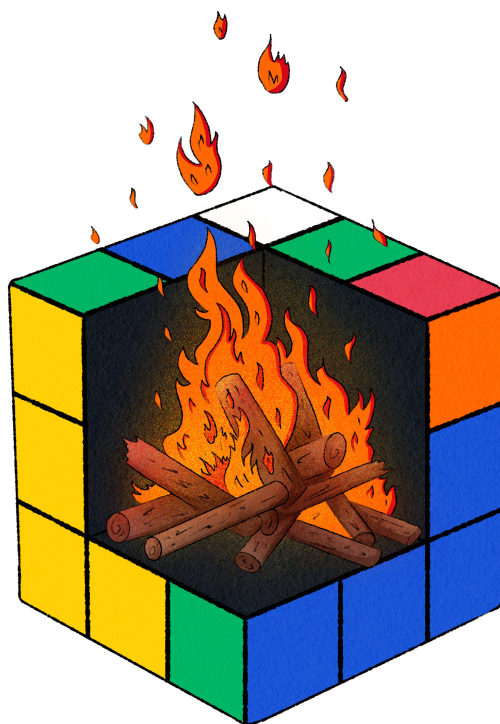


Figure 3. *Many diseases bear my trace. To target me, has begun the race. I am a fire to be doused or stoked. Yet still uncatchable like smoke.*

But what if we focus on the clinically approved strategies? For instance, the antipsychotic drug caripazine (CAR), a dopamine receptor partial agonist, has been shown to modulate multidrug resistance in cancer cells^[113]. More importantly, CAR increases 7-DHC levels, thereby decreasing neuronal susceptibility to ferroptosis in ischemic brain injury^[114]. Among clinically approved iron chelators, deferiprone (DFP) and deferasirox (DFX), have shown effective inhibition of ferroptosis in animal models of cardiac and kidney injury, as well as neurodegeneration^[1,115,116]. However, the major limitation of this therapeutic approach is the proven toxicity associated with long-term treatment. Other candidates include sorafenib, approved for liver and kidney cancers^[117], which as an off-target effect, was reported to inhibit the system x_c^- transporter (although refuted in a subsequent study^[118]), and sulfasalazine, which acts through the same mechanism but is used for rheumatoid arthritis and ulcerative colitis^[119,120]. It is, however, important to note that sulfasalazine is a rather poor system x_c^- inhibitor, requiring extremely high doses, which were even lethal in clinical studies designed to treat glioblastoma^[121]. Another FDA-approved molecule, N-acetylcysteine (NAC), widely used as a mucolytic agent and antidote for acetaminophen poisoning, is also gaining attention as an anti-ferroptotic drug by rapidly replenishing the intracellular cysteine pool^[122]. One unique example of compensatory therapy against impaired GPX4 function is a high-vitamin E diet, reported in a case of the rare genetic disorder Spondylometaphyseal Dysplasia Sedaghatian type (SSMD)^[123,124]. Vitamin E directly incorporates into cell membranes and quenches lipid radicals, acting as an inhibitor of ferroptosis and serving as an already established supportive therapy^[10].

Among therapeutic approaches for inhibiting ferroptosis, lipoxstatins represent one of the most extensively studied classes of compounds. In particular, Lipoxstatin-1 has demonstrated significant potential across a range of diseases driven by lipid peroxidation^[15,125]. A notable example is its protective effect in ischemia-reperfusion injury, where it has been shown to shield both kidney and liver from lethal damage^[126]. This class of molecules has proven effective in various applications, including organ preservation for transplantation, and holds promise as a potent anti-ferroptotic agent for both systemic and central nervous system applications^[124]. Collectively, these studies highlight not only the strong current interest in this area but also the complexity of the therapeutic landscape, given that ferroptosis is a multifaceted mechanism involving whole biological systems, which makes it particularly challenging to target and manipulate.

5. Riddle #4: It Takes Two to Tango or to Spark a Fiery Quarrel – How Do Cells Engage in the Intriguing Dance of Ferroptosis?

Dying cells possess their own language, the so-called damage-associated molecular patterns (DAMPs), which are typically immunostimulatory^[127]. Most DAMPs actually become accessible only upon plasma membrane rupture. Just like other forms of necrotic cell death, distinguishable from apoptosis^[128], ferroptosis ultimately leads to membrane rupture and the release of the cellular content. Indeed, lipid peroxidation damages the plasma membrane^[31,32,129,130], increasing the tension on this cell structure, leading to ion channel opening, osmotic swelling, and eventually plasma membrane rupture^[131,132]. Ferroptotic cells have been shown to release two well-known DAMPs, namely high mobility group protein B1 and ATP^[133], along with cytokines, especially TNF and interferon- β ^[134], and macrophage migration inhibitory factor^[99]. While these DAMPs exhibit innate immune activity and are also released by necrotic cells, other chemokines known to be released by apoptotic or necroptotic cells, such as CXCL1 and , are not released during ferroptosis^[99]. Interestingly, ferroptotic cells appear particularly prone to release anabolic metabolites, such as those from the pentose-phosphate pathway, tricarboxylic acid cycle, and methionine cycle, along with oxylipins and nucleotides, including oxidized 8-hydroxy-2'-deoxyguanosine, compared to cells dying from other modalities like apoptosis and necroptosis^[99], making those nucleotides potential ferroptosis-specific DAMPs. Ferroptotic cells also expose the ER protein calreticulin and specific oxidized phospholipids to the outer leaflet of the plasma membrane^[133,135], which may serve as signals for macrophage phagocytosis through Toll-like receptor 2, both *in vitro* and *in vivo*^[136]. Whether ferroptotic cells release or expose other (ferroptosis-specific) DAMPs remains largely unknown. Moreover, are the DAMPs released by ferroptotic cells sufficient for them to be noticed? Regardless of the cell death modality, there is an ongoing debate about which of the numerous known DAMPs are essential activators of inflammation^[137], an identity that may vary from one cell death modality to another. Additionally, the time elapsing between the initiation of membrane damage and cell bursting, which is also influenced by the activation of membrane repair mechanisms, may affect how dying cells communicate with their environment. Notably, the endosomal sorting complex required for transport III (ESCRT-III), a critical membrane repair machinery, is activated during ferroptosis execution and may thus modulate the secretion of DAMPs by ferroptotic cells^[138,139].

One notable example of pathological intercellular dialogue occurs between cancer cells and immune cells in the tumor microenvironment (TME). When it comes to adaptive immunity and cancer, the concept of proinflammatory response or death translates to immunogenic cell death^[140]. To be considered immunogenic, cell death must occur in a context of failed adaptation to stress (i.e., pathogenic), be associated with the release of DAMPs and proinflammatory cytokines in sufficient quantities (i.e., adjuvanticity), and under microenvironmental conditions favorable to the recruitment of dendritic cells (i.e., permissivity) and the subsequent priming of T cells (i.e., antigenicity), as well as for T cell infiltration and effector functions^[133,141].

Ferroptosis, although not immunologically silent and rather cytotoxically and adjuvantly loud, presents conflicting evidence regarding its antigenicity and permissivity. Some studies suggest that ferroptotic cancer cells impede dendritic cell maturation and antigen-presenting capacity, thereby reducing anti-tumor immune responses^[134,135,142]. In contrast, others indicate that early ferroptosis in cancer cells may promote dendritic cell maturation and prophylactic vaccination effectiveness^[143]. Additionally, ferroptotic cancer cells may promote the acquisition of a given phenotype by other cells in the TME, as is the case with the immunosuppressive nature of tumor-infiltrating neutrophils, that secrete PUFA-loaded vesicles^[144], or the lipolytic nature of tumor-associated adipocytes that release anti-ferroptotic lipids^[145]. However, not only can dying cancer cells influence immune responses in the TME, but immune cells themselves can either promote or undergo ferroptosis. On the one hand, CD8⁺ T cells in the TME were shown to secrete interferon gamma (IFN- γ), resulting in SLC7A11 downregulation^[146–148] and ACSL4 upregulation^[149] in cancer cells, thus strongly promoting ferroptosis and immunosurveillance^[146,149]. On the other hand, immune cells may also undergo ferroptosis, yet show significant variability in their sensitivity to this cell death modality^[150–154]. Notably, the PUFA-phospholipid landscape varies dramatically between immune cells and with their activation, and contributes, at least in part, to defining immune cell sensitivity to ferroptosis^[155]. Ferroptosis in dendritic cells may impair their functions, thereby reducing their ability to prime CD8⁺ T cells and compromising anti-tumor immunity^[156]. Moreover, CD36-mediated lipid accumulation triggers lipid peroxidation and ferroptosis in tumor-infiltrating CD8⁺ T cells, also impairing their anti-tumor functions^[157,158]. Neutrophils, which are generally immunosuppressive, can be both susceptible and resistant to ferroptosis, possibly depending on their metabolic state^[159,160]. Notably, tumor-associated macrophages may also secrete some immunomodulatory metabolites, like itaconate, to promote the NRF2 (aka NFE2L2, NFE2 like bZIP transcription factor 2)-SLC7A11-dependent resistance of cancer to both ferroptosis and immune checkpoint blockade^[161,162]. Altogether, the immunogenicity of ferroptosis seems largely context-dependent and influenced by the unique cellular and metabolic landscape of the TME. Ultimately, whether the immune system “sees the fire” of ferroptosis may depend less on the flames themselves and more on where, and in whom, they burn.

Since ferroptosis is thus a language that transcends species boundaries, it can be involved in inter-species dialogues, such as those observed between a pathogen and its host (Figure 4). Several studies have suggested that ferroptosis plays a role in infections and pathogenicity. For example, *Plasmodium falciparum* releases products that sensitize cells of the blood-brain barrier to ferroptosis, thereby increasing microvascular permeability in the brain and worsening cerebral malaria^[163]. Similarly, *Pseudomonas aeruginosa*

induces ferroptosis in human bronchial epithelial cells by expressing a lipoxygenase that oxidizes host arachidonic acid-containing phospholipids^[164]. As a further example, *Mycobacterium tuberculosis* triggers a cascade that leads to decreased GPX4 expression, thereby fostering ferroptosis in host cells while promoting its own dissemination^[165]. Viruses such as Hepatitis B and SARS-CoV-2 also appear to have engineered systems capable of triggering ferroptosis in host cells^[166,167]. On the contrary, there is evidence that hepatocytes can commit a ferroptotic-like suicide in response to Hepatitis C infection in order to restrict viral replication^[168]. Whether such ferroptotic suicide occurs in other host cells under pathogenic struggles remains largely unclear. The dialogue of ferroptosis thus extends far beyond species, and may in fact be acting as a hidden weapon in the everlasting conflict between invading pathogens and their hosts.

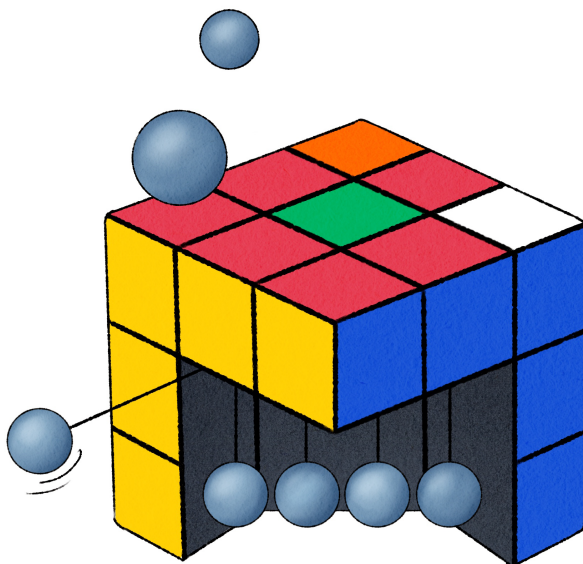


Figure 4. *I am not antigenic, but I make sounds. In cell' solidarity or hardship, I resound. I may be both the action and the reaction. Giving rise to near and far repercussions.*

In more physiological contexts, cells may unite their metabolic forces to prevent ferroptosis from occurring in their neighbors. A truly fascinating example of such metabolic cooperation can be found in the brain, where neurons and astrocytes closely communicate to enable intense neuronal electrochemistry, all while restraining oxidative stress. Neurons can afford to divert glucose from glycolysis to produce large amounts of NADPH through the pentose-phosphate pathway, only because astrocytes provide them with lactate for mitochondrial respiration^[169-171]. Such collaboration also exists regarding the supply of GSH: astrocytes supply cysteine-glycine dipeptides to neurons through the γ -glutamyl cycle for the synthesis of GSH to compensate for the neurons' inability to import cystine due to their lack of system x_c^- transporter^[172]. Similar support is provided by oligodendrocytes, which, for instance, transfer ferritin to prevent labile-iron-mediated ferroptotic axonal damage^[173]. Although these metabolic cooperations seem essential for protecting neurons against ferroptosis and thus ensuring cerebral functions, they can turn sour in pathological conditions. For instance, the susceptibility of microglia to iron dysregulation and ferroptosis can cause neuronal lipid peroxidation and ferroptosis-induced neurotoxicity^[174]. Moreover, sublethal ferroptotic stress in microglia may drive astrocytes toward a neurotoxic phenotype, fostering non-cell-autonomous neuronal death^[175]. These findings challenge our understanding of cellular relationships in the brain relating to ferroptosis. Perhaps the most important question is when and how the collaborative interplay becomes ferroptotically deadly? This ferroptotic interplay may also occur between neurons and cells outside of the brain. An intriguing example in the context of Alzheimer's disease highlights how gut microbiota dysbiosis reduces the abundance of *Bacteroides*, which normally secrete lysophosphatidylcholine to reduce ACSL4 expression in neurons and prevent their ferroptosis^[176]. Although broader confirmation is lacking, these studies inspire us to further investigate the collaborative yet pathologically impaired ferroptotic dialogue between specialized cell types in the body.

6. Riddle #5: If Ferroptosis Obeys No Signal But Is Always Suppressed, Does It Qualify as Truly Regulated, or Does It Defy the Very Concept?

Apoptosis is lit by caspases, necroptosis by kinases, and pyroptosis by inflammasomes^[177]. Each form awaits a trigger that sets off a well-defined series of cascades and ultimately reaches a point of no return. According to our current knowledge, ferroptosis seems to wait for nothing but sits uncharted within the canon of regulated cell death. It seems always there, latent, needing only the absence of defenses. One could even say its regulation is not activation, but rather suppression: the activity of GPX4 or FSP1, the recycling of GSH, the buffering of iron, and the distribution of fatty acids in membranes^[178]. Therefore, can we truly call ferroptosis "regulated" if its essence is the absence of regulation? One might even question whether ferroptosis is a death pathway at all, or rather the

revelation of life's constant battle against entropy and the flow of electrons, i.e., the oxidation of vulnerable lipids involving iron and oxygen.

Stepping back for a moment, we might first ask ourselves what exactly defines a cell death pathway as being “regulated” (Figure 5)? According to the Nomenclature Committee on Cell Death, regulated cell death differs from accidental cell death in its ability to be controlled by a dedicated molecular and cellular machinery, making it modulable and capable of being either delayed or accelerated by pharmacological or genetic interventions^[179]. As it is caused by fundamental chemical reactions that can be considered accidental^[11], the very concept of ferroptosis blurs the line between accidental and regulated cell death programs. Ferroptosis may therefore simply appear to be a cellular sabotage, an unexpected and uncontrollable accident resulting from aberrant interactions between metabolic cues, particularly occurring under pathological conditions^[109]. Yet ferroptosis is indeed classified as a form of regulated cell death, as it is triggered by oxidative perturbations in the intracellular microenvironment, is under the constitutive control of GPX4, among others, and can be inhibited by lipophilic radical trapping antioxidants or - owing its name - iron chelators^[179]. Ferroptosis is thus a cell death that has its own machinery and can be controlled pharmacologically and genetically by modulating the function of specific proteins and signaling pathways^[180,181]. However, beyond the strict definition of the term ‘regulated’, what really leads us to reconsider whether ferroptosis should be considered “regulated cell death”?

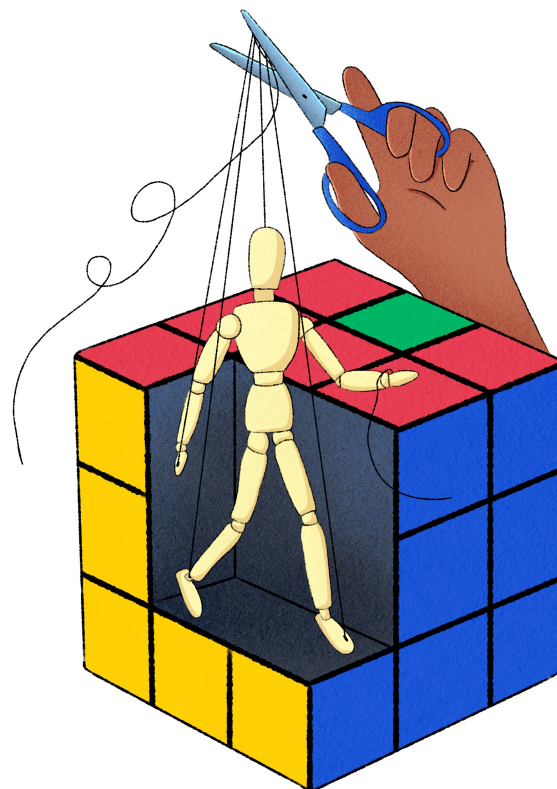


Figure 5. *For other cell deaths, I am a fool. As I seem to follow no rules. Am I a puppet held by unknown lines? Or merely sabotage without signs?*

Perhaps what raises more doubt about ferroptosis being a regulated form of cell death is the fact that it challenges our view of what a classic cell death cascade looks like, as suggested by other experts in the field^[182]. For decades, signaling pathways have been conceptualized as networks of interactions between proteins and other biomolecules, such as metabolites, which positively or negatively impinge on each other^[183]. Cell death signaling pathways are described in particular as cascades of events based on interactions between transcription factors, enzymes, cytokines, and metabolites^[183]. Ferroptosis challenges this classical pathway narrative because it is best captured as a cell death relying on highly context-dependent mechanisms that converge on a unique biochemical event, that is, again, unrestrained lipid peroxidation^[182]. Indeed, a plethora of actors that may influence the likelihood of redox defense failure and thus modulate cell sensitivity to ferroptosis in a highly context-dependent manner have been uncovered over the years^[178]. Although these discoveries have contributed to our understanding of ferroptosis, they have above all highlighted the complexity of ferroptosis as a cell death paradigm centered on ancient chemical mechanisms, shrouded in a dark veil of regulators that vary to a greater or lesser extent depending on the context. Moreover, ferroptosis is integrated into a network of multiple cell death modalities that are interrelated. For instance, expression signatures from necroptosis, pyroptosis, ferroptosis, and parthanatos were all found in the retina under ischemia reperfusion injury, with each cell death modality appearing to be involved at different time points of injury^[184]. In itself, ferroptosis may therefore challenge our view of cell death signaling cascades, but does it really make it any less regulated?

Another obscure question remains open: what makes the difference between life and ferroptotic death? All modalities of regulated cell death are considered to include a “point of no return”, a moment when adaptive responses have failed and the cell is irreversibly doomed to die^[179]. For example, the permeabilization of the mitochondrial outer membrane or the activation and oligomerization of MLKL at the plasma membrane were considered to be the points of no return in a molecular pathway toward apoptosis^[185] or necroptosis^[186], respectively. However, recently, evidence has been accumulating to question the existence of such a point of no return^[187-189]. In particular, it appears increasingly clear that regulated cell death pathways may not have a single point of no return, but rather several, giving cells the opportunity to respond and survive along their path to death, at least to some extent. As a process driven by the uncontrolled generation of lipid peroxides^[29,30,130], one may stipulate that ferroptosis fits perfectly into this new paradigm and does not appear to have a single molecular point of no return. Instead, we suggest that the point of no return in ferroptosis may be more of a peroxidation threshold. Once lipid peroxidation and membrane damage exceed the cell's defense capabilities, membrane integrity is lost^[132], leading to death. This concept also questions whether there exists a minimum proportion of the phospholipid pool that must be oxidized before cells irreversibly toggle to ferroptosis.

Depending on the strength of its defense systems, a cell can theoretically undergo ferroptosis without reaching a point of no return, allowing it to survive. This would imply that the cell somehow implements counter mechanisms that act as negative feedback loops, sending the message to prevent death at all costs. Although rare, there are a few examples of such negative feedback in cells undergoing ferroptosis. The endosomal sorting complex required for transport (ESCRT) mechanism, which is activated in response to membrane damage as a repair mechanism in several cell death pathways, including necroptosis^[190] and pyroptosis^[191-193], is also thought to be engaged by ferroptosis-prone cells^[138-139]. This repair mechanism is activated upon calcium ion influx when the plasma membrane is already damaged^[194] and therefore represents a late feedback attempt to delay plasma membrane rupture. Another negative feedback mechanism could be an activation of the antioxidant response via the transcription factor NRF2, a key regulator of cellular redox homeostasis. While NRF2 abundance is maintained at low levels through Kelch-like ECH-associated protein 1 (KEAP1)-dependent ubiquitination and proteasomal degradation under basal conditions, NRF2 protein levels increase significantly in response to oxidative stress. This is facilitated by the oxidation of key cysteine residues in KEAP1, preventing the degradation of NRF2 and allowing it to translocate to the nucleus, where it promotes antioxidant transcriptional programs that help cells recover homeostasis^[195]. NRF2 activation generally promotes ferroptosis resistance by upregulating the expression of several proteins whose function is closely related to the mechanism of ferroptosis, including GSH biosynthetic enzymes^[196], FSP1^[197,198], SLC7A11^[195] and ferritin^[199], among others. However, these mechanisms are far from universal, and under some conditions, NRF2 instead promotes ferroptosis by upregulating the export of GSH out of the cell^[200]. A further example of such negative feedback is the activation of the key tumor suppressor p53. It is typically activated in response to stress stimuli, including oncogenic activation, DNA damage, and metabolic imbalance^[201,202]. Depending on the type and intensity of the stress, p53 can activate multiple cellular effector processes, such as cell cycle arrest, senescence, DNA repair pathways, metabolic adaptation, or cell death by apoptosis^[203,204]. p53 activation may also sensitize certain cancer cells to ferroptosis induced by low levels of tert-butyl hydroperoxide, a common ROS-inducing agent^[205]. Mechanistically, p53 activation represses the expression of SLC7A11^[205]. p53 thereby limits cystine import, leading to GSH depletion^[205], and prevents the interaction of SLC7A11 with ALOX12, which normally inhibits ALOX12 activity. Furthermore, p53 stabilization, which generally causes cell cycle arrest, increases sensitivity to ferroptosis induced by GPX4 inhibitors, but not by α_c^- system inhibitors^[206]. However, in other contexts, p53 stabilization may instead suppress ferroptosis^[207,208]. p53 can therefore act both as a sensitizer of and a protector against ferroptosis, depending on the context and mode of ferroptosis induction. A question common to all these negative feedback mechanisms is whether they are not only necessary but also sufficient to prevent ferroptosis from reaching its end. Furthermore, in the same way that some cancer cells survive treatment and acquire a specific drug persister phenotype associated with profound changes in their cellular behavior, including a markedly higher sensitivity to ferroptosis^[49], can cancer cells survive ferroptotic insults and exhibit similar alterations in their behavior? A recent study has suggested such an acquisition of ferroptosis tolerance^[38], but this remains to be further confirmed. Perhaps ferroptosis is both a form of regulated cell death and a cellular sabotage, a pathway of cell death that feeds on redox chaos. Maybe it forces us to rethink our view of classical cascades and our understanding of cell survival as an endless act of keeping death at bay.

7. Concluding Remarks and Outlook

In little more than a decade, ferroptosis has transitioned from being a biochemical curiosity into a defining challenge for the entire cell death field, prompting the emergence of ever more interesting and, simultaneously, still hard-to-address issues. And similar to all good riddles, each apparent answer has only deepened its surrounding mystery, prompting in turn new questions (Figure 6). We thus slowly acknowledge: ferroptosis resists neat categorization or shall we provocatively say subjugation? At the same time, it is arguably always there, waiting, yet never truly summoned; a death pathway without a canonical signal, a program which seems to only unfold when protection falters. In this inversion lies the (maybe just semantic) paradox: is it regulated if its only regulation is suppression? Or is ferroptosis the shadow cast by life's constant vigilance, proof that survival itself is nothing more than the art of holding oxidation under control? While we and, in fact, an increasing number of extraordinary laboratories worldwide search for its purpose, we should maybe consider that perhaps ferroptosis has none. Maybe – and there is something unsettling in this when looking at this question from a cell death angle – it is less a pathway than a consequence, sometimes more like an echo of ancient and basic redox

chemistry that still reverberates through our cells. And yet, its fingerprints appear everywhere: in the catastrophic phenotypes of GPX4 deletion, in the rare but devastating human syndromes of GPX4 mutation, in the smoldering hints of pathology across models of cancer, ischemia, and neurodegeneration. And still, frustratingly, we lack the smoking gun, the unambiguous signature, the ultimate decisive proof of its role in human diseases beyond ultra-rare genetic syndromes.



Figure 6. Surely, I leave questions behind; Still challenging researchers' minds; Like a Rubik's Cube with no definitive solution; Opening up all possible future horizons?

The presented riddles of ferroptosis thus remain highly suggestive but topical: why it exists, how deadly it is, whether it has a physiological role beyond accident, where in the cell it begins, and whether it is genuinely part of the canon of regulated death or forever the odd one out. The decade ahead will likely not entirely resolve these questions so much as sharpen their edges. New tools will bring us closer to understanding ferroptosis in its native habitats, while new biomarkers may enable us to track its fleeting presence in human tissues. New therapeutics may also teach us precisely when to utilize ferroptosis as a therapeutic tool and when to counteract it. But the deeper challenge will be conceptual: to decide whether ferroptosis is a program to die, or simply the price of being alive in a world based on electrons, iron and oxygen. Perhaps the true lesson is that life does not regulate death so much as it postpones it, or, differently put, that ferroptosis is not the exception to the rule, but the rule itself, finally exposed. Or even more tantalizing, perhaps ferroptosis is not a program at all, but the reflection in life's own eyes: the glimpse of death that appears the moment we dare to blink.

Declarations

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Authors contribution

Levkina A, Vermonden P: Conceptualization, writing-original draft, writing review & editing.

Wahida A: Conceptualization, supervision, writing-original draft, writing review & editing.

Conrad M: Conceptualization, funding acquisition, supervision, writing review & editing.

Conflicts of interest

Marcus Conrad is an Editorial Board Member of *Ferroptosis and Oxidative Stress*, and holds patents for some of the compounds described herein. No other conflicts of interest to declare.

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Consent to participate

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