



Key questions in ferroptosis

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Ferroptosis, defined as iron-catalyzed necrotic cell death, has attracted tremendous attention over the past decade, resulting in tens of thousands of peer-reviewed publications. This surge of interest is primarily driven by two concepts: (i) the potential to eliminate cancer cells through ferroptosis, and (ii) the hypothesis that inhibiting ferroptosis could prevent tissue damage in a range of common disorders, including stroke, myocardial infarction, acute kidney, liver, and lung injuries, intoxications, adverse drug effects, as well as clinical scenarios such as solid organ transplantation. In my view, this enthusiasm has created a “gold rush” among researchers, which has, at least partially, overshadowed some fundamental questions that have remained unresolved since ferroptosis was first described. In a deliberately subjective manner, I reflect on some of these questions, aiming both to remind early-career researchers of these blind spots on the path to clinical translation and to encourage established investigators to continue the scientific debate.

First contemplation: The lack of a clear definition of ferroptosis—it is NOT a pathway!

Ferroptosis fundamentally requires iron. Fenton reactions drive lipid peroxidation, ultimately leading to plasma membrane rupture. This process is counteracted by a variety of genetically regulated systems, including proteins, hormones, and small molecules. These systems include, but are not limited to, thioredoxin, glutathione peroxidase 4 (GPX4), ferroptosis suppressor protein 1, hydroperoxides, estrogens, and ether lipids. Each of these ferroptosis-regulating systems, and potentially many others yet to be identified, contributes to the ferroptotic threshold of an individual cell. Consequently, none of these systems alone can serve as a definitive marker of ferroptosis. For example, kidney tubules cannot survive without GPX4^[1], whereas the absence of this selenoprotein does not affect the myocardium, which clearly undergoes ferroptosis during the reperfusion phase following myocardial infarction^[2,3]. Therefore, the definition of ferroptosis must focus on iron-catalyzed necrosis.

Contemplation 2: There is no biomarker of ferroptosis!

Lipid peroxidation can occur under many cellular conditions, but only some instances result from Fenton reactions. Therefore, detecting lipid peroxidation alone cannot be taken as evidence of ferroptosis. Similarly, terminal deoxynucleotidyl transferase dUTP nick end labeling assays can yield positive results in multiple forms of cell death, including apoptosis, necroptosis, pyroptosis, parthanatos, cuproptosis, lysosomal cell death, and others^[4]. At present, there is no specific tissue or serum marker for ferroptosis. This represents perhaps the greatest challenge in the field, as it limits the ability to conduct clinical trials with ferrostatins.

Contemplation 3: The immunogenicity of ferroptosis.

Damage-associated molecular patterns (DAMPs) are released from any necrotic cell and contribute to necroinflammation^[5]. While DAMP recognition generally promotes dendritic cell cross-priming and activation of the adaptive immune system^[6], in the case of ferroptosis, oxidized phospholipids act as potent inhibitors of dendritic cell cross-priming^[7]. As a result, the adaptive immune response may be suppressed in ferroptotic tissues^[8]. This may explain why only a minimal infiltration of adaptive immune cells is observed in necrotic tissues following ischemia-reperfusion injury in the brain, heart, liver, lung, kidney, and other organs.

Contemplation 4: How does ferroptosis integrate into the web of regulated cell death pathways?

The caspase-kinase system that governs regulated cell death pathways in apoptosis, necroptosis, and pyroptosis, and links these pathways to inflammasomes, appears to be entirely independent of ferroptosis^[9]. From an evolutionary perspective, the iron-dependent reaction that drives lipid peroxidation is older and is also found in plants, as demonstrated in *Arabidopsis thaliana*^[10]. This raises an important question: how have the complex regulated cell death systems seemingly “ignored” ferroptosis or pro-ferroptotic conditions? A more detailed investigation of the interplay between these pathways is clearly warranted.



Contemplation 5: Why does ferroptosis propagate to neighboring cells in some but not all conditions?

In certain cases, lipid peroxidation that spreads across a lipid bilayer does not stop at the boundary of neighboring cells. This phenomenon, referred to as cell-death propagation or a “wave of death,” is most prominently observed in isolated kidney tubules of male mice^[11]. Time-lapse imaging is required to capture this process, but it is clearly absent in some cell-culture assays, such as when GPX4 is genetically deleted from specific cell lines. In vivo, however, deletion of GPX4 in kidney tubules leads to synchronized nephron loss^[1]. The differences between cell culture and in vivo or ex vivo models are evident, but what underlies this fundamental discrepancy? Importantly, cell culture conditions that do show ferroptosis propagation are available, and it has been demonstrated that the wave of death can be halted by certain ferrostatins^[12]. It is therefore essential to study these cell culture models in greater detail. Imagine if we could prevent cell-death propagation in stroke or myocardial infarction, it would represent a major advance and highlights the ongoing enthusiasm in ferroptosis research.

Contemplation 6: What is the physiological function of ferroptosis?

Some of our data suggest that the ferroptotic threshold is increased by estrogens in pre-menopausal females, coordinated with the menstrual cycle, which may confer a selective advantage^[11]. However, the only known physiological process that requires cell-death propagation is the degeneration of the Mullerian and Wolffian ducts during embryonic development.

Another perspective is that the selective advantage at the organismal level lies with anti-ferroptotic systems rather than with the lethal reaction itself. Iron has always been present, and after the Pre-Cambrian, oxygen became freely available on Earth. Any lipid bilayer would be rapidly destroyed by ferroptosis if anti-ferroptotic systems were not in place to protect it. This simple yet fundamental concept may explain the physiological function of anti-ferroptotic systems.

Final contemplation 7: How do we move on to clinical translation?

What would happen if cell-death propagation were inhibited during embryonic development? Are ferrostatins teratogenic, or are ferroptosis inducers teratogenic because they trigger ferroptosis in multiple systems, such as kidney tubules, adrenal glands, pancreatic islets, and other hormone-producing cells that appear particularly sensitive to ferroptosis? Given the potent on-target effects described during the ferroptosis “gold rush,” any serious consideration of clinical translation must prioritize safety. On a positive note, there are several promising opportunities. In solid organ transplantation, inhibitors of ferroptosis can be added to the perfusate during machine perfusion. Ferrostatins could be delivered via a cardiac catheter, similar to contrast media, directly to the area at risk during reperfusion after stenting. A similar approach could be applied when stenting cerebral arteries during stroke. Ferrostatins could also be administered to freshly resuscitated patients upon stabilization in the emergency room or even during transport in an ambulance. Resuscitation after cardiac arrest causes “whole-body ischemia-reperfusion” injury, a common condition in human medicine for which no animal model exists. These strategies highlight multiple opportunities to translate ferroptosis research into clinical practice, with the potential to significantly improve human health.

Declarations**Authors contribution**

The author contributed solely to the article.

Conflicts of interest

Andreas Linkermann is an Editorial Board member of *Ferroptosis and Oxidative Stress*. No other conflicts of interest to declare.

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References

1. Friedmann Angeli JP, Schneider M, Proneth B, Tyurina YY, Tyurin VA, Hammond VJ, et al. Inactivation of the ferroptosis regulator Gpx4 triggers acute renal failure in mice. *Nat Cell Biol.* 2014;16(12):1180-1191. [DOI]
2. Fang X, Wang H, Han D, Xie E, Yang X, Wei J, et al. Ferroptosis as a target for protection against cardiomyopathy. *Proc Natl Acad Sci U.S.A.* 2019;116(7):2672-2680. [DOI]
3. Li W, Feng G, Gauthier JM, Lokshina I, Higashikubo R, Evans S, et al. Ferroptotic cell death and TLR4/Trif signaling initiate neutrophil recruitment after heart transplantation. *J Clin Invest.* 2019;129(6):2293-2304. [DOI]
4. Galluzzi L, Vitale I, Aaronson SA, Abrams JM, Adam D, Agostinis P, et al. Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018. *Cell Death Differ.* 2018;25(3):486-541. [DOI]
5. Sarhan M, Land WG, Tonnus W, Hugo CP, Linkermann A. Origin and consequences of necroinflammation. *Physiol Rev.* 2018;98(2):727-780. [DOI]
6. Yatim N, Jusforgues-Saklani H, Orozco S, Schulz O, Barreira da Silva R, Reis e Sousa C, et al. RIPK1 and NF-kappaB signaling in dying cells determines cross-priming of CD8(+) T cells. *Science.* 2015;350(6258):328-334. [DOI]
7. Wiernicki B, Maschalidi S, Pinney J, Adjemian S, Vanden Berghe T, Ravichandran KS, et al. Cancer cells dying from ferroptosis impede dendritic cell-mediated anti-tumor immunity. *Nat Commun.* 2022;13(1):3676. [DOI]
8. Kim R, Hashimoto A, Markosyan N, Tyurin VA, Tyurina YY, Kar G, et al. Ferroptosis of tumour neutrophils causes immune suppression in cancer. *Nature.* 2022;612(7939):338-346. [DOI]
9. Tonnus W, Belavgeni A, Beuschlein F, Eisenhofer G, Fassnacht M, Kroiss M, et al. The role of regulated necrosis in endocrine diseases. *Nat Rev Endocrinol.* 2021;17:497-510. [DOI]
10. Distéfano AM, Martin MV, Córdoba JP, Bellido AM, D'Ippólito S, Colman SL, et al. Heat stress induces ferroptosis-like cell death in plants. *J Cell Biol.* 2017;216(2):463-476. [DOI]
11. Tonnus W, Maremonti F, Gavali S, Schlecht MN, Gembardt F, Belavgeni A, et al. Multiple oestradiol functions inhibit ferroptosis and acute kidney injury. *Nature.* 2025;13:1-9. [DOI]
12. Kim SE, Zhang L, Ma K, Riegman M, Chen F, Ingold I, et al. Ultrasmall nanoparticles induce ferroptosis in nutrient-deprived cancer cells and suppress tumour growth. *Nat Nanotechnol.* 2016;11(11):977-985. [DOI]

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