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INVITED REVIEW

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Ferroptosis: bug or feature?

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Summary

Ferroptosis is an iron-dependent, oxidative form of non-apoptotic cell death. This form of cell death does not share morphological, biochemical, or genetic similarities with classic necrosis, necroptosis, parthanatos, or other forms of non-apoptotic cell death. Ferroptosis can be triggered by depleting the cell of the amino acid cysteine, or by inhibiting the phospholipid hydroperoxidase glutathione peroxidase 4 (GPX4). Why certain stimuli trigger ferroptosis instead of another form of cell death, and whether this process could be adaptive in vivo, are two major unanswered questions concerning this process. Emerging evidence and consideration of related non-apoptotic pathways suggest that ferroptosis could be an adaptive process, albeit one regulated and executed in a manner very different from apoptosis and other forms of cell death.

KEYWORDS
apoptosis, cysteine, glutathione, necrosis, reactive oxygen species, regulated cell death

1 | INTRODUCTION

It's not a bug, it's an undocumented feature.
(Unknown software developer)

Damaged or unwanted cells can be eliminated from the body via regulated cell death (RCD). RCD is essential for normal development and homeostasis, and excessive or insufficient RCD can contribute to the pathology of many human diseases, including neurodegeneration, autoimmunity, and cancer.[1] RCD is frequently equated with caspase-dependent apoptosis, the first RCD pathway to be characterized at the genetic and biochemical levels.[2,3] More recently, a growing number of RCD events have been shown to involve non-apoptotic pathways, including necroptosis, pyroptosis, parthanatos, autosis, ferroptosis, and others.[4–7] The nature, regulation, functional independence, and physiological relevance of these non-apoptotic cell death pathways remain topics of intense interest.[6,8,9]

Apart from the distinction between apoptotic and non-apoptotic pathways, a separate distinction has been drawn between cell death processes that are actively unleashed upon the cell by dedicated machinery, termed "suicide", and those that occur when the operation of some essential process in the cell is disrupted, termed "sabotage"[10,11] (Figure 1). Apoptosis, necroptosis, and pyroptosis are examples of cell suicide programs executed by dedicated pathways involving key pro-death effector proteins such as BCL2-associated X protein (BAX), mixed lineage kinase domain-like protein (MLKL), and gasdermin D, respectively.[12–15] Key steps in cell suicide pathways are mediated by the transcriptional upregulation, post-translational modification, or sub-cellular relocalization of these pro-death proteins. By contrast, for candidate cell sabotage pathways such as ferroptosis and parthanatos, the involvement of specific, dedicated pro-death proteins is less clear (Figure 1). Instead, death results when the aberrant inactivation or hyperactivation of specific proteins leads to a lethal metabolic imbalance within the cell. The cell is effectively "sabotaged" by its own ongoing normal cellular metabolic activity, such as the consumption of ATP or the production of lipid hydroperoxides, and if these normal activities are inhibited death is prevented.

Cell suicide pathways have well-established roles in development, homeostasis, and disease, consistent with being evolved "features" of biological systems.[1,12–15] Cell sabotage pathways are important (and druggable) routes to pathological cell death in vivo,[16–20] but do not have well-established roles in development or the maintenance of homeostasis. These observations raise two interesting and related questions. First, why do certain stimuli trigger sabotage instead of suicide? Second, why does cell sabotage exist in the first place and could such

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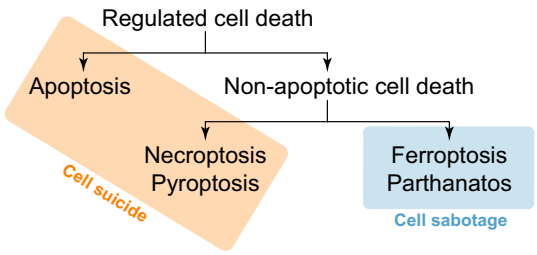

FIGURE 1 Distinguishing between different forms of regulated cell death. Examples of different regulated cell death pathways and processes. Each pathway can be classified as apoptotic or non-apoptotic. Additionally, each pathway can be recognized as a form of cell "suicide", where specific pro-death proteins are expressed and/or post-translationally modified to promote death, or as a form of cell "sabotage", where cell death results from disruption of the operation of an essential process, leading to cellular dysfunction and death without the involvement of dedicated cell death machinery

processes actually be adaptive? Here, I use the example of ferroptosis in an attempt to answer these questions. Using a metaphor drawn from the realm of computer science, I will argue that cell sabotage is most likely not a "bug", but rather an adaptive "feature" of mammalian cells.

2 | SUMMARY OF THE FERROPTOSIS PATHWAY

The ferroptosis pathway has been recently reviewed in detail[21,22] and therefore only a brief summary is provided here, including reference to some recent findings. Reduced glutathione (GSH) is a thiol-containing tripeptide (γ-L-glutamyl-L-cysteinylglycine) that is essential for cellular antioxidant defense.[23] GSH can donate reducing equivalents to reactions catalyzed by GSH-dependent glutathione transferases (GSTs), glutathione peroxidases (GPXs), and other enzymes, including the essential phospholipid hydroperoxidase glutathione peroxidase 4 (GPX4).[24,25] GPX4 opposes iron- and O_2-dependent lipid peroxidation by converting lipid hydroperoxides (L-OOH) to non-toxic lipid alcohols (L-OH).[24] In many cells, GSH synthesis is dependent upon the continuous import of cystine (Cys-Cys disulfide, Cys_2) by the cell surface Cys_2/glutamate antiporter system x_c^-[26,27]. Other routes to Cys import or synthesis, such as the transsulfuration pathway, operate in some cells.[28] Disruption of this intracellular thiol antioxidant network leads to the non-apoptotic, iron-dependent, oxidative form of cell death termed ferroptosis.

Ferroptosis can be triggered by physiological conditions (e.g. high extracellular glutamate) or small molecules (e.g. erastin, sulfasalazine, sorafenib) that block system x_c^--mediated Cys_2 import. Ferroptosis can also be triggered by genetic deletion of *Gpx4*, or by treatment with small molecules that trigger GPX4 degradation (e.g. FIN56) or covalently inhibit GPX4 function (e.g. RSL3) (Figure 2, left and center panels).[25,29–41] Interestingly, Cys/GSH depletion and/or GPX4 inactivation alone is not sufficient for ferroptosis. Lethal lipid ROS accumulation requires the activation of polyunsaturated fatty acids (PUFAs) by acyl-CoA synthetase long-chain family member 4 (ACSL4) and their incorporation into membrane lysophospholipids by lysophosphatidylcholine acyltransferase 3 (LPCAT3).[42–44] While the details remain somewhat controversial, the peroxidation of phospholipid PUFAs is likely catalyzed by one or more lipoxygenase (LOX) family enzymes.[35,36,44] These enzymes contain active site di-iron centers and iron chelators may block ferroptosis by chelating this iron and inactivating LOX function.[45,46] Thus, ferroptosis execution requires the coincident depletion of GSH and/or inactivation of GPX4 and the presence of oxidizable PUFAs incorporated into phospholipids.

The uniqueness of ferroptosis is now well established. Cells undergoing ferroptosis do not exhibit morphological changes or biochemical alterations consistent with apoptosis, such as chromatin margination or cleavage of poly ADP-ribose polymerase (PARP).[29,30,47] Ferroptosis is not attenuated by caspase inhibitors (zVAD-fmk, Q-VD-OPh), deletion of the intrinsic apoptotic effectors BAX and BCL-2 antagonist/killer 1 (BAK), or small molecule inhibitors of mitochondrial permeability transition pore (MPTP)-dependent necrosis (cyclosporine A) or RIPK1-dependent necroptosis (e.g. low concentrations of necrostatin-1).[29,31,33,47,48] Moreover, ferroptotic cell death does not require Ca^{2+}

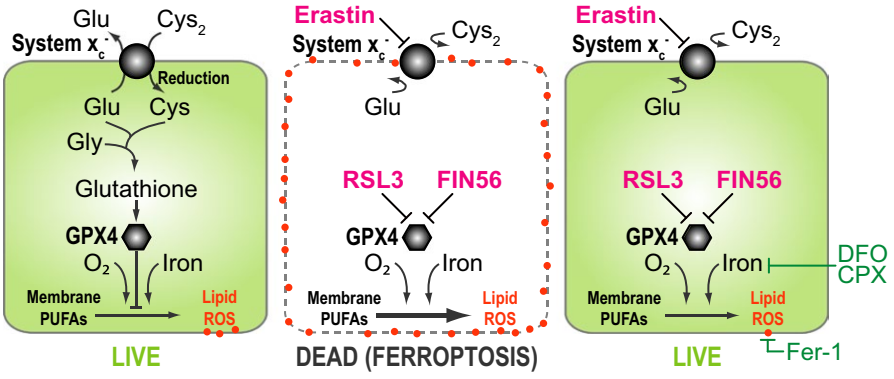

FIGURE 2 Induction and inhibition of ferroptosis. System x_c^- imports cystine (Cys_2), which is used to synthesize glutathione. Glutathione is used by GPX4 to prevent lipid reactive oxygen species (ROS) accumulation. Erastin is a small molecule that can inhibit system x_c^-, while RSL3 and FIN56 are small molecules that can inhibit GPX4 function. Inhibition at either step results in the iron- and O_2-dependent accumulation of lipid ROS from oxidized polyunsaturated fatty acids (PUFAs). Iron chelators such as deferoxamine (DFO) and ciclopirox (CPX), and antioxidants such as ferrostatin-1 (Fer-1), prevent lipid ROS accumulation and ferroptosis

influx or the function of the mitochondrial electron transport chain.[31] Unlike apoptosis and other forms of non-apoptotic cell death, the execution of ferroptosis is not known to require the expression or post-translational activation of any specific dedicated pro-death protein(s). However, cell death can be suppressed by iron-binding compounds such as deferoxamine (DFO) and ciclopirox (CPX),[29–31] and by small molecule free radical scavengers such as ferrostatin-1 (Fer-1)[19,31,36] (Figure 2, right panel). Blocking transferrin-mediated iron import or recycling of iron-containing storage proteins (i.e. ferritin) also attenuates ferroptosis,[20,49] consistent with the iron-dependent nature of this process.

3 | WHY DO CERTAIN STIMULI TRIGGER FERROPTOSIS?

Cell fate is closely linked to the metabolic state of the cell.[50] Depriving cells of metabolites such as glucose, glutamine, or leucine is sufficient to trigger caspase-mediated apoptosis.[51–53] So, why does Cys deprivation or direct GPX4 inactivation lead to ferroptosis? Why do these stresses not simply trigger apoptosis?

3.1 | Timing

One possible answer is that pro-ferroptotic stimuli do activate apoptotic pathways, but that ferroptosis is simply executed before any of the characteristic markers of apoptosis can be observed. This explanation seems unlikely, however, for two reasons. First, in culture, ferroptotic cell death induced by system x_c^- inhibition can take as long as 24 hours in certain cell lines, which is well within the timeframe needed to execute apoptosis in response to stresses such as proteasome inhibition [(30, 31) and S. J. D., unpublished]. Second, specific inhibitors of ferroptosis have been identified (e.g. Fer-1) that do not block apoptosis yet prevent cell death in response to pro-ferroptotic stimuli indefinitely.[31] This suggests that ferroptosis does not simply "beat apoptosis to the punch", but rather that it is executed without any involvement of apoptosis.

3.2 | Apoptosis blockade

A second possibility is that metabolic or other changes associated with the induction of ferroptosis biochemically inhibit the execution of apoptosis. Cells about to undergo ferroptosis due to cysteine deprivation have approximately 10% the normal level of intracellular GSH.[19] The reducing power of GSH may be needed for the processing and activation of caspases 3 and 8,[54,55] and cells depleted of GSH could therefore be unable to activate caspases properly. In U-937 cells, inhibiting de novo GSH synthesis with buthionine sulfoximine (BSO) switches the mode of cell death in response to cisplatin from apoptosis to necrosis.[56] However, this apoptosis-necrosis switch is not a general response to GSH depletion: BSO-treatment does not prevent the induction of apoptosis in response to etoposide, camptothecin, or x-ray irradiation.[56] Besides, the apoptotic machinery upstream of caspase activation is evidently not engaged in cells undergoing ferroptosis: deletion of canonical apoptotic genes (e.g. *Bax*, *Bak*) has no effect on ferroptosis and no release of cytochrome C is detected in response to erastin treatment.[30,31] Further studies will be required to determine whether, under ferroptosis-inducing conditions, apoptosis is blocked at some level upstream of Bax and Bak. However, tentatively, the simplest model is that apoptotic pathways are not engaged following exposure to pro-ferroptotic stimuli.

3.3 | A "bug" in the system

In software development, a bug is defined as a flaw in the code leading to unintended (or unpredictable) results when that code is executed. One view of ferroptosis, given its unusual nature, is that it is the biological equivalent of a software bug, namely a flaw in the execution of cell death in response to certain metabolic perturbations, leading to an unintended phenotype. Moreover, it could be argued that this bug is only revealed in vitro (e.g. in tissue culture) or in response to non-physiological cues (e.g. synthetic small molecule inhibitors of system x_c^- or GPX4). However, several recent lines of evidence argue against this interpretation. First, even in cell culture, ferroptosis can be induced under low (2%) oxygen conditions with similar efficiency as in cells grown under ambient (21%) oxygen, indicating that this oxidative form of cell death is unlikely simply an epiphenomenon of growth at high oxygen tensions.[32] Second, ferroptosis can be induced in mouse xenograft tumors by engineered nanoparticles that disrupt iron homeostasis, demonstrating that ferroptosis can be induced in vivo.[57] Third, ferroptosis can be induced in rat hippocampal slice and primary oligodendrocyte models by high concentration of extracellular glutamate or depletion of extracellular cystine, respectively, mimicking physiological conditions encountered during stroke and periventricular leukomalacia.[19,31] Indeed, ferroptosis can be triggered in fully in vivo models of ischemia-reperfusion injury, indicating that cells exposed to certain pathological conditions undergo this process.[17,20] Fourth, genetic deletion of *Gpx4* results in ferroptosis in numerous tissues in vivo, indicating that normal development requires the constant suppression of ferroptosis.[25,36,38–40] Fifth, the p53 tumor suppressor protein may induce ferroptosis as a homeostatic mechanism to prevent tumor formation.[58,59] Sixth, an iron- and lipid ROS-dependent "ferroptosis-like" lethal process has recently been observed in response to moderate heat stress in the plant model system *Arabidopsis thaliana*, indicating that ferroptosis and related processes could be conserved through evolution.[60] Together, these data argue that ferroptosis can be triggered in vivo, in many cell types, by diverse physiological stresses and pathological conditions. Thus, we propose that ferroptosis is not a "bug". While the discovery of ferroptosis might have been facilitated by in vitro conditions that sensitize to this process, such as a greater reliance on system x_c^- activity,[61–63] ferroptosis could in fact be an adaptive feature of mammalian cells.

4 | COULD FERROPTOSIS BE A "FEATURE" OF MAMMALIAN CELLS?

If ferroptosis occurs in vivo, what benefit could activation of this process provide that is not afforded by apoptosis and other forms

of non-apoptotic cell death? Below, I suggest two possible and non-mutually exclusive answers to this question.

4.1 | Direct control

Pro-apoptotic stresses such as DNA topoisomerase inhibition or endoplasmic reticulum stress are sensed and transduced through complex pathways involving kinase-mediated signal transduction, transcriptional upregulation of pro-death effectors, mitochondrial outer membrane permeabilization and cytochrome C release, caspase activation and caspase-mediated proteolytic protein cleavage.[64,65] Death can be negatively regulated by specific proteins at each one of these levels, ensuring pathway activation only under the appropriate conditions.[66] By contrast, so far as is known, the ferroptosis pathway is relatively simple: depletion of intracellular Cys leads to depletion of GSH, inactivation of GPX4, and the resultant accumulation of toxic lipid ROS. Kinases, proteases, transcription or translation, or any major intracellular organelle system, are not apparently needed for the execution of death. While the sensitivity to ferroptosis varies between cell lines, this likely correlates with differences in basal metabolic state (e.g. NADPH abundance[67]), and specific negative regulators of ferroptosis beyond the GSH-GPX4 axis itself are not known. Thus, Cys depletion (and more directly, GPX4 inactivation) provides a very specific and direct means of causing cell death: all lethal inputs and outputs lie along a single, short biochemical pathway (Cys import → GSH synthesis → GPX4 function → Inhibition of lipid peroxidation). The availability of such a direct means to initiate cell death in response to a single metabolic input (i.e. Cys or GSH levels), separate from the operation of the apoptotic machinery, may be beneficial under certain circumstances. These circumstances cannot be currently predicted, but it is notable that intracellular Cys concentrations are lower than most other amino acids in the cell.[19,68] Thus, cells may operate at a threshold where the induction of ferroptosis would be favored if the supply of intracellular Cys is disrupted even transiently. For example, transient downregulation of Cys import could be used to eliminate an unwanted cell (i.e. to suppress tumor formation[58]). Competition between cells for limited amounts of Cys present in the environment could also be a means to select the fittest cells from a population for further growth, for example during T-cell proliferation,[69] while rapidly eliminating those that are unfit. In this way, linking cell survival directly to the levels of a limiting amino acid could provide a simple means of regulating cell viability, independently of other biochemical pathways.

4.2 | Evolved pathway insulation

As noted above, DNA damage, endoplasmic reticulum stress and other pro-apoptotic stresses are detected and transduced by intracellular surveillance mechanisms that interface directly with the core apoptotic machinery.[64,65,70] Depriving cells of glucose, glutamine, or leucine can trigger caspase-mediated apoptosis, demonstrating that metabolic stress per se is not a trigger for non-apoptotic cell death or cell sabotage.[51–53] Therefore, the observation that Cys deprivation, specifically, triggers ferroptosis and not apoptosis is likely significant. One possibility is that ferroptosis has evolved to be *insulated* from apoptosis, and that this is because ferroptosis is adaptive.

Apoptosis is an immunologically silent process whose activation leads to the proteolytic destruction and/or packaging into apoptotic bodies of antigens that would normally trigger an immune response.[71] In the context of tumor suppression, or the response to pathogen infection, non-apoptotic cell death is likely desirable as a means to recruit a beneficial immune response.[72,73] Necroptosis, a non-apoptotic RCD pathway classified here as a form of cell suicide (Figure 1), is triggered when pathogen-derived inhibitors of caspase activation prevent apoptosis from occurring (e.g. by inhibiting the function of capase-8[66]). Necroptosis is highly immunogenic, which may be beneficial in the case of viral infections but detrimental when this process contributes to neuronal cell death.[74,75] Parthanatos, like ferroptosis, is a candidate form of cell sabotage.[10] High levels of alkylating DNA damage result in hyperactivated PARP and rapid ATP depletion, either by consumption of NAD^{+}[76] or by PARylation and inhibition of hexokinase,[77] both of which ultimately disrupt glycolysis. Parthanatos is pro-inflammatory, which may enhance the clearance of tumors in vivo following therapy when this form of cell death is induced.[78–81] One possibility is that ferroptosis operates according to a similar logic. During ischemia-reperfusion injury in the kidney, cells undergo ferroptosis and this appears to generate a chemoattractant signal.[17] In a completely different context, the induction of ferroptosis in mouse tumor xenografts using ultrasmall nanoparticles results in infiltration of immune cells into the tumor mass.[57] Both reports are consistent with the notion that the induction of ferroptosis is immunogenic. An interesting question is whether ferroptosis involves the release of specific damage-associated molecular patterns (DAMPs)/alarmins and, if so, whether these are unique to ferroptosis or common across different forms of non-apoptotic cell death.[82] Of further note, infection of cells with human immunodeficiency virus (HIV), Kaposi's associated sarcoma herpesvirus and other viruses inhibits GSH synthesis or otherwise enhance intracellular ROS accumulation.[83–86] Such changes may facilitate viral propagation, but simultaneously sensitize infected cells to ferroptosis. The stimulation of an immune response by ferroptosis could explain the existence of this process as a distinct and adaptive process.

5 | LOOKING AHEAD

I argue here that ferroptosis may not be a bug, but rather an unanticipated feature of mammalian cells. Additional evidence in support of this hypothesis could be sought experimentally. For example, this hypothesis predicts that in vivo ferroptosis (e.g. in response to ischemia-reperfusion[17,20]) should stimulate adaptive physiological responses, such as the recruitment of immune effectors[17,57]. Further studies of the immune consequences of ferroptosis are highly warranted. A second direction would be to pinpoint the specific physiological triggers of ferroptosis that result in this phenotype during ischemia-reperfusion injury in vivo. Obvious candidates include a reduction in extracellular Cys and/or an increase in extracellular glutamate, but this

remains to be defined. A third direction would be to identify additional physiological triggers for ferroptosis. In this connection, one intriguing candidate trigger has recently been suggested by Kagan, Conrad, Bayir, and colleagues, who noted that the LOX enzyme secreted by the pathogen *Pseudomonas aeruginosa* (i.e. *Pa*_LOX[87]) may destroy epithelial cells by inducing ferroptosis.[44] A fourth direction would be to identify molecular switches that insulate ferroptosis from apoptosis, or vice versa. Intriguingly, proteomic studies identified the key pro-ferroptotic lipid regulator ACSL4 as a target of caspase cleavage during bortezomib-induced apoptosis.[88] While speculative, inactivation of this enzyme during apoptosis may block the insertion of oxidizable fatty acids (i.e. PUFAs) into the membrane and thereby limit the ability of the cell to undergo ferroptosis. Such a mechanism is akin to the cleavage of PARP by caspases during apoptosis,[89] which may serve to inactivate PARP and limit PARP-dependent rapid ATP depletion and parthanatos.[90,91] Together, evidence along these lines would support the notion that ferroptosis is an adaptive feature of mammalian cells.

Cell sabotage pathways such as ferroptosis and parthanatos are of evident medical relevance and inherent basic biological interest. Do additional forms of cell sabotage exist and, if so, could they be discovered in a rational manner? Metabolic networks appear to be fertile ground for the discovery of cell sabotage phenotypes but, as noted above, metabolic perturbations are typically thought to trigger classic caspase-mediated apoptosis.[51,53,92] An important caveat is that the commonly used "apoptosis-specific" indicator Annexin-V can label cells undergoing both apoptotic and non-apoptotic cell death,[93] and studies using this marker may, for example, underestimate the occurrence of ferroptosis in situations where cysteine or glutathione is depleted.[94,95] Where could we look for new cell sabotage phenotypes? As suggested by the study of ferroptosis, examining the consequences of inactivating specialized metabolite detoxification pathways may provide one route to the identification of novel sabotage phenotypes. As described above, the proximate cause of ferroptosis is the accumulation of lethal lipid ROS. This occurs because of the insufficient conversion of lipid hydroperoxides to lipid alcohols by GPX4 when the GSH-GPX4 axis is inactivated. Thus, examining other toxic metabolites and associated detoxification pathways may provide one route to the discovery of new cell sabotage pathways. In addition to lipid peroxides, cells naturally generate or accumulate a number of other toxic or potentially toxic metabolites as byproducts of metabolism.[96] For example, methylglyoxal (MG, 2-oxopropanal), formed as a byproduct of glycolysis, can covalently modify (glycate) proteins, nucleic acids and lipids, leading to cell growth inhibition and ultimately cell death, which in at least some cases is non-apoptotic.[97–100] In mammalian cells, MG is detoxified by the glyoxalase pathway, which converts MG to D-lactate. Whether any endogenous stimuli can promote the accumulation of MG, either by enhancing glycolysis or inhibiting the glyoxalase pathway is not clear, but could lead to a cell sabotage phenotype that is useful in the treatment of cancer.[101] Further examination of this and other examples of failed or insufficient metabolite detoxification may lead to the identification of further biomedically relevant examples of cell sabotage.

To help pinpoint potential new forms of cell sabotage, it will be important to sharpen our definition of such processes. The concept of cell sabotage[10] contains two essential elements. First, that cell death is due to ongoing cellular activity, which contributes to cell death when some other part of the cellular biochemical or metabolic network is perturbed.[10] The second element is that cell death is orchestrated by proteins whose main function is essential for some other process, and not likely to be selected during evolution for a specific role in cell death. The two elements of cell sabotage are clearly met by ferroptosis, which results from an imbalance between the accumulation and detoxification of lipid ROS, processes that involve a set of essential enzymes necessary for cell survival. However, the notion that ongoing cellular activity is essential for cell death is not unique to ferroptosis. Even during apoptosis, ongoing cellular activity can be essential to cell death. For example, apoptotic cell death induced by proteasome inhibition requires ongoing protein synthesis.[102,103] Likewise, apoptotic cell death induced by DNA topoisomerase inhibition requires active DNA replication in S phase and/or mRNA transcription.[104–106] Also, under conditions of complete caspase inhibition, mitochondrial outer membrane permeabilization (MOMP) ultimately results in cell death due to ATP depletion[107]; ATP is presumably consumed by enzymatic activity that, if inhibited, would prevent or slow ATP depletion and cell death. Thus, ongoing cellular activity can be essential to the induction of both caspase-dependent and independent apoptosis, as well as ferroptosis. Likewise, many classic apoptosis pathway proteins can play important pro-survival roles,[108,109] suggesting that few proteins are likely to have exclusive roles in cell death. In these ways, the defining elements of cell sabotage are also associated to some degree with cell suicide and the line between these cell death processes is more blurred than imagined.

Finally, as we learn more about different candidate cell sabotage phenotypes, important differences in the operational logic of these pathways become clear. For example, while ferroptosis is triggered by *inactivation* of GSH-dependent antioxidant networks, parthanatos is triggered by *hyperactivation* of PARP-dependent enzymatic activity. Another candidate form of cell sabotage, the autophagy-related process termed autosis,[7] does not appear to be caused by any specific protein inactivation or hyperactivation, but rather a failure to restrain the normal operation of the autophagic machinery in response to nutrient deprivation. Thus, in the same manner that RCD has been sub-divided into apoptotic and non-apoptotic branches, it is possible to envision cell sabotage phenotypes being sub-divided into different classes based on the different mechanisms leading to cell death.

6 | CONCLUSIONS

Various cell death events have been described at the cellular level dating as far back as the late 19th century [reviewed in (110)]. The knowledge that cell death is a regulated process did not emerge until the latter half of the 20th century,[111] and it was not until the beginning of the 21st century that the existence and physiological relevance of non-apoptotic cell death was formally recognized.[6] Within this context, it seems likely that our understanding of ferroptosis and other

forms of cell sabotage is incomplete and that further evidence could be adduced that these processes represent adaptive features of biological systems. Since selection acts on phenotypes, not directly on genes or proteins, it is possible that evolution could have selected for regulatory networks (or the lack thereof) to ensure insulation of cell sabotage pathways such as ferroptosis from the regulatory pathways that control apoptotic cell death. The beneficial effects of cell sabotage under certain physiological situations (e.g. recruitment of immune cells to help restore homeostasis to damaged tissues) could ensure these pathways are retained during evolution as opposed to the selection for variants that link metabolic perturbations to apoptosis and trigger immunologically silent cell death. A better understanding of cell sabotage may lead us to understand that what sometimes initially appears to be a bug in our biological systems is indeed an undocumented feature.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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