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Letter to the editor: Iron, apoptosis, and ferroptosis

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To the editor:

A unique chemistry led to the evolutionary selection of iron for a wide range of fundamental cell functions, and the availability of this particular metal has become essential for almost every form of life. Iron concentrations in the environment were initially inadequate to meet the requirements for life and this necessitated the development of defined pathways to acquire critical metal. Concurrently, iron-catalyzed generation of radicals presented a potential for oxidative stress demanding that iron homeostasis be tightly controlled. Therefore, iron import, storage, and export are carefully regulated, and life exists at the precise interface between iron-deficiency and -sufficiency. Following an absolute iron-deficiency (e.g. anti-transferrin receptor antibodies and exposure to extracellular chelators), there is obstruction of the cell cycle at the S phase, engagement of MAP kinases, caspases, and proto-oncogene proteins, and initiation of a regulated cell death recognized as apoptosis [1].

More recently, ferroptosis regulated cell death was discovered. The definition of ferroptosis included cell death which was distinct from apoptosis, iron-dependent, and characterized by an accumulation of lipid peroxides [2]. In ferroptosis, it was suggested that accumulated iron catalyzed hydroxyl radical which, along with activation of enzymic pathways, resulted in elevated cell levels of lipid peroxides and cell denaturation. Ferroptosis was first described following cell exposure to erastin which was postulated to inhibit the cystine/glutamate antiporter leading to glutathione depletion, inactivation of glutathione peroxidase 4 (GPX4), an accumulation of lipid peroxides, and cell death [3].

An alternative explanation of the association between ferroptosis and disrupted iron homeostasis, the true hallmark feature of this pathway for regulated cell death, is proposed by other investigation. Ferroptosis has been repeatedly described in cells exposed to compounds and substances recognized chemically to form coordination (or chelation) complexes with iron and diseases following such exposures. These compounds

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and substances are numerous and include: microbials, endotoxin, particles and fibers, environmental pollutants (e.g. polychlorinated biphenyls, dioxin, and paraquat), toxins and venoms, anthracyclines, bleomycin, antibiotics, phenols and polyphenols, catecholamines, polychlorinated aromatic hydrocarbons, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, naphthoquinones, benzopyrene, tetrazolium salts, fatty acids, and lipoic acid. Exposure to these compounds and substances results in both a cell accumulation and a concurrent, functional deficiency of iron [4, 5]. Dependent on molecular weight, lipid solubility, and charge, the compound or substance is internalized and, as a result of its coordination chemistry, it complexes intracellular iron depriving the cell of its own metal. The exposed cell is then functionally iron-deficient. This triggers a response by the cell to reverse the loss of requisite iron which includes increasing the expression of importers such as transferrin receptor [6]. If increased import of iron is successful, cell concentrations rise, and metal levels will be sufficient to meet both cell requirements for continued function and complexation by the exposed compound or substance [7]. While iron concentrations can be elevated, cells can continue to be lacking in metal as a result of its sequestration by the exposure. If either enough iron is complexed by the compound and substance or the cell response to increase metal is inadequate, cell death is predicted.

It is counterintuitive to propose that exposure to compounds and substances with a capacity to complex iron results in an increased availability of the metal to support hydroxyl radical generation. For iron to support electron transfer and produce hydroxyl radical, an empty or labile coordination site is required. The compound or substance complexes iron and assumes coordination sites on cell metal. Accordingly, the availability of metal for electron transfer following such an exposure will decrease. There is no catalysis of hydroxyl radical but rather there can be a suppression in the generation of reactive oxygen species [5]. Instead of reflecting an accumulation of catalytically active metal, lipid peroxides can participate in the cell response to reverse the iron-deficiency following exposure to these compounds and substances. Lipid peroxidation products of arachidonic acid can be generated with and participate in the response to metal-deficiency. As one example, prostaglandin E2 (PGE_2) is upregulated with iron-deficiency while iron-sufficiency downregulates production [8,9]. Diminished glutathione levels and involvement of the cystine and glutathione pathways similarly support their recognized participation in the response to cell iron-deficiency rather than an overload [10]. As a result of its ability to complex the metal, glutathione contributes to aspects of iron homeostasis including its import and trafficking through the cytoplasm [11]. It is anticipated that, following exposure to compounds and substances with a capacity to complex iron, a cell will consume glutathione in an attempt to import the metal and reverse an iron-deficiency.

Other features of ferroptosis support this pathway of regulated cell death as being associated with a functional iron-deficiency. The proteins involved in ferroptosis are regulated by transcriptional factors associated with cell metal-deficiency (e.g. Nrf2) [12]. Morphologic characteristics of ferroptosis can be shared with those observed with iron-deficiency (e.g. decreased mitochondria cristae). In addition, ferritinophagy was suggested to participate in ferroptotic cell death by promoting the degradation of iron storage protein resulting in free iron which generates reactive oxygen species through the Fenton reaction to induce lipid peroxidation. However, ferritinophagy is a process in which iron stored in ferritin can be

utilized during metal-depleted conditions. The observation of this phenomenon following cell exposures to iron chelators supports a participation of ferritinophagy in response to iron-deficiency [13].

It is concluded that the pathogenesis of ferroptosis can be understood in terms of iron homeostasis. This pathway of regulated cell death is initiated by a functional iron-deficiency following exposure to compounds and substances which complex iron or associated disease. Therefore, ferroptosis is a pathway of regulated cell death which is not distinct from apoptosis which is described following absolute iron-deficiency. In support of this, a disruption in iron homeostasis with a functional iron-deficiency was delineated following several exposures and cell death originally defined as apoptosis but more recently recognized as ferroptosis [6, 14, 15]. Evidence supports that apoptosis and ferroptosis share a common pathway of iron-deficiency which can be absolute or functional.

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