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Nutritional and Metabolic Control of Ferroptosis: Mechanisms and Biological Relevance in Humans and Animals

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ABSTRACT

Ferroptosis is a non-necrotic, iron-dependent cell death that is caused by lipid peroxidation overload and antioxidant defenses breakdowns. In comparison to apoptosis or necrosis, ferroptosis is developed because of metabolic vulnerabilities, especially iron imbalances, glutathione deficiency, glutathione peroxidase 4 suppression and phospholipid oxidation. Nutritional conditions have been identified as potent regulators of ferroptotic susceptibility since diet affects antioxidant stores, membrane lipids, redox metabolism and iron condition. This review identically describes the biochemical processes involved in ferroptosis, particularly the role of iron redox cycling, polyunsaturated fatty acid peroxidation, antioxidant enzyme and other lipid repair pathways. It also discusses the role of nutrients like selenium, vitamin E, Coenzyme Q10, sulfur related amino acids, iron and dietary fatty acids in the regulation of ferroptotic signaling. Lastly, biological usefulness of ferroptosis in humans and animals is addressed, including its role in cancer biology, neurodegeneration, infectious disease, metabolic diseases and veterinary diseases. Nutritional management is suggested as the potential solution to tune ferroptosis for improving health and preventing tissue damage and increasing resilience to disease.

Keywords: Ferroptosis, Iron metabolism, Lipid peroxidation, Glutathione, Glutathione peroxidase 4

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Introduction

Programmed cell death is essential for maintaining tissue homeostasis and eliminating damaged, dysfunctional or metabolically compromised cells [1]. Although apoptosis, necroptosis and pyroptosis are established paradigms of regulated cell death, the recognition of ferroptosis has created a paradigm shift [2]. Ferroptosis refers to an iron-dependent, non-apoptotic, regulated cell death involving the uncontrolled peroxidation of polyunsaturated phospholipids and lipid repair system failure, especially glutathione - glutathione peroxidase 4 (GPX4) axis. In comparison to caspase-dependent apoptosis, ferroptosis is typified by disastrous plasma membrane harm, mitochondrial shrinkage, condensed mitochondrial membranes, and speedy metabolic breakdown, but no fragmentation of nuclei or chromatin condensation [3].

The idea of ferroptosis was formally introduced in 2012 by Dixon. It has been noted as early as the 1950s-60s that cystine or cysteine deprivation provoked non-apoptotic cell death in cultured cells [4]. In the 1970s, it was clear that cysteine starvation stimulated glutathione depletion and overly accumulated reactive oxygen species (ROS) [5]. It has been found in the 2000s that GPX4 is necessary to inhibit the process of cell death caused by lipid peroxidation, which was a significant breakthrough in the research of oxidative injury [6]. Following the identification of the erastin and RSL3-induced death pathways, ferroptosis was eventually discovered in 2012 with the discovery of parallel suppressor systems such as FSP1-CoQ10, GCH1 - BH4 axis and mitochondrial DHODH-mediated protection [7]. Ferroptosis is closely coupled with cellular metabolism, iron uptake and iron storage, amino acid use, NADPH generation, mitochondrial ROS and membrane lipid structure have all met each other to dictate cellular vulnerability. Such intensely metabolic entanglement renders ferroptosis highly sensitive to nutritional status. Nutrients balance antioxidant defenses, redox buffering capacity, membrane lipid patterns and intracellular iron processes: these factors define ferroptotic thresholds in humans and animals. Since the diets of livestock, human dietary habits and environmental stress factors affect such biochemical processes, ferroptosis is a cross-species-conserved metabolic process of cellular damage [6]. The nutritional and metabolic regulation of ferroptosis has thus become an important issue in the biomedical sciences, animal nutrition, veterinary medicine, toxicology and health management.

Concept and Mechanistic Basis of Ferroptosis

Ferroptosis is a unique cell death type, associated with caspase activation or standard DNA fragmentation, but rather occurs when the production of lipid peroxides is higher than the capacity of the antioxidant systems presents in the cell [3]. Ferroptosis is mechanistically regulated by iron redox cycling and expansion of the labile iron pool, peroxidation of polyunsaturated fatty acid (PUFA) containing phospholipids and failure of antioxidant defenses, in particular, GSH-GPX4 axis. The assembly of these processes eventually destabilizes membrane integrity and promotes cell death [2].

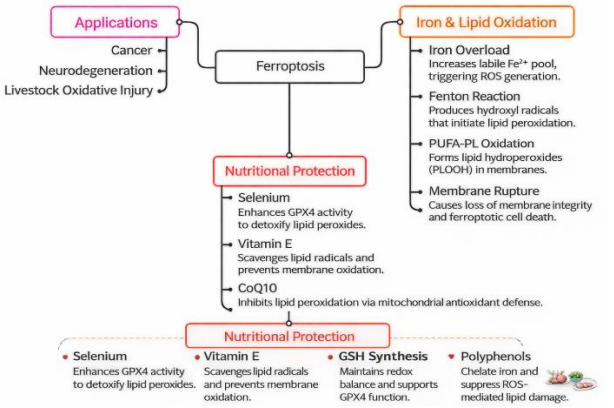

Figure 1: Integrated schematic overview of ferroptosis highlighting iron-driven lipid peroxidation, nutritional antioxidant defense, and translational applications

Iron Homeostasis, Labile Iron Pool and Redox Cycling

Iron is indispensable for numerous physiological processes, including oxygen transport, mitochondrial respiration and DNA synthesis. However, when iron homeostasis is disrupted, its redox activity becomes cytotoxic. Cellular iron uptake occurs primarily via transferrin receptor-mediated endocytosis. Within endosomes, ferric iron (Fe^{3+}) is reduced to ferrous iron (Fe^{2+}), which is then released into the cytoplasm. A fraction of intracellular Fe^{2+} contributes to the labile iron pool (LIP), a metabolically active and redox-reactive iron reservoir. The pathological significance of the LIP lies in its ability to catalyze Fenton chemistry.

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^{\bullet} + OH^{-}$$

The hydroxyl radical ($OH^{\bullet}$) generated is highly reactive and capable of abstracting hydrogen atoms from PUFA side chains in membrane phospholipids, thereby initiating lipid peroxidation chain reactions. Conditions that increase the LIP, such as ferritin degradation decreased ferritin synthesis, iron overload, or chronic inflammation, significantly elevate ferroptotic susceptibility. Similar iron dysregulation patterns are observed in metabolic disorders, inflammatory diseases and certain nutritional imbalances in animals and humans, underscoring the conserved and pathophysiological relevance of ferroptosis across species [2, 8].

PUFA-Phospholipids as Core Substrates of Ferroptosis

The major execution substrates of ferroptosis are PUFA-containing phospholipids. The insertion of PUFAs into membrane phospholipids is

heavily controlled by some enzymes. The conversion of the free PUFAs to PUFA-CoA derivatives is catalyzed by Acyl-CoA synthetase long-chain family member 4 and the conversion of PUFA-CoA to phosphatidylethanolamines and other phospholipids is catalyzed by the lyso phosphatidylcholine acyltransferase 3. Neurons, hepatocytes, and fast-growing cancer cells, which have a high ACSL4 expression, exhibit an augmented ferroptotic vulnerability because of the enhancement of oxidizable PUFA-PLs. After being incorporated into membranes, PUFA-PLs can be oxidized in two main different ways: (1) non-enzymatically via auto-oxidation by reactive oxygen species and Fenton-derived radicals and (2) via enzymatic oxidation by lipoxygenases, cytochrome P450 oxidoreductase (POR) and oxidoreductases. Lipid hydroperoxide accumulation disrupts bilayer architecture, changes membrane fluidity, and disrupts ion gradients. Excessive levels of peroxide proved to lead to membrane rupture and ferroptotic cell death when the level surpassed cellular detoxification ability [9].

Cysteine Availability, Glutathione Depletion, and GPX4 Inactivation

The main ferroptotic defense system is the cysteine-glutathione-GPX4 axis. System Xc-cystine uptake is the precursor of glutathione synthesis. The tripeptide antioxidant, Glutathione (GSH) serves as a reducing substrate of GPX4 which is a selenium-dependent enzyme in direct conversion of toxic lipid hydroperoxides to non-toxic lipid alcohols. Any impairment of this axis triggers ferroptosis. The Gpx4 activity is impaired by inhibition of system Xc -, cysteine starvation, impaired GSH biosynthesis, or selenium deficiency. Direct GPX4 inhibition leads to the accumulation of lipid peroxide due to a rapid and unregulated burst, therefore, GPX4 inactivation is the most direct and strong cause of ferroptosis cell death. This protection system can be disrupted by nutritional deficiencies, oxidative stress and metabolic imbalance [10].

Parallel Ferroptosis-Suppressing Pathways

In addition to GPX4, there are other ferroptosis-inhibitory mechanisms in cells, which offer metabolic redundancy. Reduced coenzyme Q10, a membrane-bound radical-trapping antioxidant that disrupts lipid peroxidation chain reactions, is restored by the ferroptosis suppressor protein 1 (FSP1)-CoQ10 pathway [8]. The GCH1BH4 axis synthesize tetrahydrobiopterin that stabilize membranes and directly eliminate lipid radicals. Also, dihydroorotate dehydrogenase plays a role in mitochondria in independent limitation of mitochondrial lipid peroxidation without the involvement of GPX4. These parallel systems emphasize the evolutionary significance of protecting membrane integrity against iron mediated oxidative damage. Ferroptosis, consequently, is the disastrous breakdown of compensatory systems of iron control, lipid metabolism and antioxidants defense [11].

Table 1: Key Molecular Drivers and Suppressors of Ferroptosis.

Category	Molecule / Gene	Primary Function	Effect on Ferroptosis
Iron metabolism	Transferrin (TF)	Iron transport	Promotes (↑)
Iron storage	Ferritin (FTH1/FTL)	Iron sequestration	Suppresses
Autophagy-related	NCOA4	Ferritinophagy	Promotes
PUFA activation	ACSL4	PUFA-CoA formation	Promotes
Phospholipid remodeling	LPCAT3	PUFA incorporation into PLs	Promotes
Antioxidant system	GPX4	Reduces lipid peroxides	Strong suppressor
Cystine transport	SLC7A11 (System Xc–)	Cystine import for GSH	Suppresses
Radical trapping	FSP1	CoQ10 reduction	Suppresses
Lipid antioxidant	BH4 (GCH1 pathway)	Radical scavenging	Suppresses
Mitochondrial defense	DHODH	Prevents mt-lipid peroxidation	Suppresses

Nutritional Determinants of Ferroptosis

The effect of nutrition on ferroptotic sensitivity is enormous since diet has a direct impact on the availability of antioxidants, structural lipid substrates, redox cofactors, and metals in Fenton chemistry [11]. Dietary patterns hence have a potent influence on ferroptosis in both human beings and animals, and nutritional interventions may be used as a viable approach to altering ferroptotic stress.

Selenium and Selenoproteins (GPX4 Axis)

The most important nutrient in terms of regulating ferroptosis is selenium because it is necessary in the formation of selenocysteine, which is an essential amino acid in the catalytic centre of GPX4. Deficiency of selenium causes a decrease of GPX4 activity, phospholipid hydroperoxide accumulation, and increased ferroptosis. Selenium deficiency in humans and livestock leads to pathologies similar to ferroptotic injury (e.g. white muscle disease in calves and Keshan disease in humans). The use of selenium supplementation restores the functioning of GPX4 and fat oxidation [12].

Vitamin E (α-Tocopherol)

The main chain-breaking antioxidant in the biological membranes is vitamin E. It also gives away a hydrogen atom to lipid peroxyl radicals and prevents the propagation of lipid oxidation, thus proving the significance of non-enzymatic defences. Vitamin E deficiency in animals creates skeletal and cardiac myopathies that are linked to severe lipid peroxidation, which fits the description of ferroptosis-like pathology [11].

Coenzyme Q10 and the FSP1 Pathway

Coenzyme Q10 (ubiquinone/ubiquinol) is an effective ferroptotic defence by FSP1CoQ10 axis. Ubiquinol caters lipid radicals and membrane integrity is stabilized regardless of GPX4. The endogenous CoQ10 synthesis is affected by nutritional precursors like riboflavin, niacin, and tyrosine. The use of CoQ10 as supplement in animals enhances antioxidant condition, decreases tissue peroxidation, and augmented the ability to endure metabolic stress [13].

Sulfur Amino Acids: Methionine & Cysteine

The rate of glutathione production is limited by cysteine. Low methionine or cysteine diets reduce GSH pools and impair GPX4 activity making cells more susceptible to ferroptosis [10]. In monogastric animals (poultry) , oxidative lesions, which are similar to ferroptosis, occur with the deficiency of sulfur amino acids [14]. Ferroptotic sensitivity is increased by cysteine depletion by fasting or metabolic stress in human beings.

Polyunsaturated Fatty Acids (PUFAs)

Arachidonic acid and adrenic acid are PUFAs with the necessary required substrates of ferroptosis because of their peroxidation-prone bis-allylic hydrogen atoms. The supplementation of dietary PUFA boosts the level of membrane PUFA-PL and predisposes cells to ferroptosis [9]. While Monounsaturated fatty acids lower the ferroptotic sensitivity by rivalry with PUFAs in their membrane incorporation. Animals that are fed diets rich in PUFA have an increased oxidative stress unless antioxidants are supplemented simultaneously.

Iron Intake and Bioavailability

The size of labile iron pool is determined by dietary iron. Iron overload facilitates the development of ROS through Fenton chemistry, enhances lipid peroxidation, and boosts ferroptosis. Conversely, ferroptosis can be inhibited by iron chelators (e.g. deferoxamine), which induce a reduction in available Fe 2+. Ferroptotic pathology is very similar to iron overload in horses and poultry [15].

Glucose, NADPH and Metabolic Flux

Dietary carbohydrates influence NADPH availability through the pentose phosphate pathway. NADPH acts as a reductive currency to regenerate GSH and CoQ10 pools [16]. Glucose starvation reduces NADPH and promotes ferroptosis, while adequate carbohydrate intake supports redox homeostasis and suppresses ferroptosis

Plant Antioxidants (Polyphenols, Organosulfur Compounds)

Plant-derived antioxidants (quercetin, curcumin, organosulfur compounds from garlic) exert anti-ferroptotic properties by scavenging lipid radicals, chelating iron, and activating Nrf2 signalling pathways. In feed-based systems, polyphenol-rich forages help reduce oxidative stress in livestock [17]

Table 2: Dietary Factors Influencing Ferroptotic Sensitivity

Nutrient	Mechanism of Action	Ferroptotic Effect	Human Relevance	Animal Relevance
Selenium	Required for GPX4 synthesis	↓ Ferroptosis	Keshan disease	White muscle disease
Vitamin E	Chain-breaking lipid antioxidant	↓ Ferroptosis	Neuroprotection	Myopathy prevention
CoQ10	Radical trapping antioxidant	↓ Ferroptosis	Cardioprotection	Stress resilience
Methionine/ Cysteine	GSH synthesis	↓ Ferroptosis	Metabolic stress	Poultry oxidative lesions
PUFA (ω-6)	Oxidizable membrane substrate	↑ Ferroptosis	Cancer vulnerability	Oxidative stress in livestock

MUFA	Competes with PUFA incorporation	↓ Ferroptosis	Protective	Improves meat stability
Iron (excess)	Expands LIP & Fenton reaction	↑ Ferroptosis	Hemochromatosis	Piglet iron overload
Polyphenols	Iron chelation + Nrf2 activation	↓ Ferroptosis	Anti-inflammatory	Feed antioxidant effect

Biological Relevance in Humans and Animals

The implications of ferroptosis on human and animal health are vast since redox unbalance, iron overload, and oxidative lipid damage are universal biological stress factors. Ferroptosis is a contributor of neurodegenerative diseases like Alzheimer and Parkinson in humans where iron build-up and lipid peroxidation are the typical characteristics [18]. Equally, ferroptosis also contributes to ischemia-reperfusion injury after stroke, myocardial infarction and organ transplantation. Overproduction of ROS in reperfusion saturates GPX4 and causes massive lipid membrane damage, which is also noticed in the ischemic organs of pigs and cattle. Many tumours that are resistant to different therapies are strongly dependent on GPX4 and system Xc- in cancer biology; therefore, ferroptotic induction is becoming a good treatment strategy. Ferroptosis has also been implicated in infectious diseases, including viral infections, such as COVID-19, where iron dysregulation via inflammation and a reduction in GPX4 expression provide a ferroptosis-prone environment [19].

Ferroptosis-like injuries are emerging in veterinary pathology in animals. The biochemical evidence of ferroptotic damage is found in the nutritional myopathies in cattle, sheep, goats, and poultry, which were traditionally associated with the shortage of selenium and vitamin E. Otherwise, the oxidative membrane damage associated with ferroptosis can be induced in poultry [20], and dairy cattle by heat stress because GSH levels are low and the production of ROS increases. Iron overload and oxidative tissue damage that is proposed to arise due to iron supplementation also occur in neonatal piglets, indicating ferroptotic effects. Mechanisms Ferroptosis. In other lipid-peroxidative neurodegenerative disorders, lipid peroxidation signaling pathways in equine myopathies and canines have also been implicated in ferroptosis. Due to its frequent exposure to environmental, nutritional, and metabolic stressors, such as heat stress, high-PUFA diets, infections, and rapid growth, ferroptosis is a biologically preserved process of tissue destruction in animal production [21].

Table 3: Ferroptosis in Human and Veterinary Diseases

Disease Category	Example	Mechanistic Link to Ferroptosis	Species
Neurodegeneration	Alzheimer's disease	Iron accumulation + lipid peroxidation	Human
Neurodegeneration	Parkinson's disease	GPX4 decline	Human
Ischemia-reperfusion	Myocardial infarction	ROS surge + GPX4 failure	Human & Pig
Cancer	Therapy-resistant tumors	GPX4 dependence	Human
Nutritional myopathy	White muscle disease	Selenium deficiency	Calves, lambs
Heat stress injury	Poultry heat stress	GSH depletion	Broilers
Iron overload	Neonatal iron toxicity	Excess LIP	Piglets
Equine myopathy	Rhabdomyolysis	Lipid peroxidation	Horses

Conclusion

Ferroptosis is an iron-dependent metabolically programmed regulated cell death type that consists of lipid peroxidation and failure of antioxidant systems. The nutritional supplements such as selenium, vitamin E, sulfur amino acids, CoQ10, iron, and dietary fatty acids can be considered potent ferroptotic vulnerability modulators. Due to the wide occurrence of metabolic stress, irregular iron balance, and oxidative injury between species, ferroptosis offers a single pathway to connect nutrition, redox biology, and disease. The implications of learning the nutritional effects on ferroptosis include a lot in the medical sector of human beings, treatment of diseases, as well as care of the animals. Dietary antioxidant optimization, iron balance, and PUFA intake can be potential measures of controlling ferroptosis and avoiding cellular damage in humans and animals.

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