Review[1]

The duality of Ferroptosis: a new illustration of the Janus god

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ABSTRACT

Ferroptosis, a regulated form of cell death driven by iron-dependent lipid peroxidation, has emerged as a critical mechanism in diverse biological contexts. Its involvement spans human diseases, aging processes, and plant immunity, positioning ferroptosis as both a challenge and an opportunity for therapeutic innovation. Plant-derived molecules represent a promising source of modulators capable of either inducing or inhibiting ferroptosis, while current research emphasizes the synthesis of small molecules, optimization of administration routes, and evaluation of localized activity in specific pathologies.

Beyond disease treatment, ferroptosis is increasingly recognized as central to the concept of healthy aging. The progressive decline in resistance to oxidative stress—exacerbated by environmental pollution and modern lifestyles—disrupts cellular redox balance, leading to metabolic and dermatological disorders. Strategies aimed at inhibiting ferroptosis hold potential to mitigate age-related damage, preserve tissue integrity, and promote longevity.

Ultimately, ferroptosis underscores the essential yet often overlooked role of iron in maintaining cellular homeostasis, highlighting its importance in both biomedical research and translational applications.

RESUMEN

La dualidad de la ferroptosis: una nueva ilustración del dios Jano. La ferroptosis, una forma regulada de muerte celular dependiente del hierro y caracterizada por la peroxidación lipídica, se ha consolidado como un mecanismo clave en múltiples procesos biológicos. Su participación se extiende desde enfermedades humanas hasta el envejecimiento y la inmunidad vegetal, lo que la convierte en un campo estratégico para la investigación biomédica y traslacional. Las moléculas derivadas de plantas ofrecen un potencial significativo como moduladores de la ferroptosis, capaces de inducirla o inhibirla, mientras que los estudios actuales se centran en el diseño de pequeñas moléculas, sus vías de administración y la actividad localizada en patologías específicas.

Más allá del tratamiento de enfermedades, la ferroptosis se vincula cada vez más con el concepto de envejecimiento saludable. La pérdida progresiva de resistencia al estrés oxidativo, agravada por la contaminación y los estilos de vida modernos, altera el equilibrio redox celular y favorece trastornos metabólicos y cutáneos. Inhibir la ferroptosis emerge como una estrategia prometedora para mitigar el daño asociado a la edad y preservar la longevidad.

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INTRODUCTION

The distinctive aspect of the Roman god Janus lies in his symbolic depiction. As the deity of transitions and duality, he is shown with two faces—one gazing backward toward the past and the other looking forward into the future. In the last decade, the emerging research area of ferroptosis has steadily attracted growing interest within medicinal chemistry.

The story began in 2003 when an unknown form of cell death was discovered during the study of an anticancer molecule, erastin, on human foreskin fibroblasts with a RAS gene mutation, which is present in approximately 30% of cancers[1]. By comparing erastin to camptothecin, a pro-apoptotic molecule, biologists concluded that the rapid, irreversible cell death caused by erastin is non-apoptotic. Subsequent studies have demonstrated that erastin depletes intracellular glutathione (GSH), an important cofactor of glutathione peroxidase (GPX4). GSH is required for the lipid repair function of GPX4. GPX4, a selenoprotein, oxidizes GSH to GS-GS, which detoxifies reactive hydrogen peroxide. Through lipid peroxidation, reactive hydrogen peroxide induces ferroptosis. Depletion of GSH and/or decreased GPX4 activity, combined with increased intracellular Fe^{2+}, can result in lipid peroxidation and cellular damage. In 2012, Scott J. Dixon from Columbia University identified the small molecule ferrostatin-1 as a potent inhibitor of this new type of cell death in cancer cells and proposed the term "ferroptosis." "Ferroptosis depends on intracellular iron but not other metals and is morphologically, biochemically, and genetically distinct from apoptosis, necrosis, and autophagy"[2].

THE MECHANISMS UNDERLYING FERROPTOSIS ARE HIGHLY COMPLEX

Maintaining iron balance is crucial for human health. Iron acts as a dynamic micronutrient, serving both as a cofactor for enzymes and as a structural element in proteins. Its essential functions include oxygen storage in myoglobin, oxygen transport through hemoglobin, and participation in cellular energy processes such as oxidases and iron–sulfur clusters within the mitochondrial electron transport chain. Mitochondria uphold cellular stability by producing ATP and releasing small amounts of reactive oxygen species (ROS) for signaling. When the coordination among iron metabolism (primarily via ferritin), lipid metabolism, redox regulation, and mitochondrial activity is disturbed, ferroptosis arises. This form of programmed cell death is driven by iron-dependent lipid peroxidation and the accumulation of reactive oxygen species.

Early studies proposed that extensive oxidation of polyunsaturated fatty acids (PUFAs) could lead to membrane rupture and cell death, but the reality is more nuanced. The lipids most prone to peroxidation are phospholipids containing PUFAs (PUFA-PLs), due to their bis-allylic sites within the membrane. Lipooxygenases (LOXs), iron-dependent enzymes, catalyze stereospecific oxidation of PUFAs, generating fatty acid hydroperoxides, and are thought to play a central regulatory role in amplifying ferroptosis. Within mitochondria, cardiolipin—a phospholipid unique to the inner membrane and essential for electron transport and ATP synthesis—represents 20–30% of keratinocyte mitochondrial lipids, making it a major target for peroxidation. Beyond mitochondrial and plasma membranes, lipid peroxidation occurs in multiple organelles. Current consensus highlights distinct roles: mitochondria (rich in iron and GPX4), lysosomes (sites of ferrostatin accumulation), peroxisomes (active in lipid peroxidation), the Golgi apparatus (ROS generation), and the endoplasmic reticulum (ER), which harbors the largest lipid reservoir in human cells.

Endoplasmic reticulum (ER) stress arises from the buildup of unfolded or misfolded proteins. Because of the close proximity between the ER and mitochondria, calcium overload occurs in the mitochondria, triggering excessive production of reactive oxygen species (ROS). The ER functions as the central site for lipid peroxidation, while other organelles act as sources of ROS, mediators of lipid peroxidation spread, and amplifiers of oxidative reactions. Regardless of where lipid peroxidation originates within the cell, its lethal effects ultimately converge at the plasma membrane. This process causes profound alterations in membrane structure, including pore formation, disruption of ion gradients, and changes in fluidity, curvature, and susceptibility to damage. Additionally, lipid peroxidation generates and transfers toxic aldehydes such as 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA), initiating inter-organelle chain reactions that culminate in a cascade of events leading to ferroptotic cell death[3 4 5].

Membrane contact sites (MCS) linking mitochondria and the nucleus—known as nucleus-associated mitochondria (NAM)—have recently been identified. These structures facilitate the transfer of elevated mitochondrial reactive oxygen species (mtROS) into the nucleus, where they interfere with DNA integrity, DNA methylation, and overall genomic stability. Such disturbances intensify cellular dysfunctions.

CONTROLLING FERROPTOSIS

Controlling ferroptosis is challenging due to the multitude of biological pathways that regulate oxidative stress. This form of programmed cell death can harm healthy cells and plays a role in the onset and progression of numerous diseases. At the same time, ferroptosis represents a pivotal research frontier because of its dual nature: inducing it in cancer cells produces anti-tumor effects, whereas inhibiting it in normal cells may help prevent certain disorders and age-related decline. Some researchers emphasize the possibility of selectively targeting cancer cells while sparing healthy ones. The central therapeutic challenge lies in achieving tumor-specific ferroptosis without triggering damage in normal tissues. Moreover, the connection between iron metabolism, ferroptosis, and tissue aging remains a promising area for further investigation.

FERROPTOSIS AND DISEASES

Ferroptosis is implicated in a wide spectrum of diseases, including neurodegenerative disorders such as Alzheimer's, Parkinson's, Huntington's, and stroke; metabolic conditions like steatohepatitis; pulmonary diseases; osteoporosis; and cardiovascular pathologies such as atherosclerosis and myocardial infarction. It also contributes to kidney dysfunction and hematological disorders. In diabetes, ferroptosis delays wound healing by promoting neutrophil-driven skin ulcer progression. More broadly, it is linked to biological processes such as senescence, inflammation, immune dysregulation, and aging, underscoring its potential as a novel therapeutic target.[6 7]

In dermatology, ferroptosis is associated with conditions including ichthyosis and psoriasis (via immune pathways), acne vulgaris (sebaceous gland inflammation), alopecia areata (autoimmune hair loss), vitiligo, and polymorphous light eruption (sun-induced skin reactions). Basal ferritin levels vary among skin cells, with the epidermis containing two to seven times more ferritin than fibroblasts, and these levels shift under stress. Environmental pollutants such as ozone—one of the most harmful outdoor agents—interact with stratum corneum lipids, generating lipid peroxides, aldehydes (e.g., 4-HNE protein adducts), and hydrogen peroxide. Ozone also depletes the skin's natural antioxidants, thereby accelerating oxidative damage and disease progression[8 9 10].

A structured comparative table that organizes ferroptosis involvement across different disease categories and biological contexts is shown below. This format makes the associations clearer and easier to use for teaching or publication notes.

Table. A comparative scheme of ferroptosis and its relationship with diseases

Disease Category	Examples	Mechanistic Role	Notes
Neurodegenerative	Alzheimer's, Parkinson's, Huntington's, stroke	Promotes neuronal death via oxidative stress	Central in progression of neurodegeneration
Metabolic/Liver	Steatohepatitis (fatty liver disease)	Lipid peroxidation and iron overload	Contributes to chronic liver injury
Pulmonary	Pulmonary diseases (unspecified)	Oxidative imbalance in lung tissue	Potential therapeutic target
Bone	Osteoporosis	Alters bone cell survival	Linked to bone fragility
Cardiovascular	Atherosclerosis, myocardial infarction	Endothelial and cardiomyocyte damage	Drives vascular and cardiac pathology
Renal	Kidney disorders	Iron-dependent cell death in renal tissue	Implicated in renal dysfunction
Hematological	Blood diseases	Dysregulated iron metabolism	Contributes to hematological abnormalities
Diabetes-related	Delayed wound healing, skin ulcers	Neutrophil-driven oxidative damage	Impairs tissue repair
Dermatological	Ichthyosis, psoriasis, acne vulgaris, alopecia areata, vitiligo, polymorphous light eruption, skin aging	Immune dysregulation, sebaceous inflammation, oxidative stress	Epidermis has 2–7× more ferritin than fibroblasts; ozone triggers lipid peroxides and antioxidant depletion
Biological Processes	Senescence, inflammation, immune disturbances, aging	Oxidative stress and iron metabolism	Suggests ferroptosis as a pharmacological target

This table highlights how ferroptosis spans multiple systems, from **neurodegeneration** to **skin pathology**, and emphasizes its dual role as both a driver of disease and a potential therapeutic target.

HOW TO MODULATE FERROPTOSIS?

This paper examines strategies to modulate ferroptosis in normal cells, emphasizing the potential of natural compounds to regulate iron balance and suppress ferroptosis by chelating excess iron or enhancing antioxidant defenses. Preventing glutathione (GSH) depletion, or that of its precursor cysteine, is fundamental. Beyond this, iron chelation and inhibition of lipid peroxidation—either directly or indirectly—represent widely applicable approaches.

Iron chelators can effectively block ferroptosis. These molecules typically contain donor atoms (oxygen, nitrogen, or sulfur) that form coordinate bonds with iron. Examples include deferoxamine, other approved synthetic agents, microbial siderophores, and natural chelators such as flavonoids, polyphenols, quercetin, isorhamnetin, and ascorbic acid.

Regulation of lipid peroxidation emerges as the central mechanism in ferroptosis control. Lipid oxidation involves both enzymatic and non-enzymatic pathways. The transcription factor NRF2 orchestrates cellular responses to oxidative stress, modulates intracellular iron levels, and regulates ROS production linked to iron overload. NF-κB, another key transcription factor, governs immune functions and inflammatory responses, both of which contribute to iron metabolism disorders and redox imbalance. Importantly, NRF2 and NF-κB both regulate GPX4 expression, a critical enzyme for maintaining redox homeostasis under stress.

Although numerous molecules can modulate ferroptosis, their effects vary depending on biological context (tissue type, cell line, normal vs. malignant cells) and concentration. Literature surveys highlight several inhibitors, including vitamins E[11], K[12], A[13], and C[14] (and derivatives); flavonoids such as luteolin[15], apigenin[16], baicalein[17], and icaritin[18]; plant-derived compounds like oleuropein[19] (olive leaves), silibinin[20] (flavonolignan), resveratrol[21] (stilbenoid), moscatilin[22] (orchids), *Bletilla striata* polysaccharides, EGCG (green tea), erianin[23] (*Dendrobium chrysotoxum*), gastrodin[24] (*Gastrodia elata*), cyanidin glucosides and anthocyanins (honeysuckle), rosmarinic acid[25], eugenol[26], and furanoeremophilane sesquiterpenoids. Other modulators include coenzyme Q10[27], NADPH[28], tetrahydrobiopterin[29], 18β-glycyrrhetinic acid[30], selenium-based synthetic molecules, miRNAs, and certain *Lactobacillus* strains[31 32].

CONCLUSION

Ferroptosis has emerged as a pivotal field of research, with implications across human disease, aging, and even plant immunity. Plant-derived molecules provide promising avenues for modulating ferroptosis, either by inducing or inhibiting this form of cell death. Current investigations emphasize the design of small molecules, their administration routes, and their localized activity depending on the pathology.

Beyond disease treatment, ferroptosis is increasingly linked to the concept of healthy aging. The gradual decline in resistance to oxidative stress—exacerbated by modern lifestyles and environmental pollution—disrupts redox balance, leading to progressive metabolic and dermatological disorders. Inhibiting ferroptosis thus represents a compelling strategy to mitigate age-related damage and foster longevity.

Ultimately, ferroptosis reminds us of the central role of iron, a fundamental yet often overlooked element, in maintaining cellular equilibrium and health.

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