FERROPTOSIS: A NOVEL MECHANISM OF CELL DEATH AND ITS THERAPEUTIC POTENTIAL

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https://doi.org/10.5281/zenodo.21214443

Abstract

Ferroptosis is a recently recognized form of regulated cell death characterized by iron-dependent lipid peroxidation and irreversible damage to cellular membranes. Unlike apoptosis, necrosis, or autophagy, ferroptosis is driven primarily by oxidative stress, intracellular iron accumulation, and the depletion of glutathione-dependent antioxidant defenses. Since its formal description in 2012, ferroptosis has become one of the fastest-growing research areas in biochemistry, molecular biology, and pharmacology due to its significant role in the pathogenesis of numerous human diseases.

The biochemical hallmark of ferroptosis is the excessive accumulation of lipid hydroperoxides resulting from impaired activity of glutathione peroxidase 4 (GPX4). Under physiological conditions, GPX4 protects membrane phospholipids from oxidative damage by reducing lipid hydroperoxides into non-toxic lipid alcohols using glutathione (GSH) as a cofactor. Depletion of intracellular GSH, inhibition of GPX4 activity, or excessive iron availability promotes uncontrolled lipid peroxidation, ultimately leading to ferroptotic cell death.

Recent studies have demonstrated that ferroptosis contributes to the development and progression of multiple pathological conditions, including cancer, ischemia-reperfusion injury, neurodegenerative disorders such as Alzheimer's and Parkinson's diseases, acute kidney injury, and chronic liver diseases. Conversely, pharmacological induction of ferroptosis has emerged as a promising therapeutic strategy for eliminating apoptosis-resistant tumor cells, particularly in aggressive and drug-resistant cancers.

Advances in molecular biology have identified several regulatory pathways involved in ferroptosis, including the **System Xc^-/GSH/GPX4 axis**, iron metabolism, lipid metabolism, and the **FSP1–CoQ10 antioxidant pathway**. These discoveries have expanded opportunities for developing novel pharmacological agents capable of either inducing or inhibiting ferroptosis depending on the clinical context.

Keywords. Ferroptosis; Iron metabolism; Lipid peroxidation; GPX4; Oxidative stress; Biochemistry; Molecular pharmacology.

Iron (Fe^{2+}) accumulation

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Reactive Oxygen Species (ROS)

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Lipid Peroxidation

▼

GPX4 Inactivation / GSH Depletion

▼

Membrane Damage

▼

FERROPTOSIS

Component	Biological Function	Role in Ferroptosis
Fe^{2+}	Iron metabolism	Promotes ROS generation through Fenton reactions
GPX4	Antioxidant enzyme	Prevents lipid peroxidation
Glutathione (GSH)	Cellular antioxidant	Required for GPX4 activity
System Xc^-	Cystine transporter	Maintains intracellular glutathione synthesis
ACSL4	Lipid metabolism enzyme	Increases susceptibility to lipid peroxidation

Component	Biological Function	Role in Ferroptosis
FSP1	Antioxidant defense	GPX4-independent protection against ferroptosis

Future Perspectives

Future research on ferroptosis is expected to focus on identifying highly selective biomarkers for early diagnosis and monitoring of ferroptosis-related diseases. Advances in multi-omics technologies, including genomics, proteomics, metabolomics, and lipidomics, will improve the understanding of the molecular networks regulating ferroptotic cell death and facilitate the discovery of novel therapeutic targets.

Another promising direction is the development of selective ferroptosis modulators. Ferroptosis inducers may provide effective treatment strategies for drug-resistant cancers, whereas ferroptosis inhibitors could offer therapeutic benefits in neurodegenerative disorders, ischemia-reperfusion injury, and chronic inflammatory diseases. The optimization of these compounds with improved specificity, safety, and pharmacokinetic properties remains an important objective in medicinal chemistry.

Artificial intelligence and machine learning are also expected to accelerate ferroptosis research by supporting target identification, drug repurposing, molecular docking, and predictive modeling of therapeutic responses. Furthermore, integrating ferroptosis-related biomarkers into personalized medicine may enable clinicians to tailor treatment strategies according to individual molecular profiles, thereby improving therapeutic efficacy while reducing adverse effects.

Despite substantial progress, additional preclinical and clinical investigations are required to validate the safety and effectiveness of ferroptosis-targeted therapies. International collaboration among biochemists, pharmacologists, clinicians, and computational scientists will be essential for translating laboratory discoveries into evidence-based clinical applications. Continued advances in this field are likely to establish ferroptosis as one of the most promising therapeutic targets in precision medicine over the coming decade.

Conclusion

Ferroptosis has emerged as a unique and highly regulated form of cell death that plays a crucial role in the pathogenesis of numerous human diseases. Increasing evidence indicates that dysregulation of iron metabolism, excessive lipid peroxidation, and impairment of antioxidant defense systems are the major

biochemical mechanisms underlying ferroptotic cell death. These discoveries have significantly expanded current understanding of disease progression at the molecular level.

Recent advances in biochemistry, molecular pharmacology, and systems biology have identified several promising molecular targets, including GPX4, System Xc^-, FSP1, ACSL4, and iron metabolism pathways, which may serve as potential therapeutic targets for future drug development. The ability to either induce or inhibit ferroptosis depending on the disease context provides new opportunities for treating cancer, neurodegenerative disorders, cardiovascular diseases, and other oxidative stress-related conditions.

In conclusion, ferroptosis represents one of the most promising research areas in modern biochemistry and precision medicine. Continued multidisciplinary research, together with advances in artificial intelligence, multi-omics technologies, and medicinal chemistry, is expected to accelerate the translation of ferroptosis-based discoveries into innovative diagnostic tools and targeted therapeutic strategies, ultimately improving patient outcomes and advancing personalized healthcare.

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