Ferroptosis in Endocrine-Metabolic Disorders: Molecular Mechanisms, Therapeutic Targets, and Precision Medicine Approaches

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Abstract

Ferroptosis is a tightly regulated process of iron-dependent cell death associated with excessive lipid peroxidation, glutathione depletion, mitochondrial damage, and oxidative membrane injury. Growing evidence implicates ferroptosis in the pathogenesis of endocrine-metabolic disorders including polycystic ovary syndrome (PCOS), recently redefined as Polyendocrine Metabolic Ovarian Syndrome (PMOS), autoimmune thyroid disease, obesity, insulin resistance, metabolic syndrome, and diabetes-associated disorders. Ferroptotic susceptibility of endocrine tissues is characterised by dysregulated iron homeostasis, elevated ferritin, aberrant hepcidin signalling, reduced glutathione peroxidase 4 (GPX4) activity, and chronic inflammation. Key molecular pathways include acyl-CoA synthetase long-chain family member 4 (ACSL4), system Xc-, nuclear factor erythroid 2-related factor 2 (Nrf2), ferroptosis suppressor protein 1 (FSP1), and mitochondrial reactive oxygen species. Therapeutic advances indicate potential roles for ferroptosis-targeted therapies including ferrostatin-1, liproxstatin-1, selenium compounds, iron chelators, mitochondria-targeted antioxidants, natural bioactive compounds, and glucagon-like peptide-1 receptor agonists. Medicinal chemistry approaches, computational drug discovery, biomarker profiling, and artificial intelligence-guided precision medicine strategies offer further opportunities for targeted anti-ferroptotic therapeutics.

Keywords

Ferroptosis, Endocrine-metabolic disorders, Iron metabolism, Oxidative stress, GPX4.