REVIEW ARTICLE

Targeting Ferroptosis Pathways: A Novel Strategy for Cancer Therapy

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Abstract: Ferroptosis is an iron-dependent nonapoptotic kind of regulated cell death resulting from the destruction of redox balance in the cytosol. Unlike apoptosis, ferroptosis is caused by an increase in intracellular iron and lipid peroxides that causes significant damage to the membrane lipid bilayer and mitochondria leading to cell death. Increased iron level in the cell promotes ROS production. Ferroptosis inducer molecules increase ROS production and inhibit the antioxidant defence mechanism to facilitate ferroptosis in cancer cells. Inhibition of GPX4, redox-active iron availability, and lipid peroxidation are major contributors to ferroptosis. Ferroptosis is involved in many diseases like heart disease, neurodegenerative disease, and cancer. Ferroptosis induction recently emerged as an attractive strategy for cancer therapy. In this review, we discuss the regulatory mechanism of ferroptosis, its different hallmarks, including genetic and metabolic regulators and inducers that promote ferroptosis in the cancer cells. Finally, the latest progress and development in ferroptosis research in different cancers focusing on proposing a novel strategy in cancer therapy are discussed.

Keywords: Ferroptosis, cancer, redox imbalance, regulated cell death, hallmarks, inducer.

1. INTRODUCTION

Cancer-uncontrolled proliferation of cells in specific parts of the body manifested as benign or malignant tumors-is one of the major causes of disease-related mortality worldwide. The mainstay of cancer treatment includes chemotherapy, radiotherapy, or/and surgery. Despite the major advancement in cancer treatment, resistance, recurrence and toxicity remain the prominent limitations [1]. The available treatment options target cancer cells by inducing programmed cell death, cell cycle arrest, and metastasis inhibition [2]. Under physiological conditions, the cell proliferation rate, cell cycle, and survival are intricately regulated *via* highly accurate functioning proteins. Any aberration in these functions leads to uncontrolled proliferation and apoptosis resistance.

One of the current strategies to eradicate tumors is by inducing regulated cell death (RCD) *via* highly coordinated signalling pathways and molecular mechanisms [3]. These include apoptosis, necroptosis, pyroptosis, and autophagy, with apoptosis as a well-known and primarily targeted pathway by cancer therapeutics [4]. Moreover, major chemotherapeutic agents and radiotherapy are known to induce programmed cell death in cancer. Although several FDA-approved drugs targeting apoptotic proteins, such as Bcl-2, are used in chemotherapy, these are associated with limitations such as recurrence and chemoresistance development [5].

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Ferroptosis is a newly emerged iron-dependent, a non-apoptotic form of RCD that promotes lipid peroxidation and causes significant damage to the lipid bilayer, consequently resulting in cell death [6]. It differs from other types of RCD at genetic, morphological, and biochemical levels [7]. For instance, it does not cause nuclear fragmentation, plasma membrane bubbling, chromatin condensation, and cellular size reduction as observed in apoptosis. Instead, it reduces the number of cristae and ruptures the outer membrane of mitochondria by disrupting the cytosolic redox balance in cells [8]. Thus, ferroptosis is a caspase-independent and redox-regulated form of RCD, in which lipid peroxidation causes oxidative degradation of the membrane lipid bilayer [9].

Ferroptosis is regulated by iron metabolism, antioxidant defence system, and lipid peroxidation [10]. The modulation of these pathways induces ferroptosis by upregulating ROS inducers and downregulating antioxidant defence systems [11]. In addition, ferroptosis induction has been implicated in several diseases such as brain stroke, steatohepatitis and haemorrhage, Alzheimer's disease, Parkinson's disease, leukaemia, and heart failure [7]. Thus, targeting ferroptosis can play an important role in treating cancer and various pathological conditions. Furthermore, ferroptosis is also involved in immune signalling pathways. Ferroptosis modulators interact with immune pathways that develop antitumor immunity, which can be more effective to show inhibitory effects in the metastasis stage.

Recent studies have suggested that ferroptosis targets multiple oncogenic pathways [12]. In this review, we present a comprehensive overview of hallmarks, mechanisms, and regulation of ferroptosis and its function in targeting cancer.

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