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REVIEW ARTICLE

Ferroptosis Inducers as Promising Radiosensitizer Agents in Cancer Radiotherapy

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Abstract: Radiotherapy (RT) failure has historically been mostly attributed to radioresistance. Ferroptosis is a type of controlled cell death that depends on iron and is caused by polyunsaturated fatty acid peroxidative damage. Utilizing a ferroptosis inducer may be a successful tactic for preventing tumor growth and radiotherapy-induced cell death. A regulated form of cell death known as ferroptosis is caused by the peroxidation of phospholipids containing polyunsaturated fatty acids in an iron-dependent manner (PUFA-PLs). The ferroptosis pathway has a number of important regulators. By regulating the formation of PUFA-PLs, the important lipid metabolism enzyme ACSL4 promotes ferroptosis, whereas SLC7A11 and (glutathione peroxidase 4) GPX4 prevent ferroptosis. In addition to introducing the ferroptosis inducer chemicals that have recently been demonstrated to have a radiosensitizer effect, this review highlights the function and methods by which ferroptosis contributes to RT-induced cell death and tumor suppression *in vitro* and *in vivo*.

Keywords: Ferroptosis, radiotherapy, radiosensitizer, radioresistance, cancer, cell death.

1. INTRODUCTION

One of the biggest hazards to human health remains to be cancer. According to data from the World Health Organization (WHO), cancer caused 8.8 million deaths globally in 2015. By 2030, it is predicted to surpass 13 million deaths. In order to reduce cancer-related mortality, a number of therapies have been developed recently to enhance cancer therapy, including surgery, radiation, chemotherapy, immunotherapy, targeted therapy, hormone therapy, stem cell transplants, and precision medicine. RT is a therapy method for cancer cells that uses high-energy photons [1]. RT activates death signaling in cancer cells by causing reactive oxygen species (ROS), DNA damage, and stress response in subcellular organelles, such as the endoplasmic reticulum (ER) and mitochondria. A small percentage of cancer cells, however, may be able to survive by activating compensatory survival signaling, such as the damage-repair signaling (*e.g.*, ROS scavenging), DNA repair, the unfolded protein response (UPR), and autophagy induction. Cancer cells that survive radiotherapy acquire radioresistance and can increase tumor regrowth and recurrence, which is characterized by rapid disease progression [2, 3]. Alternative ways to improve the efficiency of RT are found in innovative technologies, including image-guided radiation therapy (IGRT) and intensity-modulated radiation therapy (IMRT) [4]. Although these modern technologies vastly improve therapeutic efficacy, difficulties, such as cancer stem cells and tumor heterogeneity make it difficult to cure malignancies with radiation alone.

Radiosensitizers are compounds that, when used in combination with radiation, result in more extensive tumor inactivation than would be predicted by the additive effects of the two treatment modalities alone. Radiosensitizers that increase tumor tissue's radiosensitivity while pharmacologically lowering normal tissue toxicity are expected to be an effective way to improve RT [5-7]. Pioneer in the field of

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