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REVIEW ARTICLE

Targeting Ferroptosis as a New Approach for Radiation Protection and Mitigation

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Abstract: Radiation-induced normal cell toxicity (RINCT) is a major factor to consider while treating any ailment with radiotherapy. Clinical irradiation of tumors necessitates an understanding of the potential efficacy of radiation protective agents in reducing radiation damage to healthy tissues and their effects on tumor tissue radiosensitivity. Ferroptosis is a relatively new form of iron-dependent cell death that has been linked to a variety of disease pathologies. The key mediators of ferroptosis have been identified as lipid peroxidation and iron metabolism. Lipid peroxidation is the result of a reaction between reactive oxygen (ROS) and reactive nitrogen species (RNS) with phosphatidylethanolamine-containing polyunsaturated fatty acids (PUFAs). Ferroptosis inhibitors have been demonstrated to have anti-inflammatory effects in animal models of disease. It was recently shown that ionizing radiation (IR) generates severe ferroptosis, a critical component of RT-mediated normal cell toxicity. These findings support the use of ferroptosis inhibitor treatments for the treatment of radiation normal cell toxicity. Targeting lipid metabolic substrates and controlling ferroptosis by radiation could reduce toxicity and improve clinical outcomes. In this study, we address the relationships between radiotherapy and various types of radiation-induced cell death, and we discuss the interactions between ferroptosis and other kinds of controlled cell death generated by radiotherapy, and we investigate combination treatment options targeting ferroptosis in radiotherapy. This review will be a foundation for future research on ferroptosis in radiotherapy. Additionally, the relevant patents on ferroptosis inhibitors with various therapeutic potentials have been discussed.

Keywords: Ferroptosis, radiotherapy, radioprotector, normal cell toxicity, malignancies, ionizing radiation.

1. INTRODUCTION

Radiotherapy is one of the most commonly used remedies for treating a variety of malignancies. In more than half of cancer patients, radiotherapy is utilized for both curative and palliative objectives. Ionizing radiation is used in radiotherapy to target and kill tumor tissue, but normal tissue can be harmed as well, resulting in toxicity. Effective cancer radiotherapy relies on the promise of destroying as few normal cells as possible while killing as many tumor cells as possible [1]. Over the last few decades, the way of radiation delivery has changed dramatically. It has progressed from traditional rectangular treatment fields to increasingly conformal radiotherapy techniques such as three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) [2]. Although new treatment techniques and fractionated irradiation improved radiotherapy efficiency and reduced normal tissue problems, clinically, a continuing extension of the therapeutic window is critical. There are two possible approaches to this problem. 1) Sensitizing tumor cells to radiotherapy without sensitizing normal cells 2) Special protection of normal cells to radiotherapy. Several studies have been undertaken to date to understand better the mechanisms of the harmful effects of IR on normal tissues. Many approaches use novel cellular and molecular biology insights to prevent/decrease normal tissue harm and/or selectively increase tumor tissue's intrinsic radiosensitivity [3]. IR causes the production of highly reactive free radicals almost immediately, leading to protein changes and DNA, RNA, and cell membrane damage. Nuclear DNA damage that cannot be repaired is assumed to be the source

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