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5 - 59 Role of Ionizing Radiation in Cell Ferroptosis Induction

Zheng Xiaogang and Li Qiang

Ionizing radiation can cause ferroptosis in several ways. DNA damage induced by ionizing radiation activates ATM and inhibits SLC7A11 GSH, and GPX4 in cells[1]. DNA damage activates the cGAS-STING signaling pathway, leading to autophagy-dependent ferroptosis[2]. Ionizing radiation induces the expression of ACSL4 and promotes the formation of lipid peroxidation substrates PUFA-PLs[3]. It causes endoplasmic reticulum (ER) stress, promotes p53 expression through PERK, and transcriptionally inhibits *SLC7A11*. It also induces lipid peroxidation in adjacent cells through bystander effects by releasing RT-MPs and exosomes into the tumor microenvironment (TME). Carbon ions activate ER stress and induce ferroptosis accompanied by apoptosis through the PERK and p53-involved pathways, and mixed-RCD plays a significant role in cancer suppression.

Inactivation of SLC7A11 or GPX4 by FINs (sulfasalazine, RSL3, ML162, FIN56) enhances the radiosensitivity of cancer cells and xenograft tumors to X-rays, and usually portends a better response and prognosis after radiotherapy [3]. Erastin inhibits GPX4 expression and enhances the radiosensitivity of breast, cervical, and NSCLC to X-rays by inducing ferroptosis. In human lung adenocarcinoma and glioma patient models, FINs (IKE, RSL3, sorafenib) and radiation synergistically enhance the tumor suppression effect of ionizing radiation. Overexpression of collectrin promotes ferroptosis by down-regulating GPX4, SLC7A11 and FTH1, thereby enhancing the radiosensitivity of HCC cells to X-rays both *in vitro* and *in vivo*.

The synergistic effect of ionizing radiation and FINs in the induction of ferroptosis provides new theoretical support for the clinical radiotherapy of ferroptosis-prone tumors.

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