5 - 58 Application of Radiopharmaceuticals in Targeted Tumor Therapies*

Zhang Taotao, Zhang Hong, Li Qiang and Di Cuixia

Radiopharmaceutical therapy uses tumor-targeting carriers to deliver cytotoxic radioactivity to tumor tissues, selectively killing tumor cells, and thus producing minimal toxic and side effects on surrounding healthy tissues[1]. The use of radiopharmaceuticals to treat tumor has become one of the important ways of tumor therapy, and has made great progress in the basic research and clinical application of tumor therapy. In general, a radiopharmaceutical consists out of three components: a carrier molecule, a radionuclide for diagnostic or therapeutic applications and a linker in between. The carrier molecules can have high affinity for different type of targets, such as receptor, antigens, or misfolded proteins (Fig. 1)[2].

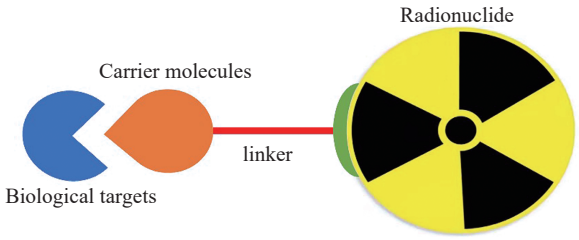

Fig. 1 (color online) General structure of radiopharmaceuticals. Radiopharmaceuticals are generally composed of carrier molecules, radionuclides and a linker between them.

Specific antibodies targeting tumor-associated antigens are used as radionuclide carriers, labeled with radionuclides, and injected into the body to specifically bind to the corresponding antigens of tumor cells for tumor therapy, which is called radioimmunotherapy[3]. Currently, radioimmunotherapy has been used to treat hematological malignancies, such as lymphoma. It is also used in the treatment of some solid tumors, such as colorectal, ovarian and prostate cancers. In particular, radioimmunotherapy targeting lymphoma have been approved by FDA for clinical application[4]. More and more radioimmunotherapy drugs are in clinical trials and have achieved good results.

Tumor cells high expression of specific receptors. Based on the principle of specific binding of receptors and ligands, the ligands or their analogues are labeled with radionuclides, and the targeting effect of the ligands is used to direct the radionuclides to the tumor tissues expressing receptors[5]. The radionuclides are concentrated in the tumor tissues to achieve the purpose of imaging or targeted therapy of tumors. The treatment for receptor dense tumors, especially for extensive and scattered metastases, is superior to other treatment methods. The corresponding ligands of tumor receptors are mostly peptides. The most widely used in clinical practice is the radionuclide labeled somatostatin analogue for the treatment of neuroendocrine tumors[6]. Meanwhile, radiopharmaceuticals targeting PSMA are developing rapidly in the clinical study of prostate cancer. Fewer studies have been reported on other tumors, and many are still in the preclinical stage.

Radiation-gene therapy, a dual anticancer strategy of radiation therapy and gene therapy through connecting radiation-inducible regulatory sequence to therapeutic gene, leading to the gene being induced to express by radiation while radiotherapy is performed and finally resulting in a double synergistic antitumor effect of radiation and gene, has become one of hotspots in the field of cancer treatment in recent years[7].

Radiopharmaceutical has been successfully applied in the clinical treatment of tumor, showing great potential in the diagnosis and treatment of tumor. However, there are still many aspects to be improved in the treatment of tumor. For example, due to the high myelotoxicity, the release of radionuclides and the catabolism of drugs in the process of delivery to target cells will cause certain damage to normal tissues, and the clinical treatment efficiency is low in solid tumors, especially in large tumors. Therefore, it is still necessary for researchers from all sides to make concerted efforts to provide more safe and effective radiopharmaceutical for clinical use, combine with other therapeutic methods for comprehensive treatment of tumor, improve therapeutic effect, promote the development of targeted radiopharmaceutical therapy, and make it better serve human health.

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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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