11 Radiotherapy and Tumor-Targeted Drug Delivery

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11.1 Introduction

Unlike heat, sonication, ultraviolet light, and photodynamic therapy (PDT), ionizing radiation has advantages that include deep tissue penetration and minimal scatter to adjacent tissues. Moreover, stereotactic radiosurgery and high dose rate brachytherapy further improve the precision of radiation dose distribution because of abrupt fall-off of dose away from tumor tissue. Ionizing radiation can therefore activate or guide drug delivery to neoplasms with greater precision compared with other forms of energy deposition into tissue.

Table 11.1 lists the mechanisms by which ionizing radiation can either guide or activate drug delivery within cancer. The first general principle is the use of monochromatic X-rays to induce auger electron emission from gold or platinum. Cisplatin (CDDP) binds to DNA and auger electrons cause DNA double strand breaks adjacent to the cisplatin conjugation to DNA (Borjesson et al. 1993; Biston et al. 2004; Hainfeld et al. 2004). The second general principle is the use of radiation to induce the expression of therapeutic genes using a radiation-inducible promoter (Weichselbaum et al. 1994; Hallahan et al. 1995). This method exploits radiation inducible promoters that cause an increased expression of the therapeutic gene within irradiated tumors. The third general principle is the use of radiation to increase proliferation of a therapeutic virus. This technique has been used to increase the efficacy of oncolytic herpes simplex virus (HSV) within irradiated neo-

Table 11.1. Radiation-directed drug delivery to tumor

Concept	Principle	Reference
Auger electron	Monochromatic X-ray activation of auger electron emission	Borjesson et al. (1993), Biston et al. (2004), Hainfeld et al. (2004)
Radiation-inducible gene therapy	Radiation-induced activation of the therapeutic gene expression	Weichselbaum et al. (1994), Hallahan et al. (1995)
Radiation regulation of viral proliferation	Radiation induced increase in proliferation of oncolytic viruses	Advani et al. (1998)
X-ray-guided drug delivery	Radiation-induced neoantigens targeted by antibodies or ligands	Hallahan et al. (2003), Geng et al. (2004)
Activation of proteolysis	Radiation activation of proteases	Demetriou et al. (2004), Winkler et al. (2004), Van Valckenborgh et al. (2005)

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plasms (Advani et al. 1998). Radiation can also be used to activate the expression of antigens within neoplasms. Although this approach can be used to increase antigen expression in cancer cells, stroma, and epithelium, the host component (blood vessels) are most attractive for both drug delivery and stability among all neoplasms. Using this approach, antibodies or ligands bind to receptors that are present only after irradiation of tumors. Proteases are activated within irradiated stroma and cancers (Demetriou et al. 2004; Winkler et al. 2004; Van Valckenborgh et al. 2005); therefore, radiation-activated proteases can cleave a therapeutic agent from a pro-drug.

This chapter focuses primarily on drug delivery targeting at radiation-induced neoantigens.

11.2 Radiation-Induced Neoantigens on Tumor Endothelium as Targets for Drug Delivery

The first concept of using radiation-induced neoantigens as targets for drug delivery was developed and proved several years ago (Hallahan et al. 2001). It was found that blood vessels express a number of cell adhesion molecules and receptors that participate in homeostasis when they are treated with ionizing radiation. Examples of radiation-induced molecules in blood vessels include intercellular adhesion molecule (ICAM)-1, E-selectin, P-selectin, and the β_3 integrin. It was also observed that the endothelium and blood components respond to oxidative stress in a similar, if not identical, manner in all tumor models. This observation suggested that targeting drug delivery to these tumor endothelium-associated, radiation-inducible neoantigens might represent a common drug delivery route for a variety of tumors. Integrin β_3-binding proteins (peptides and antibodies) conjugated to fluorochromes were located within the lumen of blood vessels immediately following irradiation as revealed by immunofluorescent and immunohistochemical staining. The peptide led conjugated radionuclides to irradiated tumors in animal models and clinical trials (Fig. 11.1).

It is well recognized that therapy of cancer is still challenging because of the nature of cancer itself. The microenvironment of solid tumor prevents the therapeutic gene product diffusion to tumor cells. Adaptive resistance arising from genomic instability in cancer is another obstacle that attenuates drug efficacy. Compared with tumor cells, the tumor-supporting tissues, such as tumor-related blood vessels, are composed of "normal" cells and would be more reluctant to be adapted with treatments. Direct contact with circulating drugs adds another benefit for tumor blood vessels as a therapeutic target. The importance of tumor-related blood vessels for tumor development, growth and metastasis has been clarified in the last few decades. Extensive research indicates that neoplasms require a functioning vascular network to provide tumor cells with oxygen and other nutrients and also to remove toxic waste products associated with cellular metabolism. For continued growth and development, tumors must generate their own networks of microvessels through the process of neovascularization (Folkman 1971). In fact, it is widely accepted that no solid tumor can grow larger than a critical size of ~1 mm^3 without developing a vascular network (Cox et al. 2004). The importance of blood vessels for tumor development, growth, and metastasis supports the concept of targeting tumor-related blood vessels for tumor control. Two related, but strategically different, approaches have been developed to test this hypothesis (Bisacchi et al. 2003; Sridhar and Shepherd 2003; Thorpe

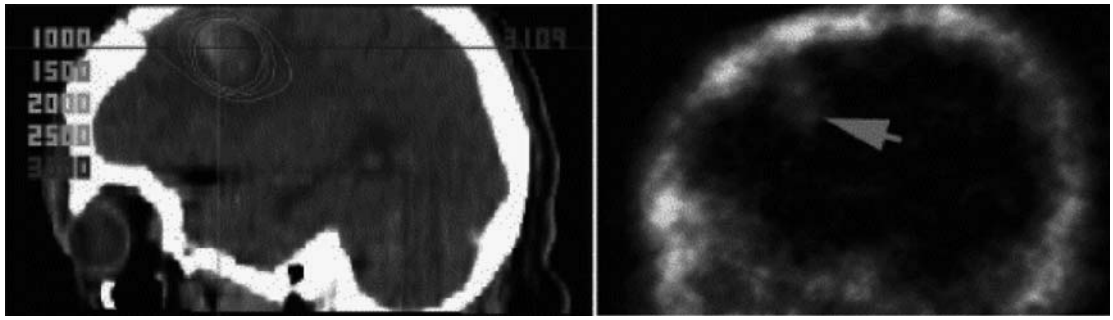

Fig. 11.1. Radiation-guided drug delivery of ^{99m}Tc-labeled biapcitide by use of an external radiation beam. The ^{99m}Tc-labeled biapcitide binding in a breast cancer brain metastasis after treatment with radiosurgery (20 Gy) is shown (*arrow*)