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Review

The role of recent nanotechnology in enhancing the efficacy of radiation therapy

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ABSTRACT

Radiation therapy is one of the most commonly used non-surgical interventions in tumor treatment and is often combined with other modalities to enhance its efficacy. Despite recent advances in radiation oncology, treatment responses, however, vary considerably between individual patients. A variety of approaches have been developed to enhance radiation response or to counteract resistance to ionizing radiation. Among them, a relatively novel class of radiation sensitizers comprises nanoparticles (NPs) which are highly efficient and selective systems in the nanometer range. NPs can either encapsulate radiation sensitizing agents, thereby protecting them from degradation, or sensitize cancer cells to ionizing radiation via their physicochemical properties, e.g. high Z number. Moreover, they can be chemically modified for active molecular targeting and the imaging of tumors. In this review we will focus on recent developments in nanotechnology, different classes and modifications of NPs and their radiation sensitizing properties.

Contents

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1. Introduction

Radiation therapy has been used in cancer therapy for more than a century and is one of the most commonly used non-surgical interventions in tumor treatment. The initial efforts to apply external radiation therapy in patients have undergone radical improvements in the last decades, resulting in combined modality approaches, including radiochemotherapy (RCT) [1]. Despite recent advances in radiation oncology, however, treatment response and survival vary considerably between individual patients. These differences are most probably caused by a variation in intrinsic tumor cell resistance to radiation and/or chemotherapy that may originate from a different genetic background or protein expression, either already existent in the patient genome (in the form of polymorphisms) and/or newly acquired in malignant cells during carcinogenesis [2]. Further improvement of radiation therapy effectiveness can be accomplished by radiation sensitizers. Radiation sensitizers (or radiosensitizers) are usually chemical or pharmacologic agents that increase the lethal effects of radiation if administered in conjunction with it [3]. An important prerequisite for a radiation sensitizer is that it exerts a differential effect between normal tissues and tumors, i.e. it should increase the sensitivity of tumors more than that of healthy tissue [3]. For this purpose, a variety of approaches including recent molecular targeted therapies have been developed [4]. These can either enhance radiation response or counteract tumor cell radiation therapy resistance. Some targeted therapies have already made their way into the clinic but more refinements should be made, for example by improving their stability and tumor cell specificity. One way of improving tumor targeting is by applying highly selective drug delivery systems, such as nanocarriers (NCs), nanoparticles (NPs) or liposomes [5]. These NCs or NPs are ranging in size between 1 and 1000 nm and vary in their mechanical and/or physicochemical characteristics. Some of them can overcome physiological barriers such as endothelial cell layers and the blood brain barrier (BBB) [6]. In addition to those that serve for delivery of therapeutic agents, NPs exist that can directly interact with ionizing radiation (graphically summarized in Fig. 1) and thereby increase cellular radiation sensitivity. Such NPs are usually made of elements with a high atomic number (high-Z NPs) and have high potential for clinical use in line with their suitability as drug delivery systems and imaging enhancers.

A number of NCs for anti-cancer therapy entered the market between 1990 and the early years of the 21st century [5]. For cytostatic agents, nanotechnology has primarily been used to improve the toxicity profile and to overcome poor aqueous drug solubility and chemical stability issue thus improving pharmacokinetic and pharmacodynamic drug profiles and enhancing the therapeutic index [7]. In 2005 for example, Abraxane®, the first generation nanoparticle formulation of the chemotherapeutic drug paclitaxel has been approved for breast cancer treatment by the Food and Drug Administration of the United States of America (US-FDA) [5].

For other sensitive compounds such as nucleic acids, proteins or peptides the protection of the active pharmaceutical ingredient (API) had major impact on therapeutic efficacy as these molecules undergo rapid enzymatic degradation in human blood [8]. The half-lives of these substances could be increased significantly by nanoencapsulation into a protective shell.

By taking advantage of the enhanced permeability and retention (EPR) effect [9,10], NCs can accumulate preferentially in tumor tissues. This passive extravasation of macromolecules into the tumor interstitial fluid (TIF) is the result of vascular endothelium lesions in solid tumors and the absence of lymphatic drainage assuring clearance of colloids from the intersitium [11]. In recent years, the existence and the effectiveness of EPR effect for tumor targeting have been subject of a controversial discussion. The rising TIF pressure and diversity of cancer diseases are major obstacles to this mechanism. Besides these aspects, biodistribution into other tissues is limiting the availability of nanoparticulate drug delivery systems in the tumor. After intravenous administration of the carrier, a number of accumulation mechanisms occur. NPs smaller than 25 nm effectively penetrate non-fenestrated endothelium while larger particles rapidly accumulate in the liver due to the fenestration of blood vessels with a pore size between 100 and 175 nm [12]. Prolonged circulation time has been reported for particles of a size between 150 and 300 nm [13]. Extravasation due to the EPR effect takes place more effectively at prolonged circulation times [10]. For NPs between 50 nm and the micrometer range, however, the greatest fraction accumulates in

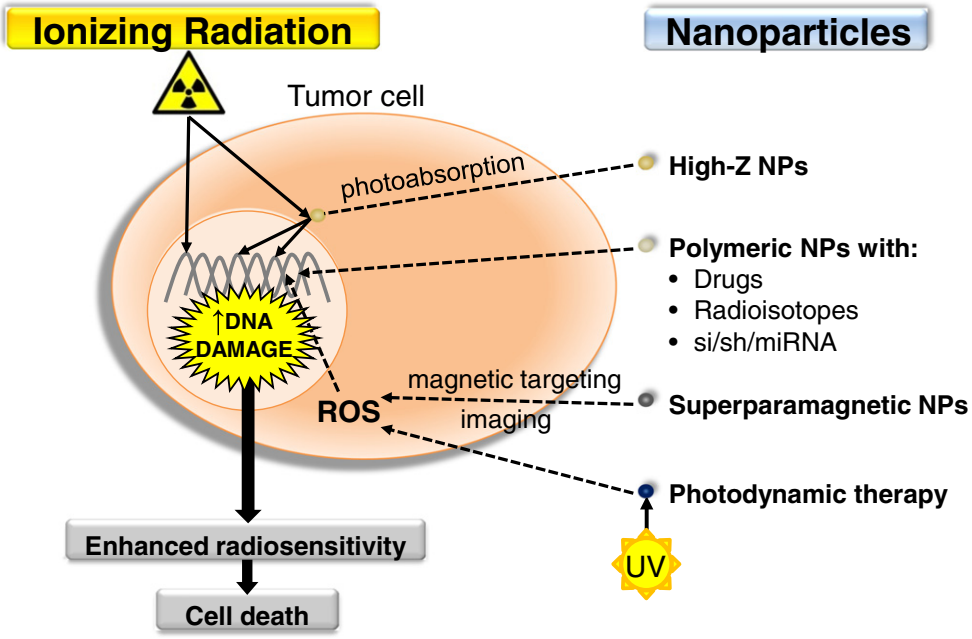

Fig. 1. Schematic representation of different types of nanoparticles (NPs) and their effects in an irradiated tumor cell. The NPs increase the amount of radiation-induced DNA damage in the cell which results in enhanced cell death. ROS: reactive oxygen species.