CLINICALLY RELEVANT

Nanomedicine: Nanotechnology, Biology, and Medicine
10 (2014) 19–34

Review

nanomedjournal.com

Nanomaterials in combating cancer: Therapeutic applications and developments

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Received 3 April 2013; accepted 4 July 2013

Abstract

The development of novel nanomaterials and their use in biomedicine has received much attention in recent years. Significant advances have been made in the synthesis of nanomaterials with controlled geometry, physicochemical properties, surface charge, and surface tailoring with bioactive polymers. These successful efforts have resulted in improved biocompatibility and active targeting of tumour tissues, leading to the development of a diverse range of nanomaterials that can recognize cancers, deliver anticancer drugs and destroy tumours by a variety of therapeutic techniques. The focus of this review is to provide an overview of the nanomaterials that have been devised for the detection and treatment of various types of cancer, as well as to underline the emerging possibilities of nanomaterials for applications in anticancer therapy.

From the Clinical Editor: In this comprehensive review, the current state-of-the art of nanomaterials for cancer diagnosis and treatment is presented. Emerging possibilities and future concepts are discussed as well.

Key words: Nanoparticles; Cancer; Polymeric nanoparticles; Qdots; AuNPs

Cancer is the uncontrolled growth of tissues and their rapid invasion without proper development and differentiation. Six biological aptitudes are considered to be 'hallmarks of cancer': proliferative signalling, evasion of growth suppressors, resistance to cell death, replicative immortality, angiogenesis, invasion and metastasis.[1] Cancer is a major cause of devastating health outcomes and economic constraints in human life. Globally, cancer rates are increasing at a distressing rate. As indicated in the Cancer Facts and Figures 2013, it is estimated that 1,660,290 new cancer cases whereas 580,350 cancer deaths are expected in the United States only.[2]

A huge amount of research has already been carried out in the field of cancer, resulting in a number of available diagnostic and treatment options, including magnetic resonance imaging (MRI), computed tomography (CT), biosensing, radiotherapy, chemotherapy, gene therapy, and immunotherapy. Radiotherapy, or radiation therapy, involves the treatment of cancer with ionizing radiation such as high-energy X-rays, gamma rays, or particle beam radiations that destroy the target tissue by damaging its DNA. Hyperthermia, the use of heat, is also being studied for its effectiveness in sensitizing tissue to radiation. Other recent research has focused on the use of radiolabeled antibodies to deliver doses of radiation directly to the cancer site (radioimmunotherapy). Radiotherapy may be used alone or in combination with chemotherapy or surgery. Although painless, it has some severe side effects such as permanent hair loss, fetal damage, skin problems, and secondary malignancies – the radiation itself is the source of mutations in healthy genes and can cause cancer. Chemotherapy, by contrast, involves a range of cytotoxic drugs such as vinblastine, doxorubicin, and taxol. The challenges here are biodistribution (non-tumour selectivity), hypersensitivity, and acquisition of multidrug resistance (MDR). Furthermore, these drugs degrade to toxic moieties, resulting in nephrotoxicity and cardiotoxicity. To devise a successful treatment regime, it is important to consider the major limitations of several therapeutic agents such as poor solubility, rapid deactivation, unfavourable pharmacokinetics, and limited biodistribution. A wide range of nanomaterials has been introduced in an effort to devise more comprehensive and versatile diagnostic and treatment solutions for malignancies.

Declaration of Interests: Authors declare no conflict of interest.

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1549-9634/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.nano.2013.07.001

The range of diagnostic/therapeutic nanomaterial tools is extensive. Drug delivery and imaging with nanomaterials benefits from the anatomical changes coupled with the pathophysiological conditions at the diseased site.[3] Nanomaterials are usually accumulated at a higher concentration at the diseased site than conventional drugs.[3] This enhanced drug targeting leads to decreased systemic toxicity and successful delivery, even to hard-to-target disease sites such as brain.[4]

Inorganic nanomaterials include quantum dots (QDs), metallic nanostructures, metal oxides, superparamagnetic iron oxides (SPIONs), gold nanoparticles (AuNPs), and carbon nanotubes (CNTs); organic nanomaterials include liposomes, natural and synthetic polymers forming nanocapsules and dendrimers.[5] Several of these are sufficiently small in size (10–100 nm) to penetrate the capillaries and be taken up by the tissues; others that are larger in size passively target and deliver at disease-specific anatomic sites.[6] Many nanomaterials are biocompatible, meaning that they do not alert the immune system, and biodegradable, breaking down to form harmless metabolic products. Moreover, a variety of materials such as QDs, AuNPs, and SPIONs exhibit unique optical, electrical, and magnetic properties,[7] which are helpful in imaging the intracellular localization and trafficking of these devices. Drugs can also be delivered at a specific site after being attached, encapsulated, absorbed, entrapped, or dissolved in the nanomaterial matrix. An emerging methodology is the use of multifunctional nanodevices, such as polymeric micelles or dendrimers, to target cancers[8] These devices contain not only the drug payload but also targeting agents such as antibodies or ligands to target specific receptors, as well as MRI contrast agents.[3,8] Recent advances in the biomedical use of nanomaterials also include gene delivery (gene therapy), delivery of antigens (vaccination), and other therapeutic applications in cardiac diseases, dental repair, and orthopaedics.[3]

This review describes a comprehensive overview of the diverse range of nanomaterials emerged for the detection and treatment of cancers as well a brief picture of some diagnostic and treatment strategies using these materials. The first section focuses on tumours as a drug delivery target. The pathology of cancer is briefly described, followed by an overview of the unique properties of nanomaterials that make them promising for tumour-targeted diagnosis and therapy. The various nanomaterials explored to date will be briefly described, including the synthetic aspects and approaches used for their application in unimodal and multimodal diagnostic imaging and therapy. A diverse range of emerging possibilities of nanomaterials in cancer therapy will be described including those which are commercialized.

How cancer differs from normal tissue

Cancer is an extensive group of diseases affecting different parts of the body. It arises from the accumulation of genetic mutations that control cell cycles. The unlimited and self-sufficient growth of cells is responsible for the major characteristics of cancers, including uncontrolled growth, invasion of adjacent tissue, metastasis, and cell immortality.[1]

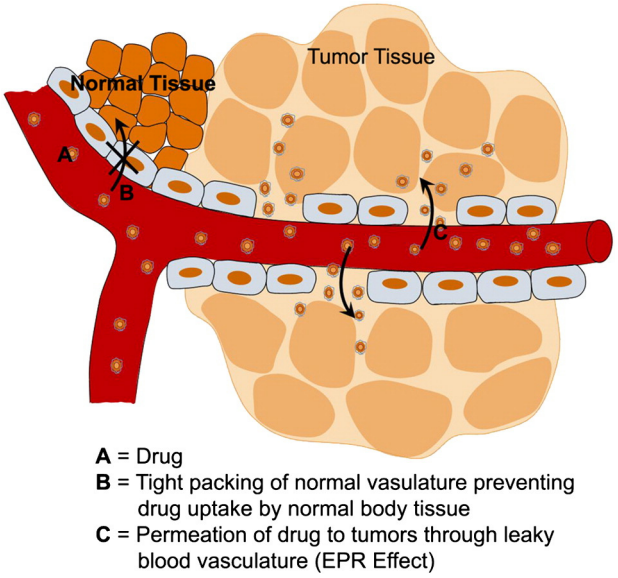

Figure 1. Nanodrug carriers are designed to stay longer in the blood and accumulate at tumour sites due to the enhanced permeability and retention (EPR) effect. The EPR effect in solid tumours is related to the anatomic and pathophysiological differences between tumour and normal tissues. For example, angiogenesis leads to high vascular density in tumours, large gaps exist between the endothelial cells in tumour blood vessels, and tumour tissues show selective extravasations and retention of macromolecular drugs. Developed nanodrugs deliver payloads based on various factors such as the increased temperature and lower pH at the site of growing tumours.

Because of their particular anatomy and physiology, it is feasible to target tumours with various nanoprobes, for diagnosis and treatment. This possibility is due to the *enhanced permeability and retention (EPR) effect,*[9] a characteristic pathological feature of tumour tissue in conjunction with low extracellular pH, hypoxia, angiogenesis, and abnormal lymphatics.

Cancers demonstrate irregular cell growth, aided by the development of a network of new blood vessels (angiogenesis), and prompted by various signals from cancerous tissues including hypoxia, low pH, hypoglycaemia, mechanical stress, immune or inflammatory responses, and genetic mutations.[10] These blood vessels are highly porous, with large spaces between the endothelial cells.[9] They are convoluted, dilated, and irregular in diameter, possess a chaotic architecture, and present a disorganized vasculature including large openings, excessive branching, fenestration.[11] With extensive leakage of blood plasma components into the tumour microenvironment, the macromolecules are not rapidly cleared from the interstitial space of the tumour, causing the EPR effect.[9] As a consequence, the passive transport of macromolecules leads to their accumulation in tumours at considerably higher concentrations than in normal tissues, mostly 10–100 times higher within 1–2 days (Figure 1).[12]

Another important property of growing tumours is their pH. Tumour tissues, with their rapid cell division, require high metabolic rates to meet their energy demands. Aerobic and anaerobic respiration inside the tumour leads to respiratory by-products, such as lactic acid and carbonic acid, being released