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Tumor Targeting Strategies

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Abstract

Nanoparticle-based drug delivery systems allow improved solubility, enhanced stability in circulation and multi-functionality. These properties and functions open many doors and create new biomedical applications for targeting drugs or imaging agents directly to the disease site. Due to the high incidence and mortality of cancer, studies are concentrating on targeted drug delivery to the tumor. This mini review presents an overview of tumor targeted drug delivery strategies under passive and active targeting sub-classes.

Keywords: Cancer; Nanotechnology; Drug targeting; Active targeting; Passive targeting

Introduction

Cancer is one of the major malignant diseases in the world. Among common cancer treatments, chemotherapy, radiotherapy, and surgery with chemotherapy have been the major treatment modalities. However, current chemotherapeutic agents are often limited by their undesirable properties, such as poor solubility, nonselective distribution and severe side effects after oral/intravenous administration, which may lead to cancer treatment failure or intolerability.

Tumor targeting strategies are classified in different ways by the pioneers of the area. It is classified as passive and active targeting by Bertrand et al. [1]; passive targeting, active targeting, physical and chemical targeting by Zhang et al.[2]; systemic targeting based on blood circulation and extravasation, and intracellular targeting by Bae et al.[3] or targeted delivery systems and stimuli responsive nanoparticles by Anselmo et al.[4].

Drug targeting can be a preferred solution for certain problems like poor drug stability, low absorption, short half-life, large distribution volume, lack of specificity and low therapeutic index.

Various nanosystems including nanoparticles, nanosponges, liposomes, dendrimers, micelles, cyclodextrins are generally used to deliver the cargo to the intended site of the body. Nanocarriers offer many advantages such as small particle size, increased drug efficacy, lowered toxicity, enhanced drug solubility, improved stability and bioavailability [2]. Drugs, genes or imaging agents can be encapsulated in a vesicle, entrapped in a matrix, or solubilized within a hydrophilic or a hydrophobic component [5].

In this mini review, targeting strategies under passive and active targeting are discussed and up to date examples are given.

Passive Targeting

Enhanced permeability and retention (EPR) effect provides accumulation of nanoparticles at the tumor site at high concentrations due to the pathophysiological differences between normal tissues and tumor tissues; this phenomenon is known as passive targeting. Although passive targeting strategy is given as a different way of targeting, indeed its accumulation effect is facilitated in receptor interaction mediated targeting.

The pathophysiological environment of tumor tissues differ from that of normal tissues, leading to the EPR effect, which is utilized for the targeted delivery of many drug delivery systems. Irregular tumor vasculature structure and lack of a lymphatic recovery system in the solid tumor provide high drug concentrations at the tumor site.

In the literature [2], optimum nanoparticle size for penetration into the fenestrated blood vessels around the tumor and for residence in the tumor region is given as in the range of 10 to 200 nm. Nanoparticles less than 200 nm size have significantly longer circulation time in blood stream due to low uptake by the reticuloendothelial system (RES) [6,7]. Therefore, it can be stated that passive targeting could be achieved with nanoparticles having prolonged blood residence time. It is important to note that, hydrophobic particles, following intravenous administration, will be coated by blood components (opsonins), which will then rapidly be taken up by RES [6]. Recognition of particles by RES, causes clearance of nanoparticles from the blood stream. In this case, using polyethylene glycol (PEG), also known as PEGylation, might be a solution, which increases the physical stability and hydrophilicity of nanoparticles and prolongs their circulation time in the blood stream by reducing their removal by the RES [8]. As it is well known, the size of porous blood vessels in majority of tumors is between 380 and 780 nm [9,10] and the maximum size of nanoparticles allowing penetration through cell membranes is approximately 500 nm [3]. Thus, optimum EPR efficiency could be obtained with nanoparticles with sizes around 400 nm [3]. Many researchers have taken advantage of this fact and thus utilized passive targeting to tumors.

Active Targeting

Active targeting is another important option for targeting of drugs, mainly for cancer treatment. Cancer progression is a dynamic process characterized by a vast array of alterations at the cellular and tissue level, which includes abnormal growth and changes in the cells, extracellular matrix, and blood vessels. These alterations are all highly inter-related [11]. Conditions like over expression of receptors at tumor cells, tumor acidity, hypoxic tumor environment are utilized to target chemotherapeutic agents to the tumor cells. The main mechanism behind active targeting is

the recognition of the ligand by its target substrate. Representative ligands include antibodies (Abs), proteins, peptides, nucleic acids, sugars, and small molecules such as vitamins. Target molecules can be proteins, sugars or lipids present in diseased organs or on the surface of cells [1].

Active targeting, also called as receptor-mediated targeting, can be classified as antibody-based, peptide-based, small molecule-based and nucleic acid aptamer-based targeting. In antibody-based targeting, full antibody or antibody fragments like $F(ab')_2$ and F(ab') can be used. Receptors including epidermal growth factor, vascular endothelial growth factor and transferrin are often used in targeted drug delivery studies due to their over expression in cancerous cells [5]. Antibody conjugated systems, which are specific to their receptors can be internalized via clathrin-mediated endocytosis. Clathrin-mediated endocytosis, historically referred to as "receptor mediated endocytosis" is the best characterized endocytotic pathway: it involves the assembly of clathrin and adaptor proteins on a region of the plasma membrane in which particular receptors are clustered to form a nascent vesicle destined for internalization [12]. Most common antibodies are CD19, rituximab (CD 20), monoclonal antibody A7, transferrin antibody, anti-human epidermal growth factor receptor-2 (HER2) scFv, anti-vascular cell adhesion molecule-1(VCAM-1), 5D4, 2C5, and DI17E6. Most recently, HER2-targeted PEGylated liposomal doxorubicin formulation has been in phase II clinical trial [4]. Fibronectin-targeted delivery [13], cancer stem cell targeting [14], epidermal growth factor receptor, G-protein coupled receptor (GPCR), folate receptor, integrin, transferrin receptor targeting [12], myeloid cell targeting [15] are strategies, which are currently investigated by researchers due to over expression of these receptors and proteins in the tumor tissue. Among these approaches, myeloid cell targeting, which is an immunotherapy-based paradigm, differs from other approaches. Immunotherapy enables the immune system to recognize and target only cancer cells, and it provides a capacity for memory, leading to extended protection.

In the literature there are several means to target cancer specifically, which lead to either self-triggered or externally activated release of the drug at target cells. Some changes in tumor microenvironment such as, pH, enzymes and hypoxia trigger drug release at the tumor site. For example, conversion of glucose to lactic acid in the tumor tissue is faster than normal tissue, which gives an opportunity to formulate pH-sensitive drug delivery systems that are capable of releasing the drug in this acidic microenvironment. Light, temperature, magnetic and acoustic changes, which are applied externally, can also activate drug release for localized tumor treatment. Thermosensitive liposomal doxorubicin, which is under phase III clinical trial is an example for temperature triggered drug release [4].

Leaky vasculature of tumors, over expression of receptors at the tumor cell surface, changes in tumor microenvironment such as pH, redox, glucose and enzymes are the conditions to be used to reach high drug concentrations at the tumor site with low side effects and maximum therapeutic effects. On the other hand, external stimuli like magnetism, temperature, acoustic, and light are the options to target the tumor alone or in combination with novel drug delivery systems. Drug delivery systems, which have already been introduced in the clinic, are promising for targeted drug delivery strategies to treat and cure not only cancer, but a large number of other diseases.

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