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The development of site-specific drug delivery nanocarriers based on receptor mediation

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ABSTRACT

Since they were first reported in 1980, site-specific drug delivery nanocarriers have progressed greatly with the development of nanotechnology and biotechnology, especially in the anti-tumor field. Currently, some of the ligand peptides like RGD have become hot targeting molecules with extensive academic studies and some receptor-medicated nanocarriers are now in clinical trials. Homing peptides have been the preferred ligands thus far due to their low molecular weight, low antigenicity, high modification ratios and low interference in vivo. The major benefit of receptor-mediated nanocarriers over passive ones may be their accumulation within tumors for longer period of time due to their binding to and/or their uptake by cancer cells, preventing them from fast redistribution into systemic circulation. The studies on receptor-mediated nanocarriers are very dynamic currently, advancing gradually from these against non-therapeutic targets to these against therapeutic targets. And recently, more studies were focused on these systems against multiple receptors and the combination therapies with receptor-mediated nanocarriers. However, we still face great challenges, especially in the understanding of receptors, the key issue for receptor-mediated delivery. This review presents the past and ongoing studies on various types of drug delivery systems based on receptor mediation, discusses the prospective and challenges, and introduces the possible trend of study in the future.

1. Introduction

Over the past 20 years, the application of nanotechnology for drug delivery has become of great interest in the pharmaceutical and biotechnology fields. The first nanotechnology-based drug delivery system, liposomes, was introduced in the 1960s. Later on, other types of nanocarriers such as nanoparticles (NPs) and polymer micelles were also reported [1]. Site-specific drug delivery (or targeted drug delivery) usually refers to a category of therapeutic systems that are able to accumulate only at diseased sites; such a delivery system was proposed a century ago by Paul Ehrlich as a 'magic bullet' [2]. Historically, site-specific drug delivery can be divided into two types: 'passive' targeting systems and 'active' targeting systems. The former is primarily due to the enhanced permeability and retention (EPR) effect. Tumors usually grow quickly, leading to highly heterogeneous and aberrant, with obviously leaky microvasculatures. As a result, particles in suitable sizes tend to readily extravasate from surrounding vessels into tumor. Up to now, based on the EPR effect, passive targeting systems have been fairly successful. A dozen of such systems, mostly based on nanocarriers, are already available on the market; these include liposomes, polymeric micelles and NPs [3]. Active targeting systems may further transport to the disease site via an interaction between the conjugated ligand and the receptors over-expressed on the target cells [4]. Active targeting systems can be based on both nanocarriers and conjugates, and the latter means the conjugation of a ligand and a drug molecule with or without a linker, which was well reviewed in the literature [5].

'Receptor' here refers to a generalized term that includes all membrane protein domains that can bind with various types of ligands, including mAbs and their fragments, proteins or protein-like molecules, homing peptides, ion channels, nucleic acid ligands (such as Aptamers), small molecules and sugars [1]. Therefore, the site-specific drug delivery nanocarriers described here can also be named as receptor-mediated nanocarriers. By conjugating targeting ligands to nanocarriers, therapeutic drug as the cargo of nanocarrier could be selectively delivered

Abbreviations: DTX, docetaxel; DOX, doxorubicin; PTX, paclitaxel; CA-4, combretastatin; PEG, polyethylene glycol; PLA, polylactic acid; DOPC, 1,2-dioleoyl-sn-glycero-3-phosphocholine; DPPC, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine; FA, folic acid; FR, folate receptor; Tf, transferrin; TfR, transferrin receptor; HP, hematoporphyrin; LDL, low density lipoprotein; LDLR, low density lipoprotein receptor; HA, hyaluronic acid; CD44, cluster of differentiation 44; ASGPR, asialoglycoprotein receptor; TL, tomato lectin; WGA, wheat germ agglutinin; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; APN, aminopeptidase N; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; Oct, octreotide; SSTR, somatostatin receptors; ClTx, chlorotoxin; VCAM, vascular cell adhesion molecule; ICAM, intercellular cell adhesion molecule; ELAM, endothelial-leukocyte adhesion molecule; TAM, Tamoxifen; HtBvLs, heterobivalent ligands; PSMA, prostate-specific membrane antigen; NP, nanoparticles; EPR, enhanced permeability and retention.

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to target cells or vasculature [6]. Receptor-mediated nanocarriers can be classified according to the affinity ligands on the nanocarrier surface or the character of the target receptors.

Receptor-mediated nanocarriers have progressed greatly with the development of nanotechnology and biotechnology, not only in the anti-tumor field but also for diseases such as arthritis, infection and advanced atherosclerotic plaques. The first study using site-specific drug delivery nanocarriers was reported in 1980, in which antibody-modified liposomes were used [1]. Since then, a great number of studies have focused on receptor-mediated nanocarriers. Homing peptide modified systems have been extensively studied due to their advantages, such as the low molecular weight, low antigenicity, high modification ratios and low interference in vivo [7]. Homing peptides such as RGD have become popular targeting molecules and are extensively researched in academia. For example, searching for 'RGD modified delivery' in Google yields more than 397,000 results. In fact, there are three types of RGD-conjugated diagnostic agents moving into clinical trials, and an octreotide-conjugated isotope (OctreoScan, Pentetreotide) was approved by the FDA in 1994 [8]. At least four receptor-mediated nanocarriers are now in clinical trials, including transferrin-conjugated NPs loaded with oxaliplatin, transferrin-modified liposomes with a wild-type p53 gene, transferrin-cyclodextrin polymer NPs complexed with siRNA, and a prostate-specific membrane antigen (PSMA)-targeted PEG-PLA NPs loaded with docetaxel (DTX) [3]. In general, receptor-mediated targeted drug delivery systems may emerge as an alternative therapy for the treatment of many diseases, especially cancers.

Current investigations on receptor-mediated delivery systems are very dynamic with the advance of life sciences, especially these on tumor biomarkers after the year 2000. These studies include delivery systems against non-therapeutic targets, such as folic acid receptors and transferrin receptors, as well as nanocarrier systems against therapeutic targets, such as vascular endothelial growth factor receptors and integrins. Recently, receptor-mediated delivery systems against multiple receptors and combination therapies based on receptor-mediated nanocarriers have attracted much attention. Here we review past and ongoing studies on various types of site-specific drug delivery systems based on receptor mediation, introduce different strategies in the development of these nanocarriers and possible future trends, and discuss prospective achievements and challenges, with an emphasis on our contributions to this field.

2. Receptor-mediated delivery systems targeting a single receptor

At the beginning, receptor-mediated delivery systems were generally designed to target a single receptor type that was over-expressed on cells (Fig. 1A(a)). With the further understanding on receptor function mechanisms, especially clustering phenomenon during some receptor–ligand interaction process, a homomultivalent drug delivery system was designed by connecting multiple copies of a ligand via a backbone linker to an appropriate nanocarrier [9,10] (Fig. 1A(b)). Such homomultivalent systems improved binding affinity towards a target compared with the corresponding monovalent ligand [10].

2.1. Receptor-mediated delivery systems against non-therapeutic targets

The first generation of receptors used to mediate drug delivery were receptors related to nutrition transport or adhesion. These included folate receptors, transferrin receptors, and asialoglycoprotein receptors. Such receptors are generally expressed on normal cells. When some diseases develop, the expression of these receptors increases significantly. The interactions of these receptors with their ligands mainly increase the selectivity and affinity between nanocarriers and cells and as a result, increase the uptake of nanocarriers by the cells. In this section, these non-therapeutic targets and recent achievements in their use in drug delivery will be discussed. Typical examples of receptor-mediated site-specific delivery systems against non-therapeutic targets are listed in Table 1.

2.1.1. Folate receptors

Folate receptors (FRs) are useful targets for tumor-specific drug delivery primarily for the following reasons: (1) they are highly up-regulated in many human cancers, and (2) as the stage/grade of the cancer worsens, the density of FR appears to increase [11]. Folic acid (FA) is a natural ligand for FR with a high affinity (Kd = ~10^{-10} mol/L). It is widely used in FR-mediated drug delivery due to its nontoxic, nonimmunogenic nature as well as its small size, low cost and easy conjugation to nanocarriers [6].

The initial FR-mediated drug tested in humans was ^{111}In-DTPA-folate, a FA-conjugated chelator that bound to FR with ~1 nM affinity [12]. Lee and Low first reported the synthesis of FA-conjugated liposomes and showed that polyethylene glycol (PEG)-based spacers were required to bridge the folate and the lipid anchor in order to allow for FR-mediated tumor cell targeting [13]. Many FR-mediated drug delivery systems (DDSs), such as liposomes, micelles and NPs, have been reported recently [14-20,24] (Table 1). These systems have significantly improved cytotoxicity and reduced the side-effects associated with the loaded therapeutics. This is because the modification of nanocarriers by FA can significantly improve the cellular uptake of nanocarriers through FR-mediated endocytosis [18]. Besides FA, FA-glutathione, with higher hydrophilicity, was also reported, and FA-glutathione modified liposomes showed better targeting efficiency than FA modified ones [20].

The same principle used in FR-mediated drug delivery can also be applied in the treatment of other diseases, such as atherosclerosis [21], systemic lupus erythematosus [22] and psoriasis [23]. For example, Thomas et al. [24] designed a FA- and methotrexate-conjugated dendrimer as a therapeutic agent for arthritis, an inflammatory disease. The conjugated dendrimer is bound and internalized into both FR-β-expressing macrophage cell lines and primary mouse macrophages in a receptor-specific manner, acting as a potent anti-inflammatory agent and reducing arthritis-induced inflammatory parameters.

However, there are also some disadvantages of the ligands folate: for example, folate is a low water solubility targeting ligand, the percentage of folate presents on the NP surface differently according to the density of folate. In a study on the "Effects of ligands with different water solubilities on self-assembly and properties of targeted nanoparticles", only 20% of the folate from PLGA–PEG–Folate was present on the NP surface while the rest remained presumably buried in the PLGA NP core due to hydrophobic interactions of PLGA and folate [25]; Furthermore, the attached therapeutic cargo must be membrane permeable, since FR+ endosomes contain no pores or channels through which hydrophilic or polymeric drugs can diffuse [12]. Nevertheless, because these limitations are easily surmountable for many cancers and their preferred therapeutic agents, the prospects for clinical success of a folate-targeted DDS seem promising [12].

2.1.2. Transferrin receptors

Transferrin receptors (TfRs) are the major route of cellular iron uptake [26]. They are over-expressed on rapidly growing and quickly multiplying cells due to their increased iron requirement [6]. Cancer cells require iron uptake via transferrin-mediated mechanism to maintain their uncontrolled growth. TfRs are therefore highly expressed on cancer cell surface [27], and their expression may be up to 100-fold greater than the average expression in normal cells [28].

TfR-mediated DDS can be prepared via the modification of nanocarriers with Transferrin (Tf), anti-TfR antibodies [28] or TfR-binding peptides (such as 7pep, HAIYPRH) [28]. Tf is a natural ligand of TfR that has a high affinity for TfR. Many nanocarriers modified with Tf have been developed to date, especially for cancer treatment [30–34] (Table 1). These nanocarriers can significantly improve the uptake of NPs by cells due to receptor-mediated clathrin-dependent endocytosis. 7pep,