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Prodrugs for improving tumor targetability and efficiency ☆

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ABSTRACT

As the mainstay in the treatment of various cancers for several decades, chemotherapy is successful but still faces challenges including non-selectivity and high toxicity. Improving the selectivity is therefore a critical step to improve the therapeutic efficacy of chemotherapy. Prodrug is one of the most promising approaches to increase the selectivity and efficacy of a chemotherapy drug. The classical prodrug approach is to improve the pharmaceutical properties (solubility, stability, permeability, irritation, distribution, etc.) via a simple chemical modification. This review will focus on various targeted prodrug designs that have been developed to increase the selectivity of chemotherapy drugs. Various tumor-targeting ligands, transporter-associated ligands, and polymers can be incorporated in a prodrug to enhance the tumor uptake. Prodrugs can also be activated by enzymes that are specifically expressed at a higher level in tumors, leading to a selective anti-tumor effect. This can be achieved by conjugating the enzyme to a tumor-specific antibody, or delivering a vector expressing the enzyme into tumor cells.

Contents

1. Introduction

Chemotherapy is successful but still faces a variety of challenges due to lack of selectivity and associated toxicity. Chemotherapy drugs act through anti-proliferative mechanism, or by arresting cell cycle at a specific phase rather than producing a toxic effect to particular types of cancer cells [1]. Therefore, these drugs, due to the poor selectivity,

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affect all rapidly proliferating and dividing cells such as red blood cells, hair follicles, gut epithelia, bone marrow, and lymphatic cells, making chemotherapy drugs unsuitable for a long-term treatment. Furthermore, chemotherapy drugs are not efficient in treating slowly growing solid tumors, whereas most human solid tumor cells do not proliferate rapidly [2]. As a result, high-dose chemotherapy is generally required to effectively inhibit the tumor proliferation, especially the resistant solid tumors. However, non-selectivity of chemotherapy drugs could result in lethal damages to the adjacent normal proliferating cells, leading to discontinuation of the therapy before all malignant cells are killed. Hence, improving the selectivity is the critical step to improve the therapeutic efficacy of a chemotherapy drug.

Among different strategies to improve the selectivity of chemotherapy drugs, targeted prodrug represents a promising approach for highly selective chemotherapy. Prodrugs are defined as chemically modified, biologically inert, small molecule drugs that are transformed *in vivo* to release the pharmacologically active drug [3]. Prodrug approach provides a remarkable tool to improve the pharmaceutical properties of the active pharmacologic agents via a simple chemical modification. Traditional prodrug design aims to: i) improve solubility in water or lipid membrane, chemical stability, oral or local absorption, and brain permeability; ii) reduce unacceptable taste, irritation or pain, pre-systemic metabolism, and toxicity [4,5]. Current review will focus on unmet needs of traditional prodrug design to improve the selectivity and targeting features.

Prodrugs can be designed to target specific antigens, peptide transporters, or enzymes that are over-expressed on tumor cells in comparison to other normal cells. This can be achieved by conjugating a tumor-specific ligand or a polymer to the chemotherapy drug via a cleavable linker [6]. The general design of a prodrug is depicted in Fig. 1. A chemotherapy prodrug may contain as many as four components: i) the parent drug or its derivative that exhibits the pharmacologic effect; ii) a metabolically labile chemical linker which links the functional group (hydroxyl, carboxylic, amine, carbonyl, and phosphate groups, etc.) of the parent drug to the rest part of the prodrug designated as the "promoiety"; iii) a polymer spacer, or an enzymatically cleavable spacer that can release the parent drug in the presence of a tumor-specific enzyme; iv) a targeting moiety for specific delivery to tumor cells.

2. Chemical linker in prodrug

To construct a prodrug, there must be a functional group on the parent drug that can be used to form a chemical bond with the promoiety. Generally, the linker should be self-immolatable or cleavable so that the parent drug can be released spontaneously or under a certain triggerable condition such as the presence of an enzyme or a change in pH. The promoiety affiliated to the parent drug provides the ability to improve the drug-like properties or overcome

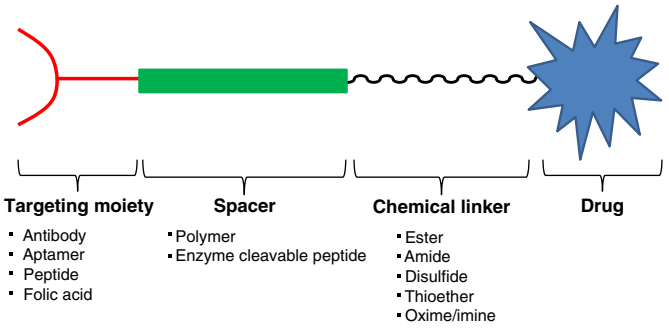
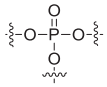
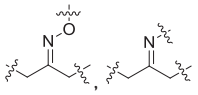
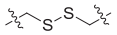
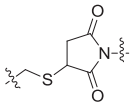


Fig. 1. General design of a prodrug.

Table 1
Common linkers used in prodrug conjugation.

	Linker	Chemical structure
Ester	Carboxyl ester	
	Carbamate ester	
	Carbonate ester	
	Phosphate ester	
Amide	Peptide bond	
Other linkers	Oxime and imine	
	Disulfide bond	
	Thioether bond	

the barriers in delivering the drug to its target cells [3]. Commonly used linkers in prodrug design are listed in Table 1.

Ester is the most common linkage in prodrug design. It is easy to synthesize and its functional groups such as hydroxyl and carboxyl acid group that are widely available in most parent drugs as well as promoiety molecules. Moreover, esterases are ubiquitously distributed in the body. Once administrated, the ester bond can be readily hydrolyzed by esterases in the blood, liver and other organs, leading to the release of the parent drug [7]. Depending on different structures of the prodrug and environmental conditions, half-life of the ester bond varies from several minutes to several hours [8,9]. For example, both EBZ-2208 and IT-101 are composed of the similar parent drug and the same ester linkage. EBZ-2208 has a half-life of only 12.3 min in human plasma [10], while the half-life of IT-101 is around 1.7 h in human plasma [11,12]. EBZ-2208 is a prodrug of the camptothecin derivative SN38 with a PEG of 40 kDa through a glycine spacer [10]. It is presumed that the linear structure of PEG and its hydrophilic property make the ester bond of the EBZ-2208 easily accessible to the activity site of esterase. On the contrary, IT-101 has a micelle-like structure that may protect the ester bond from esterases. Different types of the ester bond also exhibit different stabilities in the body. For instance, carbamate ester is more stable in comparison to carboxyl ester, phosphate ester, and carbonate ester [3].

Amide bond is another commonly used linkage in prodrug. It is the derivative of an amine and a carboxyl group. Amide has a relatively higher enzymatic stability than ester bond. Most of the amide bonds are stable for several hours or even several days in the plasma in the absence of specific enzymes. However, majority of the amide bonds in prodrugs are designed to be cleavable by a specific enzyme to increase the targetability or reduce the toxicity. Peptide linkers such as GFLG and SSKYQ are probably the best examples of this type of amide bond. The tetrapeptide linker GFLG is specifically cleaved by lysosomal enzyme in tumors. SSKYQ is a substrate peptide of the prostate specific antigen (PSA), an enzyme that is only active in prostate tumors. This type of linker shows a reliable stability in the blood circulation and only the parent drug in the target cells. GFLG has been successfully adopted in PK1, PK2, PNU166945, DX-8951 and other prodrugs that are under