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Review article

pH-responsive polymer–drug conjugates: Design and progress

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ABSTRACT

Polymer–drug conjugates are becoming established as a shining platform for drug delivery. Incorporation of pH-responsive linker between drug and polymer is expected to realize triggered release of bioactive agents from conjugates in specific sites, either in mildly acidic extracellular matrices of tumor tissues or, after cellular internalization, in acidic endosomes and lysosomes. As an emerging drug delivery system, such pH-responsive polymer–drug conjugates are able to selectively deliver and activate drug molecules while reducing their systemic side-effects. In this review, we present the recent advances in pH-responsive polymer–drug conjugates with different chemical structures and architectures, and attempt to clarify their mechanism of action, synthesis and characterization technology. Furthermore, several promising approaches for the future will also be suggested.

Contents

1. Introduction

During the past decade, the research and development of tumor-targeted drug delivery systems have received a rising interest for their potential to address some significant therapeutic issues like poor treatment response and serious adverse effects for clinical practice [1]. Generally, drug targeting consists of two components, selective drug delivery to the target sites and specific drug release at the target sites [2]. Apart from introducing cell-targeting biomolecules for specific delivery, stimuli-responsive drug systems based on different internal environments in human body can also enable

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controlled drug delivery, serving as an active research field for targeted therapeutics recently.

Stimuli-responsivity is a state of responsiveness, and stimuli-responsive drug systems can produce specific response according to small external changes in physiological environments. These changes includes internal (e.g. pH, redox potential, ionic strength and lysosomal enzymes) and external (e.g. light, ultrasound, temperature, electric and magnetic field) stimuli. For example, compared to normal extracellular matrices and blood (pH = 7.4), some intracellular compartments show lower pH values, such as the endosomes and lysosomes with a pH profile of 4.5–6.5. Owing to rapid proliferation-induced glucose consumption and lactic acid accumulation, the pH condition in tumor tissues are frequently 0.5–1.0 units lower compared with healthy tissues [3,4].

As an important signal, the existing pH difference can be considered as an ideal trigger for selectively releasing cytotoxic agents in tumor tissues and/or within tumor cells. Recently, many drug delivery systems with extraordinary pH-responsivity have been studied, such as liposomes [5,6], micelles [7,8], nanoparticles [9,10], nanogels [11,12], dendritic core-multishell nanocarriers [13] and so on. Although numerous devices are available and have achieved significant progression, polymer–drug conjugates are still preferred due to distinct advantages.

A commonly used model of polymer–drug conjugate in numerous researches was shown in Fig. 1. It contains a biocompatible water-soluble polymer backbone, hydrophobic bioactive agent(s) usually bound to the polymer via a biological response linker, and targeting moiety [14]. The polymer carrier is employed to deliver drugs, increase their aqueous solubility and protect cargoes from rapid exclusion from the body. And with increasing molecular weight of polymer, the corresponding conjugate tends to specifically accumulate in solid tumors due to the enhanced permeability and retention (EPR) effect [15]. In polymer–drug conjugates, several drug molecules are covalently linked to one polymer backbone. Compared to other polymeric systems which physically encapsulate drugs into polymer substrates, the main advancements of conjugation strategy are high drug loading, sustained drug release and good stability without undesirable drug leaking. All of these hold the key to therapeutic effect.

In the field of polymer–drug conjugates, the pH-responsivity is mainly achieved by using acid-sensitive chemical bond between drug and polymer carrier. This stimuli-responsive system holds great promise to improve therapeutic efficacy due to enhanced specificity, increased cell uptake and intracellular delivery while influencing as few healthy cells as possible. More importantly, such system offers an interesting opportunity for drug delivery where the delivery system becomes an active participant instead of passive platform for optimizing therapy. However, the drug molecules, sometimes, do not contain essential functional groups to form pH-responsive chemical bond. As a result, additional chemical modification for drugs is necessary, and the area derived from modifier is defined as spacer. Proper selection of chemical bond and spacer provides the possibility to control the rate and the site of drug release and thereby, in many cases, its activation. Furthermore, the introduction of targeting moiety like antibody could further realize the site-specific drug activation effectively.

In this review, we focus on the recent advances in pH-responsive polymer–drug conjugates, from action mechanism to synthesis and characterization. In addition, using selected examples from literatures, conjugate molecules with different chemical structures and architectures are presented, providing a preliminary overview on pH-responsive polymer–drug conjugates.

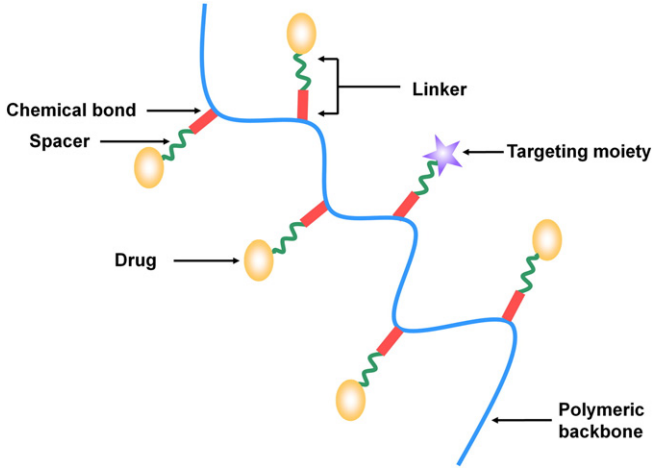

Fig. 1. Schematic illustration of polymer–drug conjugates.

2. Action mechanism of pH-responsive polymer–drug conjugates

Rational design of pH-responsive polymer–drug conjugates should be based on the action mechanism. Typically, the tailor-made linker of conjugates is capable of responding to changes in the environmental pH level. It can be cleaved hydrolytically, and the hydrolysis rate shows a close negative correlation with the surrounding pH value. Due to poor oral bioavailability of macromolecular drug, intravenous administration is widely adopted and has been the preferred route in the field of polymer–drug conjugates [16]. After intravenous administration, conjugate molecules could immediately enter the blood circulation. The pH-responsive linker between drug and polymer is expected to remain sufficient stability, which ensures conjugates to reach disease tissues without a substantial chemical change during transit environment (bloodstream, pH = 7.4). On arrival within pathological sites like tumor interstitium, macromolecular polymer–drug conjugates will entry into cells through endocytosis, which is quite different from free drug molecules that diffuse into cells via the plasma membrane [17]. Endocytosis contains two broad categories: phagocytosis and pinocytosis [18]. Phagocytosis, the internalization of large particles (0.25–10 μm), is typically restricted to professional phagocytes, like macrophages, monocytes and neutrophils. In contrast, pinocytosis, the continuous internalization of small fluid and solutes, is present in virtually all types of cells and has four distinct pathways: clathrin-mediated endocytosis, caveolae-dependent endocytosis, and clathrin- and caveolin-independent endocytosis. Usually, several endocytic mechanisms take place simultaneously during cell entry. Depending on the physicochemical characteristics of polymers and the nature of the target cells, conjugate molecules are mainly uptaken by cells via three types: fluid-phase, adsorptive, and receptor-mediated endocytosis. Fluid-phase pinocytosis is constitutively generated when there is no interaction between conjugates and cell surface. Consequently, the uptake rate is slow and directly proportional to the concentration of conjugates in the extracellular fluid. Introduction of hydrophobic moieties [19] or positive charges [20] to conjugate molecules, greater efficiency of endocytosis will be achieved by nonspecific binding with plasma membranes. This process is defined as adsorptive endocytosis. After equipment with cell-specific targeting moieties, the conjugates are internalized selectively via receptor-mediated endocytosis, and not only the rate of cellular uptake, but also biodistribution will be changed accordingly [21,22].

Subsequently, polymer–drug conjugates are exposed to various intracellular compartments characterized by different hostile environments, and the pH value gradually decreases from cytosolic pH 7.4 to endosomal pH of 5–6, and eventually acidifying to pH 4.5–5.0 in the lysosomal compartments. In this process, polymer–drug conjugates with specific linkers will be destroyed. The designed linker is susceptible to be hydrolyzed to release parent drugs in such acidic condition, thereby achieving tumor-targeted drug delivery [23].