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Review

Internal stimuli-responsive nanocarriers for drug delivery: Design strategies and applications

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ABSTRACT

The design of internal stimuli-responsive nanocarriers has been extensively used for delivery of various active compounds including drugs, peptides and genes. These nanosystems are not only designed for improved solubility, enhanced bioavailability, and prolonged blood circulation time, furthermore, they can be tailored chemically to achieve selective drug release at the desired sites of action, which can enable them to bypass physiological or pathological obstacles and achieve enhanced therapeutic efficacy. This review presents current functional moieties responsive to a variety of internal stimuli, including pH, redox, enzyme, temperature. Their design strategies and biomedical applications are also highlighted in detail. It is expected that this review can provide inspiration and impetus for exploiting more promising internal stimuli-responsive nano-systems for drug delivery.

Contents

1. Introduction

During the past several decades, an increasing number of chemotherapeutic agents have come into the market to improve anticancer diagnosis and therapy [1], however, the lack of clinical effectiveness always is scientists' headache owning to their nonspecific targeting property and rapid blood excretion rate [2]. Notably, high dosage of drugs in application is liable to cause multidrug resistance (MDR), which makes it more difficult to achieve disease treatment. To improve the therapeutic efficiency, a great many efforts have been made to enhance the drug accumulation at pathological sites as well as minimize the side-effects. Nanomedicine, developed from nanotechnology, have attracted

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tremendous attention and become an ideal candidate for efficient drug delivery [3]. For years, various nanocarriers including micelles, liposomes, polymeric nanoparticles, inorganic nanoparticles [4], dendrimers, as well as drug-polymer conjugates have been put forward throughout the field of nanomedical science for the delivery of different active cargos (drugs, genes, imaging agents, etc.) [5–10]. For instance, the utilization of poly(ethylene glycol)-poly($_{D,L}$-lactic-co-glycolic acid) (PEG-PLGA) nanoparticles in doxorubicin (DOX) delivery could dramatically reduce the cardiotoxicity of DOX which was priority to free drug solution [11].

Due to the benefit of nanometer scale-range, these nanoformulations could accumulate preferentially in diseased tissues via the enhanced permeability and retention (EPR) effect and result in increased stability, enhanced bioavailability, prolonged blood circulation time, and higher targeted property [12]. However, several delivery barriers like insufficient targeted property and inadequate intracellular release obviously limit their further application. In recent years, various targeted ligands such as folic acid (FA), galactose, RGD (Arginine-Glycine-Aspartic acid) peptide and some antibodies have been successfully conjugated to nanocarriers for active targeted drug delivery, leading to enhanced intracellular uptake and therapeutic efficiency [13]. It is noticeable that nanoformulations even with active targeting modification suffer from inadequate release at targeted sites, which presents a challenge to the design of current drug carriers. Stimuli-responsive nanocarriers are specialized nanosized drug delivery carriers that are equipped with environmental sensitive modalities within their structures. These nanocarriers can release their encapsulated cargos in response to specific environmental stimuli and surprisingly provide a new horizon for the development of nanoformulations [14]. In general, these stimuli can be divided into two modes: internal stimuli composing pH, temperature, redox potential and enzymes; and external stimuli that are triggered externally with the factors containing electromagnetically-, light-, radiation- and ultrasound-responsiveness [15]. Obviously, internal triggers are fundamentally of priority based on the intrinsic distinctions between physiological sites and diseased tissues especially in tumor and inflammatory microenvironments. These pathological changes induced distinctions such as pH gradients, redox difference, and enzyme expression therorically rendered the internal stimuli-responsive nanoformulations great merits of self-controlled drug release profile. Notably, some systemic-biochemistry parameters variation can also be utilized for stimuli-responsive drug nanocarrier design, like extra- and intracellular pH gradients and gastrointestinal pH gradients. By contrast, the external stimuli-sensitivity can be achieved only with the aid of environmental remote apparatus, which may have a potential negative impact on patients and be inconvenient to operate autonomously [16,17].

The benefits of internal-stimuli responsive nanoformulations are essentially evident, because the stimuli specifically exist in inherent pathological or physiological sites. Such specificity prompts the nanoformulations to release their cargo precisely in a tailored manner at desired target sites with reduced adverse effects, achieving self-controlled drug release pattern. The review provides a comprehensive outline of internal stimuli-responsive nanocarriers, including the design strategies, the type of carrier materials, mechanisms of drug release, and their corresponding biomedical applications such as cancer and inflammation therapy, with the emphasis on recent progress and current challenges in the field.

2. Design strategies and internal stimuli-responsive materials

The intrinsic properties are the basis in the design of internal stimuli-responsive nanocarriers with the main focus on internal stimuli like pH value, glutathione (GSH) concentration, enzyme specific overexpression and hyperthermic as illustrated in Fig. 1. The differences in biological parameters between normal tissues and pathological tissues were shown in Table 1. Basically, the characteristics of these triggers in pathological tissues are different from that in normal sites, thus the utility of these triggers provides new strategies in designing nanovehicles for drug delivery with higher on-target property and enhanced cellular uptake efficiency. To achieve more efficient agent delivery, multiple stimuli-responsive triggers could be used synergistically for enhanced intracellular uptake of nanocarriers. The targeting moieties are always functioned to the surface carriers via chemical reaction [18,19] or physical absorption [20] to achieve specific targeting delivery. For example, hyaluronic acid (HA), an ideal targeting moiety, could be not only conjugated to the carriers via amide reaction via its carboxyl groups [21] but also absorbed especially to the pores of mesoporous silica nanoparticles (MSNs) [22].

In general, the pH in extracellular microenvironment of tumor sites is slightly acidic compared with that in blood and normal tissues, and further decrease in pH value is observed in intracellular compartments like endosomes and lysosomes [23]. These pH gradients endow the pH value with the potential for internal stimuli-responsive nanocarrier design and the “proton sponge” effect helps smart nanocarriers to cleave in intracellular compartments. However, it should be considered that the responsive cleavage of nanocarriers may be delayed and the

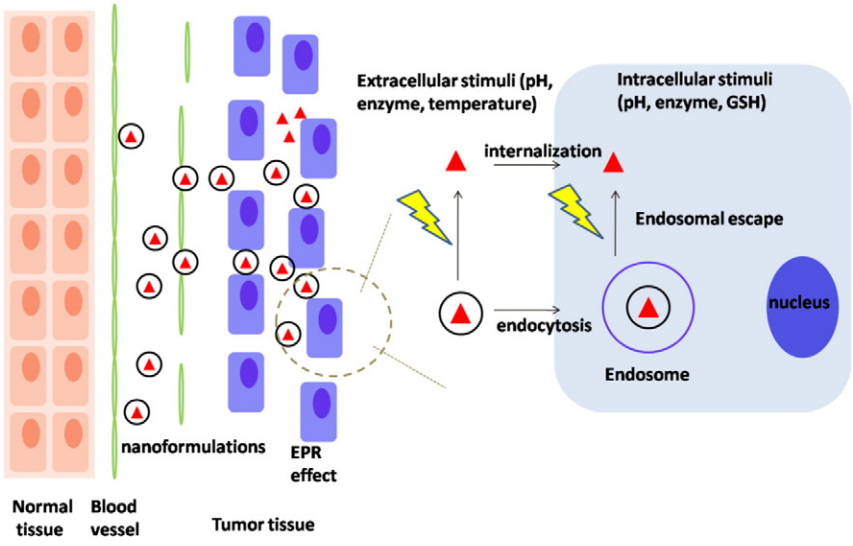

Fig. 1. Design strategies of internal stimuli-responsive drug nanocarriers.