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Review

Stimuli-sensitive nanopreparations for combination cancer therapy

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ABSTRACT

Nanocarriers have revolutionized drug delivery practices over the past couple of decades, primarily due to the advances in materials chemistry, nanotechnology and nanomedicine. This in turn, has spurred the development of a number of novel nanocarrier-based platforms and treatment strategies for cancer. It is now clear that to manage a disease as complex as cancer, a single or stand-alone treatment strategy may not suffice. Present day drug delivery strategies progressively lean towards "multi-pronged" combination approaches to make cancer treatments more effective. To that end, nanocarriers which simultaneously incorporate multiple drugs that affect different pathways and act through different mechanisms, or combinations of drugs with biological therapeutics like genes, antibodies, proteins or siRNAs have been the focus of recent active research. Furthermore, nanocarriers which respond to a variety of intrinsic cues afforded by the tumor microenvironment like low pH, elevated redox potential, over-expressed enzymes and hyperthermia as well as to externally applied stimuli such as magnetic field, ultrasound or light have been developed to trigger site-specific drug release. In this review, we focus specifically on nanocarriers that simultaneously exhibit stimuli-sensitivity and incorporate various combinations of conventional small molecule chemotherapeutic agents and biologics. We provide an overview of the different internal and external stimuli most relevant to cancer, and discuss selected examples of stimuli-sensitive combination nanopreparations from the recent literature with respect to each stimulus. Finally, we discuss multifunctional stimuli-sensitive nanopreparations which incorporate various combinations of drugs, biologics and targeting ligands within a single carrier that form so-called "smart" nanopreparations.

Contents

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1. Introduction

Drug delivery approaches in cancer have evolved enormously over the past few decades with an improved understanding of the disease at the cellular and molecular levels, the availability of a variety of fabrication materials for engineering delivery systems (polymers, metals, mesoporous materials, lipids, nanocrystals and DNA-like scaffolds) and integrated efforts from many different disciplines including biology, chemistry, materials science, biomedical sciences and engineering. By far, the greatest thrust for drug delivery in recent times has come from advances in nanotechnology that have revolutionized the field of nanomedicine by introducing a host of nanoscale systems for delivery of therapeutics. An impressive array of nanopreparations has been designed with varying sizes, architecture and surface properties [1]. This list includes, but is not limited to liposomes, polymeric micelles and nanoparticles, dendrimers, nanocrystals, nanocapsules, metallic nanoparticles, solid lipid nanoparticles, nanoemulsions, carbon nanotubes and nanogels [2–5]. These nanopreparations overcome a number of drawbacks seen with the use of free drugs and therapeutics that pose a significant barrier to effective therapy. Some of the main advantages of nanopreparations include their ability to incorporate payloads with different solubilities, an improvement in pharmacokinetic (PK) and pharmacodynamic (PD) properties of the drug without additional modifications of drug molecules, an enhanced stability and longevity of therapeutics in the circulation, an ability to be modified with respect to their surface chemistry for tissue or cell-specific delivery to minimize side-effects, and the ability to tune the release of therapeutic payloads [3,6].

Beyond the popular modifications of nanopreparations that impart longevity to drugs in the circulation and the addition of ligands to specifically target payloads to cells, substantial efforts have been recently directed towards developing “smart” nanocarriers. These “smart” or stimuli-sensitive nanopreparations (SSNs) are designed to behave dynamically in response to various internal cues in the microenvironment or to certain external cues to release their therapeutic payloads, and offer exceptional spatial and temporal control over the release of their cargoes in the process [1,7]. The internal cues or triggers which are commonly encountered in tumors include a lowered interstitial pH [8,9], high intracellular glutathione levels [10,11], various enzymes over-expressed or differentially expressed by tumors [12,13] and an increase in temperature (hyperthermia) that accompanies inflammation [14–16]. External physical stimuli such as ultrasound, magnetic field or induced hyperthermia accompanying the application of ultrasound or external magnetic field can also be employed to facilitate an “on-demand” release of payloads from the SSNs [1,5]. So far, cancer therapies have been the main beneficiaries and also the main focus of research for the development of SSNs. This is not surprising, considering the complexity of cancer and the need to continuously develop sophisticated approaches for treating it. The treatment for cancer typically involves multi-drug regimens, to achieve therapeutic synergy, and is routinely employed as a standard clinical practice. With advancements in high-throughput gene sequencing, systems biology and a focus on personalized medicine to tailor treatments to an individual patient's genetic make-up, new molecular disease targets are being discovered at a rapid pace [17–19]. Consequently, the use of molecularly targeted biologics like therapeutic antibodies, siRNA, DNA, proteins and oligonucleotides is steadily gaining momentum and strengthening the current armamentarium of treatments available for cancer and other diseases. To that end, combinations of small molecule drugs with molecularly targeted therapies have been the focus of active investigation, in addition to combinations of conventional chemotherapeutic agents for the treatment of cancer. Nanocarriers, with their inherent benefits afford an ideal platform, and play a critical role in the success of combination therapies for conventional chemotherapy drugs and molecular targeted therapies alike.

As mentioned before, cancer is a complex disease for which a single drug or even a stand-alone molecularly-targeted therapeutic may not suffice. Nanocarriers have been investigated extensively over the past few decades and have become the mainstay for development of novel treatments for cancer. The goal of this review is to discuss such novel nanopreparations which are responsive to various stimuli and which can also simultaneously incorporate agents for combination cancer therapy. We focus separately on each stimulus, internal and external and discuss relevant examples of nanopreparations for combination therapy under each category. Finally, we also discuss some interesting examples from the recent literature on the development of multifunctional SSNs for cancer that incorporate combination therapeutics and also offer the capability for targeted delivery.

2. Nanopreparations: Concepts and targeting strategies

2.1. Passive and active targeting strategies for nanopreparations

Nanopreparations have been designed and evaluated using many parameters that affect drug delivery to tumors. They have the ability to exploit the tumor microenvironment and reach the tumor tissue to deliver their payload locally. The pathophysiological difference between the solid tumors and the normal tissues is that the tumors have a tortuous and poorly differentiated vasculature with large gaps of about 100–600 nm between its endothelial cells, a feature that is absent in most healthy tissues [20,21]. This feature of solid tumors allows the extravasation of molecules with sizes up to several hundred nanometers. The lack of functional lymphatics in tumors also prevents normal clearance of the extravasated nanocarriers due to fluid retention and accumulation. This phenomenon of extravasation and poor drainage is termed the enhanced permeability and retention (EPR) effect [22]. Utilization of the EPR effect is one of the pivotal strategies applied for delivery of nanocarriers to the tumors and, based solely on the pathophysiological characteristics of the target tissues is referred to as ‘passive targeting’ [23–25]. The size of nanocarriers is one of the crucial factors influencing the EPR effect. A very small sized carrier promotes leakage into the capillaries while a very large sized carrier is more likely to be cleared by the reticuloenothelial system (RES) and be incapable of extravasation through the tumor's endothelial gaps [25]. Enhancing the hydrophilicity of nanocarrier surfaces by coating with polymers like polyethylene glycol (PEG) has resulted in systems with prolonged circulation that are capable of evading RES recognition and elimination and so exploit the EPR effect by multiple passages through the tumor sites [23,24,26,27]. Passive targeting, however, faces challenges related to non-uniform pore size and porosity of vessels based on tumor-types, failure of drugs to uniformly diffuse in the entire tumor and an elevated interstitial fluid pressure in most tumors which also occludes homogenous drug delivery [24]. Improved specificity can be imparted by active targeting, which involves making nanocarriers selective for target tissues [28]. Active targeting involves attaching ligands to nanocarriers, which recognize a target within the tumor-affected organ, tissue, cell or intracellular organelle [20,21,27,28]. Local or systemic administration of nanocarriers surface-modified with a specific recognition moiety either through ligand- or receptor-mediated targeting (binding to specific ligands/receptors unique to tumor cells) or by means of stimuli-sensitive drug nanocarriers (triggered drug release specifically at the tumor site) provides the attributes of target specificity in tumors along with more homogenous distribution throughout a tumor tissue [25]. Active targeting thus aids cell-recognition and enhances target cell uptake [20,27].

2.2. Stimuli-sensitive nanopreparations: General concepts

Stimuli-sensitive drug delivery, or smart delivery, is a very popular form of active targeting which has received a lot of attention since it delivers the cargo at the desired site and at the required time. These

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