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Review

Factors controlling the pharmacokinetics, biodistribution and intratumoral penetration of nanoparticles

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ABSTRACT

Nanoparticle drug delivery to the tumor is impacted by multiple factors: nanoparticles must evade clearance by renal filtration and the reticuloendothelial system, extravasate through the enlarged endothelial gaps in tumors, penetrate through dense stroma in the tumor microenvironment to reach the tumor cells, remain in the tumor tissue for a prolonged period of time, and finally release the active agent to induce pharmacological effect. The physicochemical properties of nanoparticles such as size, shape, surface charge, surface chemistry (PEGylation, ligand conjugation) and composition affect the pharmacokinetics, biodistribution, intratumoral penetration and tumor bioavailability. On the other hand, tumor biology (blood flow, perfusion, permeability, interstitial fluid pressure and stroma content) and patient characteristics (age, gender, tumor type, tumor location, body composition and prior treatments) also have impact on drug delivery by nanoparticles. It is now believed that both nanoparticles and the tumor microenvironment have to be optimized or adjusted for optimal delivery. This review provides a comprehensive summary of how these nanoparticle and biological factors impact nanoparticle delivery to tumors, with discussion on how the tumor microenvironment can be adjusted and how patients can be stratified by imaging methods to receive the maximal benefit of nanomedicine. Perspectives and future directions are also provided.

Contents

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1. Introduction

Nanomedicine therapies are broadly defined as active pharmaceutical ingredients formulated in delivery vehicles exhibiting an average size between 10 and 200 nm, and these encompass liposomes, micelles, polymeric nanoparticles, dendrimers, and macromolecules. Properly formulated nanoparticles evade the 5 nm renal filtration cutoff [1–3] and exhibit prolonged blood circulation, giving these particles an increased opportunity to interact with tumor tissues. Unlike normal blood vessels which feature a tightly sealed endothelium, tumor vasculature tends to be abnormally permeable to macromolecules and nanoparticles, and furthermore, lymphatic drainage is generally impaired in tumors: as a result of these pathological features, nanoparticles selectively accumulate in this biological cul-de-sac. On the other hand, low molecular weight drugs can non-selectively diffuse through the endothelial layer of normal tissues, inducing significant off-target toxicity at therapeutic doses. The enhanced permeability and retention (EPR) effect is the central hypothesis and science of nanomedicine, and tumors that present with high permeability are good candidates for this class of therapy.

Nanoparticles display distinctive pharmacokinetics (PK) and biodistribution (BD) compared to small molecules, and the altered *in vivo* biofate in turn alters the toxicity and efficacy profile of each drug. There are three major phases in nanoparticle drug delivery (Fig. 1): (1) systemic circulation and reticuloendothelial system (RES) interaction, (2) extravasation and tumor penetration, and lastly, (3) interaction with the target cells. This review focuses on the effect of nanoparticle composition and physicochemical properties on the interactions with the biological systems in these three phases, and how those interactions affect nanoparticle biofate.

2. Blood circulation and RES interaction

The first phase of delivery involves the systemic circulation and interaction with the RES, a global system of macrophages in the liver, spleen, and bone marrow, but with respect to nanoparticle clearance, the liver and spleen are the most active. Macrophages are phagocytic cells, and will engulf particles bearing recognized opsonins (serum proteins) that have adsorbed to nanoparticles [4–6]. For example, Nagayama et al. [7] demonstrated that the increased amount of complement protein C3 and immunoglobulin G (IgG) adsorbed onto the 50-nm polystyrene nanoparticles in the serum was directly reflected in the increased rate of uptake of the nanoparticles by Kupffer cells. Factors affecting opsonization and the RES interaction include PEGylation, size, composition, zeta potential, and shape of nanoparticles. Interaction of nanoparticles with the RES is a significant determinant of blood circulation time and rates of clearance. Nanoparticles with a decreased blood circulation time usually display reduced tumor uptake and efficacy.

2.1. Strategies to reduce RES interactions

2.1.1. Surface decoration

The most widely used surface decoration technique is introduction of polyethylene glycol (PEG), which is a hydrophilic polymer, to the surface of nanoparticles to reduce serum protein binding through a process of steric hindrance. PEG has been deployed in various types of nanoparticles, including liposomes, polymeric nanoparticles, and hybrid nanoparticles [8]. Sadzuko et al. [9] reported that PEGylation led to a 3-fold reduction in RES uptake, a 6-fold higher plasma area under the curve (AUC), and a 3-fold increased tumor uptake of a liposomal drug, leading to enhanced antitumor efficacy. Similar results have been reported by others with different types of nanoparticles [10–12]. PEG creates a border around nanoparticles and provides a nonspecific steric hindrance barrier preventing access of proteins [13,14]. The molecular weight (MW) of PEG and the amount used has an influence on performance. Fang et al. [15] studied protein adsorption on 100–200 nm PEGylated nanoparticles containing a range of PEG MW (2, 5, and 10 kDa), and determined that 10 kDa PEG was the most effective. Ernsting et al. [16] prepared PEGylated cellulose drug conjugates which exhibited self-assembly properties dependent on hydrophobic/hydrophilic balance, and for this system a 2 kDa PEG was optimal. Walkey et al. [17] utilized label-free liquid chromatography tandem mass spectrometry to determine serum protein binding to gold nanoparticles possessing different surface PEG densities. They reported that gold nanoparticles with different PEG densities attract different clusters of serum proteins, and the cluster of proteins binding to low PEG density particles (<0.16 PEG/nm^2) facilitated macrophage uptake. On the other hand, the cluster of proteins that bound to high PEG density particles (>0.64 PEG/nm^2) did not trigger serum-dependent phagocytosis, and the uptake by macrophage was less efficient (Fig. 2). While PEG reduces RES interactions, PEG also has an impact on particle properties including stability and drug release, and for each composition the MW and wt.% of PEG have to be experimentally optimized. This is a well-known consideration in liposomal formulation: DSPE-PEG$_{2000}$ is a common component of PEGylated liposomes, but it has detergent properties, and will destabilize liposomes when exceeding 8 mol% [18].

Despite the benefits that PEG confers, PEGylation is suspected to induce immune responses and hypersensitivity, especially when an immunostimulatory agent is included such as siRNA and pDNA [19–21]. Ishida et al. [22] and Judge et al. [23] demonstrated that the

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