Nano Today xxx (xxxx) xxx

Contents lists available at ScienceDirect

Nano Today

journal homepage: www.elsevier.com/locate/nanotoday

Review

Engineered nanomedicines with enhanced tumor penetration

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ARTICLE INFO

Article history:
Received 12 June 2019
Received in revised form
22 September 2019
Accepted 30 September 2019
Available online xxx

Keywords:
Polymer nanoparticle
Targeted delivery
Tumor penetration
Controlled drug release
Cancer therapy

ABSTRACT

Nanomedicine has been extensively explored to enhance the efficacy of chemotherapy with modest therapeutic efficacy in the clinic, owing to various factors. A primary factor is inefficient tumor penetration caused by specific tumor microenvironments, such as insufficient blood supply, high-density tumor cells and extracellular matrix, and increased interstitial fluid pressure. To date, several strategies, including the modulation of tumor microenvironments and optimization of nanoparticle properties, have been reported to improve the tumor penetration of nanomedicines, but these traditional strategies still have limitations. Recently, with unique strategies like tumor-penetrating peptide-mediated transcellular transport, the multifunctional transformable nanoparticles have emerged as an advanced generation of nanomedicine with superior tumor penetration capabilities. In this review, the latest development and limitations of nanomedicines are summarized, and prospects for improving tumor penetration are discussed.

Contents

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https://doi.org/10.1016/j.nantod.2019.100800
1748-0132/

Introduction

Nanoparticle-based cancer treatment has been in development for nearly half a century and has tremendously advanced the delivery of chemotherapeutic drugs and various new therapeutic agents, including molecular targeting agents, peptides, proteins, and genes [1–3]. However, many biological barriers still hinder the transport of nanomedicines, and considerable research efforts are being made to overcome these barriers. Nanomedicines have prolonged drug circulation and reduced drug toxicity in the cases of several nanoformulated drugs approved by the US Food and Drug Administration, such as doxorubicin liposome (DOXIL®), albumin-bound paclitaxel (PTX; Abraxane®), and irinotecan liposome (Onivyde®). Nanomedicines also enhance drug accumulation at the desired tumor sites through passive and/or active targeting [4–6]. However, the clinical results of these targeted nanomedicines have so far been modest, and some like BIND-014 have failed in clinical trials. Of the many proposed hypotheses to explain the current predicament of nanomedicines, poor tumor penetration is dominant.

The poor penetration of nanomedicines at the tumor sites is mainly attributed to tumor microenvironments and is also related to the properties of nanoparticles. First, the heterogeneous blood supply, which is sufficient at the tumor periphery but diminished in the tumor center, requires that nanoparticles travel increased distances to the tumor center [7]. Second, interstitial fluid pressure (IFP) is elevated from the tumor periphery to the tumor center, hindering nanoparticle diffusion to deep tumor sites after extravasation from peripheral blood vessels [8]. Moreover, the dense extracellular matrix (ECM) further impedes the transport of nanoparticles through the small pores within the matrix [9–11]. In addition to these biological barriers, the unique properties of nanoparticles compared with those of small molecules lead to more significant challenges. For example, nanosized delivery systems are less amenable to extravasation and diffusion after their accumulation at the tumor periphery. Moreover, there are complicated and even contradictory relations between nanoparticle properties and *in vivo* tumor penetration at several steps of the drug delivery process. Overall, the poor tumor penetration of nanomedicines is a consequence of both the tumor microenvironments and the inherent properties of nanoparticles.

Many efforts have been made to improve the tumor penetration of nanomedicines, primarily by modulating tumor microenvironments and optimizing nanoparticle properties (Fig. 1) [12–15]. However, these strategies are limited by the complex tumor microenvironments and delivery cascades. On one hand, although modulating the blood vessels or the tumor ECM alters tumor microenvironments and enables better nanoparticle distribution and diffusion, changes caused by external forces might destroy or affect the tumor microenvironments, ultimately hindering repeated treatment or even causing tumor metastasis. On the other hand, the ideal sizes, shapes, and charges of nanoparticles can be optimized *via* screening to enhance tumor penetration. However, these optimized properties usually depend on tumor types and must be further evaluated as they may affect or even obstruct other drug delivery processes. To overcome these limitations, many tailored nanoplatforms with penetration-assisted ligands or transformable properties, such as shrinkable size or reversible charge, have been explored. This review focuses on strategies to facilitate tumor transport of nanoparticles with a particular emphasis on rationally designed nanoplatforms.

Primary challenges for tumor penetration of nanoplatforms

The challenges for tumor penetration of nanoparticles are due to tumor microenvironments as well as the physical and chemical properties of nanoparticles themselves (Fig. 2).

Nanoparticle transport inside tumors mainly depends on the vasculature and the distribution of blood vessels [12,16,17]. Owing to the rapid proliferation of tumor cells, the burdens of oxygen and nutrition supply not only accelerate the formation of new blood vessels but also induce the irregular vasculature and heterogeneity of these blood vessels at the tumor sites [18]. Such irregular and heterogenous vessels lead to decreased and heterogeneous tumor blood flow, further hindering the tumor penetration of nanoparticles [19]. First, decreased blood flow limits nanoparticle perfusion at the tumor site [20,21]. Recent research showed that the enhanced permeability and retention (EPR) effect of nanoparticles was mediated by vascular bursts, which were also related to blood flow and tumor density [16]. Second, in the center of the tumor tissue, proliferating cancer cells exert substantial stress and compress both blood and lymphatic vessels, leading to vessel collapse [22] and causing functional blood and lymphatic vessels to be concentrated at the tumor periphery but scarce in the tumor center [23]. The distribution of vessels is heterogeneous over the distance from the tumor periphery to the center, which can be up to hundreds of micrometers, further exacerbating the poor penetration of nanoparticles.

After extravasation from the blood vessels to interstitial tumor spaces, dense ECM and elevated IFP further hinder nanoparticle transport [10,11,24]. The ECM is formed by proteins, glycoproteins, proteoglycans, and polysaccharides produced by epithelial, endothelial, and other stromal cells. Pores within the ECM are typically narrow, less than hundreds of nanometers, and block nanoparticle transport through steric restriction and electrostatic interactions [25–27]. In healthy tissues, IFP is nearly 0 mm Hg, whereas solid tumors typically show IFP values of 5–40 mm Hg, reaching 75−130 mm Hg 75 in some types of tumors [8,28–30]. This elevated IFP significantly slows the diffusion of large nanoparticles and even forces nanoparticles back into the blood supply [29].

Additionally, the tumor ECM contributes to the binding site barrier (BSB) for some ligand-modified nanoparticles [31,32]. The BSB was initially in the case of delivery of antibodies, which could be trapped by cells peripheral to the blood vessels, hindering their penetration into tumors [33]. The BSB has also been shown to restrict nanoparticle diffusion, preventing nanoparticles from reaching sites deep within the tumors, possibly owing to the nanoparticles being trapped by the tumor ECM or captured by stromal cells near the blood vessels [34].

Nanoparticles have unique properties that further complicate their delivery to tumors. A significant characteristic of nanoparticles is their size. Although tumor vessels are leakier than healthy blood vessels, vessel pores are permeable to nanoparticles only at certain sites, but not throughout the vessels [35], causing variation in nanoparticle extravasation and distribution [16]. The tumor sites with few eruptions can be treated only by nanoparticles penetrating from other sites, significantly increasing the distance and therefore the difficulty of transport. In addition, owing to the modification of functional ligands, nanoparticles are more readily trapped by the ECM, prohibiting their diffusion in interstitial tumor spaces. In summary, owing to their unique properties, the transport of nanoparticles from well-perfused to poorly-perfused sites are further hampered by narrow pores within the ECM and surface interactions of the nanoparticles with the surrounding environments [36].

Please cite this article as: J. Ding, J. Chen, L. Gao et al., Engineered nanomedicines with enhanced tumor penetration, Nano Today, https://doi.org/10.1016/j.nantod.2019.100800