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Perspective

Tumor-targeted nanomedicines for cancer theranostics

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ABSTRACT

Chemotherapeutic drugs have multiple drawbacks, including severe side effects and suboptimal therapeutic efficacy. Nanomedicines assist in improving the biodistribution and target accumulation of chemotherapeutic drugs, and are therefore able to enhance the balance between efficacy and toxicity. Multiple types of nanomedicines have been evaluated over the years, including liposomes, polymer-drug conjugates and polymeric micelles, which rely on strategies such as passive targeting, active targeting and triggered release for improved tumor-directed drug delivery. Based on the notion that tumors and metastases are highly heterogeneous, it is important to integrate imaging properties in nanomedicine formulations in order to enable non-invasive and quantitative assessment of targeting efficiency. By allowing for patient pre-selection, such next generation nanotheranostics are useful for facilitating clinical translation and personalizing nanomedicine treatments.

1. Introduction

Cancer is not one, but many heterogeneous diseases characterized by rapid and uncontrolled cellular expansion as a result of genetic and epigenetic alterations, and it annually affects millions of people worldwide [1]. Current therapies for cancer include surgery, radiotherapy, chemotherapy and immunotherapy. Early diagnosis of tumors facilitates the treatment of patients with surgery and/or with radiotherapy, however, in patients with tumors that cannot be resected or irradiated, or that have already metastasized, the only available treatment options are chemotherapy and immunotherapy [2]. The clinical usefulness of chemotherapy is limited by the low ability of drug molecules to reach tumors [3], by the fact that tumors tend to become resistant during the course of therapy [4–6] and by the development of immediate and long-term severe side effects [7–9], together compromising the efficiency of chemotherapy treatment.

Drug targeting strategies that enable tumor-targeted drug delivery and alter the balance between efficacy and toxicity of chemotherapeutic drugs are highly needed to overcome such limitations of chemotherapy [2,10]. In recent years, nanotechnology-based drug delivery systems have been extensively investigated to realize tumor-targeted chemotherapy. These so-called 'nanomedicines' aim at targeted delivery of chemotherapeutic drugs to the tumor site utilizing strategies such as passive targeting, active targeting and triggered drug release, while at the same time decreasing accumulation in off-target tissues, together leading to an improved therapeutic index [11,12]. Clinically relevant nanomedicines are liposomes, polymer-drug conjugates and polymeric micelles (Fig. 1A) [13–16]. Unlike conventional small molecule drugs, which are rapidly cleared from the blood circulation, nanomedicines have prolonged circulation half-lives, increased bioavailability and enhanced tumor disposition (Table 1, Fig. 1B). However, to achieve tumor-targeted drug delivery, nanoparticulate drug delivery systems have to overcome several biological barriers as presented in Fig. 1C [17].

The first nanomedicine formulation that was approved by the US Food and Drug Administration (FDA) is Doxil (PEGylated liposomal doxorubicin) [18]. The most pronounced improvement of

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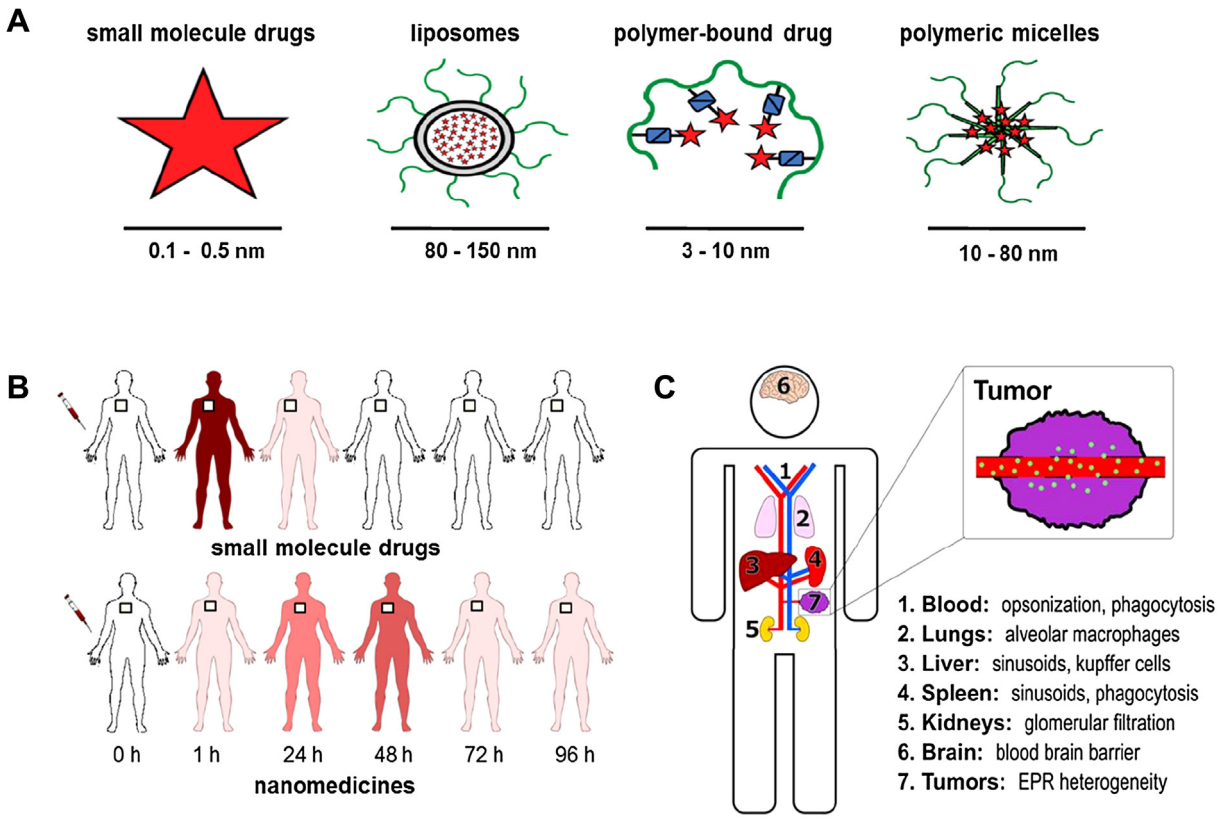

Fig. 1. Nanomedicines and tumor targeting. A. Representative examples of nanomedicines. Drugs are depicted as red stars, polymers in green, drug linkers in blue, and liposomal bilayers in grey (adapted with permission from [13]). B. Schematic representation of the biodistribution of conventional small molecule drugs vs. nanomedicine formulations upon intravenous administration. Compared to small molecule drugs, nanomedicines circulate for prolonged periods of time and achieve higher concentrations at the tumor site (tumors are depicted as squares). C. Various barriers that nanomedicines have to overcome to achieve efficient tumor-targeted drug delivery.

Doxil compared to free doxorubicin is the substantially reduced cardiotoxicity, which compromises the clinical use of free doxorubicin [19]. The clinical success of Doxil has led to the development of many other nanomedicine formulations [20]. Besides lipid-based formulations, these also include polymer-drug conjugates and polymeric micelles [21,22] (Fig. 1). The latter are especially attractive for the delivery of chemotherapeutic drugs with low water-solubility, and approximately a dozen of nanomedicines based on polymeric micelles are currently in clinical trials for different types of cancers.

To better understand the in vivo fate of nanomedicines, and to obtain information on pharmacokinetics, target site accumulation and therapeutic efficacy, it is of great value to integrate therapy with non-invasive imaging [23,24]. Such information can be used to assess the suitability of nanomedicine-based therapeutic interventions, via the pre-selection of patients most likely to respond to nanotherapy. This review summarizes the basic principles of nanoparticle-based tumor targeting, and it discusses the benefit of integrating imaging to pre-select patients and personalize nanomedicine treatments.

2. Mechanisms of nanomedicine-based tumor targeting

2.1. General considerations

When designing nanocarriers for tumor targeting, it is essential to consider their physicochemical characteristics including size and surface properties to attain optimal accumulation at the pathological site. For example, intense interactions between nanoparticles and serum proteins may cause rapid clearance from the circulation. The surface properties of nanocarriers, such as the charge and hydrophobicity affect protein opsonisation resulting in activation of the complement system and rapid uptake by phagocytes. Compared to hydrophobic and positively charged particles, neutral and hydrophilic particles are generally less prone to opsonisation [25,26]. Apart from surface properties, particle size also critically affects the in vivo fate of nanomedicines. Hydrophilic nanoparticles smaller than ~5 nm are efficiently eliminated via renal filtration whereas larger nanoparticles (>~200 nm) tend to rapidly accumulate in healthy organs such as liver, spleen and lungs [17,27]. Interestingly, nanocarriers with sizes between ~5 and ~250 nm can extravasate from leaky tumor vessels allowing for efficient accumulation over time, in part also because tumors tend to lack functional lymphatic drainage [28,29].

Even if sufficient tumor accumulation is reached, the therapeutic efficacy of nanomedicines greatly depends on the penetration depth of the formulations into the tumor interstitium [30,31]. Both tumor microenvironment and the physicochemical characteristics of the nanocarriers are key factors affecting penetration. The tumor microenvironment is generally characterized by extensive stromal components such as collagen, hyaluronan, proteoglycans networks, as well as by a high interstitial fluid pressure, which altogether present a formidable biological barrier for efficient tumor penetration [32]. Among the different strategies used to enable tumor penetration, the most straightforward method is minimizing the size of the nanocarriers [33]. In the following sections, we discuss targeting strategies used to improve the accumulation and retention of nanomedicines at the tumor site, and to increase the therapeutic efficacy of the compounds through modulation of their drug release properties.