Journal of Controlled Release 201 (2015) 78–89

Contents lists available at ScienceDirect

Journal of Controlled Release

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

Review

Improving drug delivery to solid tumors: Priming the tumor microenvironment

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ARTICLE INFO

Article history:
Received 25 July 2014
Accepted 16 December 2014
Available online 17 December 2014

Keywords:
Drug efficacy
Tumor microenvironment
Solid stress
Tumor priming
Tumor stroma
Vascular normalization

ABSTRACT

Malignant transformation and growth of the tumor mass tend to induce changes in the surrounding microenvironment. Abnormality of the tumor microenvironment provides a driving force leading not only to tumor progression, including invasion and metastasis, but also to acquisition of drug resistance, including pharmacokinetic (drug delivery-related) and pharmacodynamic (sensitivity-related) resistance. Drug delivery systems exploiting the enhanced permeability and retention (EPR) effect and active targeting moieties were expected to be able to cope with delivery-related drug resistance. However, recent evidence supports a considerable barrier role of tumors *via* various mechanisms, which results in imperfect or inefficient EPR and/or targeting effect. The components of the tumor microenvironment such as abnormal tumor vascular system, deregulated composition of the extracellular matrix, and interstitial hypertension (elevated interstitial fluid pressure) collectively or cooperatively hinder the drug distribution, which is prerequisite to the efficacy of nanoparticles and small-molecule drugs used in cancer medicine. Hence, the abnormal tumor microenvironment has recently been suggested to be a promising target for the improvement of drug delivery to improve therapeutic efficacy. Strategies to modulate the abnormal tumor microenvironment, referred to here as "solid tumor priming" (vascular normalization and/or solid stress alleviation leading to improvement in blood perfusion and convective molecular movement), have shown promising results in the enhancement of drug delivery and anticancer efficacy. These strategies may provide a novel avenue for the development of new chemotherapeutics and combination chemotherapeutic regimens as well as reassessment of previously ineffective agents.

Contents

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http://dx.doi.org/10.1016/j.jconrel.2014.12.018
0168-3659/

1. Introduction

Solid tumors show chemotherapeutic resistance due to a number of well-known mechanisms, which include the activity of alternative drug export pumps, alterations in gene expression and metabolic pathways that affect the metabolism of cytotoxic drugs, and deregulation of DNA repair and subsequent apoptosis induction. Along with these well-described mechanisms, the tumor microenvironment and/or barriers that limit drug delivery have gained a great deal of attention; their understanding is needed to address the issues related to the limited efficacy of cancer chemotherapy [1]. On the other hand, the conditions in the tumor microenvironment, such as hypoxic and acidic conditions in some regions, are known to cause considerable variations in the cell proliferation rate, and these abnormalities can result in antitumor drug resistance. Most anticancer drugs used for the treatment of solid tumors show modest effects, in part due to their limited penetration into tumor tissues [2,3]. The penetration barriers in tumor tissue that limit drug delivery are associated with patho-physiological components of the solid tumor microenvironment, which include abnormal and poorly perfused vasculature and avascular area of tumors with little convection, either due to overproduction of immature vessels or intratumoral pressure ("solid stress" as described below) applied on tumor vasculature and the parenchymal tissue [4].

In order to kill all tumor cells, systemically administered anti-cancer drugs need to be distributed all the way through the tumor vascular network, to cross vessel walls and penetrate the interstitial space, finally reaching each tumor cell at a sufficient concentration [3]. Tumor cells, which proliferate more rapidly than capillary endothelial cells, force tumor vessels apart and thus create an abnormal vascular architecture unfavorable for drug delivery [5]. Tumor cells are often located >100 μm away from the nearby vessels, whereas in normal tissues, cells reside closer to blood vessels, within a range of 50–100 μm [6,7]. This complicates the delivery of drug molecules because they have to travel a longer distance from blood vessels and to cross a space where there are many barriers for molecular movement, which results in insufficient drug penetration [3]. Even commonly used cytotoxic agents (doxorubicin and paclitaxel) are unable to penetrate more than 40–50 μm from blood vessels [2,8]. The poor penetration of these conventional drugs is known to contribute to their low efficacy that further hampers the therapeutic course complicated by disease recurrence and high dose-related toxicity. Hence, drug distribution improvement strategies may represent a basic and important solution for better cancer treatment outcomes [7].

1.1. Anti-cancer nanoparticles and enhanced permeability and retention effect

Nanoscale drug delivery systems (nanoparticles, NPs; sometimes called nanomedicines) take potential advantage of abnormalities of tumor vasculature which promote NP accumulation in the perivascular tumor region, which has been termed the "enhanced permeability and retention" (EPR) effect by H. Maeda [9]. The excessive leakiness of tumor vasculature due to large gaps between endothelial cells favors the release of macromolecular NPs into the space around tumor vessels, and NP retention is considerably increased due to poor lymphatic drainage. The cut-off size of the tumor vasculature pores (≥200 nm) [10] provides a great opportunity for macromolecular drug delivery systems (DDS) (micelles, liposomes, gold NPs, carbon NPs *etc.*) to selectively accumulate in the tumor [11]. The variable properties of nanocarriers (size, surface charge, biocompatibility, and release profile) and the availability of permeability factors, including bradykinin, nitric oxide (NO), angiotensin-converting enzyme (ACE) inhibitors, and prostaglandins, can influence the EPR effect; therefore, NP design and therapeutic regimen must be optimized to obtain maximum targeting and therapeutic efficiency [12].

The potential advantages of NPs over conventional small-molecule chemotherapeutic drugs include prolonged circulation due to reduced renal or hepatic clearance and decreased distribution volume, leading to site-specific delivery with minimal nonspecific accumulation and providing enhanced therapeutic index [13]. For example, large micelles (5–100 nm) can easily escape renal excretion but are still small enough for enhanced extravasation from leaky tumor vasculature. Due to the large size of the micelles, along with other beneficial properties, many micelle-based formulations are already under clinical trials that support their use as optimal DDS [14]. The extensive work by V.P. Torchilin and his colleagues on drug carrier systems further facilitates their use for targeted delivery of chemotherapeutics into tumor cells [15,16]. To overcome the undesirable actions of the reticuloendothelial system, DDS have been optimized by coating with polyethylene glycol (PEG),or PEGylation, which has dramatically improved tumor targeting [14,17]. In fact, PEGylation improves the longevity of DDS, an effect that was first described for liposomes [16,18]; other PEGylated particles also show prolonged *in vivo* circulation, which promotes tumor selectivity [19].

1.2. Translational challenges for nanomedicine delivery

Extensive research during the two previous decades has shown that these cancer-targeting NPs have achieved their major goal of overcoming the host toxicity issues, but their clinical efficacy has been persistently unsatisfactory [20]. Some of the FDA approved NPs, such as liposomal doxorubicin (Doxil/Caelyx) [21–23], daunorubicincitrate liposomes (DaunoXome) [24] and albumin-bound paclitaxel (Abraxane) [25] show less host toxicity than conventional chemotherapy, but only mild improvements have been seen in the overall patient survival rate [26]. Multiple factors may contribute to the much anticipated clinical outcomes of cancer-targeting NPs [27]. Due to low blood perfusion and tumor vessel heterogeneity, however, convective flow and extravasation are not necessarily sufficient for the EPR effect to become beneficial for these NPs. Furthermore, the physical properties of drugs, such as size, charge, polarity, and configuration, may show negative impacts on the EPR effect and its related processes [28–30], as illustrated by the PEG dilemma, where the hydrated PEG moiety hinders the binding of PEGylated NPs to tumor cell receptors [31].

The design of NPs, tumor heterogeneity, and abnormal characteristics of the tumor microenvironment may all reduce the clinical efficacy of these formulations [32,33]. The variable pore cut-off size due to tumor heterogeneity may not favor the preferential extravasation of large NPs through the EPR effect. Therefore, the EPR effect alone is not necessarily sufficient to favor the delivery of NPs, and abnormal tumor microenvironment may inhibit their potential activity [26,27]. Likewise, heterogeneous intratumoral dissemination of NPs appears to be a major challenge for their efficient clinical translation [34]. The EPR heterogeneity due to diverse tumor conditions with variable hypoxia and compressed vascular system decreases the EPR effect [12]. The factors that influence the EPR effect can be summarized as follows: (i) the extent of angiogenesis and presence of functional lymphatic vessels; (ii) the extent of tumor growth adjacent to the vasculature and the degree of mechanical stress generated due to tumor hyperplasia and tumor