Major Advances and Emerging Concepts of EPR-Enhancing Strategies

Subjects: Oncology

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The enhanced permeability and retention (EPR) effect is dynamic and a phenomenon of tumor blood vessels, which is mostly dependent on blood flow. Animal models of solid tumors rich in blood flow demonstrated enhanced EPR effects. The strategies to enhance the EPR effect can be broadly classified into pharmacological and physical-based approaches.

Keywords: EPR-based therapy ; passive targeting ; heterogeneity ; solid tumor

1. Introduction

Cancer tumors generate an uncommon extracellular matrix, making it challenging for anticancer drugs to infiltrate [1]. In the late 1980s, preferential accumulation of macromolecules into cancer cells was observed. Japanese researchers Hiroshi Maeda and Yasuhiro Matsumura first described the enhanced permeability and retention (EPR) effect in 1986 [2]. This observation was due to the presence of fenestration in damaged tumor blood vessels and poor lymphatic drainage. In hypoxic conditions or inflammation, blood vessels become more permeable. The fast-growing tumor cells in a hypoxic state tend to put in action more blood vessels or submerge existing ones to confront. New blood vessels created due to the process of neovascularization are leaky as they have large fenestrations ranging from 200 to 2000 nm (pore), depending on tumor type, TME (tumor microenvironment), etc. [1]. During the formation of tumors, lymphatic functions are disrupted, resulting in minimal uptake of interstitial fluids, which contributes to the retention of NPs in the tumors as they are not cleared, and stored in the tumor interstitium. This effect is known as the enhanced permeation and retention (EPR) effect. Usually, in normal tissues, the drainage of extracellular fluid into lymphatic vessels often happens at an average flow rate of 0.1 to 2 μm/s, maintaining continuous drainage and renewal [3]. However, when a tumor is formed, the lymphatic function is disrupted resulting in minimal interstitial fluid uptake [1].

The EPR effect is a unique feature of solid tumors related to characteristics of tumors including defective vascular architecture, large space between endothelial cells in blood vessels, abundant vascular mediators, vascular endothelial growth factor, and diminished lymphatic recovery. Therefore, tumor blood vessels are leaky compared to normal blood vessels due to the defective endothelial cells and more vascular permeability, as well as vastly expressed vascular mediators including bradykinin, NO, and VEGF, resulting in selective accumulation of nanodrugs into tumor tissues with little or no distribution in normal cells [4]. Among others, the most prominent pathophysiological factors contributing to EPR-targeted passive tumor targeting include active transcytosis across the blood vessel wall for NPs extravasation and phagocytic uptake by TAMs as a mechanism of NPs retention [2].

The strategies to enhance the EPR effect can be broadly classified into pharmacological and physical-based approaches. The pharmacological approaches involve the administration of a drug to interfere with the tumor microenvironment and thereby enhancing the accumulation of nanoparticles at the tumor site. Whereas physical approaches involve the use of an external physical stimulus such as heat or radiation to temporarily improve the permeability in the tumor tissues. These strategies to enhance the EPR are used in both preclinical and clinical settings. The following sections discuss the recent advancements in EPR-enhancing strategies.

2. Tumor Vasculature Modulation

In clinical settings, one of the main challenges for the delivery of macromolecules and nanomedicine to the cancer site is due to the heterogeneity of the EPR effect in solid tumors [5]. Several factors result in the heterogeneity of the tumor such as stage and size of the tumor, primary metastatic nature, and pathological characteristics. Two main approaches are employed to restore effective blood perfusion to the tumor site. This results in the mitigation of tumor heterogeneity and vasculature, normalizing disorganized tumor vasculature, and unblocking the occluded vessels are the two main approaches in achieving uniform drug delivery to the tumor site [6][7][8].

3. Normalization of Vasculature

One of the classical approaches is to administer antiangiogenic compounds and deprive the tumor tissue of oxygen and nutrients. In clinical settings, this approach has been proven to be ineffective when used alone [9]. Recently, research groups such as Jain, et al., have used the combination therapy of angiogenesis inhibitors along with chemotherapy [10], where the angiogenesis modulators are used to normalize the vasculature and improve the EPR effect–mediated drug delivery and efficacy of the cancer treatment. An intermediate dose of anti-VEGF receptor two antibodies (DC101) was used to successfully normalize the blood vasculature in and around the tumor site, thereby reducing the necrotic and hypoxic regions [11]. Further, the research group administered a combination of Doxil (around 125 nm in size) or Abaxane (around 12 nm in size) in breast tumor-bearing mice and observed a significant (around threefold) accumulation of smaller nanoparticles [12]. This concludes the DC101 improved tumor vascular normalization leading to a smaller and homogenous pore on the tumor vessel wall [11]. Another class of drugs used to aid in vascular normalization is tyrosine kinase inhibitors (TKIs), a small molecule class of drugs. Several research groups employed treatment with erlotinib, an EPR enhancer which is a TKI against epidermal growth factor receptor (EGFR). This improved the accumulation of human serum albumin-bound paclitaxel (HAS-PTX) in vivo in tumor-bearing mice such as head and neck carcinoma cells (SCC7), colon carcinoma cells (CT26), and breast cancer cells (4T1) [13]. A significant tumor size reduction was observed in models with combination therapy of erlotinib and has-PTX in comparison to the HAS-PTX group alone. A higher vascular normalization resulted in a higher distribution of hasHSA-PTX to the tumor site. Another TKI, Imatinib, inhibits VEGF-independent angiogenesis and also improves the delivery of nanoparticles to the tumor site, which was observed in A459 xenograft tumor models (lung carcinoma) [14]. Most research groups have reported that vascular normalization results in pore size reduction in the tumor vasculature. One of the problems with vascular normalization is the accumulation and quick clearance of small-sized nanoparticles. Research groups such as Xiao et al. used a combination of cediranib (VEGFR TKI) and enzyme-responsive size changeable gold nanoparticles (from around 40 nm to 300 nm upon enzymatic activity) [15]. The size-changeable gold nanoparticles have shown an around twofold increase in the tumor size suppression in the subcutaneous 4T1 tumor model than the fixed size nanoparticles. The increase in size led to increased residence time in the tumor tissue and improved the antitumor effect of size-changeable gold nanoparticles that increased with the coadministration of cediranib. In addition, celecoxib a cyclooxygenase-2 (COX-2) inhibitors also act as an angiogenesis inhibitor and result in vascular normalization and improved EPR effect in the tumor site [16]. The choice of therapy for vascular normalization must be chosen wisely since this approach is effective in delivering small-sized nanomedicines in comparison to the larger ones.

4. Fibrinolytic Co-Therapy

Cancer mortality and morbidity are contributed to by a hypercoagulative state of malignancy in patients [17]. Vascular occlusion in tumors can be caused due to several factors such as tissue factors that secrete proinflammatory cytokines being overexpressed by tumor cells, platelet activation due to cytokine-activated endothelial cells, and leukocytes overexpressing tissue factors. All these factors result not only in vascular occlusion but also tumor heterogeneity of the EPR effect and thereby resulting in poor drug delivery. Fibrinolytic therapy helps in dissolving fibrins in occluded vessels and improving the tumor vasculature [18][19][20][21][22]. Research groups such as Zhang et al. preadministered tissue plasminogen activator (tPA) with paclitaxel-loaded nanoparticles to de-compress the tumor vessels in A549 tumor xenograft mice. The tPA is a thrombolytic drug that degrades fibrins, and the pretreatment decreased the number of fibrins at the tumor vessel walls. The pretreatment group showed a higher accumulation and enhanced penetration depth of 115 nm nanoparticles at the tumor site in comparison to the saline group [23]. In another study, researchers reported that pretreatment with tPA has not affected biodistribution. However, improved the penetration of Doxil® into B16F10 tumors [24]. Although co-therapy with fibrinolytic has shown promise and great potential in increasing the EPR effect in delivering nanomedicine, tPA's low half-life and specificity remain a challenge.

5. Bradykinin Mediators and Bradykinin

Activation of bradykinin receptors B1 and B2 results in increased vasodilation, disruption of endothelial adherens junctions, and actomyosin cytoskeletal contraction of endothelial cells [25]. Several tumors overexpress kinin receptors resulting in higher permeability of tumor vasculature. Since the half-life of bradykinin is short lived and it has the risk of pain induction, some research groups use drugs that inhibit angiotensin-converting enzyme (ACE). These ACE inhibitors (ACEi) inhibit the conversion of angiotensin I to angiotensin II and thereby inhibiting the degradation of bradykinin. ACEi drugs such as enalapril are used to improve the permeability of the vasculature further and improve the accumulation of nanomedicine at the tumor site. Some research groups have used captopril which is a more potent ACEi than enalapril.

Captopril usage has improved the accumulation of paclitaxel-loaded nanoparticles in U87 glioma xenograft tumors [26][27][28].

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