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Cancer Nanomedicine: Strategies to Enhance Tumor Delivery and Immunotherapy

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Abstract

Nanomaterials with unique size and integrated features allow novel mechanisms for cancer therapy, so nanomedicine offers more possibilities for effective and safe cancer treatment. However, inefficient tumor delivery remains a major challenge in the clinic. In this commentary, we first discuss new designs of nanomedicine to increase tumor accumulation by active targeting strategies. Nanomedicine can be used to improve active targeting via ligand-receptor binding, cell penetration, or specific cell membrane coating, leading to improved therapeutic efficacy and reduced systemic toxicity. In addition, immune cells are demonstrated as an important component in tumors, and play a critical role in tumor progression and metastasis, here we address tumor-targeting nanomedicine provide unique approaches to remodel the immunosuppressive tumor microenvironment and promote antitumor immune responses.

Introduction

Cancer nanomedicine was originally developed for more efficient delivery of chemotherapeutic agents into tumor, and has been extensively employed as a therapeutic for cancer treatment owing to its unique features in drug delivery, diagnosis and imaging, as well as the therapeutic nature of some nanomaterials themselves [1,2]. The enhanced permeability and retention (EPR) effect has been considered as the major discipline for development of cancer nanomedicine [3]. By this way, nanomedicines can passively accumulate in tumor due to the large inter-endothelial gaps and the absence of lymphatic drainage [4,5]. However, the translation of nanomedicine has been limited due to the low clinical effectiveness of EPR effect. According to a retrospective analysis of published studies during 2005-2015, it was founded that only 0.7% of nanoparticle was delivered to solid tumor following systemic administration [6]. Recently, Sindhwani et al. found that the gaps of leaky vessels are not responsible for the penetration into tumor over several different types of tumors [7], as tumor vasculature is mostly continuous, and gaps occur at a very low frequency. It is crucial to explore new strategies to bypass the bottlenecks of traditional nanomedicine delivery.

Besides passive accumulation by EPR effect, nanomaterials can integrate novel mechanisms for active tumor-targeted delivery. Taking advantage of molecular markers over-expressing on tumor tissues compared to normal cells, incorporating specific ligands or antibodies should be considered to promote nanoparticle accumulation in solid tumors. Nanomedicine with penetration-assisted peptides or transformable properties, such as reversible charge, have been explored to increase internalization of drugs through active transport [8].

Immunotherapy could evoke host immunity to kill cancer cells, showing considerable and long-lasting clinical benefit in several tumor types. However, failure of effector T cells to infiltrate into tumors and immunosuppressive environment in tumors limit antitumor immune responses [9]. Nanomedicine aiming at enhancing immunotherapy could act by mechanisms distinct from chemotherapy. Some immune cells, especially myeloid cells, are native targets for nanomedicine. A thorough understanding of the nano-bio interaction will enable the optimal design of nano-immunotherapies targeting immunosuppressive tumor microenvironment and lymphoid tissues, subsequently triggering the release of tumor antigens and intracellular danger signals, which can boost systemic antitumor immune responses.

In this commentary, we discuss mainly the development of nanomedicine that increase tumor accumulation by active targeting strategies, and further reverse tumor immune environment to promote cancer immunotherapy.

Active Delivery of Nanomedicine into Tumor

With deeper understanding of *in vivo* nano-cellular interactions, we could switch our delivery strategies to enhance active transport drugs into target cells.

Protein interaction can be integrated in the cell-nanoparticle interaction. Taking advantage of molecular markers overexpressing on tumor tissues compared to normal cells, ligand-conjugated nanoparticles could enhance the uptake and release of the therapeutic cargo, such as small-molecule drugs and nucleic acids at the tumor site while reduce side effects relative to conventional therapeutics. It has been shown in cancer therapy that the presence of targeting ligands enhances the cellular uptake of nanoparticles through receptor mediated endocytosis [10,11]. Meanwhile monoclonal antibodies (some approved by the FDA as therapeutic antibodies [12-14]) have been widely used as conjugated molecules and showed efficiency [14-16]. For example, paclitaxel-loaded nanoparticle/Herceptin(Trastuzumab, a humanized anti-HER2 monoclonal antibody) complexes had 22.4% higher cytotoxicity in HER2-overexpressing breast cancer cells compared to paclitaxel-loaded nanoparticles and displayed a dependency on their HER2 expression levels[15].

Tumor-penetrating peptides have been widely used to promote tumor accumulation of nanoparticles as a tumor-targeting strategy [17-20]. iRGD has been identified as a tumor-penetrating peptide using peptide library displayed on T7 phage [21]. They showed that iRGD targeted to tumors through a three-step process: 1) the RGD motif mediated binding to αv integrins on tumor endothelium; 2) a proteolytic cleavage exposing a binding motif for neuropilin-1; 3) penetration into cells and tissue. iRGD have been utilized to increase tumor penetration of nanoparticles in experimental tumors *in vivo*, and in human tumors *ex vivo* [18,22,23]. In a separate example, Kazuki et al. coated Nab-paclitaxel with iRGD. When injected intravenously, the iRGD-abraxane accumulated in the tumor 11-fold more than nontargeted abraxane in BT474 xenograft models, and significantly inhibited the tumor growth [21].

Cell membrane-coated nanoparticle is a novel platform with prolonged circulation. By coating specific cell membrane directly onto the surface of nanoparticles, the resulting particles could gain the native functionalities of the source cells via associated surface markers [24,25]. It was demonstrated that the membrane-coated nanoparticle could significantly enhance the uptake of cells with corresponding receptors. Krishnamurthy et al. have coated monocyte membrane around PLGA nanoparticles loaded with DOX [26]. The surface marker CD49d, a primary ligand to vascular cell adhesion molecule 1 (VCAM-1), was retained on the membrane-coated nanoparticle. When incubated with mouse skeletal myocyte cells with minimal VCAM-1 and many other cell adhesion molecules, the coated and uncoated particles showed little difference. On the contrary, in metastatic MCF-7 cell lines expressing VCAM-1, membrane-coated nanoparticle showed greater cellular uptake and cytotoxicity when compared to non-coated nanoparticle controls (IC_{50}: 12 μM vs. 4 μM). Besides the utilization of existing markers, some functionalization strategies have been developed to introduce additional ligands onto the surface of nanoparticles. Zhilan et al. reported a CDX peptide-incorporated red blood cell membrane-coated nanoparticle. Owing to the high binding affinity between candoxin-derived CDX peptide and nicotinic acetylcholine receptors (nAChRs) expressed on the surface of brain endothelial cells, the nanoparticles showed promising brain targeting efficiency both *in vitro* and *in vivo* [27].

Cationic conjugates are reported to increase caveolae-mediated endocytosis and transcytosis, which enables transendothelial and transcellular transport, and a relatively uniform distribution throughout the tumor [28]. Shen et al. designed a charge reversal nanoparticle, with γ-glutamyl transpeptidase-responsive camptothecin–polymer conjugate. The overexpressed γ-glutamyl transpeptidase on the luminal endothelial cells of the tumor blood vessels cleaves the γ-glutamyl moieties of the conjugate to generate positively charged primary amines. The conjugate accumulated in tumor 3.2-fold more than nanoparticles without γ-glutamyl transpeptidase in HepG2 xenograft tumor model and yielded a 99% tumor-inhibition rate in large tumor [29].

With many advances in ligand engineering and formulation optimization of nanoparticle, active delivery will become a common therapeutic method in the next generation of cancer nanomedicine. Recent study first discovered that in nanomedicine delivery, active transcytosis contributed more in transporting AuNPs into solid tumors than passive EPR [7], but detailed mechanism is not well understood. The role of different trans-endothelial pathways with respect to extravasation of varying nanoparticle types and surface chemistry needs to be further explored.

Nanomedicine Design to Enhance Cancer Immunotherapy

Traditional nanomedicine design focuses on improving

chemotherapy to directly destroy rapidly growing tumor cells. With the explosive development of immunotherapy, many researchers find that, a considerable or even major part of cells in tumor is immune cells [30]. In this pathological state, immune cells tend to help tumor cells suppress or escape immune response and promote tumor growth [31]. It has been demonstrated that a large fraction of systemically administered nanomedicine is taken up by non-tumor cells [32], including immune cells within secondary lymphoid tissues or tumor microenvironment. With the unique feature of immune cell targeting, nanomedicine could provide opportunities to promote the tumor microenvironment remodeling and continued cancer cell killing.

Tumor-associated macrophages (TAMs) are significant components of the immunosuppressive tumor microenvironment (ITME), displaying an anti-inflammatory M2 polarization to support tumor growth and suppress CD8+ T cell recruitment to TME, thus correlated with poor prognosis [33-36]. One of the key features of macrophages is their plasticity, which enables them to change their phenotype in the tumor microenvironment. Once the immunosuppressive immune cells have been re-programmed, these pro-inflammatory M1 phenotypes could contribute to the antitumor activities [37,38].

Taking advantage of their propensity to phagocytose nanoparticles and microparticles, designing nanomedicine aiming to regulate the immunosuppressive activity of TAM is an attractive approach. Rodell et al. reported engineered cyclodextrin nanoparticles which displayed high TAM affinity while perpetuating a considerable loading efficiency of TLR7 and TLR8 agonist R848. After systemic administration, the formulation could alter TAM phenotype and subsequently improve immune response [39]. Some researchers present functionalized ligand onto nanoparticles to enhance macrophage-targeting capability and remodel their function [40,41]. Kulkarni et al. conjugated signal-regulatory protein-α (SIRPα)-blocking antibodies onto LNPs, while simultaneously loaded a small-molecule inhibitor of macrophage colony-stimulating factor 1 receptor (CSF1R). The SIRPα-blocking antibody significantly enhanced binding of nanoparticles and macrophage, and both the functionalized ligand and drug helped to reprogram TAMs to a pro-inflammatory phenotype, leading to tumor regression and survival [42].

Danger signal delivery especially STING agonists is a potential strategy that has been shown to stimulate innate immune response and remodel the tumor microenvironment. One major challenge of this strategy is promoting cytosolic drug delivery. Some advances have been achieved lately [43,44]. Daniel et al. reported polymersomes for cGAMP delivery. The pH-responsive formulation could mediate endosomal escape of cGAMP and increase drug activity by several orders of magnitude compared to free cGAMP. Treatment with this nanomedicine resulted in an 11-fold decrease in the tumour growth rate and significant increase in the survival time relative to free cGAMP [45]. Though some novel materials have been developed for efficient danger signal delivery, one requirement for immunostimulation is that the cells have functional sensor proteins. STING heterogeneity and epigenetic silencing in tumors remains a problem [46]. Protein-based biomimicking nanomedicine as a drug delivery carrier could solve this problem. Yanpu et al. developed recombinant TM-deficient STING protein as cGAMP carrier to induce near-complete self-assembly of STINGΔTM (14 nm) into tetramers (29 nm), which is necessary for the binding and phosphorylation of TBK1 and initiation of downstream pathway. The formulation can trigger STING signaling independent of endogenous STING [47]. When applied as adjuvant, cGAMP-STINGΔTM induced strong humoral and cellular immune responses *in vivo* and showed great antitumor therapeutic efficacy.

Nanomedicine following *in situ* injection could be trapped in the tumor's dense extracellular matrix composed of a collagen-rich hydrogel [48,49]. Immunomodulatory agents delivered in this way could maximize accumulation in the TME, while minimize systemic immunostimulation and cell death. A number of clinical trials are currently evaluating direct intratumoral injection of immunotherapies [50]. Yingzhong et al. intratumorally administered an ionizable lipid to induce robust immunogenic cell death (ICD) and enhance tumor cell transfection. With encapsulated self-replicating IL-12 RNA, the formulation led to rejection of large established tumors and immune memory [51]. This multifunctional single-agent immunotherapeutic is benefit to clinical translation.

Targeting the innate and adaptive immune systems with nanoparticles provides new pathways for immunotherapy. It is hopeful that nanotechnology-based immunotherapy could be an important complement to current therapies that focus on tumor cells.

Perspective

Non-efficient delivery to the targeted diseased tissue is the major challenge for nanomedicine translation [52]. Some researchers grafted anti-fouling coatings such as PEG [53] and leukocyte membranes [54] to the nanoparticle surface in order to reduce nanoparticle sequestration by the liver and resident cells, showing enhanced circulation time and improved accumulation in tumors. Interestingly, recent study showed that, via adjustment of the lipid type (permanent cationic and anionic or ionizable cationic) and

its molar percentages, lipid nanoparticles (LNPs) could be systematically engineered to deliver mRNA into specific organs [55]. Similar result has shown in RNA-lipoplexes vaccine, where near-neutral and slightly negative particles (optimized charge ratio of 1.3:2) provided an exclusively splenic target [56]. Facing the poor tumor accumulation and challenged EPR effect, the strategies to enhance tumor target in an active mechanism are desired. And further efforts to elucidate the mechanisms underlying active transport are required to facilitate its clinical translation.

Immune cells in tumor have been recognized as a considerable target for precise and effective nanomedicine design. Recent progress about reprogramming of myeloid cells at molecular and genetic level provide new opportunities for nanomedicine. In addition, further understanding of nano-bio interaction contribute to bio-inspired platform and proper administration route to enhance immunotherapy. However, there is a growing need to further characterization of the tumor immune microenvironment and its distinct classes and subclasses, which relate to the likelihood of response to immunotherapeutics [57]. And experimental models maximally matching patient tumors and immune compartments are desired.

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