



Macrophages mediated biomimetic drug delivery systems

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Abstract

Taking advantage of their enhanced permeability and retention (EPR) effect, nanomedicines have been extensively studied for targeted drug delivery to tumor tissues. However, tumor heterogeneity restricts the EPR effect and drug penetration into tumors, and nano-formulations only generate a limited therapeutic improvement in clinical settings. Macrophages have the inherent ability of tumor homing, stealth in blood circulation, and phagocytosis of particles. In this short review, we categorize and discuss in-depth recent works using macrophages as carriers for delivery in this growing field of bioinspired research.

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Introduction

Over the past decades, nanomedicines comprised of cytotoxic chemotherapeutic agents and nano-carriers by conjugation or encapsulation, generally with size ranging from 10 nm to 200 nm, have been approved efficiently for cancer therapy by virtue of their increased tumor accumulation and targeting via the enhanced permeability and retention effect (EPR) [1,2]. Although nanomedicines have remarkably reduced the side effects of small molecular chemotherapeutics, less enhanced therapeutic efficacy have been obtained. One of several examples is Doxil, a PEGylated liposome-encapsulated form of doxorubicin that has been approved for treatment of Kaposi's sarcoma and other cancers [3]. Unlike the mature and tightly organized microvasculature in normal tissues, which are impermeable to nanomedicines, tumor microvasculature has a disorganized and defective architecture with wide fenestrations of tens to hundreds nanometers, thus allowing for the extrava-

sation of nanomedicines [4,5]. Moreover, because tumor tissues lack effective lymphatic drainage, they exhibit abnormal molecular and fluid transport dynamics and can trap nanomedicines that extravasate from the blood. Thus, rational design of next-generation nanomedicines with nano-property integration and synchronization could be a promising strategy to improve therapeutic efficacy [6].

Macrophages as Drug Delivery Cellular Carriers

Recently, the biomimetic delivery system (BDS) has been emerging as a novel strategy to actively carry payloads to the tumor sites. The BDS shows its superiority over other cancer targeted drug delivery systems in the aspects of inherent tumor-homing tendency and biocompatibility [7]. Macrophages, as its name implies, are characteristic of non-immunogenicity, which endow them long enough blood-circulation times, and impressive phagocytosis that enables them to internalize and



withstand considerable drug loadings [8], both of which are prerequisites for drug delivery carriers. Additionally, compared with mesenchymal or neural stem cells, macrophages are circulating cells that are more abundant, and can be more easily separated, loaded *in vitro* with drugs, and reintroduced into the circulation. Of most importance, macrophages constitute a dominant leukocyte population in tumors (up to 50% of the cell tumor mass) [9-11]. Independent of the EPR effect, macrophages exhibit an intrinsic homing property mediated by various chemo-attractants, enabling them to migrate to tumors [12]. For example, one of the body's responses to the presence of a malignant neoplasm is the recruitment of peripheral blood monocytes into the tumor, induced into the tumor mass by a chemoattractive gradient. Once the monocytes cross the endothelial basement membrane, they differentiate into macrophages which can infiltrate a tumor referred as tumor-associated macrophages or TAMs.

Several drug-delivery systems using macrophages have been reported, with excellent therapeutic effects [13-15]. In this treatment scenario, macrophages would be permitted to take up nanoparticle-based therapeutics and deliver them into the tumor site. Once recruited into the tumor, the macrophages can still maintain the cargo nanoparticles and then migrate/chemotax to the hypoxic regions of the tumor. Once in place, the nanoparticle-based therapeutic function could be initiated and result in total tumor destruction and remission with a greatly decreased risk of tumor regrowth and metastasis.

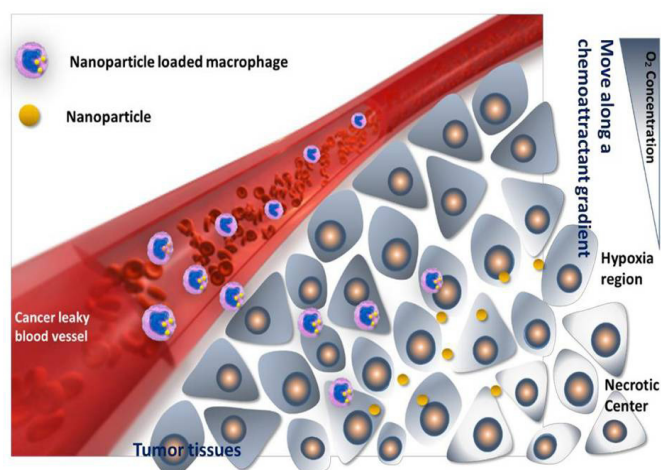


Figure 1: Schematic of Macrophage mediated biomimetic drug delivery into the hypoxic region of tumor.

Some investigators suggested combining cell mediated BDS with photothermal therapy [16-20]. Clare et al. demonstrated Au nanoshells laden macrophages, which can be taken up into a tumor and once in place, to succumb to Au nanoshell-based photoinduced cell death using NIR light. The disadvantages associated with this method lie in its inconvenience to operate, as precise instruments are required. Other reports tried to load chemotherapeutic agents containing nanomaterials into cellular vehicles [15,21,22]. Zhang et al. constructed a BDS by loading meaningful amount of doxorubicin into macrophage without affecting the viability of the cells and the BDS shows a promising anti-cancer efficacy in terms of tumor suppression, life span prolongation and metastasis inhibition, with reduced toxicity. However, the drug loading content seems too low to be clinically meaningful in most cases. To reduce the harmfulness of treating agents to the cellular vehicles themselves, some studies anchored drug containing nanomaterials at the surface of cells by chemical reactions [23-26], while others developed a BDS by

linking prodrug to the related enzyme expressing macrophages [27,28]. Yang et al. demonstrate the feasibility of immobilizing nanoparticles including polyamidoamine (PAMAM) dendrimers and quantum dots (Qdots) to the macrophage surface through cell surface chemical modification. Troyer et al. designed a system based on InCE-expressed macrophage cell delivery that can carry both a prodrug and an activated enzyme to the cancer site. The prodrug/activated enzyme system can prolong the life of *i.p.* pancreatic tumor bearing mice significantly. These systems exhibited minimal toxicity to the cellular vehicles and healthy tissues, but perhaps the complicated operating procedures resist their possible clinical application. Alternatively, ligand-receptor interaction is a method that requires no cellular modification [29,30]. By taking advantage of the specific interactions between HA and macrophages, Rubner and Mitragotri developed HA-functionalized cellular back-packs, which exhibited a strong attachment to macrophages and impressive phagocytosis-resistance [30]. However, the attachment's potential interference with specific cellular functions and the transendothelial migration process is a concern.

Challenges and Future Prospects

Although taking advantages of macrophages may fabricate truly "active" nanomedicines towards tumors and some systems have shown potential for cancer treatment, the field is still in its infancy and several key challenges remain.

The off-target recruitment of macrophages has not entered the spotlight, but it may be a crucial issue for the future clinical applications. Various complications of cancer could result in the recruitment of macrophages into unwanted sites. For instance, as in other nanomedicine systems, the liver, spleen and even lung are the organs that sequester these drug-loaded macrophages [31,32]; the toxicity to these organs may prevent the clinical translation of these delivery systems.

The direct-loading of small molecules in macrophages leads to unsatisfactory loading composition or fast drug release, resulting in limited drug delivery to target cells [33]. The cells stopped proliferating after drug loading and size expansion. So when it comes into possible clinical application, perhaps the low amount of drug concentration and complicated operating procedures may impeded its way.

Nevertheless, as an emerging technology, macrophage based active nanomedicine has opened new perspectives on overcoming the current limitations of EPR-based drugdelivery systems for cancer treatment. In future, great efforts should be made in the rational design of a delivery system that synchronizes the functions of macrophages and nanomedicines to address the existing problems and achieve high therapeutic efficacy.

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