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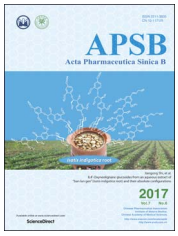

REVIEW

Leukocyte-derived biomimetic nanoparticulate drug delivery systems for cancer therapy

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Abstract Precise drug delivery to tumors with low system toxicity is one of the most important and challenging tasks for pharmaceutical researchers. Despite progress in the field of nanotherapeutics, the use of artificially synthesized nanocarriers still faces several challenges, including rapid clearance from blood circulation and limited capability of overcoming multiple physiological barriers, which hamper the clinical application of nanoparticle-based therapies. Since leukocytes (including monocytes/macrophages, neutrophils, dendritic cells and lymphocytes) target tumors and can migrate across physiological barriers, leukocytes are increasing utilized as carriers to transfer nanoparticles to tumors. In this review we specifically focus on the molecular and cellular mechanisms of leukocytes that can be exploited as a vehicle to deliver nanoparticles to tumors and summarize the latest research on how leukocytes can be harnessed to improve therapeutic end-points. We also discuss the challenges and opportunities of this leukocyte-derived nanoparticle drug delivery system.

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1. Introduction

Nanotechnology has made a great impact on medicine, especially on cancer therapy, over the past several decades[1–3]. Doxil® the doxorubicin HCl liposome injection, is used to treat over 300,000 patients annually for Kaposi's sarcoma and ovarian cancer after failure or intolerance to prior systemic chemotherapy[4,5]. The introduction of nanotechnology enables a spatiotemporally-specified drug release pattern in cancer therapy and thus improves the pharmacokinetics of drugs, reduces adverse-effects of traditional chemotherapeutics administration, and contributes to better compliance in patients[6]. Nanotechnology offers another chance for chemical and biological entities that were once excluded due to their toxicity, rapid clearance, and off-target deposition[7].

Nanoparticulate drug delivery systems are mainly constructed of synthetic lipid or polymer-based macromolecules that either physically encapsulate or chemically conjugate the drugs[8]. Despite the enormous progress in the field of nanotherapeutics, the use of artificially synthesized nanocarriers still faces several challenges, including rapid clearance from blood circulation, off-target effects and ineffectively nanoparticle transfer in patients with advanced forms of cancer[6,9]. Most nanoparticle formulations are administered systemically, and accumulate in the tumor mainly *via* enhanced permeability and retention (EPR) effects[1,10], which is generally thought to be the result of intra-tumor leaky vasculature and poor lymphatic drainage in the tumor region. However, data derived from clinical experiments suggest that the EPR effects in patients are limited[11–13]. Furthermore, nanoparticles will encounter multiple physiological barriers that influence their effectiveness, such as blood circulation, nanoparticle-protein interaction, extravasation into tumor tissue or the tumor microenvironment (TME), phagocytic sequestration and renal clearance[13,14]. Therefore, new tactics are needed to improve the therapeutic performance of nanoparticles.

To overcome these obstacles and push the limits of nanoparticle performance, there has been a recent paradigm shift towards cell-based strategies in carrier design[15]. In contrast to the relatively simple components and structures of nanocarriers, cells have a wealth of tactics to avoid attack from the immune system[16]; furthermore, nanocarriers are able to cross impermeable biological barriers and target specific regions[6]. Owing to these attractive features, cell-based targeting tactics are very exciting for the field of drug delivery due to their high specificity and long-term persistence.

Using mammalian autologous or donor-matched cells as the drug carriers has been proposed as a potential approach to efficiently deliver therapeutics to target tissues, and has gained considerable attention from researchers[9]. Red blood cells (RBC) and leukocytes are the most thoroughly investigated cell types. Owing to a long lifetime of nearly 3–4 months in body, RBC membrane coating has emerged as a promising method to prolong the circulation time of nanoparticles in the body. However, this approach lacks the ability to specifically target tumors. Since then, leukocytes have attracted attention. They function as the "military forces" in the body, capturing and destroying foreign targets that have been recognized as "invaders". Furthermore, the inherit homing ability of leukocytes to inflamed/tumor regions makes them promising carrier candidates for targeting delivery of chemotherapeutics and TME regulators[17].

One applicable strategy of leukocyte-derived drug delivery is to take advantage of the biocompatibility and bio-functions of living leukocytes to extend the *in vivo* lifetime of drugs and to use leukocytes to target inflamed tissues for site-specific drug delivery. To this end, nanoparticles can be either incorporated or surface-immobilized on leukocytes in a "hitchhiking strategy" (Fig. 1). The other approach is to coat nanoparticles with leukocyte-derived membrane components, which is generally known as a "ghost-cell" strategy (Fig. 1). The "ghost cell" still preserves the intact membrane proteolipid components on the surface after an extraction and isolation process. The nanoparticles coated with plasma membranes[18] or cell-derived extracellular vesicles[19] can preserve the physicochemical properties of synthetic nanomaterials while acquiring complex cellular functions derived from leukocytes.

Here we review recent progress on leukocyte-derived nanoparticulate drug delivery systems. We start with an overview of features of leukocytes—monocytes/macrophages, neutrophils, dendritic cells and lymphocytes—that favor nanoparticle drug delivery, and also summarize recent applications that show how researchers design delivery platforms based on these features. At the end, we point out the challenges and opportunities of applications that use leukocytes in the construction of nanoparticulate drug delivery systems.

2. Cellular and molecular mechanisms involved in tumor targeting of leukocytes

In every step of tumor progression, leukocytes are recruited into the TME through leukocyte infiltration/extravasation[20], and participate in the regulation of immune surveillance[21]. The infiltration is regulated by various chemokines and cytokines produced by tumor cells and other cells that occupy the TME[8]. Once leukocytes infiltrate into tumor tissues they establish an inflammatory microenvironment[22], where leukocytes are engaged in a dynamic and extensive crosstalk with surrounding tumor cells[23]. Since tumor-infiltrating leukocytes are indispensable components in the progression of the tumor and TME, and each type of cell has its own set of unique characteristics[24], a deep understanding of the roles of different types of leukocytes that are involved in immune surveillance would help us to develop novel targeted delivery strategies to kill tumor cells and regulate the TME. We summarize the basic properties of leukocytes in Table 1.

2.1. *Monocytes/macrophages*

Macrophages, derived from monocytes, are vital regulators of the innate immune system[8]. The typical feature of macrophages is that they tend to migrate toward pathological regions, typically inflammation sites and tumors, along chemoattractant gradients[20]. Tumors and the surrounding stroma cells can secret chemoattractants, such as colony stimulating factor-1 (CSF-1) and chemokine ligand 2 (CCL2)[25,26], to recruit macrophages and monocytes to migrate to tumor tissue. Macrophages also tend to localize in hypoxic areas. Therefore, this tumor-tropic property of macrophages can be employed in the delivery of drug/diagnosis agents. Moreover, extracellular materials such as polysaccharides, complement, endotoxins and Fc-segment of immunoglobulins and low density lipoproteins can be recognized and internalized by macrophages, providing an opportunity to load nanoparticles into macrophages[27]. As a result, macrophages are attractive as carriers for therapeutic delivery.

Owing to intracellular degradation, loading bare drug directly into macrophages would probably lead to premature drug inactivation combined with uncontrolled drug release[27], result in limited

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