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Drug delivery to macrophages: Challenges and opportunities

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ABSTRACT

Macrophages are prevalent in the body and have roles in almost every aspect of human biology. They have often been considered a subject to avoid during drug delivery. However, with recent understanding of their diverse functions in diseases, macrophages have gained increasing interest as important therapeutic targets. To develop drug carriers to macrophages, it is important to understand their biological roles and requirements for efficient targeting. This review provides an overview of representative carriers and various approaches to address challenges in drug delivery to macrophages such as biodistribution, cellular uptake, intracellular trafficking, and drug release.

1. Introduction

Macrophages play various roles in mammalian biology, including development, homeostasis, repair, and innate immunity [1]. Accordingly, macrophages have been an important subject of drug delivery research. Macrophages are the main hosts of intracellular pathogens in chronic infectious diseases and, thus, pursued as a therapeutic target for intracellular delivery of antibiotics. Moreover, macrophages have gained increasing interest as a therapeutic target for cancer immunotherapy due to their complex roles in tumor microenvironment. Although traditional drug delivery research has often viewed macrophages as an undesirable interceptor of drug carriers, it is worthwhile to consider the biological roles of macrophages in a broader therapeutic context and actively exploit them as a target for drug delivery. In this review, we discuss various approaches to deliver drugs to macrophages in recent literature, their contribution to therapeutic outcomes, and remaining challenges in macrophage-targeted drug delivery.

2. Biological roles of macrophages

The best-known source of tissue-resident macrophages is blood monocytes, derived from hematopoietic stem cells in the bone marrow, which undergo several differentiation steps to commit to a monocyte lineage [2] (Fig. 1a). Circulating monocytes are recruited to various tissues and differentiated into macrophages according to the environmental cues [3,4]. In addition, recent studies find that tissue-resident macrophages may also be derived from embryonic precursors, such as microglial cells from yolk sac and Langerhans cells from fetal liver, and maintained by self-renewal [5]. Tissue-resident macrophages provide diverse functions according to the anatomical locations. Kupffer cells in the liver are mainly involved in waste disposal process, such as clearance of microbes and cell debris from the blood [6]; alveolar macrophages in the lungs serve as the first-line defender against inhaled pathogens [7]; and red pulp macrophages in the spleen are responsible for removal of senescent erythrocytes and iron flux regulation [8]. In addition to the reticuloendothelial system (RES), several other tissues have resident macrophages with distinct functions, such as osteoclasts (mineral disruption) and bone marrow macrophages (erythropoiesis support) in the bone, microglia cells (immune surveillance) in the brain, intestinal macrophages (intestinal homeostasis maintenance) in the gastrointestinal tract, and Langerhans cells (interaction with T lymphocytes) in the skin [6].

Macrophages may be categorized along a linear scale according to their activation status: M1 macrophages (classically activated macrophages) on one extreme and M2 macrophages (alternatively activated macrophages) on the other (Fig. 1b) [2]. Activation into the M1 phenotype occurs via cellular or exogenous stimuli like interferon-γ (IFN-γ), tumor-necrosis factor (TNF), and lipopolysaccharide (LPS). M1 macrophages secret pro-inflammatory cytokines and oxygen and nitrogen radicals to help destroy foreign organisms and tumor cells [2,9]. On the other hand, polarization into the M2 phenotype involves interleukin-4 (IL-4), IL-13, and transforming growth factor β (TGF-β), leading to the production of immunosuppressive cytokine IL-10 [10]. M2 macrophages are involved in the resolution of inflammatory responses, by participating in debris scavenging, tissue remodeling, and angiogenesis [2,9,10].

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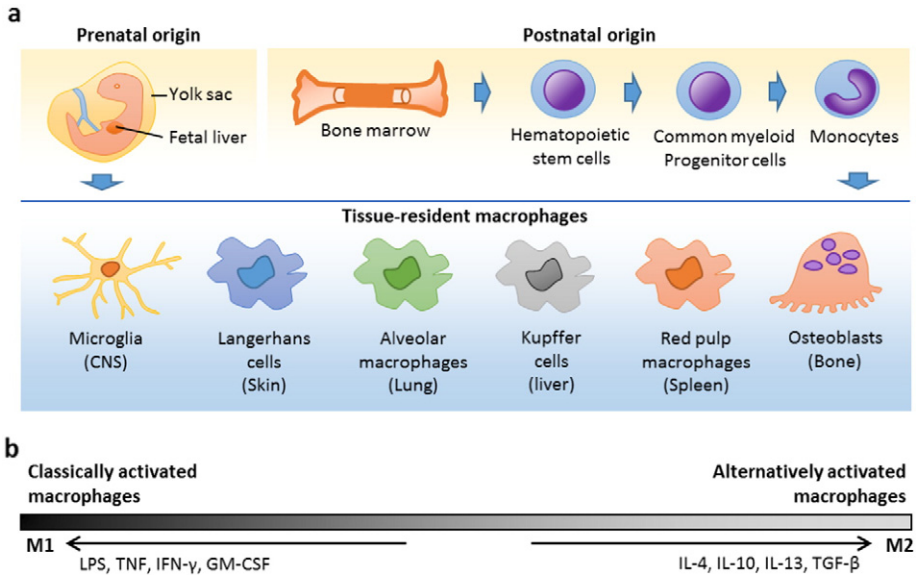

Fig. 1. (a) Origin of tissue-resident macrophages: bone marrow-originated monocytes (most well-known), fetal liver-derived monocytes, and yolk sac-derived macrophages [6]. (b) Linear scale designating two activation states of macrophages, M1 and M2, and responsible stimuli. Figures adapted from [2].

Recently, tumor-associated macrophages (TAMs), macrophages localized in tumors or tumor-enriched niche, have gained significant interest in the field of cancer therapy [11–13]. TAMs are a prominent component of solid tumors, often comprising a major fraction of the cell mass [11]. TAMs are derived from monocytes recruited by tumor cells via soluble mediators like chemokine (C–C) ligand 2 (CCL2) [14]. In' monocytes are exposed to anti-inflammatory molecules like IL-4, IL-10, TGF-β and prostaglandin E2 and polarized to M2-like macrophages [11,14]. These macrophages possess poor antigen presenting ability and produce soluble factors to suppress anti-tumor immune systems [11]. For example, TAMs suppress the production of IL-12, a cell-stimulating cytokine to promote anti-tumor activities of natural killer cells, T helper 1 cells (Th 1), and $CD4^+$ T cells [15]. In addition, TAMs produce chemokine CCL22 to mediate trafficking of regulatory T cells (Treg) and suppress tumor-specific T cell immunity [16]. TAMs can also encourage tumor invasion via non-immune processes, for example, by producing a high concentration of vascular endothelial growth factor (VEGF), which promotes vasculogenesis and angiogenesis [17].

3. Macrophages in drug delivery

3.1. Macrophages as a target for drug delivery

Macrophages have long been an important target for drug delivery. For example, antibacterial agents are delivered to macrophages for the treatment of intracellular infections, such as tuberculosis, salmonellosis, and brucellosis. These infections are caused by bacteria residing in host cells, which allow them to replicate, survive, and cause damages to the host. Macrophages provide an immune-privileged niche and act as reservoirs for these intracellular pathogens [18,19]. *Leishmania donovani*, a deadly intracellular protozoan, also inhabits and proliferates in macrophages to cause visceral leishmaniosis [20–22]. Infections with these pathogens are currently managed by antibiotics, but the therapeutic outcomes are disappointing due to their inefficient delivery to the pathogens in macrophages [23,24]. Drug delivery systems that can target macrophages are expected to enhance co-localization of antibiotics and intracellular pathogens and, thus, improve the therapeutic effects.

Macrophages are latent reservoirs for human immunodeficiency virus type-1 (HIV-1) [25]. Macrophages allow the entry of HIV-1 via CD4, which interacts with the envelope glycoprotein gp120 of the virus [26]. Macrophages can resist the cytopathic effect of HIV-1 and disseminate the virus throughout the body, thus making an important therapeutic target for the treatment of HIV-1 infection [26]. Macrophages have also been pursued as a therapeutic target for the treatment of Gaucher disease, a genetic disorder leading to the deficiency of lysosomal enzyme activities [27]. Since this enzyme dysfunction mainly occurs in macrophages, efforts have been made to deliver replacement enzymes or enzyme activators specifically to macrophages [27–29]. In addition, macrophages play a critical role in rheumatoid arthritis (RA), as their overpopulation in the inflamed synovial membranes leads to acute and chronic damages to the joints [30]. Hence, drug delivery systems that can specifically inactivate or deplete macrophages in the joints have been of interest in the field of RA therapy [31–33].

In cancer therapy, macrophages have typically been considered an undesirable mechanism for premature clearance of drug delivery systems and, thus, a subject to avoid during circulation. However, with the increasing awareness of the complex roles of TAMs in tumor progression, macrophages are revisited as a potential target in cancer therapy [12,14,34]. TAMs have been targeted in two ways in cancer therapy: one is to deplete TAMs and prevent its tumor-promoting activities, and the other is to reprogram TAMs into more M1-like pro-inflammatory phenotypes and enhance their immunostimulatory properties. These approaches employ chemotherapeutic agents [14,35–37], bisphosphonates [38,39], inhibitors of specific signaling pathways [40], or cytokines [41]. Trabectedin is a new marine alkaloid with anticancer activities, recently approved for the treatment of soft tissue sarcoma [36,42]. Germano et al. reported that trabectedin caused selective depletion of monocytes and macrophages in blood, spleens, and tumors and reduction of angiogenesis, suggesting that TAM inhibition may be the main mechanism of its anticancer activities [37]. Docetaxel, a taxane anti-mitotic agent, was suggested to play multiple roles in modulation of myeloid-derived suppressor cells (MDSC) in tumor-bearing hosts: it promoted the apoptosis of immunosuppressive MDSCs in 4T1-neu mammary tumor-bearing mice and also induced polarization of MDSCs toward an M1-like phenotype [43]. Bisphosphonates such as zoledronate and alendronate are generally used for the treatment of cancer-induced bone diseases and known to have direct anti-tumor effects [39]. In addition, bisphosphonates are readily taken up by macrophages to induce their apoptosis and inhibit the production of pro-angiogenic matrix metallopeptidase 9 (MMP-9) [39]. It was also shown that zoledronate helped TAMs to restore M1 antitumoral phenotype, extending the overall survival of tumor-bearing mice [44]. Inhibitors of colony-stimulating factor 1 receptor (CFS1R) blocked the CSF1/CSF1R signaling pathway, which decreased the