

Role of macrophage in nanomedicine-based disease treatment

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ABSTRACT

Macrophages are a major component of the immunoresponse. Diversity and plasticity are two of the hallmarks of macrophages, which allow them to act as proinflammatory, anti-inflammatory, and homeostatic agents. Research has found that cancer and many inflammatory or autoimmune disorders are correlated with activation and tissue infiltration of macrophages. Recent developments in macrophage nanomedicine-based disease treatment are proving to be timely owing to the increasing inadequacy of traditional treatment. Here, we review the role of macrophages in nanomedicine-based disease treatment. First, we present a brief background on macrophages and nanomedicine. Then, we delve into applications of macrophages as a target for disease treatment and delivery systems and summarize the applications of macrophage-derived extracellular vesicles. Finally, we provide an outlook on the clinical utility of macrophages in nanomedicine-based disease treatment.

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1. Introduction

1.1. Overview of macrophage

In the development of disease, leukocytes, that is, white blood cells (WBCs), are activated for immunoreaction and target the invading pathogens. WBCs comprise several subtypes, including neutrophils, lymphocytes, monocytes, eosinophils, and basophils, which can be identified by different surface markers. All of these subtypes work independently as well as cooperatively, and their importance in disease mechanisms has been extensively studied and described (Murray & Wynn, 2011b; Wynn et al., 2013; DeNardo & Ruffell, 2019).

As part of the innate immune system, macrophages have high plasticity and respond to their microenvironment by changing their phenotype (Locati et al., 2020). Similar to dendritic cells, macrophages recognize 'nonself' through membrane-bound or intracellular pattern-recognition receptors (PRRs) and prompt the secretion of inflammatory cytokines and chemokines, after which they participate in further immune responses (DeNardo & Ruffell, 2019). To fit into different microenvironments, macrophages can be polarized into classically activated M1-macrophages, alternatively activated M2-macrophages and other phenotypes. It is generally accepted that macrophage polarization is a tightly regulated process under the control of gene transcriptional networks in response to microenvironmental stimuli, which affects macrophage phenotype resulting in infinite numbers of phenotypes and a spectrum of diverse behaviors (Lawrence &

Natoli, 2011; Xue et al., 2014). The widely accepted nomenclature distinguishing M1- and M2-macrophages is a matter of much discussion. The term 'classically activated' is used to designate the effector macrophages that are produced during cell-mediated immune responses. M1 macrophages play a major role in proinflammation and antimicrobial mechanisms. Following tissue injury or bacterial, protozoan, and viral infections, M1 macrophages express proinflammatory cytokines including tumor necrosis factor (TNF), interleukins -1 (IL-1), IL-12, and IL-23, and inducible nitric oxide synthase, which is an essential step in destroying the pathogen (Nahrendorf & Swirski, 2016). The pro-inflammatory cytokines that are produced by M1 macrophages are an important component of host defense, but they can also cause extensive damage to the host, leading to many diseases, such as Crohn's disease (Buisson et al., 2016), multiple sclerosis (Nally et al., 2019), and rheumatoid arthritis (Keewan & Naser, 2020). The term 'alternatively activated' macrophages was proposed for macrophages that are generated in the presence of IL-4 upregulating the expression of the mannose receptor (Stein et al., 1992). This seems a bit inaccurate as it implies that this is the only alternative activation mechanism for macrophages; whereas recent studies have demonstrated other mechanisms of alternative activation (Hurdal et al., 2019). Mounting evidence suggests that the M2 designation encompass cells with dramatic differences in their biochemistry and physiology and include essentially all other types of macrophages, except M1 (Mosser & Edwards, 2008) M2 macrophages have an immunosuppressive function and

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participate in pathogen clearance, tissue repair, and tumor progression. For example, transforming growth factor- β 1 (TGF β 1), produced by M2 macrophages, is involved in wound repair and tissue regeneration (Roberts et al., 1986); these macrophages are referred to as wound-healing macrophages. M2 macrophages have also been proven to be associated with tumorigenesis promotion (Murray & Wynn, 2011a). More in-depth studies revealed that the M2 phenotype can be subdivided into M2a (induced by IL-4 or IL-13), M2b (induced by IL-10), and M2c (induced by a combination of immune complexes and lipopolysaccharide) (Mantovani et al., 2004). Newer findings argue against such a simple categorization, pointing to the requirement for higher-resolution approaches to decode the complexity of macrophage activation. Apart from the previously mentioned phenotypes, tumor-associated macrophages (TAMs) are increasingly viewed as being of great relevance in the tumor microenvironment (TME). As the major tumor-infiltrating immune cell population, TAMs commonly help cancer cells by promoting tumor immune escape, angiogenesis, tumor growth, and metastasis (Scali et al., 2016; Ngambenjawong et al., 2017). The dissimilarity in function between various macrophage polarization states makes the balance of macrophages essential for body homeostasis. Thus, nanomedicine can enhance therapeutic efficacy by regulating M1/M2 macrophages to an equilibrium state, such as converting tumor-associated macrophages from M2 to M1 (Ovais et al., 2019; Figueiredo et al., 2020).

1.2. Overview of nanomedicine

In many diseases, traditional treatment strategies have limited therapeutic effects, making the advent of nanomedicine an unparalleled opportunity to advance the treatment of such diseases. The field of nanomedicine is developing rapidly on many fronts, including drug delivery, vaccine development, antibacterial development, diagnosis and imaging tools, wearable devices, implants, and high-throughput screening platforms (Pelaz et al., 2017). Many research findings are being translated into viable clinical products. Nanoparticles (NPs) are essential components of nanomedicine and have many unique advantages, including large surface-to-volume ratio, small size, the ability to encapsulate various drugs, and tunable surface chemistry. This holds the potential of delivering new kinds of treatment potentially superior to conventional disease therapies (Xu et al., 2015). Various materials have already been synthesized into NPs.

NPs have been used to deliver a wide range of therapeutics for cancer treatment, which have the capabilities of improving the safety and efficacy of clinically approved encapsulated antineoplastic payloads, including doxorubicin (DOXIL) (Gabizon et al., 2016; Gao et al., 2018), irinotecan (Onivyde) (Liu et al., 2019), paclitaxel (Abraxane) (Dancy et al., 2020; Su et al., 2020), and vincristine (Marqibo) (Zhao et al., 2017). Many other NPs, targeting related cytotoxic payloads such as daunorubicin (Halley et al., 2016), cytarabine (Wei & Tiong, 2017), platinum derivatives (Zeng et al., 2020), and more recently, molecularly targeted inhibitors are

undergoing clinical development for cancer treatment (Min et al., 2015). Extensive studies have demonstrated that NPs have the following potential applications: (i) extending drug release and systemic pharmacokinetics, (ii) reducing the need for toxic drug solvents and prolonging the time of intravenous infusions, (iii) facilitating combination treatments, and (iv) increasing targeted tumoral drug accumulation (Prabhakar et al., 2013).

In addition, antibody-drug conjugates (ADCs) is an emerging emphasis in nanomedicine for the treatment of a variety of cancers. ADCs are composed of monoclonal antibodies (mAbs) conjugated to potent cytotoxic drugs through various linker technologies (Beck et al., 2017). The major advantage of ADCs is that they can deliver cytotoxic drugs selectively to target cancer cells through cancer-associated membrane receptors, thereby overcoming the limitations of traditional chemotherapy and targeted therapies. ADCs exert anticancer activity by multiple mechanisms. ADCs recognize and attached to a specific target, after which, the ADC-antigen complex is internalized by endocytosis (Chari, 2008). Through a series of cellular reactions, the cytotoxic drug is released to the cytosol, inducing apoptosis (Chalouni & Doll, 2018). ADCs also induce other mechanisms including antibody-dependent cytotoxicity and/or complement-dependent cytotoxicity (Khera & Thurber, 2018). Currently, 5 ADC drugs have been approved and more than 100 ADCs are in clinical trials (Chau et al., 2019). We will also talk about this in its current applications later in the review.

Cellular uptake of nanomedicines is generally through phagocytosis (particles larger than 0.5 μ m) and pinocytosis (uptake of fluids and solutes) (Patel et al., 2019). Phagocytosis is restricted to specialized phagocytic cells such as macrophages, neutrophils, monocytes, and dendritic cells. The phagocytic process begins with particle recognition and binding with receptors on the surface of the host cell, leading to the engulfment of particles into the cell and subsequent formation of phagosomes. Through a series of physical processes, the particle is transferred to late phagosomes and ultimately lysosomes, forming a phagolysosome (Sahay et al., 2010) (see Figure 2(A)). The physicochemical properties of nanomedicines often determine the efficiency of phagocytosis and the targeting effect of macrophages to the particles; these include shape, size, surface charge, suitable ligands, and so on. Table 1 lists several factors that affect the absorption of nanomedicines by macrophages.

Drug targeting of macrophages can be achieved via two strategies: passive targeting and active targeting. Tumoral drug accumulation is related to passive targeting by enhanced permeability and retention (EPR) effects, including irregular tumor vasculature, dysfunctional lymphatics, and increased cellular uptake (Khawar et al., 2015). Tumor cells create new blood vessels from existing ones to resist hypoxia and low nutrition. The newly created blood vessels possess hyperpermeability due to the components of discontinuous endothelium, which is referred to as EPR. The selective leakage of macromolecules larger than 40 kDa from tumor vessels and their accumulation in tumor tissues does not occur in normal tissues (Fang et al., 2003; 2011). NPs leak from the

Table 1. Factors affecting the targeted absorption of nanomedicines.

	Brief description	References
Factors		
Size	There are different sizes of particles suitable for different macrophage lines and different materials. Only appropriate particles can activate macrophages and be internalized. In a certain range, uptake efficiency of macrophage increases with particles' size. Furthermore, larger nanoparticles are more likely to cause M1-type polarization of macrophages.	(Ahsan et al., 2002; Ma et al., 2015; Jasinski et al., 2018)
Shape	Nanoparticles of different shapes have different endocytosis mechanisms, while spherical ones are usually relatively easy to internalize. The acicular and rod-like particles are more potent cytotoxic.	(Zhao et al., 2013; Li et al., 2016; Forest et al., 2017; Jasinski et al., 2018)
Surface charge	Charged nanoparticles are more effective in binding and delivering drugs than neutral particles. With the increase of net charge, cell uptake increased. Cations and anions with the same net charge have their advantages and disadvantages in different materials.	(Xu et al., 2009; He et al., 2010; Maurizi et al., 2015)
Ligands		
Mannose receptor	Mannose receptor is widely expressed on the surface of macrophages. Because of high affinity for mannose oligosaccharides, it's used to enhance the uptake of mannoseylated antigen in macrophage specific delivery. In particular, mannose receptors are highly expressed in TAMs, which are associated with tumor invasion, proliferation and metastasis in the microenvironment.	(Ruan et al., 2014; Ganbold & Baigude, 2018; Hagimori et al., 2018)
Folate receptor	Folate receptor is a glycoprotein with high affinity for folate, which is highly expressed in activated macrophages. Folate receptor can increase macrophage uptake through folate receptor-mediated endocytosis and selectively deliver to the site of inflammation.	(Varghese et al., 2014; Mohammadi et al., 2016; Yang et al., 2021)
CD64	CD64 is a transmembrane glycoprotein belonging to the immunoglobulin superfamily. There're some advantages for targeting macrophage, such as a strict myeloid cell distribution and the ability to bind and rapidly internalize monomer IgG. Furthermore, CD64 is up-regulated only under pro-inflammatory conditions and helps to distinguish M1 from M2 macrophage.	(Thepen et al., 2000; Moura et al., 2014; Hristodorov et al., 2015)
CD44	CD44 is a cell surface glycoprotein, which can bind to hyaluronic acid, regulate toll like receptor activation, and then enhance phagocytosis of phagocytes.	(Tran et al., 2015; Amash et al., 2016; Qadri et al., 2018)
Dectin-1	Dectin-1 is a non-conditioning β - glucan receptor overexpressed in macrophages, which plays an important role in phagocytosis of yeast by macrophages.	(Brown et al., 2002; Ohman et al., 2014)
Scavenger receptor	Macrophage take up low-density lipoprotein via scavenger receptors (SR). It also recognizes a number of distinct ligands including microbial components and mediates opsonin independent recognition and elimination. SR family are widely used in molecular targeted macrophages, including Marco, SR-A, SR-B and so on.	(Chao et al., 2013; Yu et al., 2015; Qian et al., 2017; Eisinger et al., 2020)
Peptides	Peptides with high specificity are also used for selective targeting macrophages. Besides, peptides are often combined with other ligands to enhance macrophage phagocytosis.	(Conde et al., 2015; Qian et al., 2017; Scodeller et al., 2017; Cheng et al., 2018)

tumor vasculature via the EPR effect and arrive at tumor cells and stroma, leading to the accumulation of high concentrations of antitumor drugs in the TME with a reduction in systemic side effects (Miao et al., 2015). Therefore, the EPR effect serves as a basis for the development of macromolecule anticancer therapies. On the other hand, to enhance the specificity of nanomedicines for macrophages, NPs may be modified to better adapt to high-affinity receptors on the surface of macrophages. NPs are internalized mainly through receptor-mediated endocytosis after interacting with their target antigen. The active targeting of nanoparticles does not affect their biological distribution but can enhance cell uptake (Howard et al., 2016). Some of the receptors expressed on the surface of macrophages and their utility in active targeting of macrophages are described in Table 1.

Due to the important role of macrophages in disease and their wide application in nanomedicine, researchers are increasingly focusing on nanomedicine-based treatments centered on macrophages. In this review, we will focus on three topics: (I) macrophage as a target for nanomedicine-based disease treatment; (II) applications of macrophage-based delivery systems; and (III) macrophage-derived extracellular vesicles as a new drug-delivery platform.

2. Macrophages as targets for nanomedicine-based disease treatment

Biologically, macrophages function in most immune responses; they have phagocytic and killing effects on pathogens. In addition, macrophages combine small immunogenic peptides with major histocompatibility complex (MHC) molecules to form a peptide-MHC complex. This complex is expressed on the cell surface for T cells to recognize and activate, by processing exogenous and endogenous antigens. As they remove and destroy pathogens, macrophages secrete reactive oxygen and nitrogen species, triggering substantial collateral tissue damage, which is associated with several diseases (Nathan & Ding, 2010). Beyond secreting certain components contributing to diseases, macrophages are directly involved in the occurrence and development of many diseases. Based on the special and varied role of macrophages in diseases, targeting macrophages holds great promise for treatment. In the era of tailored medicine, macrophage targeting treatment combined with nanomedicine has gained increasing interest owing to its therapeutic potential in treating a large variety of diseases. Nanomedicines with active and accurate targeting ability should first overcome three barriers: the reticuloendothelial

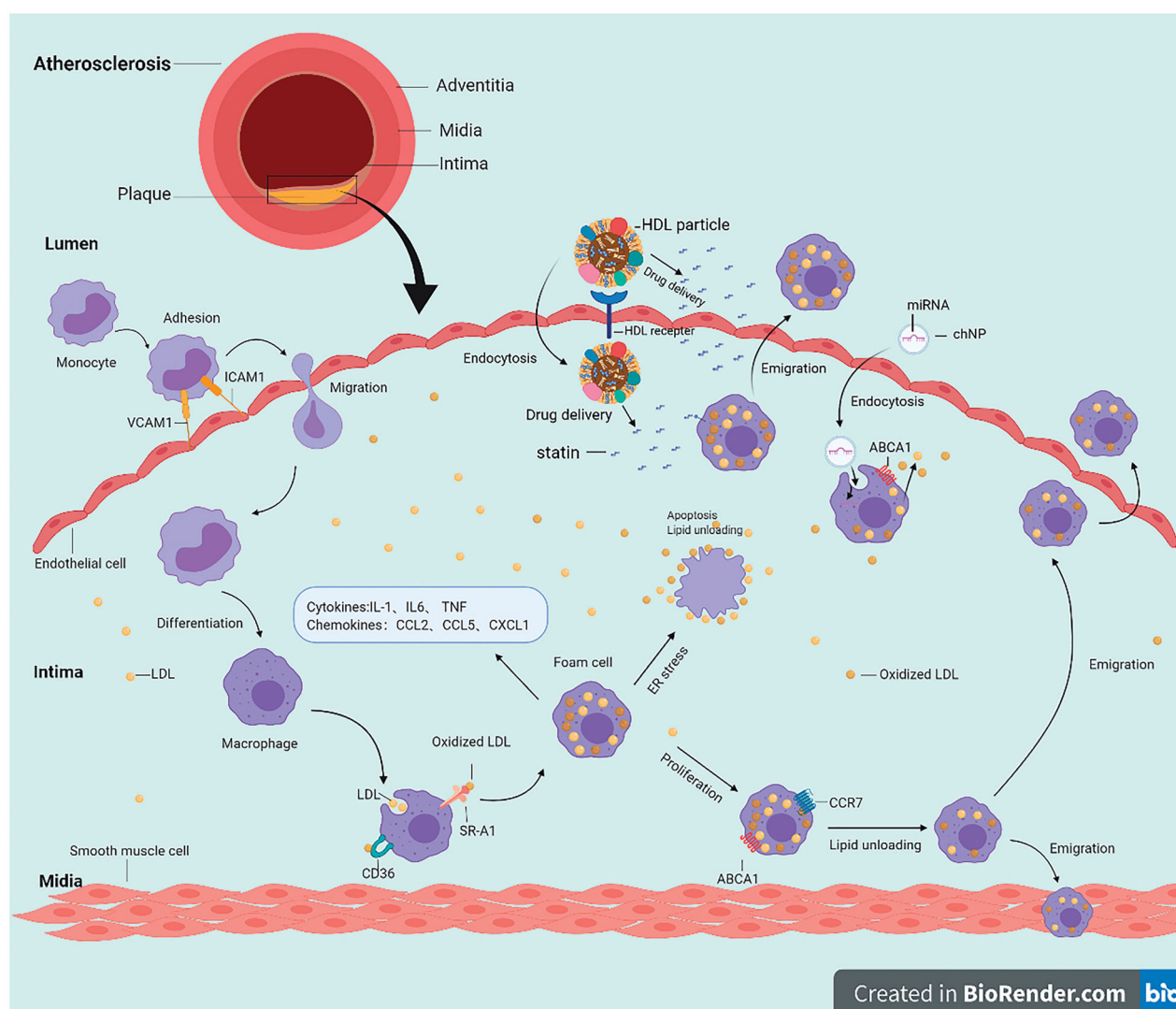


Figure 1. Mechanisms of regulating monocyte recruitment and formation of foam cells in plaques. Hyperlipidemia increases the number of monocytes. The increased levels of expressions of intercellular adhesion molecule 1 (ICAM1) and vascular adhesion molecule 1 (VCAM1) promote the infiltration of monocytes into the intima. The part of recruited monocytes differentiates into macrophages, which have a variety of scavenger surface receptors for oxidized LDL modified low-density lipoprotein (oxLDL). Then macrophages ingest oxLDL via scavenger receptor-mediated pathways, (including scavenger receptor A (SRA and CD36), and LDL by direct phagocytosis, which leads to the formation of the foam cells that are a hallmark of the atherosclerotic plaque. Oxidized LDL stimulates macrophages to produce pro-inflammatory cytokines and chemokines that enhance the inflammatory response. Overwhelming ingestion of LDL and oxLDL contributes to cellular apoptosis of macrophages resulting in the exposure of apoptotic material which potentiates inflammation with more monocyte recruitment. The ABCA1 and CCR7 expression are upregulated in foam cells. ABCA1 can reverse the accumulation of foam cells and CCR7 helps macrophage emigration from the plaque through reverse transmigration to the lumen or trafficking to the adventitial lymphatics. Based on the above principles, HDL NPs and CHNPs are well constructed.

system, vascular endothelium, and specifically suitable ligands attached to the nanoplateforms (Chen et al., 2017). In the following sections, we will discuss several representative active macrophage targeting strategies.

2.1. Macrophages as targets for inflammation

In normal immune regulations, the inflammatory response is a self-limiting process that includes an induction phase and a resolution phase. Alterations in the immunological mechanisms involved in the resolution phase give rise to excessive and persistent inflammation (Steinbach & Plevy, 2014). Undue chemokines, cytokines, and proinflammatory mediators from macrophages are closely associated with many human diseases, such as pneumonia, rheumatoid arthritis,

systemic lupus erythematosus, Crohn's disease, psoriasis, atherosclerosis, and ischemic heart disease (Singh et al., 2017). Given these facts, macrophages represent a new class of targets for promoting remission in patients with inflammation.

2.1.1. Targeting for atherosclerosis

It has been proposed that inflammation participates in the progression of atherosclerotic lesions and also influences the stability of atheromatous plaques (Libby, 2002). In general, atherosclerosis is a result of excess cholesterol circulating in the bloodstream, for which hypercholesterolemia is responsible (Li et al., 2014). In the arterial intima, macrophages derived from monocytes actively ingest the normal and modified lipid. Lack of a suitable negative feedback mechanism for uptake and abundance of lipids leads to a

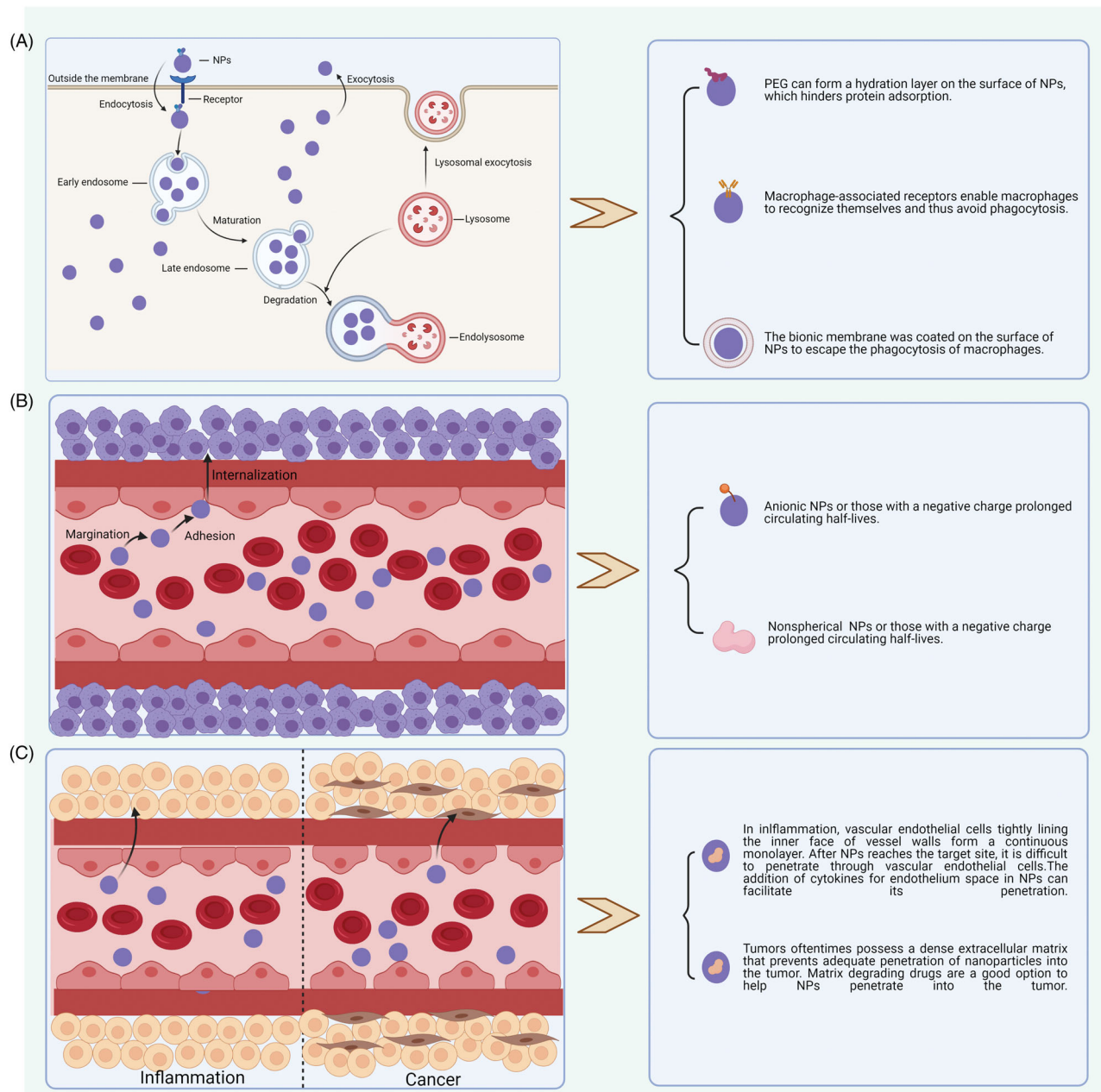


Figure 2. Obstacles encountered when NPs enter the body, and strategies to overcome these obstacles. (A) In blood vessels, plasma proteins attach to the surface of NPs and initiate the phagocytosis of NPs by mononuclear phagocyte system (MPS). It is engulfed by early endosomes in macrophages. The early endosomes matured into the late endosomes, which could degrade NPs after lysosomal fusion. The NPs can overflow at any point in the process. In order to overcome the endocytosis of the NPs by MPS, the NPs surface can be hydrated, or the bionic membrane can be placed on the surface, or the macrophages cannot recognize the NPs. (B) All NPs undergo migration, attachment and internalization in blood vessels. To prolong the half-life of NPs in the blood vessel, the ionic properties or shape of NPs can be changed. (C) The permeability of vascular endothelium to NPs is different in inflammation and cancer. In inflammation, endothelial cells line up tightly. In order for NPs to penetrate the target, it is necessary to add drugs that enlarge the endothelium space. In cancer, the vascular endothelial cells are loosely arranged, but the matrix contains fibroblasts that block the internalization of NPs. In order for NPs to penetrate into the target, it is necessary to add anti-cellulose drugs.

significantly higher accumulation of lipids in the macrophages, which eventually causes the formation of foam cells and promotes the progression of disease (Moore & Tabas, 2011; Singh et al., 2014). It is well established that the presence of cholesterol ester-enriched foam cells is the hallmark of atherosclerotic plaques (see Figure 1). The previous study showed that inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase ameliorated atherosclerotic diseases (Senokuchi et al., 2005). Reverse cholesterol transport

(RCT) is also an essential route for the disposal of cholesterol (Yu et al., 2019). HDL mediates the transport of cholesterol from the periphery to the liver, which subsequently uptakes HDL cholesterol and secretes hepatobiliary cholesterol, which is finally excreted via the feces (van der, 2010; Fisher et al., 2012). Multiple lines of evidence support the fact that enhancing foam cell cholesterol efflux by HDL particles, the first step of RCT, is a promising antiatherogenic strategy (Ouimet et al., 2019). Tang et al. designed a treatment

option, which was the administration of the short-term HMG-CoA reductase inhibitor simvastatin in a high-density lipoprotein (HDL) NP (S-HDL) combined with on-going oral statin treatment; it had already been determined that the combination could pharmacologically treat inflammation in atherosclerosis and generate long-term therapeutic benefits (Tang et al., 2015). For their own physical and biological characteristics, HDL particles are capable of targeting macrophages. In the construction of nanomaterials to treat atherosclerosis, HDL particles primarily act as a carrier to deliver drugs that protect statins from serum catabolism and increase the bioavailability of statins. Similarly, the combined use of simvastatin-loaded discoidal reconstituted HDL (ST-d-rHDL) that has plaque-targeting and cholesterol removal ability, and β -cyclodextrin (β -CD) that promotes cholesterol efflux, can increase cell membrane permeability and fluidity and enhance drug absorption that benefits the treatment of atherosclerosis (He et al., 2020). Nevertheless, one disadvantage of this combination is the difficulty of delivering the free β -CD and ST-d-rHDL to the macrophage/foam cells. In subsequent studies, β -CD could be designed to be anchored to ST-d-rHDL to form an integral model using nanomaterials, making it more appropriate for further clinical application. Apart from HDL, studies have also shown that adenosine triphosphate-binding cassette transporter (ABCA1) also relates to RCT (Frambach et al., 2020). It has been demonstrated that miR-33, an intronic microRNA (miRNA), which is a transcriptional regulator of cholesterol synthesis, reduces cholesterol efflux to apolipoprotein A1 by inhibiting the expression of the ABCA1 (Rayner et al., 2010). Nguyen et al. developed chitosan nanoparticles (chNPs) that could deliver miR-33 to macrophages and determined that the chNPs functioned to regulate ABCA1 expression and cholesterol efflux (Nguyen et al., 2019).

However, attenuating inflammation by reducing local macrophage accumulation is the more straightforward way for atherosclerosis treatment. Recently, a macrophage-specific nanotherapy based on single-walled carbon nanotubes loaded with a chemical inhibitor of the antiphagocytic CD47-SIRP α signaling axis was demonstrated to have the potential for implementing 'Trojan horse' NPs to prevent atherosclerotic cardiovascular disease (Flores et al., 2020). This nanotherapy targets early lesional macrophages, achieving disease prevention. Nanomedicine-based disease treatment targeting early lesions may be a hotspot in future research.

2.1.2. Targeting for osteoarticular diseases

The pathogenesis of some osteoarticular diseases (OADs), such as osteoarthritis (OA), rheumatoid arthritis (RA), osteoporosis, systemic lupus erythematosus, and so on, is related to macrophages. First, we will consider OADs as an example. OADs are degenerative joint diseases characterized by the loss of cartilage, changes in subchondral bone, formation of osteophytes, and inflammation of the synovium, usually involving the knee, hip, and distal interphalangeal joints (Xie et al., 2019). OADs manifest such a severe macrophage inflammatory response that a vast number of inflammatory cells secrete a high level of proinflammatory cytokines in the

OA area (Crielaard et al., 2012). Moreover, the polarization of synovial M1 macrophage exacerbates OA partially through R-spondin-2 (Rspo2) (Zhang et al., 2018). Since M1 macrophages are a potential therapeutic target for OA treatment, Chen, Liu and coworkers (Chen, Liu, et al., 2019) successfully constructed a novel photothermal-triggered NO generation platform targeting macrophages for the precise therapy of OA. They combined photothermal agents, NO, and Notch1-siRNA into a single particle to achieve drug release control. NPs can maintain controlled release of the drug in the plasma for a longer time period due to diffusion, solvent, chemical reaction, and stimuli-controlled release. The above-mentioned photothermal agents are good examples. In the following section, we will also discuss other NPs that have stimuli-controlled release.

M1 macrophages exhibit a unique metabolic characteristic called the Warburg effect and also known as aerobic glycolysis (Regdon et al., 2019). Warburg effect is a distinctive form of cellular metabolisms with high levels of glucose uptake and increased conversion of glucose to lactose in the glycolytic pathway. Among these, induced production of iNOS and H₂O₂ drives the repolarization of macrophages (Orihuela et al., 2016). Inspired by these findings, Tang et al. developed modified zeolitic imidazolate framework-8 (ZIF-8) NPs loaded with *s*-methylisothiouria hemisulfate salt (SMT) for gas regulation and metabolic reprogramming of synovial macrophages in OA (Zhou et al., 2020). Moreover, Chen, Liu et al. constructed photothermal-triggered NO nanogenerators NO-Hb@siRNA@PLGA-PEG (NHsPP) by assembling photothermal agents and NO molecules within NPs. The combination of various kinds of nanomaterials may thus compensate for individual defects and this practice is now becoming mainstream.

Fukui and colleagues found that RA patients displayed an increased M1/M2 ratio, which promotes osteoclastogenesis (Fukui et al., 2018). RA is an immune-mediated inflammatory disease that results in synovitis, cartilage destruction, and even loss of joint function (Ni et al., 2020). The pathogenesis of RA is complicated and still not completely clarified. Macrophages in RA under oxygen-deficient conditions increased expression of hypoxia-inducible factor-1 α (HIF-1 α) and induced the generation of reactive oxygen species (ROS) (Wang et al., 2017). Recent publications, inspired by these results, reported on the development of manganese ferrite and ceria nanoparticle-anchored mesoporous silica nanoparticles (MFC-MSNs). Not only did these MFC-MSNs scavenge ROS and produce O₂, leading to efficient polarization of M1 to M2 macrophages, but they also encapsulated the anti-rheumatic drug methotrexate as a drug-delivery vehicle to achieve sustained release (Kim et al., 2019). Similarly, Jain et al. packaged an anti-inflammatory cytokine, IL-10, encoding plasmid DNA into non-condensing alginate-based NPs. In particular, the surface of the nano-carriers was modified with tuftsin peptide to achieve active macrophage targeting (Jain et al., 2015). Early research findings of high levels of expression of vasoactive intestinal peptide (VIP) receptor, folate receptor-beta (FR- β), toll-like receptors, and other relative-receptors on the surface of macrophages in RA supported this direct targeting strategy (Xiao et al., 2019). Conjugates of

G5 PAMAM dendrimer methotrexate (G5-MTX) can specifically bind to folate receptor-overexpressing macrophages. Further, G5-MTX is demonstrated to have therapeutic and preventive effects on an adjuvant-induced inflammatory arthritis model (Thomas et al., 2011; Qi et al., 2015). Targeting low doses of VIP self-associated with sterically stabilized micelles (SSMs) has been developed for RA (Sethi et al., 2013). These studies suggest appropriate NPs are promising for the treatment of RA and other inflammatory disorders. Moreover, from the perspective of gene therapy, the biggest bottleneck is safe and efficient delivery in conjunction with target-specific intracellular localization. This is also a problem urgently requiring further research.

2.1.3. Targeting for inflammatory bowel disease

Inflammatory bowel disease (IBD), such as Crohn's disease and ulcerative colitis (UC), is a chronic relapsing disorder associated with uncontrolled inflammation in the gastrointestinal tract (Xiao & Merlin, 2012). Accumulating evidence has shown that inappropriate macrophages and DCs are associated with human IBD pathogenesis (Steinbach & Plevy, 2014; Na et al., 2019). Moreover, tumor necrosis factor- α (TNF- α), derived from macrophages, is an essential factor that contributes to IBD (Adegbola et al., 2018). There is accumulating research targeting TNF- α for the treatment of IBD. Orally targeted galactosylated chitosan poly(lactic-co-glycolic acid) NPs loaded with TNF- α siRNA are demonstrated to have the capability of reducing inflammation (Huang, Guo, et al., 2018). Kriegel and coworkers set up an NPs-in-microsphere oral system (NiMOS) through encapsulating TNF- α -specific small interfering RNA (siRNA) into type B gelatin NPs and entrapping the above NPs in poly(epsilon-caprolactone) (PCL) microspheres (Kriegel & Amiji, 2011). His system has the following advantages: (1) Oral instead of conventional drug administration methods are used to achieve localized treatments, and (2) smaller doses are suggested to be equally efficacious with fewer side effects. Analogously, Xiao et al. synthesized a mannosylated reducible cationic polymer (PPM) and further assembled NPs, assisted by sodium triphosphate (TPP). This combination was proven to be non-toxic in vitro experiments and remarkably reduced TNF- α levels by targeting macrophages (Xiao et al., 2013). Silencing of certain genes using siRNA is now common for the treatment of diseases owing to related gene overexpression and the level of establishment of the technology. However, the safety and effectiveness of this technique in clinical applications remain to be seen. Due to their low stability, local-targeted delivery of miRNAs is still challenging.

Because of the significant involvement of macrophages in the pathogenesis of several types of inflammation, they are considered relevant therapeutic targets. As mentioned above, various nanomaterials are used to design and synthesize NPs based on complex disease mechanisms. Advancing knowledge of the characteristics and roles of macrophages in inflammation is driving the development of more sites in macrophages as potential targets in nanomedicine.

2.2. Macrophages as a target for cancer

TAMs are the key components in the TME (Dehne et al., 2017). There are two major TAM subtypes, M1 and M2. M1 macrophages are tumor inhibitory, while M2 macrophages are tumor promotive. It is increasingly recognized that TAMs potentiate tumor progression and metastasis (Pollard, 2004). TAMs secrete signal extracellular vesicles (EVs) and molecules for promoting tumor initiation and development, such as transforming growth factor β (TGF- β), vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF) (Sevic et al., 2019). Moreover, TAMs participate in resistance against chemotherapy and radiotherapy, solid tumor angiogenesis, tumor migration, invasion, metastasis, and immunosuppression (Chen, Song, et al., 2019). For instance, TAMs drive early transcoelomic metastasis of ovarian cancer by promoting spheroid formation (Yin et al., 2016). Compared with traditional cancer treatments, drug delivery is an advanced, safe, and efficient system. Next, we will summarize the current nanomedicine-based cancer treatment targeting macrophages.

In breast cancer, TAMs are endowed with the capacity for angiogenesis and cancer cell migration, and invasion (Tariq et al., 2017). Therefore, the design of NPs targeting breast cancer TAMs has attracted much attention recently. The 2-ethyl-butyl cyanoacrylate (PEBCA) NPs containing the cytotoxic drug cabazitaxel (CBZ) is designed for the polarization of M2 to M1 macrophages and manifests a remarkably good therapeutic effect in the triple-negative PDX mouse model (Fusser et al., 2019). Mesoporous Prussian blue (MPB) NPs with low molecular weight hyaluronic acid (LMWHA) surface modification (LMWHA-MPB) are synthesized for macrophage conversion and O₂ generation. After uptake by M2 macrophages, LMWHA-MPB remodels the phenotype of TAMs (M2→M1) and shows an anti-metastatic effect on 4T1 cells (Zhang, Zhang, et al., 2019). Jiang and coworkers found that CD137 can facilitate the differentiation of monocytes/macrophages into osteoclasts, which is conducive for establishing a microenvironment suitable for the colonization of tumor cells and promoting bone metastases of breast cancer in the advanced stages. Thus, anti-CD137 blocking antibodies were infused into an F4/80-targeted liposomal NP to inhibit monocytes/macrophage differentiation (Jiang et al., 2019).

The therapeutic effects of traditional treatment options, including surgery, adjuvant chemotherapy, and radiotherapy are limited, and most melanoma patients develop drug resistance and disease recurrence (Early Breast Cancer Trialists' Collaborative Group, 2011; Wagle et al., 2011). Compared with traditional treatments, cancer immunotherapy provides an advantage for restoring the antitumor immunity in the TME (Mellman et al., 2011). Macrophages are a breakthrough for melanoma immunotherapy. M2-like TAM dual-targeting nanoparticles (M2NPs) loaded with anti-colony stimulating factor-1 receptor (anti-CSF-1R) siRNA are used for the elimination of M2-like TAMs. α -peptide (a scavenger receptor B type 1 [SR-B1] targeting peptide) linked with M2pep (an M2 macrophage binding peptide) is responsible for dual-targeting of macrophages (Qian et al., 2017). Dual targeting represents scientific progress in realizing

precision therapy. Additionally, ferumoxytol (FMT) combined with the TLR3 agonist poly (I:C) (PIC) and FP-NPs (NPs composed of amino-modified FMT [FMT-NH₂] surface-functionalized with PIC) was explored for macrophage polarization to promote melanoma regression (Zhao et al., 2018). The Food and Drug Administration (FDA)-approved iron supplement ferumoxytol and other iron oxide NPs have been used for treating iron deficiency as contrast agents for magnetic resonance imaging and as drug carriers. The benefits and the safety of ferumoxytol have been proven in several studies. Further, ferumoxytol has attracted attention due to its promising therapeutic effects on the growth of early mammary cancers and lung cancer metastases in the liver and lungs (Zanganeh et al., 2016). Meanwhile, ferumoxytol has been applied in the assessment of TAMs in murine melanoma by low-field relaxometry *in vivo* (Baroni et al., 2020). TAM subtypes show a wide heterogeneity; however, the function of specific TAM subsets is unclear. Etzerodt et al. used antibody-conjugated lipid NPs (LNPs; α CD163-LNP) to effectively deplete CD163⁺ TAMs. They showed that non-targeted cytotoxic LNPs significantly reduced the total number of TAMs, but were not as effective in reducing tumor growth as that of CD163-targeted LNPs. This study suggests that CD163⁺ TAMs have a strong immunosuppressive function in melanoma, and the specific depletion of CD163⁺ macrophages leads to a large number of activated T cells, infiltration, and tumor regression (Etzerodt et al., 2019). These results suggest a new therapeutic strategy to specifically target TAM subsets as a complement to the non-response to immunotherapy.

TAMs account for up to a third of malignant glioma (Fleige et al., 2001). Medical treatment options for malignant glioma are limited due to the inability of most drugs to penetrate the blood-brain barrier (BBB) (Mo et al., 2018). However, TAMs have a natural ability to traverse the intact and compromised BBB and undergo differentiation into long-lived brain-resident macrophages and microglia (Hickey, 1999). Therefore, TAMs are a target for the design of nanomedicines as well as carriers in drug systems. Next, we discuss treatment methods as a target. Simvastatin (SV) and fenretinide (4-hydroxy(phenyl)retinamide; [4-HPR]) are proven to be reliable for antitumor effects (Tiwari et al., 2006; Gaist et al., 2013; Chen et al., 2016). Mo and coworkers wrapped SV and 4-HPR with a TPGS-TAT-embedded lactoferrin NP system, repolarizing the TAMs from the M2 phenotype to M1 by regulating the STAT6 pathway (Mo et al., 2018). Likewise, Jin et al. developed a nanomedicine strategy consisting of a multifunctional liposome for codelivery of SV, paclitaxel (PTX), and legumain targeting cholesterol metabolism to reverse EMT and repolarize TAMs to treat drug-resistant cancers (Jin et al., 2019). These deliveries and therapeutic strategies deal well with the difficulties of a lack of effective BBB-permeable drugs and efficient brain delivery methods for glioma treatment. More studies that focus on macrophages as the carrier in drug systems will be discussed in detail below. Similarly, the high abundance of TAMs in colorectal cancer and their plasticity have become attractive targets for pharmacological intervention. Liu and colleagues successfully

developed Ru-based NPs, Ru@ICG-BLZ NPs, which could repolarize TAMs into M1 macrophages and further produce hyperthermia and ROS to eliminate cancer cells (Liu et al., 2019).

Nanotechnology-based photothermal therapy has attracted great attention in the past decade; we also will describe its advantages and disadvantages below. Pancreatic cancer is another difficult-to-treat cancer due to its high invasiveness and drug resistance, which can be attributed to a pervasive infiltration of M2 macrophages (Kurahara et al., 2011). The significance of M2-polarized TAMs in pancreatic cancer is beyond doubt. Nab-paclitaxel (trade name Abraxane), which consists of an NP albumin-bound formulation of paclitaxel and gemcitabines, as the first-line treatment for pancreatic cancer is an example of the adoption of nanomaterials in the clinic (Cullis et al., 2017), representing an important advance from basic research to clinical applications.

All strategies mentioned above directly use TAMs as targets. With nanomedicine sustaining innovations, there is a breakthrough improvement from single targeting to dual targeting. In other words, the designed NPs can target TAMs as well as other cells like cancer cells. Recently, Zhang et al. created twin-like core-shell NPs (TCN) for synchronous biodistribution. TCN contains two types of NPs, namely sorafenib (SF) loaded cationic lipid-based nanoparticles (SF-CLN) for targeting hepatocellular carcinoma (HCC) cells and mannose-modified IMD-0354 loaded cationic lipid-based NPs (M-IMD-CLN) targeting for TAMs. The safety and efficacy of the technique have been demonstrated *in vitro* (Wang, Zhang, et al., 2019). Further studies could enable its applications for other separated cell targeting combination therapy strategies in clinics. It is worth mentioning that although ADCs mainly target specific tumor antigens, the side effects on immune cells must also be considered because antibodies can bind to macrophages and other immune cells through Fc receptors. In particular, some ADCs deliver cytotoxic loads to TAMs. APOMAB (chDAB4) is a kind of antibody that targets dead tumor cells. Staudacher et al. reported that TAMs can process chDAB4 and chDAB4 ADC *in vitro*, and release free drugs to kill 'bystander' Lewis lung. In addition, consumption of TAMs reduces the concentration of drugs in the tumor and reduces the anti-tumor activity of chdab4 ADC (Staudacher et al., 2020). Similarly, Li et al. showed that ADCs can bind to F4/80⁺ TAMs, whose abundance is consistent with the anti-tumor activity of ADCs *in vivo* in lymphoma and breast cancer models. It is likely that TAMs internalize ADCs through Fc-Fc γ R interaction and then process ADCs, releasing the payload (Li et al., 2017).

3. Applications of macrophage-based delivery system

In recent years, cell-based drug delivery, especially to the tumor sites, has attracted much attention (Ayer & Klok, 2017; Pang et al., 2017). In contrast to traditional drug administration, cell-based drug delivery has multiple advantages including the following: (1) enhanced drug efficacy, (2) sustained

release of the drug, and (3) prolonged drug half-life. Currently, leukocytes are popular drug carriers owing to their specific tropism to diseased tissue (Lameijer et al., 2013). However, the choice of cells as carriers requires more careful attention since different cells have unique characteristics. Macrophages participate in the pathophysiology of conditions such as inflammatory disease, cancer, and neurodegeneration. Surprising results were achieved by exploiting macrophages as vehicles combined with nanomedicines for therapy. Macrophage-based delivery systems are frequently referred to as Trojan horses (Choi et al., 2007). They can escape the immune system and cross blood–vessel barriers to reach the hypoxic regions of tumors. Earlier, Lu et al. confirmed that monocyte-derived macrophage (MDM)-mediated delivery of small molecular agents is feasible. They used superparamagnetic iron oxide NPs (SPIONs) as evaluating tools and found that macrophages loaded with SPIONs with appropriate configurations could achieve an excellent therapeutic effect in an LPS-induced acute neuroinflammation mouse model (Tong et al., 2016). Subsequently, Huang et al. tried to use peritoneal macrophages as carriers for the delivery of SN38-NPs for cancer treatment. No obvious toxic effect of the SN38-NPs on macrophages in an A549 subcutaneous tumor model was observed, and the SN38-NP-loaded macrophages showed potent antitumor effects *in vitro* and *in vivo* (Huang, Sun, et al., 2018).

Other than what has already been mentioned, macrophages can be used as therapeutic targets for malignant glioma, it is also an undertaker of cell-based delivery systems. Gold nanoshell-loaded macrophages were applied in human glioma treatment *in vitro*, and the results validated a decrease in proliferation of tumor cells with an increase in nanoshell-loaded macrophages (Madsen et al., 2012). Gold nanostructures are currently considered potential photothermal transducers and drug carriers owing to their absorption of near-infrared light and converting it to heat (Thakor et al., 2011; Wang et al., 2012). In photothermal therapy (PTT), a photothermal (PT) agent targets diseased tissues and cells using a specific wavelength of light and the vibrational energy/heat released (Zhang, Du, et al., 2019; Yang et al., 2019). An et al. developed a macrophage-mediated delivery system with a high loading potential for tumor hypoxia photoacoustic (PA) imaging and enhanced PTT with small gold nanorods (AuNRs) as a model theranostics agent. In a mouse tumor model, they determined that this system can enhance tumor ablation and decrease the risk of tumor recurrence (An et al., 2019). Similarly, Chiu et al. synthesized doxorubicin (DOX)-loaded AuNR/albumin core-shell nanoplatform (NR@DOX:SA) and exploited macrophage-mediated delivery to load this nanoplatform to achieve enhanced antitumor effects (Chiu et al., 2017). To date, most cancer therapies for gold nanostructures are based solely on photothermal effects. However, combination therapy with chemotherapeutic agents may be an emerging strategy for treating cancer. A biomimetic delivery system (BDS) for prostate cancer therapy involving loading doxorubicin (DOX)-loaded reduced graphene oxide (rGO) into a mouse macrophage-like cell line (RAW264.7) was established in a recent study by Qiang and

coworkers (Qiang et al., 2019). Combining this with a stimuli-release triggered by a near-infrared laser (NIR) served as an effective combination of chemotherapy and photothermal therapy to ensure active targeting of tumor cells and controlled drug release.

PTT-based drug delivery is a type of drug release system activated in response to external induction and time and/or locally controlled triggers. These include non-physiological triggers, such as temperature and ultrasound, as well as electrical and magnetic triggers. Recently, a magnetic hyperthermia-controlled drug release system was reported in which macrophages delivered the combination of silica-coated SPION cores with mesoporous silica shells (Ullah et al., 2019). When exposed to an external alternating magnetic field (AMF), SPIONs induced local heat increasing the temperature and triggering the release of encapsulated drugs (Kumar & Mohammad, 2011). This approach is implemented such that under certain conditions, drugs are released but no nonspecific release of the drug is observed. Compared with the side effects of systemic administration, controlled drug delivery provides a possibility for accurate topical administration to reduce the systemic effects of drugs.

Parkinson's disease (PD) is a progressive and severely disabling neurodegenerative movement disorder and the most common cause of Parkinsonian symptoms (Parkinsonism), characterized by tremor, bradykinesia, and rigidity (De Pablo-Fernández et al., 2018). The need to develop neuroprotectants and control neuroinflammation for the protection of the brain against injury cannot be overstated. Similar to the case of malignant glioma, the BBB is a major obstacle to the delivery of therapeutic drugs for PD. Haney and coworkers forged the concept of macrophage delivery of protein antioxidants to attenuate neuroinflammation and nigrostriatal degeneration in PD. They successfully incorporated the redox enzyme catalase into a polyion complex micelle ('nanozyme'), and used bone marrow-derived macrophages as carriers to deliver nanozymes to the lesion locations (Haney et al., 2011). Brain diseases, such as central nervous system (CNS) disorders and brain cancers, are some of the most prevalent, devastating, and yet poorly treated diseases. Macrophages, whether they participate in the development of diseases or can cross the BBB, are potentially effective for the treatment of disease. The pathways for drug delivery shown here may be used for the treatment of these brain diseases.

In delivery systems, macrophages are not only carriers but also slow-release reservoirs. In many cases, macrophages firmly incorporate the NPs during storage. Upon contact with an appropriate cell location or stimulated by PTT, they will be triggered to release the encapsulated NPs. This strategy overcomes the limitation of inefficient drug delivery by realizing controlled release.

4. Macrophage-derived extracellular vesicles as a new drug-delivery platform

Extracellular vesicles (EVs) are secreted by membrane vesicle cells. Not only are they waste carriers, but they are also capable of exchanging signals between cells by transferring

components such as nucleic acids, lipids, and proteins (Colombo et al., 2014; van Niel et al., 2018). EVs can be broadly categorized as exosomes and microparticles. In essence, exosomes (30–100 nm in diameter) are intraluminal vesicles (ILVs) formed by the inward budding of the endosomal membrane during the maturation of multivesicular endosomes (MVEs), which are intermediates within the endosomal system, and secreted upon fusion of MVEs with the cell surface (Stremersch et al., 2016; van Niel et al., 2018). On the other hand, microparticles (MPs), which are 100–1000 nm in diameter, are vesicle-like structures that are released to the outside of cells by the cell membrane surrounding the contents of cells by inducing changes in the cytoskeleton when cells are stimulated by activation or apoptosis (Mause & Weber, 2010). These structures, which lie between the molecular and cellular levels, can be used as carriers for the communication of information and substances between cells and for the storage and transportation of substances and information in cells (Li et al., 2020). EVs derived from different cells have different functions. Recent studies have shown that EVs can function as efficient carriers of chemotherapeutic drugs (Ran et al., 2016; Ye et al., 2018; Guo et al., 2019), RNA drugs (Chen et al., 2020; Leidal et al., 2020), and anti-inflammatory drugs (Go et al., 2019; Kalinec et al., 2019). Here, we highlight the role of macrophage-derived EVs in the treatment of disease.

Macrophage-derived EVs have aroused increasing interest in recent years. Holder and coworkers proved that the human placenta internalizes macrophage-derived exosomes in a time- and dose-dependent manner via clathrin-dependent endocytosis. Subsequently, macrophage exosomes induced the release of proinflammatory cytokines by the placenta responding to maternal inflammation and infection and preventing damage to the fetus (Holder et al., 2016). Moreover, exosomes from M1-polarized macrophages exhibit chemotaxis toward lymph nodes, primarily after ingestion by local macrophages and dendritic cells, and induce the release of a pool of Th1 cytokines. Meanwhile, Cheng et al. found that exosomes derived from M1-polarized macrophages could be used as a vaccine adjuvant (Cheng et al., 2017). In epithelial ovarian cancer, miR-223 from macrophage-derived exosomes is closely associated with chemotherapy resistance (Zhu et al., 2019). With further study of EVs, their importance in diseases is highlighted from mechanisms of action to treatments. The body of research evidence highlighted above suggests that macrophage-derived EVs are related to diseases. Therefore, the use of single macrophage-derived EVs or macrophage-derived EVs encapsulating drugs is believed to represent promising approaches to treatment. For example, exosome-mimetic nanovesicles derived from M1 macrophages (M1NVs) have acquired the capability of repolarizing M2 TAMs to M1. In addition to inducing antitumor immune responses by releasing proinflammatory cytokines, M1NVs can also potentiate the antitumor efficacy of checkpoint inhibitor (aPD-L1) therapy (Choo et al., 2018). However, research efforts have focused more on macrophage-derived EV encapsulating drugs. M1 macrophage-derived exosomes acting as carriers to deliver PTX into tumor tissues showed

that this delivery system in 4T1 tumor-bearing mice enhances the antitumor efficacy of PTX (Wang, Wang et al., 2019). M2 macrophage-derived exosomes (M2 Exo) electroporated with FDA-approved hexyl 5-aminolevulinate hydrochlorides (HAL) that undergo intrinsic biosynthesis and metabolism of heme generating anti-inflammatory carbon monoxide and bilirubin, are used for atherosclerosis treatment owing to their release of anti-inflammatory cytokines (Wu et al., 2020). These studies demonstrated macrophage-derived exosomes are a novel drug-delivery strategy and their effectiveness and security suggest promising clinical applications.

Macrophage-derived MPs are also widely and frequently used in nanomedicine. A macrophage-derived microvesicle (MMV)-coated poly (lactic-co-glycolic acid) (PLGA) NP (MNP) was developed for targeting RA (Li et al., 2019). Using MNP to encapsulate tacrolimus and applying it to mice revealed significant suppression of the progression of RA. This demonstrated that MNP is an efficient biomimetic vehicle for RA targeting and treatment, and may be applicable to other diseases. Macrophage-derived MVs efficiently delivered DEX into an inflamed kidney and exhibited a superior capacity to suppress renal inflammation and fibrosis (Tang et al., 2019). Rayamajhi and coworkers hybridized small EVs with synthetic liposomes to engineer vesicles less than 200 nm in size to mimic the size of exosomes, named hybrid exosomes. After loading water-soluble doxorubicin, hybrid exosome toxicity against cancer cells was enhanced owing to the pH-sensitive release of the drug in the acidic cancer environment (Rayamajhi et al., 2019).

5. Conclusions and challenges

In summary, we report that macrophages play a key role in the pathogenesis of various diseases and portray the current status of macrophages in nanomedicine. Current nanotechnologies can design and generate NPs that specifically target macrophages as well as the macrophage-based delivery system of NPs. Furthermore, macrophages nanomedicine-based disease treatment has raised exciting expectations for many medical problems in inflammatory/autoimmune disorders and cancers. Notably, infiltration of macrophages into tumors is a common phenomenon in malignant tumors, which has good prospects for the development of strategies focusing on macrophages using nanotechnology. In this review, we have shown several examples in which TNPs directly target macrophages or are delivered to lesion locations via macrophage-based delivery systems or macrophage-derived EVs.

However, there are still many problems to be solved to realize the full practical applications. How can NPs be delivered for better targeting of macrophages? In different diseases, surface-marker proteins of macrophages may undergo changes. The rational design of NPs is crucial for increasing the targeting efficiency or specificity to macrophages. How to fabricate NPs to achieve controlled release after successful delivery is an interesting and important area to explore. We need to understand that there are many obstacles to NPs after entering the body. We've

already mentioned a few of them such as mononuclear phagocyte system, hemorheology and blood vessel fluid dynamics, intratumoral pressure and nanoparticle extravasation and so on (Blanco et al., 2015), and there are many ways to overcome them (see Figure 2).

In contrast to traditional drugs, nanomedicine offers certain advantages in passive or active targeting, pharmacokinetics, and reducing toxic and side effects. They show great potential in the fields of malignant tumor, regenerative medicine, and other diseases. There are a large number of related clinical trials currently, but few have been approved. Although some regulatory guidelines are in place for such products in some countries, they lack the specifications and guidelines for their use in a clinical setting, which further hampers their use in clinical practice (Hussaarts et al., 2017). Nanomedicine has several problems. Firstly, the active principal component (API) of nanomedicines is a major consideration for regulation. Drug combination with nanomedicine is more complex compared to that of common drugs. A small change may cause a major change in biological characteristics, structure, and function (Duncan & Gaspar, 2011). Secondly, in terms of safety assessment, with small size and unique physicochemical properties, nanomedicines are significantly different from traditional drug's pharmacokinetic and toxicology profile. And the preparation of nanomedicines is complex. These result in new requirements for quality control and pharmacokinetic analysis. Some routine toxicological tests may not be applicable or need to be adjusted (Liu et al., 2020). Thirdly, there are strict procedures for the handling, storage, and use of nanomedicines in clinical practice, and any error may affect patients. Precise control of transport and storage temperatures use and dilution of appropriate solvents and rate of administration are required (Flühmann et al., 2019). This means that both nurses and doctors have a high level of control over drugs and rich knowledge of nanomedicines. Although nanomedicines have been approved for use, they are still in the minority due to strict regulations and price issues. In other words, there is not enough clinical data nor an understanding of the side effects of drugs at this time.

Therefore, the ethical issues of nanomedicines also deserve our attention. Although all nanomedicines are tested in vivo in animals and in vitro in cells before entering clinical trials to ensure safety and efficacy, the uncertainty that human subjects face when they first receive a nanomedicine product in clinical trials cannot be eliminated. Ethical codes and regulations require that the potential benefits to humans and society should be reasonably considered and the risks minimized in relation to the potential benefits of humans subjects (Emanuel et al., 2000). It is urgent to accelerate the clinical researches of nanomedicines and obtain more clinical data. Regulatory authorities should formulate and improve regulatory requirements. Besides, it is reasonable to standardize drug evaluation under multidisciplinary cooperation including cell biology, toxicology, biomedical engineering, analytical chemistry, and so on.

Author contributions

SS, HX, and MG wrote the draft. YJ reviewed and edited the manuscript before submission. SW, SZ, and PM, commented and added extra information.

Disclosure statement

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