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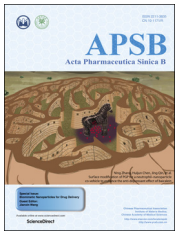

REVIEW

Biomimetic nanoparticles for inflammation targeting

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Abstract There have been many recent exciting developments in biomimetic nanoparticles for biomedical applications. Inflammation, a protective response involving immune cells, blood vessels, and molecular mediators directed against harmful stimuli, is closely associated with many human diseases. As a result, biomimetic nanoparticles mimicking immune cells can help achieve molecular imaging and precise drug delivery to these inflammatory sites. This review is focused on inflammation-targeting biomimetic nanoparticles and will provide an in-depth look at the design of these nanoparticles to maximize their benefits for disease diagnosis and treatment.

Abbreviations: apoE$^{-/-}$ mice, Apolipoprotein e knockout mice; CAM, cellular adhesion molecule; CCL5, chemokine (C-C motif) ligand 5; CD40L, cluster of differentiation 40 ligand; CTC, circulating tumor cell; CTL, cytotoxic T cell or CD8$^+$ T cell; CXCL4, chemokine (C-X-C motif) ligand 4; CXCR1, chemokine (C-X-C motif) receptor 1; Cy7, cyanine 7; DC, dendritic cell; DSPE-PEG, distearoyl Phosphoethanolamine-poly(ethylene glycol); GPIbα, glycoprotein Ibα; GPIV, glycoprotein IV; GPIX, glycoprotein IX; GPV, glycoprotein V; GPVI, glycoprotein VI; HUVEC, umbilical cord vascular endothelial cell; IBD, inflammatory bowel disease; ICAM-1, intercellular cellular adhesion molecule-1; IgG, immunoglobulin G; IL, interleukin; LFA-1, lymphocyte function associated antigen-1; LLV, leukocyte-like vector; LPS, lipopolysaccharide; Mac-1, macrophage adhesion molecule-1; MHC, major histocompatibility complex; MRI, magnetic resonance imaging; NM-NP, neutrophil membrane-coated nanoparticle; PECAM-1, platelet-endothelial cellular adhesion molecule-1; PLA-PEG, poly(lactic acid)-poly(ethylene glycol); PLGA, poly(lactic-*co*-glycolic acid); PNP, platelet membrane-cloaked nanoparticle; PSGL-1, P-selectin glycoprotein ligand-1; RA, rheumatoid arthritis; RBC, red blood cell; SLe^X, sialyl lewis X; SPIO, super paramagnetic iron oxide; TGF-β, transforming growth factor β; Th cell, T-helper cell or CD4$^+$ T cell; TNF-α, tumor necrosis factor-α; VCAM-1, vascular cellular adhesion molecule-1; VLA-4, very late antigen-4; VWF, Von Willebrand factor

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1. Introduction

Inflammation, a protective response involving immune cells, blood vessels, and molecular mediators against harmful stimuli such as pathogens, damaged cells, or irritants, has been considered as a mechanism of innate immunity to eliminate the initial cause of cell injury, clear out necrotic cells and damaged tissues, and to initiate tissue repair[1]. Inflammation can be classified by whether it is caused by infection or not, or classified as either acute or chronic. In most cases, as the body's automatic defense response, inflammation is beneficial. However, in some cases, inflammation is harmful, such as the attack on body's own tissues.

Inflammation has a close relationship with a vast variety of human diseases, including pneumonia, rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, psoriasis, atherosclerosis, ischemic heart disease, and even cancers[2]. It has been proven that inflammation plays a fundamental role in the progress of these disorders. For instance, inflammation mediates all the stages of atherosclerosis from initiation through progression and, ultimately, the thrombotic complications of atherosclerosis[3]. As a result, targeting inflammation offers a promising solution for diagnosis and treatment of these diseases.

Nanoparticle drug delivery systems possessing the advantages of biodegradability, biocompatibility, non-toxicity, and prolonged circulation provide a versatile platform for inflammation targeting[4,5]. Nanoparticles come in a large variety of forms (liposomes, polymer nanoparticles, polymersomes, hybrid nanoparticles, inorganic nanoparticles, solid lipid nanoparticles, biomimetic nanoparticles, etc.) and a broad range of sizes (from a few nanometers to 1000 nm). The outstanding features are their distinctive size, shape, and surface properties for tissue penetration *via* a passive or active targeting mechanism.

Recently, biomimetic nanoparticles have gained increasing attention from researchers worldwide since biomimetic nanoparticles can combine the advantages of both synthetic nanomaterials and natural materials, making it possible for molecular imaging and precise drug delivery using a biomimetic strategy[6]. Many natural mechanisms of the immune system engaged in an inflammatory response can be mimicked by biomimetic nanoparticles in order to achieve inflammation targeting, which is often ignored in the traditional design of nanomedicine. This review will focus mainly on the design of biomimetic nanoparticles with the capability of molecular imaging and precise drug delivery. As far as we know, this is the first review focusing on biomimetic nanoparticles for inflammation targeting, and will provide an in-depth look at the design of these nanoparticles to maximize their benefits for disease diagnosis and treatment.

2. The connection between inflammation and diseases

Inflammation occurs in a large group of human diseases. The immune system is often involved with inflammatory disorders, as demonstrated in the following examples of inflammation-related diseases.

2.1. *Inflammation in rheumatoid arthritis and systemic lupus erythematosus*

New onset arthritis is not uncommon, with about half of arthritis patients resolving their symptoms spontaneously in several months[7,8]. However, for the rest, the inflammation that leads to arthritis cannot be resolved, contributing to a switch toward chronic disease characterized by leukocyte accumulation and stromal cell accumulation inside the synovium. Rheumatoid arthritis (RA) is the most prevalent arthritis with persistent inflammation involved in its progression[9]. A symmetrical peripheral inflammatory polyarthritis is one of the symptoms of RA. Many immune cells participate in the inflammation during the onset of RA. After the onset of clinically evident joint disease, the normally hypocellular synovial membrane becomes hyperplastic. This inflamed synovium contains a superficial lining layer of synovial fibroblasts and macrophages overlying a layer that contains an intense cellular infiltrate including macrophages, T cells (both $CD4^+$ T cells and $CD8^+$ T cells), B cells, plasma cells, natural killer (NK) cells, mast cells, and fibroblasts. Synovial macrophages are activated *via* a number of routes including the binding of immune complexes to Fcγ receptors, the ligation of Toll-like receptors[10], and direct T cell contact[11]. Such activated macrophages are an important source of proinflammatory cytokines including tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), IL-6, IL-15, and IL-23. Activated T cells play a direct role in macrophage activation and also produce IL-17 which can itself activate macrophages as well as fibroblasts and osteoclasts. B cells and plasma cells produce proinflammatory cytokines and autoantibodies and may play a role in local T-cell activation *via* the presentation of peptides on major histocompatibility complex (MHC) class II molecules. These infiltrating cells and their cytokines drive the process of bone and cartilage destruction, which is mediated predominantly by fibroblasts and osteoclasts[12]. RA also shows linkage with inflammatory diseases of the skin, lungs and vascular systems[8]. Although systemic lupus erythematosus shares different symptoms with RA, the role of inflammation during its occurring is almost the same[13].

2.2. *Inflammation in the gastrointestinal tract*

Inflammation of the gastrointestinal tract can be considered a mechanism of preservation, a way in which the host can protect itself from invading pathogens and noxious stimuli. The inflammatory response acts to remove and inactivate the damaging substance, and is aided by an array of cell-derived proteases and reactive oxygen products, as well as soluble mediators. Inflammation is normally self-limiting. However, in some cases, inflammation can be chronic, leading to excessive tissue injury, as long as the factors initiating inflammation persist[14].

Helicobacter pylori infection is associated with inflammation inside gastrointestinal tract. *Helicobacter pylori* colonize more than half of the population in the world and represent the major risk factor that leads to peptic ulceration, gastric adenocarcinoma, and gastric lymphoma. The damage to the gastric mucosa results from the host's immune response to *Helicobacter pylori* infection rather than the bacterium itself. During the innate immune response to infection, the bacterium elicits a rapid recruitment of neutrophils, followed later by T lymphocytes, B lymphocytes, plasma cells, and macrophages. Activated neutrophils contribute to the epithelial cell damage by releasing proteolytic enzymes and reactive oxygen species. Pro-inflammatory cytokines, such as IL-1β, IL-2, IL-6, IL-8 and TNF-α, are also upregulated[15].

Crohn's disease and ulcerative colitis are the two major types of inflammatory bowel disease (IBD). In IBD, the immune system in the bowel is disturbed. A leaky epithelial barrier allows luminal antigens access to the submucosa and thus exposure to granulocytes

and regulatory lymphocytes. Degranulation of neutrophils and mast cells leads to the release of tissue-damaging proteases, pro-inflammatory cytokines and vasoactive peptides. The epithelial layer itself expresses Toll-like receptors which are important for the detection of bacterial components. The mechanisms involved in antigen recognition are also compromised in IBD—dendritic cells (DCs) incorrectly recognizing commensal bacteria as pathogens, triggering activation of naive T cells into T-helper cells or natural killer cells. Furthermore, atypical antigen-presenting cells may turn into effective activators of naive T cells. Activated T cells also show a delayed apoptosis, and persist in the mucosa. Such inappropriate T-cell activation and accumulation contributes to inflammation of the mucosa[16].

2.3. *Inflammation in skin diseases*

Psoriasis is a skin disease caused by chronic inflammation. In a genetically primed individual, there is an intricate relationship between the innate immune system and the adaptive immune system when responding to unidentified antigens. The immune cells including T cells, DCs, monocytes, and macrophages are thought to contribute to psoriasis progression. Of the T-cell subsets, cytotoxic T cells ($CD8^+$ T cells, CTLs) are mainly located inside epithelial tissue, in close approximation with keratinocytes and Langerhans cells, while at the same time, T-helper cells ($CD4^+$ T cells, Th) are mainly positioned inside the papillary dermis. T cells inside the epithelium are thought to participate in the pathogenesis of psoriasis[17]. T-helper 1 cells are thought to be an activated memory T-cell phenotype participating in the onset of psoriasis, and T-helper 17 cells are another important element with a potential impact on psoriasis pathogenesis[18]. DCs with antigen-presenting ability have the capacity to direct the adaptive immune system by activating T cells, B cells and NK cells. When the number of dermal DCs is increasing, the cytokine production in autologous T cells will also be increasing inside psoriasis lesions[19].

2.4. *Inflammation in cardiovascular diseases*

Inflammation is an important pathophysiological symptom during vascular disease, cardiac ischemic injury and cerebral ischemic injury. Evidence shows that inflammation participates in atherosclerosis from the onset of atherosclerosis to the progression of atherosclerotic lesions. Inflammation also affects the stability of atheromatous plaques[20,21]. In addition, the role of inflammation is also important during cardiac ischemic injury and cerebral ischemic injury[22,23].

There is good evidence for locally active inflammation as a major cause of plaque formation and plaque composition[24]. A mature plaque comprises a central core of necrotic tissues and fat infiltration surrounded by inflammatory cells. Atheromatous plaques are covered with a cap rich in cells and fibrous tissues, the so-called fibrous cap. This cap seals procoagulant and platelet-activating materials within the vessel wall and prevents them from interacting with blood coagulation factors and platelets. The cap is composed primarily of smooth muscle cells and collagen secreted by smooth muscle cells. The cap structure and properties are determined by inflammation. Active infiltration of inflammatory cells in the cap results in cytokine and metalloproteinase production, which suppresses collagen production, induces smooth muscle cell apoptosis, and degrades preexisting fibrous tissues[25]. When the cap is replaced with inflammatory and necrotic tissues, the fibrous cap becomes thin and vulnerable to rupture[26].

2.5. *Inflammation in cancer*

The idea that inflammation had a close connection with cancer was first brought up by Rudolph Virchow in 1863, when he proved the existence of leukocytes in tumor tissues[27]. The epidemiological data also indicate a convincing connection between chronic inflammation and malignant transformation of inflamed tissue into cancer. Those cells and mediators that contribute to inflammation also help to create tumor microenvironment. In some cancers, inflammation just precedes cancer development, but in other cancers it is the oncogenic changes that lead to the tumor-promoting inflammation. Angiogenesis and metastasis of tumors is also connected with inflammation.

Cancer cells recruit neutrophils and macrophages *via* the expression of cytokines[28]. The network made up by cytokines and chemokines participates in tumor-related inflammation and can regulate both normal cells and tumor cells in the tumor microenvironment. Proinflammatory mediators, such as proteases, eicosanoids, cytokines, and chemokines are usually overexpressed by neoplastic cells. Several cytokines, such as TNF-α, IL-6, IL-17, IL-12, IL-23, IL-10, and transforming growth factor-β (TGF-β), make up the tumor microenvironment and are able to facilitate the development of the tumor[29].

2.6. *Inflammation in other diseases*

Inflammation inside the lung is normal as a basic physiologic response, but it can also be linked with specific respiratory illnesses, especially for chronic inflammation. Chronic inflammation has a close relationship with many lung diseases like asthma, chronic obstructive pulmonary disease, bronchiectasis and interstitial lung disease[30–32]. Although the purpose of inflammation is for defense, an over-exuberant response from the immune system may contribute to serious respiratory diseases and acute inflammation can also lead to lung diseases. The inhalation of a pathogen, toxin or specific allergen can all lead to the responses from the immune system, causing the exacerbation of bronchiectasis, chronic obstructive pulmonary disease and asthma[33].

Inflammation inside the central nervous system occurs after brain injury. The proximal cause may be an anoxic event such as a stroke, chronic neurodegeneration or an infectious process. In each instance, glial cells including astrocytes and bone marrow-derived microglia, the resident macrophages of the central nervous system, are activated and participate in the inflammatory response[34]. Additional components of neural inflammation, such as polymorphonuclear leukocytes, lymphocytes, and macrophages, then arrive from the periphery[35,36].

3. Inflammation-involved molecules and immune cells

Leukocytes, including neutrophils, lymphocytes, monocytes and granulocytes, all directly participate in the onset of inflammation. As demonstrated in Fig. 1A, at the beginning of inflammation, capture and rolling as the interactions between leukocytes and inflamed endothelial cells are mediated primarily by interaction between selectins and oligosaccharide residues of glycoprotein ligands expressed mainly on leukocytes. Afterwards, firm adhesion and transmigration are mainly mediated by leukocyte integrin's

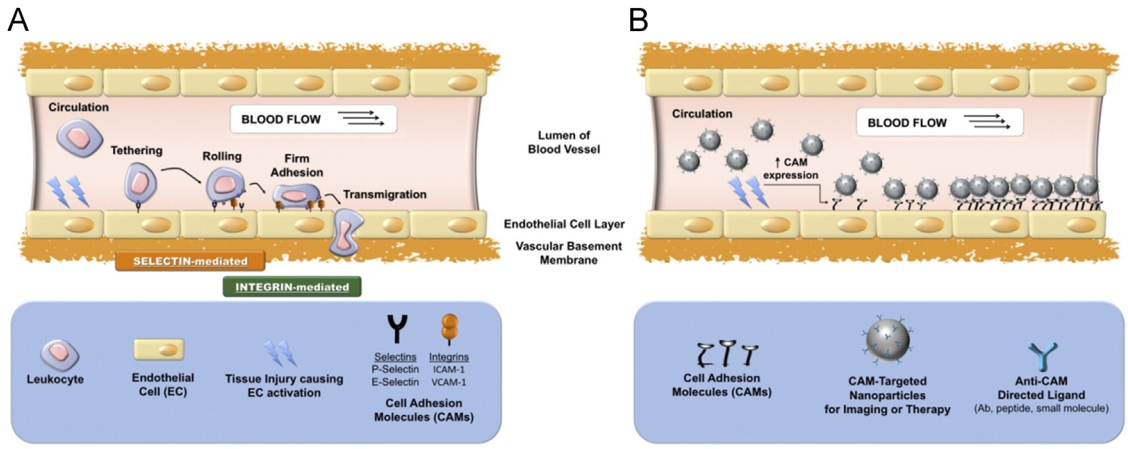

Figure 1 Schematic of how leukocytes adhere to inflammation sites and how nanoparticles mimic this mechanism. Cited with permission from Ref. 5. Copyright Elsevier, 2011.

interacting with cellular adhesion molecules (CAMs), an important part of immunoglobulin superfamily. As a result, selectins and CAMs are two main kinds of inflammation-involved molecules, and leukocytes are the main inflammation-involved cells. By mimicking the interaction between selectins or CAMs on inflammatory endothelial cells and leukocytes, biomimetic nanoparticles can achieve inflammation-targeted drug delivery (Fig. 1B). Apart from leukocytes, platelets also contribute to inflammation. As inflammation is always accompanied with vessel wound, platelets can be activated at the inflammation site and clot the wounded area, providing hemostasis in first stage. Thus, biomimetic nanoparticles mimicking activated platelets could also make inflammation targeting drug delivery possible.

3.1. *Selectins*

Selectins play an important role in both tethering and rolling of leukocytes, although these processes are further facilitated by several integrin (especially when selectin deficiency occurs). The selectins are a three-member family (L-, P-, and E-selectin) that share a highly conserved extracellular N-terminal Ca^{2+}-dependent C type lectin domain. All selectins contain a transmembrane domain and a cytoplasmic tail. The main structural difference between different selectins is the number of consensus repeat units. All selectins bind, through their lectin domain, to sialyl forms of oligosaccharides displayed on various mucin-like glycoproteins, for example, sialyl lewis X (SLe^X). P-selectin glycoprotein ligand-1 (PSGL-1) is one of the most extensively distinguished ligands for all three selectins (P-selectin, E-selectin, L-selectin) on leukocytes[37].

P-selectin (CD62P) is produced in cytoplasmic secretory α-granule of platelets and endothelial cells. Stimulation with vasoactive mediators such as thrombin or histamine leads to rapid mobilization of endothelial P-selectins toward the external plasma membrane of endothelial cells allowing leukocytes to interact. Thus, P-selectin contributes to early leukocyte recruitment in inflammation and infection. P-selectin expression at the cell surface is transient due to internalization by endocytosis for reuse. In addition to this rapid expression, P-selectin can be transcriptionally up-regulated in human endothelial cells by cytokines such as IL-4, whereas in murine endothelial cells, TNF-α and lipopolysaccharide (LPS) can induce its expression. Interactions between P-selectin on activated platelets and its main counter ligand PSGL-1 on leukocytes results in leukocyte–platelet interactions that are pertinent for wound healing and contribute to leukocyte recruitment during inflammation[38].

E-selectin (CD62E) expression is mostly restricted to activated endothelial cells, with the exception of skin microvessels and bone marrow where it is constitutively expressed. E-selectin requires *de novo* mRNA and protein synthesis, and its expression on the surface of endothelial cells can be triggered by IL-1β or TNF-α with maximal expression at 4 h, falling toward baseline level by 24 h. In comparison with P-selectin, E-selectin internalization is much slower and it is directed to lysosomes for degradation instead of being recycled[39].

L-selectin (CD62L) exclusively and constitutively exists on the surface of leukocytes, particularly neutrophils, monocytes, and naive lymphocytes (but not memory lymphocytes). It serves as a key receptor for lymphocyte's homing to secondary lymphoid organs from peripheral sites of injury and inflammation. Its location on the tips of microvilli facilitates its interaction with endothelial cells, allows high receptor concentrations and also evades the electrostatic repulsion of the negative cell surface. Upon leukocyte activation, L-selectin is rapidly shed. Although this mechanism is not fully elucidated, it is known that this shedding can be blocked by inhibitors of zinc-based metalloproteases[40].

3.2. *CAMs*

Following the initial rolling process mediated by selectins and their ligands, leukocytes are activated coincident with a decrease in the rolling velocity of leukocytes. Afterwards, a transition to firm adhesion between leukocytes and endothelial cells occurs. Adherent leukocytes can become elongated and flatten onto the endothelium, decreasing their protrusion into the vessel lumen, and thus their tendency to detach.

Firm adhesion is established by the binding interaction of integrins with CAMs including intercellular CAM-1 (ICAM-1, CD54), vascular CAM-1 (VCAM-1, CD106) and platelet-endothelial CAM-1 (PECAM-1, CD31). These immunoglobulins are expressed basally on the resting endothelium, and can be upregulated during inflammation.

VCAM-1 is encoded by the *VCAM-1* gene, which is also named CD106. The main function of VCAM-1 is to serve as a cell adhesion molecule. After cytokine stimulus, VCAM-1 will be

expressed mainly on endothelial cells. VCAM-1 is a natural endothelial ligand for very late antigen-4 (VLA-4), which is expressed on most leukocytes' surface and belongs to the integrin family. The adhesion of lymphocytes, monocytes, eosinophils, and basophils on inflamed vascular endothelium tissue is mediated mainly by VLA-4. It is also important in signal transduction between leukocytes and endothelial cells during the development of atherosclerosis and rheumatoid arthritis. Furthermore, VCAM-1 can contribute to trans-endothelial migration of leukocytes *via* the paracellular pathway by causing gap formation between adjacent endothelial cells[41].

ICAM-1 also belongs to the immunoglobulin superfamily as an adhesion molecule. The expression of ICAM-1 is low on resting vascular endothelial cells. As a transmembrane protein expressed on leukocytes and endothelial cells, ICAM-1 is important in stabilizing cell interaction and promoting the migration of leukocytes across endothelial tissues. The ICAM-1 receptors include lymphocyte function associated antigen-1 (LFA-1) and macrophage adhesion molecule-1 (Mac-1), which belong to the integrin family. LFA-1 and Mac-1 expressed on the leukocyte surface can help them target sites of inflammation. LFA-1 is the main receptor of ICAM-1, while the affinity between Mac-1 and ICAM-1 is low. Fibrinogen is also one of the ICAM-1 ligands[42].

PECAM-1, also known as CD31, is expressed on the membrane of platelets, monocytes, neutrophils, and other T-cells, participating in intercellular junctions with endothelial cells. PECAM-1 gets involved in leukocyte transmigration, angiogenesis, and integrin activation. PECAM-1 also exists in some vascular tumor tissues including epithelioid hemangioendothelioma and epithelioid sarcoma-like hemangioendothelioma. In immunohistochemistry, PECAM-1 is usually utilized to prove the existence of endothelial cells in histological tissues, which helps to assess tumor angiogenesis, a marker to determine whether rapid growth of tumor is occurring[43].

3.3. Leukocytes

Leukocytes, also called white blood cells, are the cells of the immune system involved in protecting the body against both infectious disease and foreign invaders. Generally, leukocytes can be divided into five types: neutrophils, eosinophils, basophils, lymphocytes, and monocytes. Leukocytes have a very close relationship with inflammation. Leukocytes can move from blood to sites of inflammation by extravasation, which directly contributes to inflammation. Some leukocytes, such as macrophages (differentiated from monocytes) can phagocytose foreign materials from bacteria and debris to dead cells. Some can release chemical cytokines that kill pathogenic organisms. Leukocytes also release mediators that contribute to the inflammatory response. Different kinds of leukocytes are involved in different diseases; granulocytes mainly participate in acute inflammation, while monocytes and lymphocytes mainly take part in chronic inflammation[44].

Extravasation, describing leukocyte movement from the blood circulation into tissues with the help of blood vessels, is worthy of further discussion. Extravasation is firstly based on chemotaxis by leukocytes. Many chemoattractants can induce leukocytes to move along a chemotactic gradient to an inflammation site. In the inflammation site, activated macrophages release cytokines, for example, IL-1 and TNF-α. These cytokines can bind to inflamed endothelial cells *via* the connection between them and G protein-coupled receptors. Instant expression of P-selectin on endothelial tissues occurs, which enables leukocytes to move along the endothelial tissue *via* the weak binding power between carbohydrate ligands (for example, SLe^X) and P-selectin. Damaged cells also release cytokines, which increases E-selectin expression on endothelial tissues. E-selectin has a function similar to P-selectin. Cytokines have the ability to increase the expression of CAMs, such as ICAM-1 and VCAM-1, on endothelial tissues, offering stronger binding for leukocytes to adhere *via* VLA-4 (VCAM-1 receptor), LFA-1 and Mac-1 (ICAM-1 receptors). Tight binding of leukocytes to endothelial cells is then available. Meanwhile, the retraction of endothelial cells enables the leukocytes to cross endothelial tissues and move into the inner tissues, which is also facilitated by cell adhesion molecules such as ICAM-1[45].

3.4. Platelets

Derived from bone marrow stem cell lineage megakaryocytes, anucleate platelets mainly function in hemostasis, initiating rapid clotting, vasoconstriction, and inflammation that leads to sterilization, tissue repair, and resolution. If the inflammatory stimulus is a lacerating wound, exuded platelets can help clot the wounded area and provide hemostasis[46]. All clotting mediators, including platelets, coagulants, plasmin, and kinins, provide a structural staging framework at the inflammatory tissue site in the form of a fibrin lattice for the purpose of aiding phagocytic debridement and wound repair[47]. In addition to "first responders" in wounds, platelets can also serve as "first responders" in cancer and metastasis[48]. Cancer is considered as a non-healing wound or chronic inflammation[49,50]. Leaky blood vessels or inflammatory reactions during carcinogenesis provide opportunities for platelets to invade tumors. Platelet mitogenic properties can stimulate tumor growth, which further promotes the invasion of tumor cells into the blood stream. In addition, platelets also facilitate their survival in circulation, adhesion to endothelial cells, extravasation of circulating tumor cells (CTCs), and enhance tumor metastasis[51,52].

In addition to being the cellular effector of hemostasis during inflammation, platelets potentially modulate inflammatory processes by interacting with leukocytes and by secreting cytokines, chemokines, and other inflammatory mediators[53]. Platelets have been reported to play a vital role in vascular inflammation initiation and acceleration by transmitting the signal to leukocytes and facilitating immune recruitment functions. Taking atherosclerosis as an example, Massberg et al.[54] showed that platelets adhered to carotid endothelium at an early stage of atherosclerosis in hypercholesterolemic $apoE^{-/-}$ mice. Prolonged blockade of platelet adhesion by antibodies against glycoprotein Ibα (GPIbα) significantly attenuated atherosclerotic lesion formation in these animals, indicating that platelet GPIbα interaction with its ligand Von Willebrand Factor (VWF) on activated endothelial cells might be responsible for platelet binding[55,56]. Once recruited to atherosclerotic lesions, platelets contain a variety of molecules that can additionally promote chemo-attraction of leukocytes (platelet activating factor, macrophage inflammatory protein-1α, and cationic proteins), stimulate smooth muscle cell and fibroblast proliferation (TGF-β, platelet-derived growth factor, and serotonin), and promote collagen synthesis. Platelets with these cytokines thereby contribute directly to lesion progression and maturation[57]. Activated platelets also shed large amounts of soluble CD40 ligand (CD40L)[58]. CD40L/CD40 interaction plays an important role in atherosclerosis because antibodies to CD40L inhibited lesion development in low-density lipoprotein receptor-deficient mice[59] and CD40L-deficient mice were extensively protected from

atherosclerosis[60]. With all of these activities of activated platelets, it is not surprising that repeated infusions of activated platelets promoted atherosclerosis in apoE$^{-/-}$ mice. Platelet function was also dependent on the presence of platelet P-selectin[61]. Several independent studies demonstrated that platelets and their adhesion receptor P-selectin played an important role in atherosclerotic lesion formation[54,62]. Activated platelets also express and secrete chemokine (C-C motif) ligand 5 (CCL5) and chemokine (C-X-C motif) ligand 4 (CXCL4), which are deposited in a P-selectin dependent manner on microvasculature, aortic endothelium, and monocytes[63]. Deposition of these proinflammatory cytokines results in activation of monocyte integrin and increased monocyte recruitment to atherosclerotic lesions[61].

4. Biomimetic nanoparticles for inflammation targeting

In the past thirty years the development of biomimetic nanoparticles for inflammation targeting was largely based on three strategies: i) Synthetic nanoparticles modified with targeting ligands that mimic cell surface proteins (also called bottom-up strategy); ii) cell membrane-coated nanoparticles (also called top-down strategy); iii) liposomes engineered with cell membrane proteins (Fig. 2). For the first strategy, the biomimetic nanoparticles are a synthetic system, where targeting ligands against CAMs and selectins are modified on nanoparticles for diagnosis, therapy, and theranostic applications of inflammation-related diseases[64]. However, for these synthetic nanoparticles, limitations remain in performance and functionality, such as short circulation, low targeting efficiency, and safety problems. In order to push the performance and functionality limits of synthetic nanoparticles, the second strategy that combines the versatility of synthetic nanomaterials and the unique functionalities of cellular membranes generates a new class of cell membrane-coated nanoparticles for effective delivery of therapeutic agents[65]. These biomimetic nanoparticles leverage the advantages of cell membranes and synthetic nanoparticles and are highlighted with three main advantages: (i) prolonged systemic circulation[66], (ii) cell-specific targeting[67], and (iii) detoxification[68]. For the third strategy, bioactive cellular components are engineered into synthetic liposomes to bridge the gap between synthetic nanoparticles and biological materials[69]. These liposomes integrated with cell membrane proteins are also endowed with cell-like long circulation and cell-specific targeting ability.

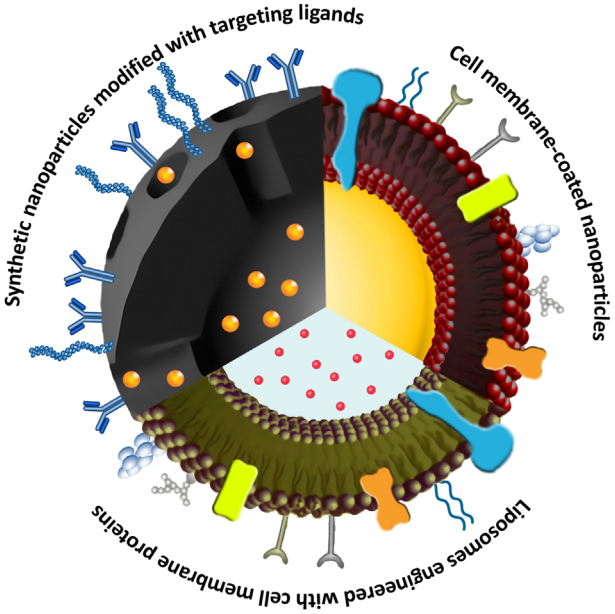

Figure 2 Schematic graph of different strategies of inflammation-targeting biomimetic nanoparticles. Orange or red balls indicate drugs encapsulated in grey synthetic nanoparticles or green liposomes.

4.1. *Synthetic nanoparticles modified with targeting ligands*

4.1.1. *Liposomes modified with targeting ligands*

A liposome is a vesicular structure with an aqueous core surrounded by a hydrophobic membrane bilayer composed of phospholipids, whose hydrophobic tail is inserted into the bilayer and hydrophilic head extends into in the water. Liposomes modified with targeting ligands on their surface can realize inflammation-directed drug delivery, enhancing local drug concentration and minimizing drug toxicity at the same time. Kang et al. found that decorating the I domain of LFA-1[70] onto the surface of liposomes could increase liposome specificity toward LPS-induced inflammation or toward inflamed human macrovascular endothelial cells and monocytes with high ICAM-1 expression *in vitro*. Using celastrol as a model drug, these ICAM-1-targeted liposomes were able to defend endothelial cells against LPS challenges, block the adhesion of monocytes toward inflamed endothelial cells, prevent leukocytes from accumulating in inflammatory tissues, and avoid the aggravation of inflammatory signals[71]. Since VCAM-1 is over-expressed on tumor vessels, modifying liposomes with anti-VCAM antibody can be used for detecting tumors. Gosk et al.[72] prepared PEGylated immunoliposomes modified with anti-VCAM antibody and found that these VCAM-1-targeted liposomes demonstrated significantly increased accumulation in Colo 677 tumor tissues, compared with liposomes modified with an irrelevant immunoglobulin G (IgG). Additional research showed that nitric oxide-loaded echogenic liposomes decorated with anti-VCAM-1 antibody could improve the targeting effect on atheroma components[73].

Inflammation-targeting liposomes could also be made by decorating PSGL-1 on liposomes with the help of a streptavidin-protein G linker. After decorating with PSGL-1, liposomes were demonstrated to have a more than 7-fold greater binding affinity toward P-selectin expressed on the membrane of activated epithelial cells *in vitro*. *In vivo* studies further proved that PSGL-1-decorated liposomes were equipped with a similar stability and circulating capability to unconjugated liposomes but a more than 3-fold greater accumulation at the tumor site[74].

4.1.2. *Polymersomes modified with targeting ligands*

Polymersome (also named polymer vesicle) is a vesicular structure with an aqueous core surrounded by a hydrophobic membrane composed of amphiphilic polymers. Similar to liposomes, polymersomes can be used to simulate cells, encapsulating and delivering drugs. Inflammation-targeting polymersomes can be developed *via* antibody decoration on polymersomes. Lin et al.[75] first functionalized polymersomes with antibodies against ICAM-1 for inflammation targeting, utilizing biotin-avidin chemistry. Avidin is a tetrameric biotin-binding protein, containing four identical subunits, each of which can bind to biotin with high affinity and specificity. The avidin–biotin complex is the strongest known non-covalent interaction ($K_d = 10^{-15}$ mol/L) between a

protein and ligand. The bond formation between biotin and avidin is very rapid, and once formed it is unaffected by extremes of pH, temperature, organic solvents and other denaturing agents[76]. As a result, avidin–biotin chemistry is extensively used for targeting ligand decoration on nanoparticles, where nanoparticles can be either decorated with biotin or avidin, while targeting ligands can be either linked to avidin or biotin. Hammer et al.[77] also developed leuko-polymersomes to mimic the two critical adhesion pathways that leukocytes utilize to achieve adhesion in the fast fluid flow of blood vessels—selectins and integrins, by linking inflammation-targeting ligands (both anti-ICAM-1 antibody and SLe^X) to polymesomes *via* biotin–avidin chemistry. It was demonstrated that these leuko-polymersomes adhered avidly and selectively to surfaces coated with P-selectin and ICAM-1 under flow and maximal adhesion occurred at intermediate densities of both SLe^X and anti-ICAM-1 antibody, owing to synergistic binding effects of the two ligands. Leuko-polymersomes were able to simulate the leukocyte adhesion at a physiological shear rate toward inflamed endothelium. Compared with leuko-polymersomes, polymersomes bearing only a single ligand bound less avidly to inflamed endothelium and with lower selectivity, indicating optional mimicry of leukocyte adhesion to inflamed endothelium required contributions from both pathways. These studies established a basis for the design of polymersomes for targeted diagnosis and treatment of inflammation-related diseases[78].

4.1.3. *Polymer nanoparticles modified with targeting ligands*

Polymer nanoparticles refer to solid particles composed of macromolecular polymers, with particle size ranging from 10 to 1000 nm. Low toxicity, good biocompatibility, and biodegradation at specific sites are the main advantages of polymer nanoparticles as drug carriers. The early attempt to prepare inflammation-targeting polymer particles was with biotinylated-SLe^X, a natural targeting ligand toward selectin, which was decorated onto the surface of avidin-modified poly(lactic-*co*-glycolic acid) (PLGA) microspheres. SLe^X-decorated PLGA microspheres simulated the natural adhesion process of leukocytes when applied to the flow chamber coated with selectins, showing low speed rolling under flow[79]. Leukocyte-inspired poly(lactic acid)-poly(ethylene glycol) (PLA-PEG) biodegradable particles (size from 1 to 2.5 μm) were also synthesized by the linkage of biotinylated antibody against E-selectin, biotinylated antibody against P selectin, biotinylated antibody against VCAM-1, and biotinylated antibody against ICAM-1 to the surface of PLA-PEG-biotin particles with the help of neutravidin. It was demonstrated that these leukocyte-inspired particles were able to target to all of the major inflammation markers overexpressed during inflammation. PLA-PEG particles decorated with antibody against E-selectin exhibited a 6-fold higher adhesion toward TNF-α-treated endothelium *in vivo* than undecorated particles. A 10-fold enhancement of PLA-PEG particle adhesion toward trauma-triggered endothelium *in vivo* was shown with the help of recombinant PSGL-1[80]. After comparison of these different targeting ligands, anti-VCAM-1 antibody was chosen for further study. PLA-PEG spheres concatenated with anti-VCAM-1 antibody exhibited selective and enhanced adhesion to inflammatory vasculature in a dextran sulfate sodium-induced mice model of colitis[81].

Except for antibodies or proteins, peptides can also be utilized as alternative targeting ligands for inflammation targeting. Cyclo (1,12)PenITDGEATDSGC (cLABL) peptide, which was demonstrated to bind with high affinity to domain-1 (D1) of ICAM-1 on the surface of inflamed endothelial cells, was decorated on PEGylated PLGA nanoparticles. It was demonstrated that cLABL-modified nanoparticles bound rapidly and efficiently to human umbilical cord vascular endothelial cells (HUVEC) with overexpressed ICAM-1. The binding capability of PLGA nanoparticles can be efficiently blocked *via* pre-incubating HUVEC with free cLABL, suggesting that the binding of PLGA nanoparticles to HUVEC was specifically mediated by surface cLABL on nanoparticles. Meanwhile, cLABL-modified nanoparticles were rapidly endocytosed and trafficked to lysosomes to a greater extent than the untargeted nanoparticles[82]. Further verification indicated that this peptide-mediated nanoparticle ultimately led to targeting delivery of therapeutic agents to inflammatory sites expressing upregulated ICAM-1[83].

4.1.4. *Polymer micelles modified with targeting ligands*

Polymer micelles with a typical core–shell structure were formed by self-assembly of polymers. The small and uniform size of micelles, good dispersibility in water, convenience for sterilizing, and controlled release of drugs make micelles perfect carriers for water-insoluble substances[84]. When modified with inflammation-targeting ligands, polymer micelles are very commonly used for diagnosis and treatment of inflammation-related diseases. By adding a cysteine group to the N-terminus of VHPKQHR peptide, a VCAM-1-binding peptide derived from phage display *in vivo*[85], the linkage of CVHPKQHR to distearoyl phosphoethanolamine-poly(ethylene glycol) 2000-maleimide (DSPE-PEG2000-maleimide) was facilitated through thioether linkage, forming DSPE-PEG2000-VHPKQHR. To achieve near-infrared imaging of inflammation, Cyanine 7 (Cy7) dye was labeled to DSPE-PEG2000-amine, forming DSPE-PEG2000-Cy7. Since amphiphilic DSPE-PEG2000 can self-assemble and turn into spherical micelles, VCAM-1-targeting micelles of 17 nm were easily prepared by mixing DSPE-PEG2000-VHPKQHR and DSPE-PEG2000-Cy7 at a molar ratio of 1:9. These micelles were able to specifically accumulate at the site of both early-stage and mid-stage atherosclerotic plaques inside $ApoE^{-/-}$ mice and reveal the existence of atherosclerotic plaque[86].

4.1.5. *Inorganic nanoparticles modified with targeting ligands*

Inorganic nanoparticles have good application prospects in the field of reaction catalysis, imaging, and electromagnetic function. Two typical inorganic nanoparticles, including iron oxide nanoparticles and gold nanoparticles, are discussed in the following sections.

Iron oxide nanoparticles have diameters between 1 and 100 nm. There are various shapes of iron oxides, such as nanorods, porous spheres, nanohusks, nanocubes, distorted cubes, and self-oriented flowers. Iron oxide nanoparticles with a size <10–20 nm exhibit an inimitable form of magnetism, which is called super paramagnetic iron oxide (SPIO)[87,88]. Iron oxide nanoparticles can be used in inflammation detection by magnetic resonance imaging (MRI), a non-invasive, non-radiative technique, which is thought to lead to cellular or even molecular resolution if optimized targeted iron oxide nanoparticles are introduced. Amstad et al.[89] developed PEG-gallol-stabilized iron oxide nanoparticles with a size of 9 ± 2 nm and modified them with biotinylated antibodies against VCAM-1 *via* the linkage between biotin and neutravidin. These small iron oxide nanoparticles demonstrated excellent specificity for VCAM-1 targeting using a quartz crystal microbalance with dissipation monitoring. Theoretically, these iron

oxide nanoparticles can be functionalized with any biotinylated ligand for molecular imaging of inflammation. R832 peptide, a cyclic heptapeptide obtained by *in vitro* phage display[90] was modified on ultrasmall superparamagnetic particles of iron oxide for efficient detection of plaques with a vulnerable morphology in an ApoE$^{-/-}$ mouse model[91]. To detect the inflammatory activation of cells in atherosclerosis, Nahrendorf et al.[85] developed a VCAM-1-targeted imaging platform by conjugating VHPKQHR peptide to 38-nm iron oxide nanoparticles with a 3-nm monocrystalline core. Noninvasive MRI of VCAM-1 by this platform not only helped identify early stages of inflammation in experimental atherosclerosis, but also enabled real-time detection of VCAM-1 expression in inflammation *in vivo*, to quantify pharmacotherapy-induced reductions in VCAM-1 expression, and to identify activated cells in human plaques[85].

Apart from VCAM-1, ICAM-1 could also be a target for inflammation-targeted imaging using iron oxide nanoparticles. Chen et al.[92] engineered nanoprobes mimicking the intermolecular interaction between activated leukocytes and inflamed endothelial cells *in vivo* by decorating SPIO nanoparticles with integrin LFA-1 I domain. Optical and MRI imaging of the whole body *in vivo* showed that these leukocyte-mimetic nanoparticles were equipped with preferential localization toward tumor vasculature, providing a likelihood for detecting tumors *via* targeting delivery to inflammatory tumor microenvironment[92].

Gold nanoparticles refer to gold particles with diameter from 5 to 300 nm and with the shape of a sphere, shell, cage, or rod[93,94]. The gold nanoparticle suspensions are usually presented in different colors from red to blue/purple because of the tunable size and the surface plasmon resonance phenomena caused by absorption of light. In addition, when irradiated with non-ionizing laser pulses, gold nanoparticle can absorb the laser energy and convert it into heat instantaneously, leading to transient thermal expansion and thus wideband ultrasonic emission (photoacoustic signal), which can be measured to produce images[95]. These unique optical and photoacoustic properties of gold nanoparticles could be used for molecular imaging of inflammation. Gold nanoshells sized 38.7 nm displaying near-infrared absorption properties were conjugated with anti-VCAM-1 antibody by a bi-functional PEG for photoacoustic imaging of atherosclerotic plaque in mice. No noticeable acute toxic effect was found in mice and the selective accumulation of these VCAM-1-targeted gold nanoshells was detected in atherosclerotic-prone regions in mice by photoacoustic imaging[96].

4.2. *Cell membrane-coated nanoparticles*

4.2.1. *Leukocyte membrane-coated nanoparticle*

To act as artificial leukocytes targeting an inflammation site, Parodi et al.[67] first developed a leukocyte-like vector (LLV) platform by coating leukocyte membrane (J774 macrophage, THP-1 monocyte, or Jurkat T lymphocyte) on nanoporous silicon particles with a diameter of 2.8 μm. These LLVs could efficiently target inflamed HUVECs triggered by TNF-α by the interaction of LFA-1 on LLVs and up-regulated ICAM-1 on HUVECs. In addition, LLVs were able to evade the immune system, be sufficiently stable *in vivo* to enhance particle circulation time, and move across the endothelial layer while eluding the lysosomal pathway. Furthermore, LLVs could recognize and bind tumor endothelium in an active, non-destructive manner. These results suggested that LLVs could successfully deliver drug or imaging agents to inflammatory vasculature.

Inflammation is a hallmark of cancer. Activated leukocytes are intrinsically able to home to inflammatory sites. Utilizing inflammation-driven mouse models, Zhang's group[97] revealed that grapefruit-derived nanovectors were enhanced for homing to inflammatory tissues after coating with inflammation-associated receptor-enriched membrane harvested from activated leukocytes (lymphoma cell line EL4 cells). Blocking LFA-1 or chemokine (C-X-C motif) receptor 1 (CXCR1) and CXCR2 on leukocyte membrane could significantly inhibit the targeting capability of these leukocyte membrane-coated nanovectors for sites of inflammation. The therapeutic potential of leukocyte membrane-coated nanovectors loaded with drugs was further proven by enhancing the chemotherapeutic effect on CT26 and 4T1 tumor-bearing mouse models and inhibiting inflammation in dextran sulfate sodium-triggered colitis mouse models[97]. Evidence showed that inflammation also occurs at tumor metastatic niches and inflammatory neutrophils possess a metastasis niche-targeting property by the intrinsic cell adhesion molecules on neutrophils. Inspired by this mechanism, Kang et al.[98] developed a nanosize neutrophil-mimicking drug delivery system by coating neutrophil membranes on the surface of PLGA nanoparticles (NM-NP). Compared with uncoated nanoparticles, NM-NP improved homing to circulating cancer cells and the premetastatic niche, prevented early metastasis and potentially inhibited the progress of already-formed metastasis after loading with carfilzomib, a second generation proteasome inhibitor.

4.2.2. *Platelet membrane-coated nanoparticles*

As inflammation is always associated with vascular damage, platelets are recruited to the damaged vessels to provide haemostasis. Therefore, nanoparticles coated with platelet membrane could be endowed with the homing capability of platelets for inflammation sites. Zhang's group[99] first demonstrated the preparation of platelet membrane-cloaked nanoparticle (PNP) consisting of a biodegradable PLGA core shielded entirely in the plasma membrane of human platelets. The resulting nanoparticles demonstrated a right-side-out unilamellar membrane coating functionalized with immunomodulatory and adhesion antigens associated with platelets such as CD47, CD55, CD59, αIIb, α2, α5, α6, β1, β3, GPIbα, Glycoprotein IV (GPIV), Glycoprotein V (GPV), Glycoprotein VI (GPVI), and Glycoprotein IX (GPIX). Compared with uncoated nanoparticles, PNP had reduced cellular uptake by macrophage-like cells and lacked particle-induced complement activation in autologous human plasma. In addition, PNP also displayed platelet-mimicking properties such as selective adhesion to damaged human and rodent vasculatures[99]. To enhance antitumor therapy, Hu et al.[100] presented a relay drug delivery strategy composed of two sequential modules: a signal transmission nanoparticle encapsulating tumor necrosis factor α (TNF-α) (designated NCA) to trigger tumor vascular inflammation and an execution platelet-coated nanoparticle holding paclitaxel (designated NCB) targeting inflammatory tumor vasculature. It was shown that NCA could specifically target the tumor blood vessels and effectively trigger inflammation, while the subsequent administration of the execution NCB could easily identify the amplified signal and accumulate at the tumor site by five-fold compared with uncoated nanoparticles. To integrate the advantages of different biological membranes, Dehaini et al.[101] created a new type of biological coating by fusing red blood cell (RBC) membrane and platelet membrane, providing a facile method for further enhancing nanoparticle functionality. It was demonstrated

that this RBC-platelet hybrid membrane-coated nanoparticle carried properties of both source cells, exhibiting long circulation and inflammation-targeting capabilities.

4.3. *Liposomes engineered with leukocyte membrane protein*

To bridge the gap between synthetic nanoparticles and biological materials, Molinaro et al.[69] first developed a leukosome platform incorporating leukocyte membrane proteins into liposomes. The resulting proteolipid vesicle leveraged the advantages of both liposomes and leukocyte membrane proteins, enabling efficient targeting to inflammatory vasculature. It was shown that leukocyte membrane proteins, such as LFA-1, Mac-1, and PSGL-1, self-tolerance-related antigen CD45, and marker-of-self CD47 were all identified on the surface of leukosomes by liquid chromatography–tandem mass spectrometry. Immunolabeling with antibodies directed against the extracellular domain of these proteins not only confirmed their presence in leukosomes, but also verified their correct orientation on the leukosome bilayer. In an ear inflammation mouse model triggered by lipopolysaccharide, leukosomes demonstrated 5-fold enhanced accumulation at one hour after injection and 8.5-fold enhanced accumulation at one day after injection in comparison with normal liposomes. Compared with normal liposomes, a notable decrease of accumulation inside non-specific organs such as spleen, kidney, liver and lung as well as a five-fold increase of circulation time was found for leukosomes. After loading with dexamethasone, an anti-inflammatory glucocorticoid, leukosomes significantly reduced the inflammatory symptoms *in vivo* compared with control liposomes[69]. By combining cell biology with nanotechnology, it was estimated that any cell type-derived membrane protein could be used for the development of biomimetic liposomes. In addition, the reconstruction of membrane proteins purified from different cellular types (leukocytes, red blood cells, platelets) will create different biomimetic liposomes that exploit the intrinsic properties of the original cells for precise drug delivery to inflammation sites.

5. Conclusions and prospectives

Biomimetic nanomedicine is still in its infancy and there are many ways to further improve the above-discussed strategies for the development of biomimetic nanoparticles for inflammation targeting. For biomimetic nanoparticles based on synthetic nanoparticles modified with targeting ligands, screening targeting ligands with high affinity with CAMs and selectins and optimizing the physiochemical characteristics of nanoparticles are important directions for better inflammation targeting, as the interaction of nanoparticles with inflammatory tissues depends on the targeting ligands on nanoparticles, while *in vivo* circulation of nanoparticles is determined by their physiochemical characteristics. Regarding cell membrane-coated nanoparticles, using specialized cell membranes (including activated cells and genetically engineered cells) or combining functions from different membrane types may further benefit their utility. For liposomes engineered with cell membrane proteins, the reconstruction of membrane proteins purified from different origins will create different biomimetic liposomes. In addition, depleting human leukocyte antigen and other blood type antigens during protein purification by special techniques will help to further enhance their application in inflammation targeting. Finally, reliable and standardized fabrication of these nanoparticles to get a stable, safe, and non-immunogenic final product is extremely important for their translation into clinics. Although the biomimetic nanoparticles, especially cell membrane-coated nanoparticles and liposomes engineered with cell membrane proteins are still relatively new, we hold the belief that inflammation targeting biomimetic nanoparticles will have a bright future in advancing the field of nanomedicine, enabling novel applications.

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References

1. Karin M, Clevers H. Reparative inflammation takes charge of tissue regeneration. *Nature* 2016;**529**:307–15.
2. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. *Cell* 2010;**140**:883–99.
3. Hartman J, Frishman WH. Inflammation and atherosclerosis: a review of the role of interleukin-6 in the development of atherosclerosis and the potential for targeted drug therapy. *Cardiol Rev* 2014;**22**:147–51.
4. Howard M, Zern BJ, Anselmo AC, Shuvaev VV, Mitragotri S, Muzykantov V. Vascular targeting of nanocarriers: perplexing aspects of the seemingly straightforward paradigm. *ACS Nano* 2014;**8**:4100–32.
5. Chacko AM, Hood ED, Zern BJ, Muzykantov VR. Targeted nanocarriers for imaging and therapy of vascular inflammation. *Curr Opin Colloid Interface Sci* 2011;**16**:215–27.
6. Fang RH, Jiang Y, Fang JC, Zhang L. Cell membrane-derived nanomaterials for biomedical applications. *Biomaterials* 2017;**128**:69–83.
7. Tunn EJ, Bacon PA. Differentiating persistent from self-limiting symmetrical synovitis in an early arthritis clinic. *Br J Rheumatol* 1993;**32**:97–103.
8. Harrison BJ, Symmons DP, Brennan P, Barrett EM, Silman AJ. Natural remission in inflammatory polyarthritis: issues of definition and prediction. *Br J Rheumatol* 1996;**35**:1096–100.
9. Symmons D, Turner G, Webb R, Asten P, Barrett E, Lunt M, et al. The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century. *Rheumatology* 2002;**41**:793–800.
10. Brentano F, Kyburz D, Schorr O, Gay R, Gay S. The role of Toll-like receptor signalling in the pathogenesis of arthritis. *Cell Immunol* 2005;**233**:90–6.
11. Brennan FM, Hayes AL, Ciesielski CJ, Green P, Foxwell BM, Feldmann M. Evidence that rheumatoid arthritis synovial T cells are similar to cytokine-activated T cells: involvement of phosphatidylinositol 3-kinase and nuclear factor κB pathways in tumor necrosis factor α production in rheumatoid arthritis. *Arthritis Rheum* 2002;**46**:31–41.
12. McInnes IB, Schett G. Cytokines in the pathogenesis of rheumatoid arthritis. *Nat Rev Immunol* 2007;**7**:429–42.
13. Frostegård J. Systemic lupus erythematosus and cardiovascular disease. *Lupus* 2008;**17**:364–7.
14. Brierley SM, Linden DR. Neuroplasticity and dysfunction after gastrointestinal inflammation. *Nat Rev Gastroenterol Hepatol* 2014;**11**:611–27.
15. Boland CR, Luciani MG, Gasche C, Goel A. Infection, inflammation, and gastrointestinal cancer. *Gut* 2005;**54**:1321–31.
16. Xavier RJ, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. *Nature* 2007;**448**:427–34.
17. Chang JC, Smith LR, Froning KJ, Schwabe BJ, Laxer JA, Caralli LL, et al. $CD8^+$ T cells in psoriatic lesions preferentially use T-cell receptor $V_\beta 3$ and/or $V_\beta 13.1$ genes. *Proc Natl Acad Sci U S A* 1994;**91**:9282–6.

18. Zheng Y, Danilenko DM, Valdez P, Kasman I, Eastham-Anderson J, Wu J, et al. Interleukin-22, a T_H17 cytokine, mediates IL-23-induced dermal inflammation and acanthosis. *Nature* 2007;**445**:648–51.
19. Nestle FO, Turka LA, Nickoloff BJ. Characterization of dermal dendritic cells in psoriasis. Autostimulation of T lymphocytes and induction of Th1 type cytokines. *J Clin Investig* 1994;**94**:202–9.
20. Ross RA, Monteith PR, McAdam JG. Case report: polymorphous haemangioendothelioma, a rare cause of persistent lymphadenopathy. *J R Nav Med Serv* 1993;**79**:80–2.
21. Libby P. Inflammation in atherosclerosis. *Nature* 2002;**420**:868–74.
22. Frangogiannis NG, Smith CW, Entman ML. The inflammatory response in myocardial infarction. *Cardiovasc Res* 2002;**53**:31–47.
23. del Zoppo G, Ginis I, Hallenbeck JM, Iadecola C, Wang X, Feuerstein GZ. Inflammation and stroke: putative role for cytokines, adhesion molecules and iNOS in brain response to ischemia. *Brain Pathol* 2000;**10**:95–112.
24. Shah PK. Role of inflammation and metalloproteinases in plaque disruption and thrombosis. *Vasc Med* 1998;**3**:199–206.
25. Robbie L, Libby P. Inflammation and atherothrombosis. *Ann N Y Acad Sci* 2001;**947**:167–80.
26. Thomas TH, Advani A. Inflammation in cardiovascular disease and regulation of the actin cytoskeleton in inflammatory cells: the actin cytoskeleton as a target. *Cardiovasc Hematol Agents Med Chem* 2006;**4**:165–82.
27. Balkwill F. Immunology for the next generation. *Nat Rev Immunol* 2005;**5**:509–12.
28. Munn LL. Cancer and inflammation. *Wiley Interdiscip Rev Syst Biol Med* 2017;**9**:e1370.
29. Balkwill F, Coussens LM. Cancer: an inflammatory link. *Nature* 2004;**431**:405–6.
30. Cowburn AS, Condliffe AM, Farahi N, Summers C, Chilvers ER. Advances in neutrophil biology: clinical implications. *Chest* 2008;**134**:606–12.
31. Galli SJ, Tsai M, Piliponsky AM. The development of allergic inflammation. *Nature* 2008;**454**:445–54.
32. Sutherland ER, Cherniack RM. Management of chronic obstructive pulmonary disease. *N Engl J Med* 2004;**350**:2689–97.
33. Kim EY, Battaile JT, Patel AC, You Y, Agapov E, Grayson MH, et al. Persistent activation of an innate immune response translates respiratory viral infection into chronic lung disease. *Nat Med* 2008;**14**:633–40.
34. Greter M, Lelios I, Croxford AL. Microglia *versus* myeloid cell nomenclature during brain inflammation. *Front Immunol* 2015;**6**:249.
35. Rothhammer V, Quintana FJ. Environmental control of autoimmune inflammation in the central nervous system. *Curr Opin Immunol* 2016;**43**:46–53.
36. Hagberg H, Mallard C. Effect of inflammation on central nervous system development and vulnerability: review. *Curr Opin Neurol* 2005;**18**:117–23.
37. Varki A. Selectin ligands. *Proc Natl Acad Sci U S A* 1994;**91**:7390–7.
38. Geng JG, Chen M, Chou KC. P-selectin cell adhesion molecule in inflammation, thrombosis, cancer growth and metastasis. *Curr Med Chem* 2004;**11**:2153–60.
39. Jutila MA. Selectins in leukocyte extravasation: function of a common epitope on L- and E-selectin. *Adv Pharmacol* 1994;**25**:235–62.
40. Stamenkovic I. The L-selectin adhesion system. *Curr Opin Hematol* 1995;**2**:68–75.
41. Dean DC, Iademarco MF, Rosen GD, Sheppard AM. The integrin $\alpha 4\beta 1$ and its counter receptor VCAM-1 in development and immune function. *Am Rev Respir Dis* 1993;**148**:S43–6.
42. Wawryk SO, Novotny JR, Wicks IP, Wilkinson D, Maher D, Salvaris E, et al. The role of the LFA-1/ICAM-1 interaction in human leukocyte homing and adhesion. *Immunol Rev* 1989;**108**:135–61.
43. DeLisser HM, Newman PJ, Albelda SM. Molecular and functional aspects of PECAM-1/CD31. *Immunol Today* 1994;**15**:490–5.
44. Kelly M, Hwang JM, Kubes P. Modulating leukocyte recruitment in inflammation. *J Allergy Clin Immunol* 2007;**120**:3–10.
45. Kreuger J, Phillipson M. Targeting vascular and leukocyte communication in angiogenesis, inflammation and fibrosis. *Nat Rev Drug Discov* 2016;**15**:125–42.
46. Gentry PA. The mammalian blood platelet: its role in haemostasis, inflammation and tissue repair. *J Comp Pathol* 1992;**107**:243–70.
47. Acikel S, Akdemir R. The relationship between inflammation, platelet activation and antiplatelet resistance. *Inflamm Allergy Drug Targets* 2010;**9**:364–81.
48. Menter DG, Kopetz S, Hawk E, Sood AK, Loree JM, Gresele P, et al. Platelet "first responders" in wound response, cancer, and metastasis. *Cancer Metastas- Rev* 2017;**36**:199–213.
49. Schäfer M, Werner S. Cancer as an overhealing wound: an old hypothesis revisited. *Nat Rev Mol Cell Biol* 2008;**9**:628–38.
50. Zitvogel L, Pietrocola F, Kroemer G. Nutrition, inflammation and cancer. *Nat Immunol* 2017;**18**:843–50.
51. Schumacher D, Strilic B, Sivaraj KK, Wettschureck N, Offermanns S. Platelet-derived nucleotides promote tumor-cell transendothelial migration and metastasis *via* $P2Y_2$ receptor. *Cancer Cell* 2013;**24**:130–7.
52. Gay LJ, Felding-Habermann B. Contribution of platelets to tumour metastasis. *Nat Rev Cancer* 2011;**11**:123–34.
53. Mannaioni PF, Di Bello MG, Masini E. Platelets and inflammation: role of platelet-derived growth factor, adhesion molecules and histamine. *Inflamm Res* 1997;**46**:4–18.
54. Massberg S, Brand K, Gruner S, Page S, Müller E, Müller I, et al. A critical role of platelet adhesion in the initiation of atherosclerotic lesion formation. *J Exp Med* 2002;**196**:887–96.
55. André P, Denis CV, Ware J, Saffaripour S, Hynes RO, Ruggeri ZM, et al. Platelets adhere to and translocate on von Willebrand factor presented by endothelium in stimulated veins. *Blood* 2000;**96**:3322–8.
56. Romo GM, Dong JF, Schade AJ, Gardiner EE, Kansas GS, Li CQ, et al. The glycoprotein Ib-IX-V complex is a platelet counterreceptor for P-selectin. *J Exp Med* 1999;**190**:803–13.
57. Ross R. Platelets, Platelet-derived growth factor, growth control, and their interactions with the vascular wall. *J Cardiovasc Pharmacol* 1985;**7**:S186–90.
58. André P, Nannizzi-Alaimo L, Prasad SK, Phillips DR. Platelet-derived CD40L: the switch-hitting player of cardiovascular disease. *Circulation* 2002;**106**:896–9.
59. Mach F, Schönbeck U, Sukhova GK, Atkinson E, Libby P. Reduction of atherosclerosis in mice by inhibition of CD40 signalling. *Nature* 1998;**394**:200–3.
60. Lutgens E, Gorelik L, Daemen MJ, de Muinck ED, Grewal IS, Koteliansky VE, et al. Requirement for CD154 in the progression of atherosclerosis. *Nat Med* 1999;**5**:1313–6.
61. Huo Y, Schober A, Forlow SB, Smith DF, Hyman MC, Jung S, et al. Circulating activated platelets exacerbate atherosclerosis in mice deficient in apolipoprotein E. *Nat Med* 2003;**9**:61–7.
62. Burger PC, Wagner DD. Platelet P-selectin facilitates atherosclerotic lesion development. *Blood* 2003;**101**:2661–6.
63. von Hundelshausen P, Weber KS, Huo Y, Proudfoot AE, Nelson PJ, Ley K, et al. RANTES deposition by platelets triggers monocyte arrest on inflamed and atherosclerotic endothelium. *Circulation* 2001;**103**:1772–7.
64. Khodabandehlou K, Masehi-Lano JJ, Poon C, Wang J, Chung EJ. Targeting cell adhesion molecules with nanoparticles using *in vivo* and flow-based *in vitro* models of atherosclerosis. *Exp Biol Med* 2017;**242**:799–812.
65. Luk BT, Zhang L. Cell membrane-camouflaged nanoparticles for drug delivery. *J Control Release* 2015;**220**:600–7.
66. Hu CM, Zhang L, Aryal S, Cheung C, Fang RH, Zhang L. Erythrocyte membrane-camouflaged polymeric nanoparticles as a biomimetic delivery platform. *Proc Natl Acad Sci U S A* 2011;**108**:10980–5.
67. Parodi A, Quattrocchi N, van de Ven AL, Chiappini C, Evangelopoulos M, Martinez JO, et al. Synthetic nanoparticles functionalized with biomimetic leukocyte membranes possess cell-like functions. *Nat Nanotechnol* 2013;**8**:61–8.
68. Hu CM, Fang RH, Luk BT, Zhang L. Nanoparticle-detained toxins for safe and effective vaccination. *Nat Nanotechnol* 2013;**8**:933–8.

69. Molinaro R, Corbo C, Martinez JO, Taraballi F, Evangelopoulos M, Minardi S, et al. Biomimetic proteolipid vesicles for targeting inflamed tissues. *Nat Mater* 2016;**15**:1037–46.
70. Marlin SD, Springer TA. Purified intercellular adhesion molecule-1 (ICAM-1) is a ligand for lymphocyte function-associated antigen 1 (LFA-1). *Cell* 1987;**51**:813–9.
71. Kang S, Park T, Chen X, Dickens G, Lee B, Lu K, et al. Tunable physiologic interactions of adhesion molecules for inflamed cell-selective drug delivery. *Biomaterials* 2011;**32**:3487–98.
72. Gosk S, Moos T, Gottstein C, Bendas G. VCAM-1 directed immunoliposomes selectively target tumor vasculature *in vivo*. *Biochim Biophys Acta* 2008;**1778**:854–63.
73. Kim H, Kee PH, Rim Y, Moody MR, Klegerman ME, Vela D, et al. Nitric oxide-enhanced molecular imaging of atheroma using vascular cellular adhesion molecule 1-targeted echogenic immunoliposomes. *Ultrasound Med Biol* 2015;**41**:1701–10.
74. Carlisle R, Seymour LW, Coussios CC. Targeting of liposomes *via* PSGL1 for enhanced tumor accumulation. *Pharm Res* 2013;**30**:352–61.
75. Lin JJ, Ghoroghchian PP, Zhang Y, Hammer DA. Adhesion of antibody-functionalized polymersomes. *Langmuir* 2006;**22**:3975–9.
76. Hofmann K, Kiso Y. An approach to the targeted attachment of peptides and proteins to solid supports. *Proc Natl Acad Sci U S A* 1976;**73**:3516–8.
77. Hammer DA, Robbins GP, Haun JB, Lin JJ, Qi W, Smith LA, et al. Leuko-polymersomes. *Faraday Discuss* 2008;**139**:129–41.
78. Robbins GP, Saunders RL, Haun JB, Rawson J, Therien MJ, Hammer DA. Tunable leuko-polymersomes that adhere specifically to inflammatory markers. *Langmuir* 2010;**26**:14089–96.
79. Eniola AO, Rodgers SD, Hammer DA. Characterization of biodegradable drug delivery vehicles with the adhesive properties of leukocytes. *Biomaterials* 2002;**23**:2167–77.
80. Sakhalkar HS, Dalal MK, Salem AK, Ansari R, Fu J, Kiani MF, et al. Leukocyte-inspired biodegradable particles that selectively and avidly adhere to inflamed endothelium *in vitro* and *in vivo*. *Proc Natl Acad Sci U S A* 2003;**100**:15895–900.
81. Sakhalkar HS, Hanes J, Fu J, Benavides U, Malgor R, Borruso CL, et al. Enhanced adhesion of ligand-conjugated biodegradable particles to colitic venules. *FASEB J* 2005;**19**:792–4.
82. Zhang N, Chittasupho C, Duangrat C, Siahaan TJ, Berkland C. PLGA nanoparticle–peptide conjugate effectively targets intercellular cell-adhesion molecule-1. *Bioconjug Chem* 2008;**19**:145–52.
83. Chittasupho C, Xie SX, Baoum A, Yakovleva T, Siahaan TJ, Berkland CJ. ICAM-1 targeting of doxorubicin-loaded PLGA nanoparticles to lung epithelial cells. *Eur J Pharm Sci* 2009;**37**:141–50.
84. Liu Z, Wang Y, Zhang N. Micelle-like nanoassemblies based on polymer–drug conjugates as an emerging platform for drug delivery. *Expert Opin Drug Deliv* 2012;**9**:805–22.
85. Nahrendorf M, Jaffer FA, Kelly KA, Sosnovik DE, Aikawa E, Libby P, et al. Noninvasive vascular cell adhesion molecule-1 imaging identifies inflammatory activation of cells in atherosclerosis. *Circulation* 2006;**114**:1504–11.
86. Mlinar LB, Chung EJ, Wonder EA, Tirrell M. Active targeting of early and mid-stage atherosclerotic plaques using self-assembled peptide amphiphile micelles. *Biomaterials* 2014;**35**:8678–86.
87. Ittrich H, Peldschus K, Raabe N, Kaul M, Adam G. Superparamagnetic iron oxide nanoparticles in biomedicine: applications and developments in diagnostics and therapy. *RöFo* 2013;**185**:1149–66.
88. Laurent S, Saei AA, Behzadi S, Panahifar A, Mahmoudi M. Superparamagnetic iron oxide nanoparticles for delivery of therapeutic agents: opportunities and challenges. *Expert Opin Drug Deliv* 2014;**11**:1449–70.
89. Amstad E, Zurcher S, Mashaghi A, Wong JY, Textor M, Reimhult E. Surface functionalization of single superparamagnetic iron oxide nanoparticles for targeted magnetic resonance imaging. *Small* 2009;**5**:1334–42.
90. Burtea C, Laurent S, Port M, Lancelot E, Ballet S, Rousseaux O, et al. Magnetic resonance molecular imaging of vascular cell adhesion molecule-1 expression in inflammatory lesions using a peptide-vectorized paramagnetic imaging probe. *J Med Chem* 2009;**52**:4725–42.
91. Burtea C, Ballet S, Laurent S, Rousseaux O, Dencausse A, Gonzalez W, et al. Development of a magnetic resonance imaging protocol for the characterization of atherosclerotic plaque by using vascular cell adhesion molecule-1 and apoptosis-targeted ultrasmall superparamagnetic iron oxide derivatives. *Arterioscler Thromb Vasc Biol* 2012;**32**:e36–48.
92. Chen X, Wong R, Khalidov I, Wang AY, Leelawattanachai J, Wang Y, et al. Inflamed leukocyte-mimetic nanoparticles for molecular imaging of inflammation. *Biomaterials* 2011;**32**:7651–61.
93. Saha K, Agasti SS, Kim C, Li X, Rotello VM. Gold nanoparticles in chemical and biological sensing. *Chem Rev* 2012;**112**:2739–79.
94. Khlebtsov N, Bogatyrev V, Dykman L, Khlebtsov B, Staroverov S, Shirokov A, et al. Analytical and theranostic applications of gold nanoparticles and multifunctional nanocomposites. *Theranostics* 2013;**3**:167–80.
95. Deán-Ben XL, Gottschalk S, Mc Larney B, Shoham S, Razansky D. Advanced optoacoustic methods for multiscale imaging of *in vivo* dynamics. *Chem Soc Rev* 2017;**46**:2158–98.
96. Rouleau L, Berti R, Ng VW, Matteau-Pelletier C, Lam T, Sabourel P, et al. VCAM-1-targeting gold nanoshell probe for photoacoustic imaging of atherosclerotic plaque in mice. *Contrast Media Mol Imaging* 2013;**8**:27–39.
97. Wang Q, Ren Y, Mu J, Egilmez NK, Zhuang X, Deng Z, et al. Grapefruit-derived nanovectors use an activated leukocyte trafficking pathway to deliver therapeutic agents to inflammatory tumor sites. *Cancer Res* 2015;**75**:2520–9.
98. Kang T, Zhu Q, Wei D, Feng J, Yao J, Jiang T, et al. Nanoparticles coated with neutrophil membranes can effectively treat cancer metastasis. *ACS Nano* 2017;**11**:1397–411.
99. Hu CM, Fang RH, Wang KC, Luk BT, Thamphiwatana S, Dehaini D, et al. Nanoparticle biointerfacing by platelet membrane cloaking. *Nature* 2015;**526**:118–21.
100. Hu Q, Sun W, Qian C, Bomba HN, Xin H, Gu Z. Relay drug delivery for amplifying targeting signal and enhancing anticancer efficacy. *Adv Mater* 2017;**29**:1605803. Available from: http://dx.doi.org/10.1002/adma.201605803 .
101. Dehaini D, Wei X, Fang RH, Masson S, Angsantikul P, Luk BT, et al. Erythrocyte–platelet hybrid membrane coating for enhanced nanoparticle functionalization. *Adv Mater* 2017;**29**:1606209. Available from: http://dx.doi.org/10.1002/adma.201606209 .