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.

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Abbreviations: apoE\textsuperscript{−/−} 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\textsuperscript{+} 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, distearyl Phosphoethanolamine-poly(ethylene glycol); GPIb\textsubscript{α}, glycoprotein Ib\textsubscript{α}; GPIV, glycoprotein IV; GPSX, 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-IP, 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; SL\textsubscript{E}, sialyl lewis X; SPIO, super paramagnetic iron oxide; TGF-β, transforming growth factor β; Th cell, T-helper cell or CD4\textsuperscript{+} 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. 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. 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. As a result, targeting inflammation offers a promising solution for diagnosis and treatment of these diseases.

Inflammation in rheumatoid arthritis and systemic lupus erythematosus shares different symptoms with RA, the role of inflammation during its occurring is almost the same.

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. 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. 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 overlaying 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, and direct T cell contact. 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 auto-antibodies 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. RA also shows linkage with inflammatory diseases of the skin, lungs and vascular systems. Although systemic lupus erythematosus shares different symptoms with RA, the role of inflammation during its occurring is almost the same.

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.

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.

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 naïve T cells into T-helper cells or natural killer cells. Furthermore, atypical antigen-presenting cells may turn into effective activators of naïve 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.

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. 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. 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.

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. In addition, the role of inflammation is also important during cardiac ischemic injury and cerebral ischemic injury.

There is good evidence for locally active inflammation as a major cause of plaque formation and plaque composition. 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. When the cap is replaced with inflammatory and necrotic tissues, the fibrous cap becomes thin and vulnerable to rupture.

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. 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. 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 interleukins, 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.

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. 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.

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. Additional components of neural inflammation, such as polymorphonuclear leukocytes, lymphocytes, and macrophages, then arrive from the periphery.

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
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 cytoplasmatic 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 different selectins is the number of consensus repeat units. All and a cytoplasmic tail. The main structural difference between type lectin domain. All selectins contain a transmembrane domain

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

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**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.
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 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 cells43.

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 ligands42.

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 tissue including epitheloid 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 occurring43.

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 inflammation44.

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, SLeα) 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-145.

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 hemostasis46. 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 repair47. In addition to “first responders” in wounds, platelets can also serve as “first responders” in cancer and metastasis48. Cancer is considered as a non-healing wound or chronic inflammation49. 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 metastasis51,52.

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 mediators53. 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 ib (GPIIb) significantly attenuated atherosclerotic lesion formation in these animals, indicating that platelet GPIIb interaction with its ligand Von Willebrand Factor (VWF) on activated endothelial cells might be responsible for platelet binding55,56. 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 maturation57. 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 mice59 and CD40L-deficient mice were extensively protected from
atherosclerosis. 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. Several independent studies demonstrated that platelets and their adhesion receptor P-selectin played an important role in atherosclerotic lesion formation. 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. Deposition of these proinflammatory cytokines results in activation of monocyte integrin and increased monocyte recruitment to atherosclerotic lesions.

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. 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. These biomimetic nanoparticles leverage the advantages of cell membranes and synthetic nanoparticles and are highlighted with three main advantages: (i) prolonged systemic circulation, (ii) cell-specific targeting, and (iii) detoxification. For the third strategy, bioactive cellular components are engineered into synthetic liposomes to bridge the gap between synthetic nanoparticles and biological materials. These liposomes integrated with cell membrane proteins are also endowed with cell-like long circulation and cell-specific targeting ability.

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 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 onto the surface of liposomes could increase liposome specificity toward LPS-induced inflammation or toward inflamed macrovascular endothelial cells and monocytes with high ICAM-1 expression in vivo. 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. Since VCAM-1 is over-expressed on tumor vessels, modifying liposomes with anti-VCAM antibody can be used for detecting tumors. Gosk et al. 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 decorated 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.

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.

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. 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. 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. 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 SLeX) to poly(ethylene glycol) 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 SLeX 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.

4.1.3. Polymer nanoparticles modified with targeting ligands
Polymer nanoparticles refer to solid particles composed of macro-molecular 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-SLeX, a natural targeting ligand toward selectin, which was decorated onto the surface of avidin-modified poly(lactic-co-glycolic acid) (PLGA) microspheres. SLeX-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. 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. 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.

Except for antibodies or proteins, peptides can also be utilized as alternative targeting ligands for inflammation targeting. Cyclo(1,12)PenITDGEATDSCG (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. Further verification indicated that this peptide-mediated nanoparticle ultimately led to targeting delivery of therapeutic agents to inflammatory sites expressing upregulated ICAM-1.

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. 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, 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.

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 iniminitive form of magnetism, which is called super paramagnetic iron oxide (SPION). Iron oxide nanoparticles can be used in inflammation detection by magnetic resonance imaging (MRI), a non-invasive, non-radioactive technique, which is thought to lead to cellular or even molecular resolution if optimized targeted iron oxide nanoparticles are introduced. Amstad et al. 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 was modified on ultrasmall superparamagnetic particles of iron oxide for efficient detection of plaques with a vulnerable morphology in an ApoE−/− mouse model. To detect the inflammatory activation of cells in atherosclerosis, Nahrendorf et al. developed a VCAM-1-targeted imaging platform by conjugating VHPQKRH peptide to 38-nm iron oxide nanoparticles with a 3-nm monocristalline 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.

Apart from VCAM-1, ICAM-1 could also be a target for inflammation-targeted imaging using iron oxide nanoparticles. Chen et al. engineered nanoprobe mimicking the intermolecular interaction between activated leukocytes and injured endothelial cells in vivo by decorating SPION 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.

Gold nanoparticles refer to gold particles with diameter from 5 to 300 nm and with the shape of a sphere, shell, cage, or rod. 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. 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.

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. 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 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. 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. developed a nanosize neutral-mimicking drug delivery system by coating neutral phospholipids 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 first demonstrated the preparation of platelet membrane-coated 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, α2, a5, α6, β1, β3, GPBαx, 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. To enhance antitumor therapy, Hu et al. 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. 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. 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. 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 prospects

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 physicochemical 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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