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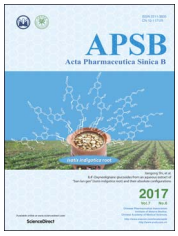

REVIEW

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

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