

Application of Nanomaterials Targeting Immune Cells in the Treatment of Chronic Inflammation

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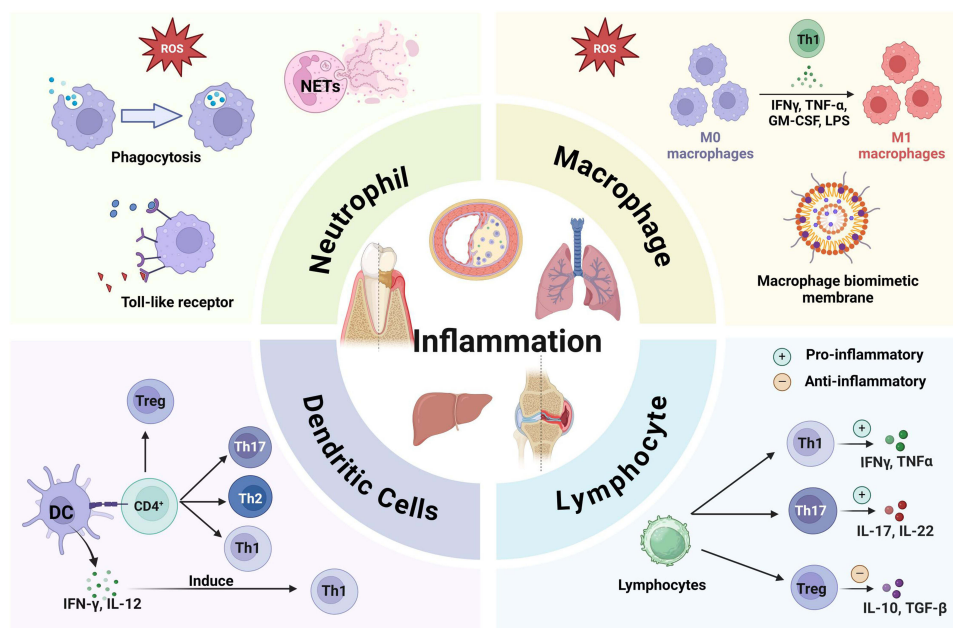
Abstract: Chronic inflammation is a common characteristic of all kinds of diseases, including autoimmune diseases, metabolic diseases, and tumors. It is distinguished by the presence of low concentrations of inflammatory factors stimulating the body for an extended period, resulting in a persistent state of infection. This condition is manifested by the aggregation and infiltration of mononuclear cells, lymphocytes, and other immune cells, leading to tissue hyperplasia and lesions. Although various anti-inflammatory medications, including glucocorticoids and non-steroidal anti-inflammatory drugs (NSAIDs), have shown strong therapeutic effects, they lack specificity and targeting ability, and require high dosages, which can lead to severe adverse reactions. Nanoparticle drug delivery mechanisms possess the capacity to minimize the effect on healthy cells or tissues due to their targeting capabilities and sustained drug release properties. However, most nanosystems can only target the inflammatory sites rather than specific types of immune cells, leaving room for further improvement in the therapeutic effects of nanomaterials. This article reviews the current research progress on the role of diverse immune cells in inflammation, focusing on the functions of neutrophils and macrophages during inflammation. It provides an overview of the domestic and international applications of nanomaterials in targeted therapy for inflammation, aiming to establish a conceptual foundation for the utilization of nanomaterials targeting immune cells in the treatment of chronic inflammation and offer new perspectives for the avoidance and management of inflammation.

Keywords: nanomaterials, periodontitis, chronic inflammation, target therapy, neutrophil, macrophage

Introduction

Inflammation is a protective reaction of the immune system to external stimuli, which maintains tissue homeostasis under various harmful conditions.¹ It is an internal defense reaction induced by immune cells and cytokines, primarily triggered by specific pattern recognition receptors expressed on myeloid-derived cells, like neutrophils, monocytes, macrophages, and dendritic cells.² The purpose of inflammation is to repair damaged tissues and eliminate various injurious factors, including pathogens. Any factor that leads to cell or tissue damage can potentially cause inflammation.³ The general process of inflammation is as follows: danger signals are released from damaged cells or pathogens, activating surrounding immune cells, which then release inflammatory mediators to recruit more immune cells to the inflammatory site. Subsequently, white blood cell migration occurs, resulting in the accumulation of neutrophils at the inflammatory site, releasing tumor necrosis factor- α (TNF) to increase vascular permeability. Monocytes release pro-inflammatory cytokines, further promoting the inflammatory response. Immune cells clear dead cells and inflammatory factors through phagocytosis or immune responses. Finally, anti-inflammatory cytokines, including interleukin-10 (IL-10), are discharged, inducing tissue regeneration, leading to the alleviation of the inflammatory response and eventual recovery. Inflammatory reactions can lead to temporary reductions in tissue function. When the inflammatory response is excessive or persistent, it promotes the development of numerous

Graphical Abstract



chronic ailments, leading to pathological changes and severe tissue damage, which may result in the progression of different chronic diseases, such as periodontitis, pneumonia, rheumatoid arthritis, cardiovascular diseases, malignant tumors, diabetes, chronic kidney disease, and autoimmune diseases.^{4,5} However, traditional anti-inflammatory drugs have issues such as poor permeability, rapid degradation, low bioavailability, and poor targeting ability, and may cause irreversible damage to normal tissues or organs. Therefore, there is a need to improve the targeted delivery of drugs and reduce their toxic side effects. Nanomaterials possess advantages such as large surface area, high drug loading capacity, strong drug stability, prolonged drug retention time at the inflammatory site, and reduced drug side effects. With the continuous development and innovation in the field of nanotechnology, nanomaterials have shown potential applications in multiple fields. Nanomaterials can not only improve bioavailability and enhance drug efficacy⁶ but also increase drug targeting by targeting specific immune cells, making them increasingly applied in the therapy of inflammation, infection and other diseases. The modulation of cytokine functions has been proposed to treat chronic inflammatory diseases, and immunotherapy that regulates host immunity has also shown promising application prospects in the treatment of infectious inflammation.⁷ Recently, many nanomaterials have been engineered to modulate the roles of immune cells and inflammation-associated cytokines to diminish inflammation, and these nanosystems have demonstrated remarkable therapeutic outcomes both *in vitro* and *in vivo*.

Immune Cells in Inflammation

Innate immune cells, neutrophil (NET), macrophages, dendritic cells (DC), mast cells (MC), and adaptive immune cells, including thymus-derived lymphocytes (T cells), bone marrow-derived lymphocytes (B cells), and plasma cells, interact with tissues to regulate inflammatory responses and host immune modulation processes, influencing the development of inflammation. When pathogens invade human tissues, the innate immune response is activated.⁸ Innate immune cells produce cytokines and chemokines that directly regulate tissue metabolism: DCs generate cytokines and interact with immune cells, while NK cells express M-CSF and release histamine, platelet-activating factors, and other factors and mediators along with MCs, thereby modulating inflammatory responses.⁹ Similarly, adaptive immune cells produce various cytokines, chemokines, and interact with other immune cells, exerting direct or indirect effects on tissue metabolism: B cells secrete cytokines and interact with immune cells, while T cells tend to release more inflammatory factors and cytokines, such as IL-6, TNF- α , IL-1 β ,

IL-17, and IL-22, interacting with other cells and mediating signaling pathways, including OPG/RANK/RANKL and TNF. Moreover, excessive innate immune responses lead to inflammation and tissue destruction, activating adaptive immune responses.^{10,11} Screening potential therapeutic targets can significantly improve the treatment of inflammation.¹² To further enhance the specificity of nanoparticles, more and more stimuli-responsive nanomaterials are being studied and developed, and the acidic pH and elevated ROS levels in the inflammatory microenvironment are commonly used response factors for the construction of stimulus-responsive nanomaterials. Therefore, a deeper understanding of the mechanisms of immune cells in chronic inflammation facilitates the development of novel therapeutic approaches and drugs, providing new strategies and methods to treat and prevent chronic inflammation.

Neutrophil

Neutrophils, the most and primary white blood cells in the human body, are among the first cells to enter inflamed sites and serve as a crucial first line of defense against infectious challenges. They rapidly migrate into tissues, directly phagocytosing and eliminating pathogenic microorganisms and their products, playing a vital role in controlling infection and resolving inflammatory responses.¹³ Neutrophils exhibit a wide range of effector mechanisms to combat pathogens, including phagocytosis and the production of reactive oxygen species (ROS), proteases, and neutrophil extracellular traps (NETs). Furthermore, neutrophils possess various specific receptors, such as integrin $\alpha\beta1$ and mannose receptors, which can quickly recognize and bind to cyclic arginine-glycine-aspartic acid peptides or mannose. Modifying drug-loaded nanoparticles with these specific ligands can increase drug concentrations at inflammatory sites by binding to specific receptors on neutrophils.¹⁴ Polymorphonuclear neutrophils express most types of Toll-like receptors, and the engagement of cell surface Toll-like receptors activates neutrophils and promotes antimicrobial functions, enabling the identification of a broad spectrum of pathogen-associated molecular patterns (PAMPs) and triggering responses to invading pathogens.¹⁵

Neutrophil Extracellular Traps (NETs)

In recent years, neutrophil extracellular traps (NETs) have been considered the culprit in neutrophil-mediated immunopathology.¹⁶ When exogenous pathogens invade or the body experiences certain inflammatory conditions, neutrophils release a fibrous network-like structure known as NETs,¹⁷ which are regarded as potential therapeutic targets. **Figure 1** NETs are comprised of DNA, histones, and MPO, with histones and MPO exhibiting significant toxicity to epithelial cells.¹⁸ Brinkmann first described NETs as bactericidal traps that promote the elimination of extracellular bacteria.¹⁹ The process of NET formation, known as NETosis, is a unique form of cell death distinct from apoptosis as well as necrosis.²⁰ NETs are a double-edged sword,²¹ with excessive production by neutrophils promoting the advancement of different ailments, such as atherosclerosis, rheumatoid arthritis, and cancer. Therefore, inhibiting NET formation or eliminating their excess may be a potential anti-inflammatory strategy.^{22–24} Research on NETs is crucial for understanding the function of the immune system and the mechanisms of inflammation and infection.

Neutrophils and Periodontitis

Periodontitis, one of the most widespread infectious inflammatory disorders within humans, is a chronic inflammatory condition triggered by local microbial communities and host immune responses, leading to periodontal tissue damage and even tooth loss.²⁵ The disease is characterized by a dysregulated neutrophil response to specific bacterial species within the subgingival biofilm. Neutrophils are the primary inflammatory cells involved in periodontitis, and neutrophil infiltration is a major feature of periodontal lesions.^{26–28} Hirschfeld et al proposed that variations in neutrophil responses to different bacteria, such as quantitative deficiencies or functional abnormalities in neutrophils against various bacteria, may be the pathogenic mechanism leading to periodontal disease.²⁹ As the most abundant immune cells, changes in neutrophil numbers or functions can exacerbate periodontal inflammation through multiple mechanisms, affecting periodontal immune homeostasis. On one hand, neutrophils participate in the progression of periodontitis,³⁰ with continuous activation of neutrophils in periodontal tissues releasing large amounts of ROS, damaging periodontal structures. On the other hand, chronic inflammation causes alterations in bone marrow hematopoietic stem cells, with newly differentiated neutrophils exhibiting enhanced activity, further aggravating tissue destruction and worsening periodontitis.³¹ The research team led by Fang Fuchun identified a neutrophil subpopulation associated with NETs in

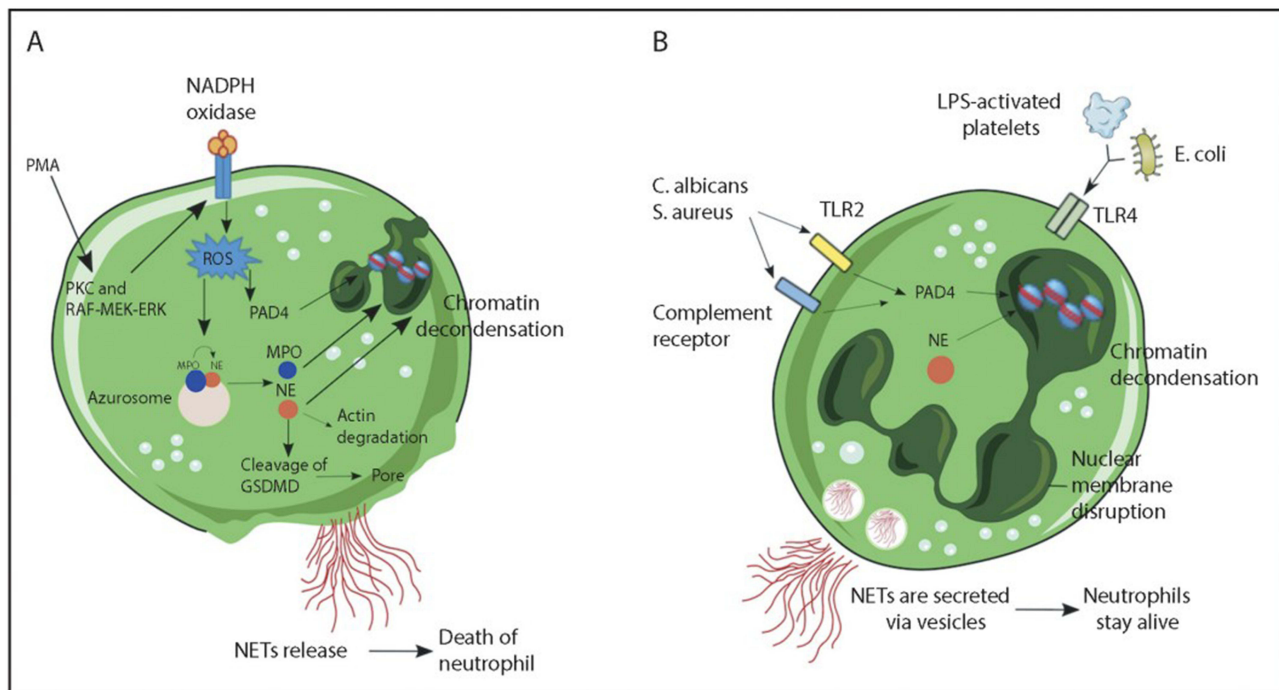


Figure 1 Mechanisms of NET formation. **(A)** PMA and other stimuli induce lytic-NET formation. Neutrophils are stimulated with PMA, resulting in the activation of NADPH oxidase via PKC and Raf-MEK-ERK signaling pathways, consequently generating ROS. Subsequently, PAD4 is activated and citrullinates arginine on histones, causing chromatin decondensation. MPO and NE are discharged from cytoplasmic azurophilic granules and then translocated to the nucleus, contributing to the unfolding of chromatin. The nuclear envelope subsequently disintegrates, discharging the chromatin into the cytosol, where it blends with cytosolic proteins. NE also cleaves GSDMD in the cytosol to its active form (GSDMD-NT), which, besides forming pores in the plasma membrane, also mediates pore formation in nuclear and granule membranes, enhancing the release of NE and other granular content. Finally, NETs are released, and the neutrophil undergoes cell death. **(B)** Nonlytic NET formation is induced by the recognition of stimuli via Toll-like receptor 2 (TLR2), TLR4, or complement receptors, independent of NADPH oxidase activation. *S. aureus* and *C. albicans* activate TLR2 and complement receptors, respectively, while *E. coli* or LPS-activated platelets activate TLR4. Along with PAD4 activation and NE translocation to the nucleus, chromatin decondensation proceeds, and protein-decorated chromatin is expelled via vesicles without plasma membrane disruption. After the release of NETs, neutrophils remain alive for further functions. Reprinted from *Blood*, Vol 133/Edition 20, Castanheira FVS, Kubes P. Neutrophils and NETs in modulating acute and chronic inflammation, Page numbers 2178–2185, Copyright 2019, with permission from Elsevier.¹⁷

gingival tissues using single-cell technology for the first time. They demonstrated the role of NETs in promoting gingival inflammation and alveolar bone resorption in severe periodontitis using a mouse model, suggesting the potential of targeting NETs for periodontitis treatment.³² Figure 2 Additionally, their experiments revealed the mechanism by which inflammatory gingival fibroblasts promote NET formation through MIF-CD74/CXCR4, providing new perspectives for the prevention and treatment of periodontitis.

Excessive NET formation or clearance disorders have a causal relationship with periodontitis. Neutrophils recruit Th17 cells to periodontal tissues by releasing NETs and chemokines such as CCL2 and CCL20, indirectly exerting tissue-destructive effects through IL-17.¹⁶ After the rupture of the cell membrane within the extracellular space, NETs are released into the tissues, exerting antimicrobial effects and subsequently removed from the tissues. If NET removal fails, persistently high levels of NETs may cause damage to periodontal tissues.³³ Non-surgical and surgical interventions have become traditional treatment modalities for periodontal therapy. Although adjunctive therapies (including antibiotics or supplements) accompany these therapies, their use is limited by antimicrobial resistance and partial effectiveness. Thus, novel approaches are required to regulate local inflammation in periodontal tissues as well as the host immune response.³⁴ In the next few years, more research is required to improve immunotherapy treatment methods and continuously comprehend the risks as well as long-term effectiveness of new approaches in treating periodontitis.³⁵

Neutrophils and Chronic Respiratory Diseases

In chronic obstructive pulmonary disease (COPD) patients, persistent NET formation has been observed, correlating with inflammation and disease severity. Research shows that neutrophils and NETs contribute to lung function decline by obstructing airways.³⁶ Chronic lung infections are associated with high levels of neutrophil proteins and DNA, believed

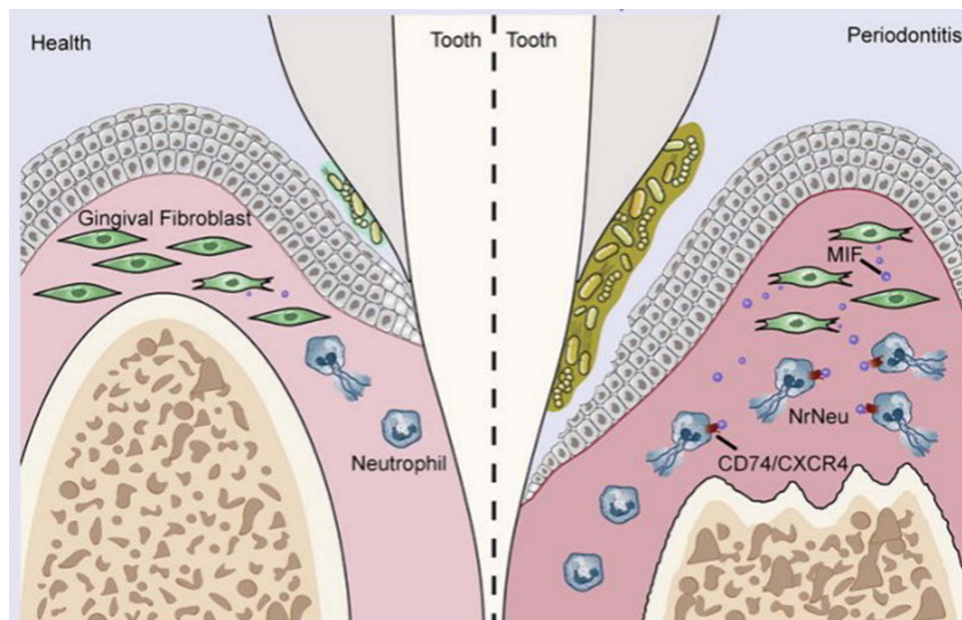


Figure 2 In inflamed gingival tissue, fibroblasts decreased while neutrophils increased; Fibroblasts induce excessive formation of NETs through MIF/CD74/CXCR4 ligand receptor axis, thereby promoting the progression of periodontitis). Reprinted from *Journal of Advanced Research*, Qiu W, Guo R, Yu H, et al. Single-cell atlas of human gingiva unveils a NETs-related neutrophil subpopulation regulating periodontal immunity, Copyright 2024, with permission from Elsevier.³²

to be caused by NETs. In addition to causing direct damage, NETs provide pro-inflammatory stimuli to macrophages, promoting inflammatory responses in CF subjects. Wang et al found that GPR84 was highly upregulated in cells isolated from bronchoalveolar lavage fluid of LPS-induced mice.³⁷ GPR84 blockade improved lung inflammation in mice by reducing neutrophil infiltration and oxidative stress. GPR84 can also induce neutrophil oxidant production by stimulating Lyn, AKT, and ERK1/2 activation. This study demonstrated the crucial role of GPR84 in neutrophil function and lung inflammation, suggesting GPR84 as a potential drug target for pneumonia.

Neutrophils and Chronic Liver Diseases

Nonalcoholic fatty liver disease (NAFLD) is presently the primary chronic liver disease, characterized by inflammation, hepatocyte injury, and fibrosis.³⁸ NAFLD is the most frequent cause of liver disease-related mortality as well as morbidity. Nonalcoholic fatty liver includes nonalcoholic fatty liver steatosis and nonalcoholic steatohepatitis (NASH). Many studies have highlighted the role of neutrophils in NASH, with hepatic neutrophil infiltration promoting NASH development and circulating neutrophils correlating with its severity. Neutrophil infiltration in the liver promotes the development of nonalcoholic steatohepatitis.^{39,40} MPO-DNA levels, a marker of NETs, are elevated in NASH patients and mouse models.⁴¹ In mouse models, the development of steatosis is independent of NETs, suggesting that NET formation is a consequence of fatty liver accumulation. When NETosis is inhibited, inflammatory responses decrease, with reduced levels of macrophages and neutrophils in the liver. Therefore, regulating key targets that recruit neutrophils to the liver may slow disease progression.⁴²

Neutrophils and Atherosclerosis

Atherosclerosis (AS) is a lipid-driven, multi-cell-mediated chronic inflammatory disease of blood vessels, primarily affecting large and medium-sized arteries. AS is featured by lipid accumulation in the arterial wall, immune cell infiltration, and the formation of a fibrous cap composed of smooth muscle cells and collagen.⁴³ One mechanism by which neutrophils promote atherosclerosis is through the formation of NETs.⁴⁴ Extracellular cholesterol crystals interact with neutrophils to induce NET release, and NETs stimulate macrophages to produce the precursor form of the inflammatory cytokine interleukin-1 β (pro-IL-1 β). Furthermore, cholesterol crystals bind to the cell surface protein CD36 on macrophages, activating inflammasomes (as shown in the figures 1-5), thereby promoting the maturation of endogenous IL-1 β and upregulating another pro-inflammatory cytokine, IL-17, produced by.⁴⁵ Consequently,

macrophages present in atherosclerotic plaques possess inflammatory and plaque-destabilizing functions. Ultimately, this triggers thrombotic complications, interrupting arterial blood supply to downstream tissues, leading to myocardial infarction and stroke.

Neutrophils and Rheumatoid Arthritis (RA)

Rheumatoid arthritis (RA) is a systemic autoimmune disease featured by continuous synovial inflammation, leading to joint cartilage and bone damage. NETs serve as a kind of source of extracellular autoantigens, and citrullinated peptides generated by histone citrullination through PAD2 and PAD4 activity are overexpressed within neutrophils. It could even be detected within the synovium of RA patients.⁴⁶ Activated neutrophils also express chemokines and chemokine receptors, promoting neutrophil migration and infiltration in RA joints.⁴⁷ Furthermore, numerous studies have observed enhanced NET formation in RA patients, and the function of NETs in the pathogenesis of rheumatoid arthritis has been investigated.

Macrophages

Macrophages are core innate immune cells in the mortal body and are an essential part of the host immune response. They are also one of the most extensively studied immune cells, playing a important role in the pathogenesis of inflammation. Macrophages are vital in the initiation, maintenance, and resolution stages of inflammation. They can rapidly migrate and accumulate at inflammatory sites, where they exert dual roles in promoting disease progression and tissue repair.⁴⁸ Under the induction of different factors, macrophages polarize into different functional phenotypes.

M1 and M2 macrophages participate in the destruction as well as repair phases of inflammatory tissues⁴⁹ **Figure 2**. When the body encounters pathogenic microbial attacks, macrophages differentiate into M1 and M2 macrophages.⁵⁰ M1 macrophages mainly participate in Th1-type immune responses and can produce a series of pro-inflammatory cytokines, including nitric oxide (NO), interleukin (IL)-1 β , IL-2, IL-6, and other inflammatory factors, promoting Th1 activation. Increasing evidence suggests that inflammation is closely related to the increase in the M1/M2 ratio of polarized macrophages.⁵¹ CD64 is a high-affinity Fc- γ receptor, considered a marker of M1 macrophages, while CD163 and CD206 have been recognised as the primary markers of M2 macrophages. For example, in synovitis, macrophages expressing CD64 (Fc- γ receptor) play a key role and are considered a marker of macrophage activation.^{52,53} ROS are naturally occurring oxidants, and their production affects macrophage differentiation, promoting their transformation into the M1 phenotype. Under physiological conditions, antioxidants can effectively neutralize ROS, thus preventing ROS-mediated tissue damage.⁵⁴

Macrophages and Chronic Inflammation

Macrophages are regulators of immune activity and body homeostasis, adopting variable activation states as a function of time and environmental cues.⁵⁵ In the pathogenesis of inflammatory lung diseases, macrophages promote the advancement as well as progression of acute or chronic inflammatory responses via secreting inflammatory cytokines/chemokines and activating transcription factors, such as in acute respiratory distress syndrome (ARDS) and chronic obstructive pulmonary disease (COPD). Eapen et al demonstrated that M2 phenotype macrophages predominate in the bronchoalveolar lavage (BALF) of COPD patients with increased cytokines, including IL-4, IL-13, IL-8, and IL-10.⁵⁶ Osama et al showed that macrophage-induced eosinophilia is closely related to the severity of COPD.⁵⁷ MCP-1 levels are elevated in sputum samples from COPD patients, and macrophages influence neutrophil recruitment by producing MCP-1, indicating that macrophages play a vital role in the development of COPD by inducing neutrophil influx.⁵⁸ Macrophages are key coordinators in the pathogenesis of lung injury/acute respiratory distress syndrome, and regulating macrophage polarization can improve the prognosis of ALI/ARDS.⁵⁹

In periodontitis, M1 and M2 macrophages participate in the destruction and repair stages of PD.⁴⁹ **Figure 3** M1 macrophages promote inflammation and activate osteoclasts by recruiting neutrophils to remove periodontal pathogens, leading to alveolar ridge resorption. M2 macrophages are involved in Th2-type immune responses⁶⁰ (**Figure 3**), increasing the expression of IL-10 and chemokines, promoting Th2 activation, and exerting immunomodulatory effects on Th2 cells. They promote apoptosis and neutrophil recruitment to terminate the inflammatory process. M2 macrophages release various anti-inflammatory factors, including IL-4 and IL-10, secrete bone morphogenetic protein (BMP)-

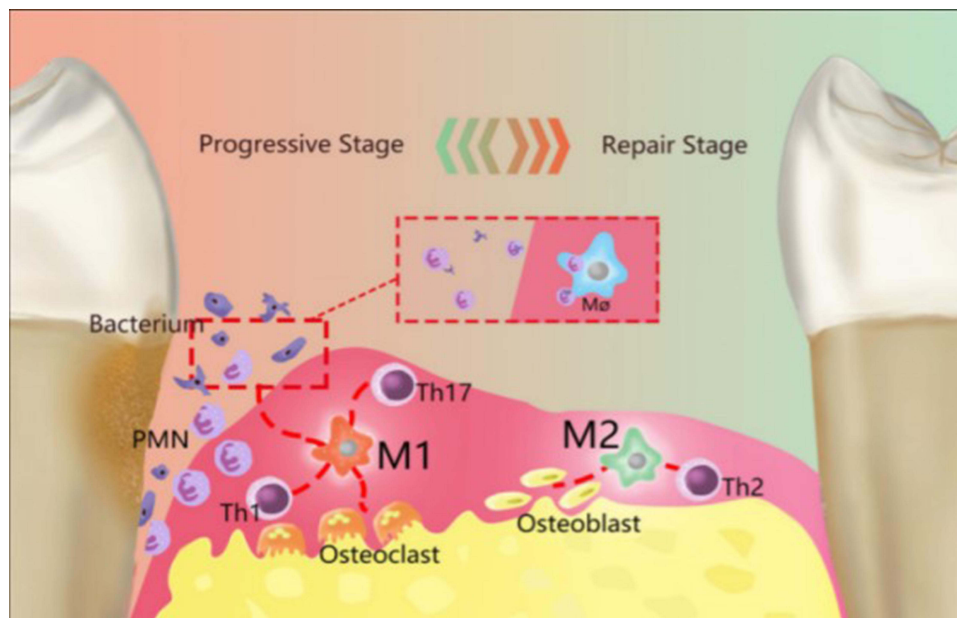


Figure 3 Polarized macrophages play a crucial role in the initiation and progression of Parkinson's disease (PD). In PD, resident macrophages polarize into two primary phenotypes, M1 and M2, which respectively govern the inflammatory development and resolution phases. M1 macrophages are primarily proinflammatory and produce a series of proinflammatory factors, working in conjunction with Th1 cells, Th2 cells, and other cells. By collaborating with Th1-type immune cells, M1 macrophages can remove periodontal pathogenic microorganisms through the recruitment of PMNs. Simultaneously, M1 macrophages activate osteoclasts, leading to the absorption of the alveolar ridge. M2 macrophages primarily play an anti-inflammatory role and are mainly involved in immune interactions with Th2 cells. M2 macrophages terminate inflammatory development via accelerating the apoptosis for M1 macrophages and PMNs, perform tissue repair through various anti-inflammatory factors, and could activate osteoblasts to recover bone tissue. Reproduced from Sun X, Gao J, Meng X, Lu X, Zhang L, Chen R. Polarized Macrophages in Periodontitis: characteristics, Function, and Molecular Signaling. *Front Immunol.* 2021;12:763334.⁴⁹

2, as well as vascular endothelial growth factor (VEGF) to participate in inflammation suppression and accelerate tissue healing, exerting anti-inflammatory and effect of angiogenesis, and activating osteoblasts to restore bone tissue.^{61,62} Additionally, M2 macrophages possess immunosuppressive, wound repair, and tumor-promoting functions.

Dendritic Cells (DCs)

The primary function of dendritic cells is to survey peripheral cells and present antigens to T cells. Exogenous stimuli activate DCs, leading to the secretion of cytokines and upregulation of surface costimulatory molecules.⁶⁴ Mature DCs present antigens to naive CD4⁺ T cells,⁶⁵ which differentiate into helper T cells (Th1, Th2, Th17) and regulatory T cells (Tregs).⁶⁶ Interferon- γ (IFN- γ) and interleukin-12 (IL-12) secreted by dendritic cells induce Th1 cell formation in an inflammatory environment.⁶⁷ Therapeutic approaches utilizing regulatory T cells (Tregs) to alleviate inflammatory tissue damage have been widely proposed. However, Tregs are unstable and may lose their function in an inflammatory environment, potentially converting into Th17 cells.⁶⁸ Regulating the Treg/Th17 balance can significantly impact the pathogenesis of inflammation.⁶⁹ Wen et al discovered that protein arginine methyltransferase 5 (PRMT5) attenuates activation and maturation by suppressing the expression of endotoxin-stimulated pro-inflammatory cytokines, ISGs, costimulatory molecules, and MHC. The inhibition of metabolic switching plays a key role in controlling activated dendritic cells, suggesting that PRMT5 is a promising therapeutic target for inflammation.^{70,71}

Lymphocytes

Different subsets of lymphocytes also participate in the inflammatory process. Helper T cells (Th1, Th17) and B lymphocytes promote inflammatory responses, while regulatory T cells (Tregs) and B10 cells significantly suppress inflammatory reactions. Studies have shown that periodontitis primarily activates CD4⁺ T cell-polarized Th1, Th2, Th17, and Tregs, mediating immune responses through characteristic cytokines. The activation of Th cells is a pivotal factor in

determining the progression of tissue damage, particularly the classical T cell subsets Th1, Th2, and Th17, which secrete various pro-inflammatory cytokines (IL-1 β , IL-17).⁷²

Therefore, in-depth exploration of the different roles of various immune cells at different stages of chronic inflammation is of great significance for the future clinical application of immunotherapy in the treatment of chronic inflammatory diseases.

Overview of Nanomaterials

Systemic administration is currently the most common method for treating many symptoms and diseases, and traditional inflammatory targeted therapies have shown promising therapeutic effects. However, most anti-inflammatory drugs are inevitably absorbed, have poor permeability through mucosal barriers, struggle to accurately reach the lesion site, have short retention times, and may even produce adverse side effects on the body, thus limiting their clinical application. Many anti-inflammatory drugs broadly suppress inflammation and are administered systemically at high dose concentrations, leading to various side effects, including immunodeficiency toxicity (eg, viral and bacterial infections) and systemic toxicity (eg, nephrotoxicity, hepatotoxicity).⁷³ Therefore, numerous researchers have focused on designing and investigating drug carriers, wound dressings, and composite drug release systems, such as nanoparticles, exosomes, and biomimetic materials, to overcome the limitations of anti-inflammatory drugs.^{74,75} Nanomaterials are a type of multifunctional novel material with particle sizes ranging from 1 to 100 nm. The prominent features of nanomaterials are their unique size, shape, and surface properties that enable tissue penetration through passive or active targeting mechanisms. The emergence of nanotechnology has provided tremendous potential for overcoming biological barriers. Firstly, nanoparticles deliver drugs in a sustained and controlled manner, degrading and releasing drugs in response to specific environmental stimuli, thereby enhancing drug solubility, improving drug stability, reducing toxicity and drug degradation, ensuring stable cellular targeting and oral retention,⁷⁶ and protecting drugs from pH effects and enzymatic degradation.⁷⁷ Secondly, surface modification of nanoparticles can enhance their ability to target inflammatory micro-environments. Thirdly, the small size of nanocarriers allows them to accumulate in inflamed epithelial cells through the enhanced permeability and retention effect, more effectively targeting inflammatory tissues.⁷⁸ The advantages of nanoscale delivery systems, such as biodegradability, biocompatibility, non-toxicity, and prolonged circulation, provide a platform for targeted therapy of inflammation.⁷⁹ Nanoscale delivery systems have been utilized as a potential method for treating various diseases, including inflammation.⁸⁰

Based on their chemical composition and structure, nanoparticle systems can be classified into organic nanoparticles, inorganic nanoparticles, and lipid-based nanoparticles. Organic nanoparticles, commonly referred to as polymeric nanoparticles, include synthetic and natural polymers. Nanoscale drug delivery systems with various structures have been widely used,⁸¹ including chitosan, poly(lactic-co-glycolic acid) (PLGA), nanohydrogels, liposomes, carbon nanoparticles, silica nanoparticles, and nanocomposites, all of which can serve as drug carriers and exhibit excellent drug loading and release capabilities,^{76,82} making them potential candidates for targeted drug delivery.⁸³

Polymeric Nanoparticles

Polymeric nanoparticles (PNPs) are solid particles ranging in size from 10 to 1000 nanometers. Examples include poly(lactic-co-glycolic acid) (PLGA) nanoparticles,⁸⁴ polycaprolactone (PCL), and hydrogel nanoparticles. Polyesters are the most commonly used polymers in nanosystems, containing ester functional groups in their polymer backbone, and their degradation can facilitate controlled drug release. Natural polymeric nanoparticles include polymers such as sodium alginate, chitosan, albumin, and gelatin.⁸⁵ Moreover, with the rapid development of nanotechnology and materials science, there has been an increasing focus on developing safer and more effective hydrogels for treating severe inflammatory conditions, such as rheumatoid arthritis, osteoarthritis, periodontitis, and ulcerative colitis. Hydrogels can be classified into natural hydrogels (eg, chitosan, hyaluronic acid, sodium alginate, cellulose, gelatin) and hydrogels prepared from synthetic biomaterials (eg, poly(lactic acid) (PLA), polyacrylamide, poly(ethylene glycol) (PEG)). Nanohydrogels are nanoparticles composed of three-dimensional hydrogel materials, formed by crosslinked swellable polymer networks with high water retention capacity. Nanohydrogels are primarily composed of synthetic polymers, biopolymers, or combinations of chemically or physically crosslinked components.⁸⁶

Nanostructured Lipid Carriers

Nanostructured lipid carriers (NLCs) are drug delivery systems that utilize solid lipids and liquid lipids as the core matrix. Compared to solid lipid nanoparticles and traditional drug delivery carriers, NLCs offer advantages including improved drug loading capacity, flexible drug release modulation, and improved stability. Moreover, NLCs exhibit good biocompatibility, low toxicity, increased solubility, reduced side effects, prolonged shelf life, and superior drug targeting and controlled release capabilities.^{87,88} In previous studies, NLCs have demonstrated effective therapeutic prospects through various administration routes, including pulmonary, local, nasal, ocular, and oral.⁸⁹ Yang et al designed a rapidly monodispersed gelatin methacryloyl@liposome (GelMA@Lipo) hybrid microgel drug delivery platform by anchoring liposomes within a photocrosslinkable GelMA matrix. Compared to the control group, the liposomes were firmly fixed in the microgel through non-covalent interactions, enabling prolonged drug retention in the joints.

Classification of Inorganic Nanomaterials

Common inorganic nanomaterials include metal nanoparticles (Ag, Pd), metal oxide-based functional nanomaterials (ZnO, TiO₂, MgO), carbon and graphene nanomaterials, and others. Compared to organic nanomaterials, inorganic nanomaterials possess unique physicochemical properties, such as optical, electrical, magnetic, ultrasonic, and catalytic properties, as well as controllable shape and size, which also offer tremendous advantages in anti-inflammatory therapy.⁹⁰ Although inorganic nanomaterials have been widely used in biomedical applications, the extensive retention time of many functional inorganic nanomaterials *in vivo* increases the possibility of harmful toxicity.⁹¹ Therefore, further enhancement of their targeting ability and bioavailability is also required.⁹²

Nanomaterials Targeting Specific Immune Cells

Although traditional nanoscale drug delivery systems have improved the therapeutic effects of drugs, nanoparticles carrying drugs with surfaces that bind to plasma proteins can activate immune responses and are easily cleared by the mononuclear phagocyte system, thereby reducing the bioavailability of the drugs.⁹³ Moreover, most systems cannot precisely target the drug to the inflammatory tissue, and the drug is released into each type of cell at the inflammation site, further reducing the therapeutic effect.^{94,95} Therefore, additional studies are required to enhance the targeting ability of nanoparticles. For example, intravenous injection of mannoseylated liposomes in rats with arthritis resulted in only partial drug delivery to the joints because liposomes are easily cleared by the reticuloendothelial system.⁹⁶ In contrast, neutrophil-based drug delivery systems can avoid clearance by the reticuloendothelial system and enhance the ability of nanoparticles to target joints.⁹⁷

In cancer treatment, the clinical progress of immunotherapy has been remarkable, and more clinical data have demonstrated that combining nanomedicines with immunotherapy can significantly improve the therapeutic effect.⁹⁸ Nanoimmunotherapy is mainly achieved through three different approaches: nanomedicines are used to (1) target cancer cells, (2) target the tumor immune microenvironment, and (3) target the peripheral immune system. In the case of inflammation, the inflammatory microenvironment is formed by immune cells, inflammation-related enzymes, and inflammatory mediators. Similar to tumors, we can use immune cells or biomarkers to provide opportunities for precise targeting of anti-inflammatory drugs. Combined with the advantages of nanomedicines, such as precise localization of inflammatory tissues, overcoming barriers, enhancing interactions with epithelium, and reducing systemic adverse reactions, targeted delivery of nanomaterials to immune cells can be achieved for the treatment of chronic inflammation. The immunomodulatory effects of nanoparticles are one of the hotspots in nanomaterial research. Currently, many nanomaterials have been found to regulate the immune system, achieving significant progress in the fields of nanomedicine and immunotherapy.⁹⁹

Macrophage-Targeted Nanomaterials

Macrophage Polarization

The main direction of macrophage polarization therapy is to induce macrophages to transform into the M2 type, thereby alleviating inflammation, promoting tissue repair, and achieving anti-inflammatory effects. The production of ROS is a major biological process in which stimulated macrophages participate in killing phagocytosed microorganisms.¹⁰⁰

However, excessive ROS may drive macrophages to transform into the M1 type, exacerbating the development of inflammation.¹⁰¹ Sun et al constructed a cerium@ce6 multifunctional nanocomposite that regulates host immunity by downregulating M1 polarization and upregulating M2 polarization in macrophages. This nanocomposite can avoid periodontitis caused by high levels of ROS, prevent oxidative stress, and improve the regenerative potential of periodontal inflammatory tissues in animal models.¹⁰² Ni et al utilized gold nanoparticles (AuNPs) to induce macrophages to transform into the M2 type by regulating the production of inflammatory and regenerative cytokines, thereby improving the periodontal inflammatory microenvironment and modulating the inflammatory response in early periodontal tissues.¹⁰³ Nanoparticles can protect drugs from the influence of pH and enzymatic degradation. By designing nanoparticles to respond to ROS, pH, or enzymatic reactions in the pathological microenvironment, drug release can be controlled.⁷⁶ Hu et al prepared a mannosylated (Man) functionalized nanoscale metal-organic framework (MOF) to load Que for targeted therapy of myocardial infarction (MI). The nanomedicine Que@MOF/Man can reprogram macrophage polarization and neutralize ROS, thereby reducing oxidative stress and targeting the inflammatory infarcted heart.¹⁰⁴ Man is a yeast polysaccharide containing D-mannose residues that can be recognized by mannose receptors. Mannose receptors are highly expressed on macrophages at inflammatory sites, promoting the inflammation-specific accumulation and targeted cellular internalization of Que@MOF/Man in macrophages. Galarraga et al exposed LPS-stimulated macrophages to extracted cranberry concentrate and found a significant decrease in M1 and a significant increase in M2, indicating that cranberry proanthocyanidins have effective anti-inflammatory effects in periodontal treatment.¹⁰⁵ Wang et al introduced the antioxidant drug quercetin into nano-octahedral cerium to construct a nanocomposite (CeO₂@QU), achieving synergistic regulation of host immunity in periodontal disease. The prepared nanocomposite not only effectively increased the M2/M1 ratio of macrophage polarization in inflammatory cell models but also promoted periodontal tissue regeneration by significantly decreasing the levels of pro-inflammatory cytokines while increasing the levels of anti-inflammatory cytokines, demonstrating therapeutic potential for local inflammation.¹⁰⁶ Shi et al developed resveratrol-loaded liposomes (Lipo-RSV) that transformed macrophages from the M1 phenotype to the M2 phenotype by stimulating p-STAT3 and suppressing p-STAT1. Lipo-RSV elevated the mRNA levels of M2-associated markers (CD206, Arg-1, and Chil3) and reduced the mRNA levels of M1 macrophage markers (CD86, iNOS, and CCR7) in stimulated macrophages. Furthermore, Lipo-RSV could scavenge ROS, inhibit NF- κ B signaling and inflammasomes, thus reducing pro-inflammatory cytokines IL-1 β , IL-6, and TNF- α , showing potential for treating periodontitis.¹⁰⁷ Wali et al prepared dexamethasone-loaded ROS-responsive polymeric nanoparticles (PFTU@DEX NPs). Due to the ability of PFTU@DEX NPs to inhibit the expression of NLRP3, Caspase1, and IL-1 β , they could effectively suppress inflammatory cells, ROS signaling pathways, and apoptosis, inducing macrophage phenotype polarization from M1 to M2, thus effectively alleviating acute lung injury.¹⁰⁸ Ma et al developed folic acid-modified DNA origami nanostructures (FA-tDONs)¹⁰⁹ by utilizing the inherent ROS and NO scavenging abilities of DNA molecules. FA-tDONs could effectively scavenge ROS and NO, actively target M1 macrophages at inflammatory sites, and promote M1-M2 transformation.

Specific Receptors

Compared to conventional nanosystems, active targeting nanocarriers that transfer cargo to disease sites with higher selectivity have shown advantages in treating inflammation, cancer, and other chronic diseases.^{110,111} Some active targeting nanoparticles have been developed to target macrophages by localizing to specific cell receptor surfaces in particular situations.¹¹² Current approaches for targeting macrophages include targeting CD44, coupling folic acid, coupling mannose, microbial mimicry, and lactoferrin modification. Yang et al designed an injectable hydrogel (Gel/FA-PDA@Leon) based on mammalian collagen and peptides.¹¹³ Gel/FA-PDA@Leon can target and deliver Leon to M1 macrophages, reducing the secretion of pro-inflammatory cytokines by inhibiting the JAK2/STAT3 inflammatory signaling pathway. The hydrogel can also protect collagen cells from the effects of ferroptosis. Gel/FA-PDA@Leon hydrogel significantly inhibits the inflammatory response associated with rheumatoid arthritis (RA) and protects the integrity of joint structures, thereby promoting the recovery of joint function, making it effective for the treatment of RA. Feng Jie et al prepared a Mannose-PEG-PCL targeted nanomedicine that actively targets macrophage membrane receptors, increasing the endocytic uptake of nanoparticles by macrophages.¹¹⁴ The nanomedicine reshapes the synovial inflammatory microenvironment by activating the AKT/STAT6 pathway. Na et al developed

a macrophage-based encapsulated hydrogel nanoformulation (MZ@PNM@GCP).¹¹⁵ MZ@PNM@GCP specifically blocks the binding of P.g. to immune cells through Toll-like receptor complex 2/1 (TLR2/1) targeting, preventing P.g. from disrupting the periodontal host immune response. Furthermore, FR2, a membrane protein overexpressed on inflammatory macrophages, can selectively recognize and internalize folic acid (FA)-modified nanodrug delivery systems into inflammatory macrophages.¹¹⁶ The Wang research group developed folic acid-modified genistein liposomes that target macrophages.¹⁰⁶ These liposomes can regulate the TLR4/MyD88/NF- κ B axis in macrophages and promote the osteogenic differentiation of PDLSCs. Sun et al constructed the M2M@PLGA/COX-siRNA delivery system, which has low toxicity and obvious targeting to the injured site, reducing inflammatory reactions and significantly improving tendon adhesion.¹¹⁷ Hyaluronic acid possesses unique biological properties that enable it to specifically combine with the overexpressed CD44 receptors on the surface of macrophages, endowing nanodrug delivery systems with the ability to target macrophages. Nanoparticles containing hyaluronic acid can be used to target macrophages for the treatment of inflammatory diseases.¹¹⁸

Nanomedicines selectively deliver drugs to the damaged regions of rheumatoid arthritis (RA) through passive targeting effects. The surfaces of nanomedicines are then modified with targeting ligands connected to specific receptors for active targeting of macrophages.⁹⁸ Jia et al constructed a pH-responsive dual-targeted nanodrug delivery system, RBA-NPs, loaded with targeting CD44 and folate receptors. The study found that intra-articular M1 macrophages were reprogrammed to M2 type through RBA. RBA-NPs can also drive M1-to-M2 phenotype conversion by downregulating glycolysis levels through blocking the ERK/HIF-1 α /GLUT1 pathway. This nanocarrier effectively delivers RBA to inflammatory sites, significantly reducing inflammatory cytokine levels and promoting tissue repair, improving the efficiency of rheumatoid arthritis treatment. The study also identified a potential molecular target for regulating macrophage reverse reprogramming through energy metabolism.¹¹⁹ Feng Naibo et al designed and constructed a dual-responsive, macrophage-targeting nanocarrier loaded with small interfering RNA (si ERN1), effectively achieving targeted therapy for rheumatoid arthritis (RA). The nanocarrier demonstrated superior therapeutic effects, immune homeostasis regulation, and cartilage protection in collagen-induced arthritis (CIA) model mice.¹²⁰ Tand et al developed an FA receptor-targeted GER nanocarrier, FA-NPs/GER. In vitro experiments confirmed that FA-NPs/GER could promote the transformation of M1 macrophages to M2 macrophages. In animal experiments, the drug selectively accumulated at inflammatory sites, significantly reducing inflammatory infiltration. Therefore, macrophage-targeted nanocarriers loaded with GER represent a safe and effective method for treating RA (Table 1).¹²¹

Natural Nanoparticles

In recent years, natural products have attracted growing interest as a potential therapy for various diseases because of their high therapeutic potential, low cost, and high safety.^{122–124} Natural products also possess antimicrobial, antioxidant, and anti-inflammatory properties. For example, plant-derived exosome-like nanoparticles (pELNs) are natural nanocarriers with sizes ranging from 50 to 500 nm. pELNs contain lipids, RNA, and other active molecules.¹²² pELNs can be derived from many plants and fruits, such as ginger, blueberries, and coconuts.¹²⁵ ELNs derived from grapefruit, carrots, and ginger induce macrophages to express IL-10 and promote the activation of nuclear factor 2 (Nrf2) in macrophages, blocking the assembly of NLRP3 inflammasomes in macrophages.¹²⁶ This suggests that G-ELNs are novel and effective drugs for blocking the assembly and activation of NLRP3 inflammasomes. NLRP3 inflammasomes regulate the release of interleukin-related inflammatory factors, and their activation promotes inflammation, making them a key factor in improving inflammatory responses. Ginseng-derived ELNs inhibit IL-4 and IL-13-induced M2-like polarization in macrophages and increase the secretion of M1-macrophage-related cytokines (including TNF- α , IL-12, and IL-6).¹²⁷

pELNs are lipid bilayer membrane nanovesicles rich in lipids, proteins, RNA, and other active molecules. They have high bioavailability and low immunogenicity, making them relatively safe. pELNs have demonstrated the capability to penetrate mammalian cells and modulate cellular functions.^{122,128} Due to their wide availability, cost-effectiveness, and ease of acquisition, pELNs can serve as better alternatives to animal-derived exosomes (ADEs).¹²⁹ pELNs not only have great potential in regulating immune function, inflammation, and tissue regeneration, but they also can act as drug carriers, cellular uptake in vivo and enhancing drug stability. Meng et al utilized exosome-like natural tea-derived carbon nanotubes to reduce ROS production, decrease the levels of pro-inflammatory cytokines TNF- α , IL-6, and IL-12, and significantly increase the levels of anti-inflammatory IL-10 secreted by macrophages, effectively preventing or reducing inflammation.¹³⁰ pELNs can also regulate inflammatory responses by blocking the activation and release of NLRP3

Table 1 Macrophage-Targeted Nanomaterials

Nanomaterials	Chronic Diseases	Mechanisms of Action	In vivo	Main Results	Reference
Que@MOF/Man	Inflammatory myocardial infarction	Reprogramming macrophage polarization and neutralizing ROS	Myocardial infarction rats	Validated the rational design of inflammation-targeting delivery strategy, alleviating oxidative stress and regulating inflammatory responses in the damaged heart, providing a therapeutic approach for MI treatment	[104]
Cerium @ce6 multifunctional nanocomposites	Periodontitis	Exerting ROS-based aPDT and anti-inflammatory effects	Animal model of periodontitis	Provides new insights for eliminating the deficiencies of aPDT in the treatment of periodontal disease and even in future clinical applications of anti-infective therapy	[102]
Gel/FA-PDA @Leon	Rheumatoid arthritis (RA)	CeO ₂ charge conversion effect, regulating local ROS levels induced by inflammatory pathways for an extended period	collagen-induced Arthritis rat model	Protecting collagen cells from ferroptosis, contributing to maintaining the structural integrity of articular cartilage and accelerating the recovery of joint function	[113]
(CeO ₂ @QU)	Periodontitis	Downregulating pro-inflammatory cytokines and upregulating anti-inflammatory cytokines	Animal model of periodontitis	Effectively clearing ROS and driving the conversion of pro-inflammatory macrophages to an anti-inflammatory phenotype to eliminate inflammation, providing a promising candidate drug for the treatment of periodontal inflammation	[106]
Lipo-RSV liposome	Periodontitis	Activating p-STAT3 and downregulating p-STAT1, converting macrophages from M1 to M2 type; Lipo-RSV clearing ROS, inhibiting NF- κ B signaling and inflammasomes, and reducing pro-inflammatory cytokines IL-1 β , IL-6, and TNF- α	Animal model of periodontitis	Lipo-RSV provides a promising antibiotic-free treatment method for periodontitis management	[107]
PFTU@DEX NPs	Pneumonia	Inhibiting the expression of NLRP3, Caspase1, and IL-1 β , effectively suppressing inflammatory cells, ROS signaling pathways, and apoptosis, and inducing macrophage phenotype polarization from M1 to M2	Lung injury rats	Reduced neutrophil infiltration, inhibited the release of proteins and inflammatory mediators, and thus decreased acute lung injury in vivo	[108]
MZ@PNM@GCP	Periodontitis	Toll-like receptor complex 2/1 (TLR2/1) targeting to block the specific binding of P.g. to immune cells, preventing P.g. from disrupting the periodontal host immune response	Animal model of periodontitis	Treating periodontal inflammation, restoring local immune function, and killing pathogens with good biocompatibility	[115]

(Continued)

Table I (Continued).

Nanomaterials	Chronic Diseases	Mechanisms of Action	In vivo	Main Results	Reference
RBA-NPs	Rheumatoid arthritis (RA)	Blocking the ERK/HIF-1 α /GLUT1 pathway to downregulate glycolysis levels, thereby driving M1-to-M2 phenotype conversion	Rat rheumatoid arthritis model	Not only developed a targeted delivery system to improve the anti-RA efficiency of RBA but also discovered a potential molecular target for regulating the reverse reprogramming of macrophages through energy metabolism	[119]
FA-NPs/GER	Rheumatoid arthritis (RA)	Promoting the transformation of M1 macrophages to M2 macrophages	Adjuvant-induced arthritis (AIA) rats	Selectively accumulating at inflammatory sites, significantly reducing inflammatory infiltration, providing a safe and effective method for treating RA	[121]

inflammasomes. Liu et al found that ELNs derived from shiitake mushrooms (S-ELNs) can inhibit the activation of NLRP3 inflammasomes by preventing the formation of inflammasomes in primary macrophages. S-ELNs also inhibit pro-inflammatory cytokines such as IL-6, thus exhibiting good anti-inflammatory activity.¹³¹ Professor Lu Jiahong's team prepared biomimetic nanoparticles (Effero-RLP) by fusing apoptotic red blood cell membranes with liposomes. The PPAR- γ agonist rosiglitazone was loaded into the biomimetic nanoparticles to regulate macrophage function and achieve anti-inflammatory effects. Experiments demonstrated that Effero-RLP has good macrophage targeting and efficient cellular uptake properties. Compared with other liposome carriers, Effero-RLP exhibited superior anti-inflammatory efficacy. In drug release experiments, Effero-RLP showed a relatively slow release rate. Therefore, Effero-RLP has great application potential in the treatment of inflammatory bowel disease¹³² Figure 4.

Neutrophil-Targeted Nanomaterials

Neutrophil Receptors

Typically activated neutrophils are considered to be primarily induced by Toll-like receptor (TLR) and interferon (IFN) γ signaling stimulation, which are enhanced during infection, stroke, and myocardial infarction. Naina et al demonstrated that the G protein-coupled receptor (GPCR) Mrgpr1 expressed by neutrophils drives anti-inflammatory neutrophils and

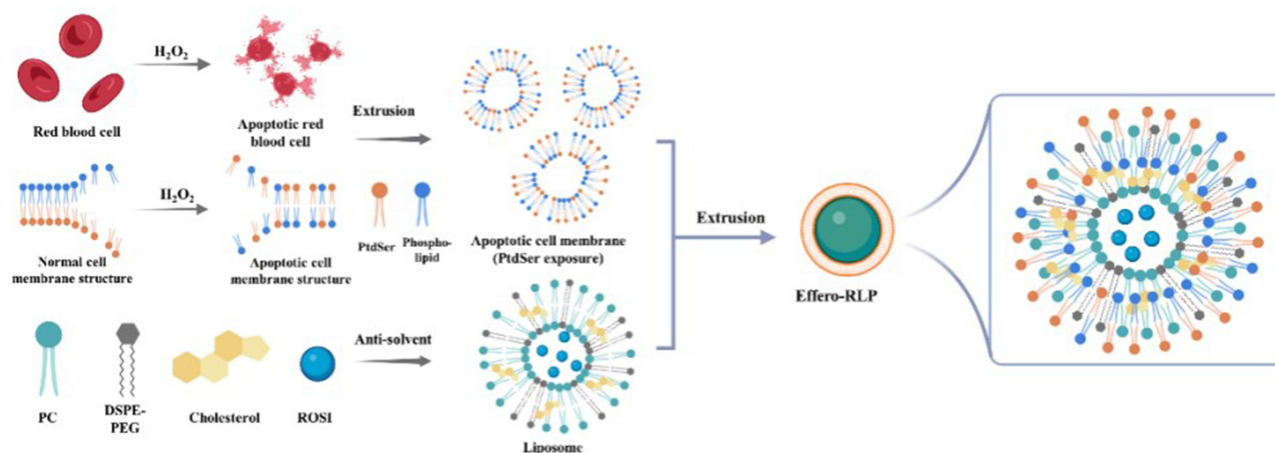


Figure 4 The preparation of LP, RLP and Effero-RLP. The schematic of apoptotic RBC membrane preparation and the fusion with liposome particles. Reproduced from Han R, Ren Z, Wang Q, et al. Synthetic Biomimetic Liposomes Harness Efferocytosis Machinery for Highly Efficient Macrophages-Targeted Drug Delivery to Alleviate Inflammation. *Adv Sci.* 2024;11(29):e2308325.¹³²

inhibits activated neutrophils, serving as a negative regulator of neutrophil killing function.¹³³ Mrgpra1-mediated signal transduction is driven by its ligand neuropeptide FF (NPFF), which determines the balance between pro-inflammatory and anti-inflammatory programming. Kang et al prepared neutrophil membrane-coated poly(lactic-co-glycolic acid) (PLGA) nanoparticles.¹³⁴ Because of the high expression of adhesion molecules and chemokine receptors on neutrophils, the neutrophil membrane coating can endow nanocarriers with the ability to target synovitis and be recruited to the synovial fluid under the chemotactic effect of IL-8. Yang et al engineered a biomimetic ApoA-I mimetic peptide-modified neutrophil membrane-encapsulated F127 polymer (R4F-NM@F127)¹³⁵ for targeted drug administration during rheumatoid arthritis (RA) therapy, effectively inhibiting synovial inflammation and reducing joint damage.

The Mrgpra1-NPFF axis mediates the counter-regulation of interferon (IFN) γ -mediated neutrophil polarization during acute lung infection, suggesting that it may balance excessive neutrophil responses. Therefore, intrinsic pathways within neutrophils determine their cell fate, function, and the extent of infection. Albumin NPs manufactured using organic solvents can specifically bind to Fc γ RIII receptors on activated neutrophils,¹³⁶ and albumin NPs can be absorbed by activated neutrophils in the blood, mediating the delivery of nanotherapeutic drugs in inflammation or tumors. This provides numerous opportunities for the rational design and engineering of targeted drug delivery to activated neutrophils. The NLRP3 inflammasome is a protein complex, it can help the body resist pathogen invasion under physiological conditions, but its overactivation may lead to excessive release of inflammatory mediators and overactivation of inflammatory cells, disrupting the immune balance within tissues and ultimately leading to various inflammatory diseases, including periodontitis. The NLRP3 inflammasome can be involved within the activation regarding neutrophils, macrophages, osteoclasts (OCs), and human periodontal ligament fibroblasts (HPLFs) and may contribute to the progression of various inflammatory as well as autoimmune conditions. Therefore, targeted therapy to regulate the function of the NLRP3 inflammasome provides a new approach for the adjuvant treatment of periodontitis.¹³⁷ The MCC950 targeted therapeutic strategy has high specificity and can significantly reduce the levels of the pro-inflammatory cytokine IL-1 β without affecting other types of inflammasomes and their corresponding inflammatory factor expression.^{138,139}

Targeted Regulation of NETs for Inflammation Treatment

The balance of NETs is crucial for maintaining health and homeostasis in the body. NETs have become potential therapeutic targets for inflammatory and autoimmune diseases. The excessive production of NETs and the degradation of their components can be inhibited by drugs, thereby achieving targeted treatment of inflammation.¹⁴⁰ Hu et al designed anti-inflammatory nanoparticles based on a luminol-conjugated α -cyclodextrin material (LaCD).¹⁴¹ The results showed that LaCD NPs could effectively inhibit neutrophil-mediated aortic aneurysm inflammation by attenuating the structure of NETs and suppressing NET-mediated pro-inflammatory events. This study demonstrated the effectiveness and potential mechanism of anti-NETosis nanotherapy for the targeted treatment of abdominal aortic aneurysms and provided a promising reference for the precise treatment of other inflammatory diseases. Chen et al designed NET-like structures using DNA and ZnO nanoparticles.¹⁴² In the anti-inflammatory assay, ZnO/DNA-HCl NG significantly inhibited the expression of TNF- α , IL-6, iNOS, and COX-2 in LPS-stimulated Raw264.7 cells. Furthermore, ZnO/DNA-HCl NG significantly alleviated the clinical symptoms of LPS-induced peritonitis in mice. Hu et al found that LaCD NPs could effectively attenuate the formation of neutrophil extracellular traps (NETs), thereby inhibiting NET-mediated pro-inflammatory events and NETosis-related inflammatory progression, demonstrating the effectiveness and potential mechanism of anti-NETosis nanotherapy for targeted treatment of inflammatory diseases.¹⁴³ Liu et al prepared RGD-modified bovine serum albumin (BSA) nanoparticles (CBR NPs). These nanoparticles could selectively target inflammatory neutrophils (INEs) in circulation and induce INE apoptosis. Simultaneously, they were able to suppress the activation of NETs through the NF- κ B pathway and block the release process of NETs, thereby inhibiting the infiltration of circulating neutrophils (INEs) into inflamed joints and reducing tissue damage by suppressing NET release.¹⁴³ Zhou et al modified the surface of Prussian blue nanoparticles (PB NPs) with a neutrophil elastase (NE)-binding peptide to target activated neutrophils. These NET-targeted nanoparticles exhibited effective treatment for antiphospholipid antibody-mediated thrombosis during pregnancy.¹⁴⁴

Biomembrane Targeting

Nanoparticles, while being the ideal drug carriers, can enhance targeting to a certain degree. However, the straightforward biofunctionalization of nanoparticles still encounters significant challenges within the complex intercellular environment. The clinical application of nanoparticles also presents some issues; once synthesized, nanoparticles are engulfed by immune cells of the immune system, triggering immune responses and toxic effects. Some nanomaterials may inherently possess biological toxicity, such as cardiotoxicity and cytotoxicity, and they can also negatively impact the environment, thus raising concerns about their safety. It is imperative to further investigate the toxicity and biocompatibility of nanomaterials. Consequently, researchers have been inspired by the bionics strategy to coat nanomedicine with a biofilm, which not only reduces rejection reactions and other adverse effects but also enhances targeting capabilities and mitigates toxic reactions. Cell membrane-mimicking nanomaterials have emerged in the fields of disease diagnosis and targeted drug delivery, becoming a new therapeutic strategy.¹⁴⁵

Nanomaterials modified with cell membrane derivatives retain antigens and cell membrane structures, enabling them to acquire the unique functions of the original cells, such as active targeting, long-term blood circulation, and immune escape.¹⁴⁶ Therefore, this biomimetic strategy demonstrates long-term circulation of nanoparticles that are difficult for the immune system to recognize. By coating nanoparticles with cell membranes, various functional proteins can be modified on the surface to form biomimetic nanoparticles, providing multiple pathways for nanoparticles to participate in physiological and pathological processes. The constructed cell membrane-coated nanoparticles retain the various characteristics and inherent targeting capabilities of the core nanoparticles. These advantages make these materials show application potential in inflammation treatment. Drug delivery systems specifically targeting the inflammatory microenvironment have been developed. Currently, various biomembrane nanocarriers have been developed, mainly including macrophage membranes, neutrophil membranes, extracellular vesicles, and hybrid cell membranes.¹⁴⁶ The most prominent are macrophage and neutrophil-targeting nanoparticles and their derived biomimetic nanoparticles.¹⁴⁶

Macrophage Cell Membrane

The macrophage membrane inherits the surface protein spectrum and biointerface characteristics of the source cells, protecting synthetic nanoparticles from being engulfed by immune cells and accurately recognizing antigens to target inflamed tissues.¹⁴⁷ Luo et al prepared alginate microspheres (Motor@M2M@SAM) combined with Janus nanomotors and M2 macrophage membranes for targeted treatment of ulcerative colitis⁶³ Figure 5. Zhao et al utilized the characteristics of the CCL2/CCR2 chemokine axis to recruit macrophages and prepared macrophage membrane-coated nanoparticles, which showed significant accumulation in breast cancer lung metastasis.¹⁴⁸ Ma et al used mouse macrophage membranes to cover nanogelatin and ChS, constructing an “egg yolk-shell” structured artificial M2 macrophage for the treatment of osteoarthritis.¹⁴⁹ Compared with nanohydrogels without cell membrane coating, the artificial M2 macrophages exhibited significant adhesion and accumulation on the surface of inflamed cartilage and synovium, producing a notable anti-inflammatory effect. Gao et al reported a biomimetic drug delivery system of macrophage membrane-coated ROS-responsive nanoparticles. The macrophage membrane not only prevented the clearance of NPs from the endothelial system and assisted NPs in entering inflamed tissues but also isolated pro-inflammatory cytokines and inhibited local inflammation, improving the therapeutic effect on atherosclerosis. This experiment demonstrated that cell membrane-coated drug delivery methods might be more suitable for treating inflammatory diseases than live cell methods.¹⁵⁰ Although macrophage membrane-camouflaged nanoparticles are currently in the embryonic stage, there is still great potential and challenges in exploring their translational models in clinical settings.

Neutrophil Cell Membrane

Recently, some nanomedicines have been used to alleviate rheumatoid arthritis (RA) by targeting functional cells modified with regulatory ligands. Other nanoparticles disguised with membranes or extracellular vesicles (EVs) of these functional cells have been employed to target and attack lesions for RA treatment.¹⁵¹ Yu et al coated self-assembled PEGylated L-arginine nanoparticles with inflammatory neutrophil membranes to construct a neutrophil membrane-based biomimetic nanopatform, NM-LANPs@Ru.¹⁵² In vivo studies on a mouse osteoarthritis model showed that the biomimetic nanopatform could specifically target inflammatory sites through dual-modal imaging,

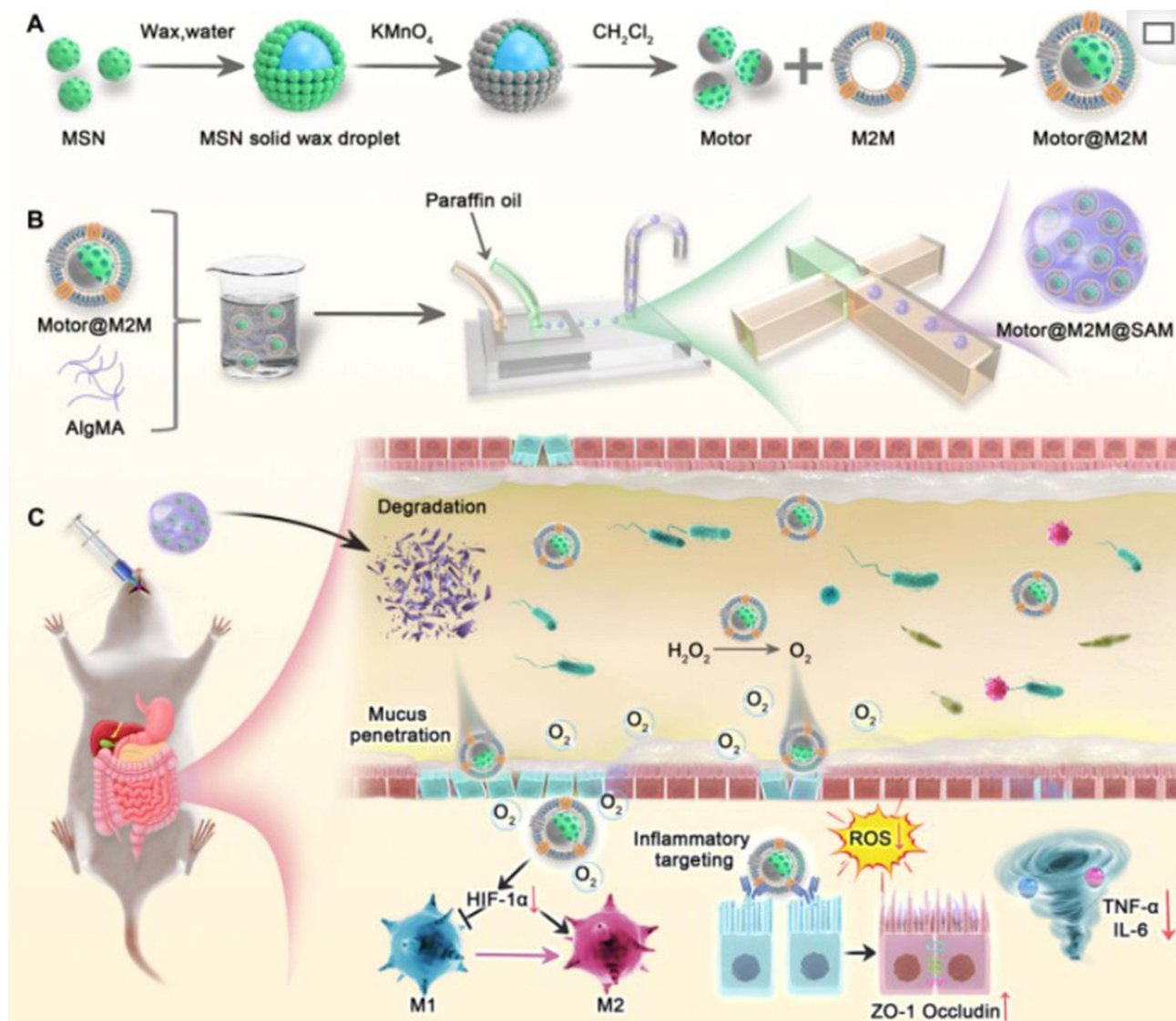


Figure 5 Schematic illustration of Motor@M2M@SAM preparation and its mechanism for UC treatment. **(A)** Scheme depicting the fabrication process of Motor@M2M. **(B)** Scheme illustrating the fabrication process of Motor@M2M@SAM using microfluidic technology. **(C)** Mechanism for UC Treatment: Upon oral administration, SAM is disrupted as it enters the colon. Subsequently, Motor@M2M is released from the hydrogel into the colonic lumen. The propelling force of O₂ bubbles, generated by the decomposition of local H₂O₂ in the inflammatory microenvironment, facilitates the penetration of Motor@M2M through the mucus layer. These nanomotors then target inflammatory colon cells through a macrophage-like function. They specifically interact with colon epithelial cells. Acting as decoys, Motor@M2M neutralizes inflammatory cytokines through receptor-ligand interactions and absorption. Ultimately, Motor@M2M exerts therapeutic effects against UC by scavenging ROS, reducing inflammation, reprogramming macrophages, repairing the epithelial barrier, and rebalancing the microbiota. Reproduced from Luo R, Liu J, Cheng Q, Shionoya M, Gao C, Wang R. Oral microsphere formulation of M2 macrophage-mimetic Janus nanomotor for targeted therapy of ulcerative colitis. *Sci Adv.* 2024;10(26):eado6798.⁶³

exhibiting higher penetration depth compared to non-membrane-coated nanomaterials. Yang Ni et al developed an R4 peptide-modified neutrophil membrane-coated biomimetic nanomedicine (R4F-NM@F127-Cel) with a clear targeting ability for SR-B1⁺ cells. By targeting the synovial membrane through the SR-B receptor, it effectively inhibited synovial inflammation and improved joint damage, providing a promising strategy for the clinical treatment of RA.¹⁵³ Wang et al developed a biomimetic neutrophil-like aggregation-induced emission (AIE) nanorobot (CM@AIE NPs). The neutrophil membrane on the surface enabled CM@AIE NPs to mimic source cells and interact with immune regulatory molecules. Additionally, the excellent photothermal properties of AIE allowed precise localization of inflammatory sites and exerted the anti-inflammatory effect of nanoparticles, minimizing damage to surrounding normal tissues.¹⁵⁴ Zang et al found that neutrophil membrane-coated nanoparticles (NM-NPs) could prevent the infiltration of neutrophils and macrophages to inflammatory sites by capturing chemokines and blocking adhesion to

inflammatory endothelial cells. NM-NPs showed a significant anti-inflammatory effect in vivo on endotoxin-induced inflammatory liver injury without drug loading. This experimental study revealed the anti-inflammatory effects and mechanisms of NM-NPs in the absence of drug loading, providing new insights and evidence for developing safer and more effective targeted drug delivery systems.¹⁵⁵

Conclusion

In chronic inflammatory diseases such as pneumonia, periodontitis and rheumatoid arthritis, controlling the progression of inflammation is a key step in treating the disease. In recent years, nanodrug delivery systems have received widespread attention due to their different functions of immune cells and extracellular matrix factors, which are highly expressed in the inflammatory microenvironment. With the increased understanding and comprehension of various aspects of inflammation, researchers have developed various nanotargeted drug delivery systems. The unique physicochemical and targeting properties of nanodrug delivery systems have created a favorable platform for drug delivery to treat inflammation. In this review, we briefly outlined the relationship between inflammation and immune cells, and reviewed nanotreatment strategies to provide insights for future advances in inflammation treatment and the design of immune-targeted nanodrug delivery systems. Overall, immune-targeted nanomaterials have shown great potential in anti-inflammation, but the greater challenge lies in clinically evaluating the risks and benefits of candidate drugs. Inducing neutrophil apoptosis, inhibiting neutrophil extracellular traps, or targeting neutrophils for drug delivery are therapeutic strategies that can help alleviate inflammation and cure diseases, but relevant research is still in the exploratory stage, and clinical application has a long way to go. Therefore, we need more scientific research to continuously improve the development of new nanotreatment strategies. Immune-targeted nanomaterials will soon provide new opportunities for inflammation treatment, thereby reducing the suffering of patients and the medical burden on society.

Advanced nanomaterials have broad application prospects and can be applied to more fields in the future, exhibiting more excellent properties. With in-depth research on the pathogenesis of various inflammations, new understandings and discoveries are constantly emerging. These new insights not only provide new targets for anti-inflammatory drugs but also offer new ideas for the development of treatment methods, which will bring better treatment options for patients. We can not only start from the perspective of immune cells and immune factors but also delve into relevant inflammatory signaling pathways (NF- κ B, MAPK, Akt, Jak/Stat, etc) to understand the role of related pathways in the disease and find effective targets for inflammation. With the deepening understanding of chronic inflammation mechanisms and the discovery of new targets, I believe that the research and development of anti-inflammatory drugs will achieve more innovations and breakthroughs. Although many specific targeted nanomaterials are relatively new, targeted anti-inflammatory nanomaterials will have a bright future in advancing the field of nanomedicine, enabling new applications to become possible.

Data Sharing Statement

No data was used for the research described in the article.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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