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Review

Macrophages in the pathogenesis of psoriasis and anti-psoriatic nanotherapies

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Abstract: Psoriasis is a common, chronic, and inflammatory skin disease. Macrophages account for about 61.3% of the inflammatory cells infiltrating psoriatic lesions. Modulating macrophage polarization, inhibiting their infiltration, and targeting the secretion of inflammatory factors and associated inflammatory pathways by these cells can alleviate psoriasis symptoms and inflammation. Moreover, nanomaterials as novel drug carriers, offer unique advantages such as large surface area, easy modification, high biocompatibility, good biodegradability, enhanced systemic adsorption, etc. Nanomaterials have great potential for efficient drug delivery and release, as well as improving therapeutic efficacy while reducing adverse effects. By systematically addressing the role of macrophages in psoriasis pathogenesis and the potential of nanomaterials in treating psoriasis through modulating macrophages, this review enhances our understanding of the disease mechanism and holds promise for novel therapeutic breakthroughs and advancements in the future treatment of psoriasis.

Keywords: psoriasis; macrophages; nanomaterials; nano-bio interaction; immunomodulation; drug delivery

1. Introduction

Psoriasis is a common chronic inflammatory skin disease that affects ~2%–3% of the global population. The incidence rate is influenced by different factors such as age, gender, geographic location, and race, as well as genetic and environmental factors, ranging from 30.3 to 321.0 per 100,000 person-years. The disease can occur at any age, especially in the age groups of 16–22 and 55–60 years. Psoriasis significantly affects the quality of patients' social life and personal life. Severe cases can result in an increase in loss of productivity by more than four times, especially in patients with poor quality of life, young age (< 40 years), and comorbidities [1,2]. Psoriasis patients are more likely to experience suicidal thoughts and even suicide attempts. In conclusion, psoriasis is a globally prevalent and costly disease that imposes a heavy burden on patients, families, and society [3,4].

In the skin lesions of psoriasis patients, there is a significant increase in the number of macrophages in the inner layer of the epidermis. This finding reveals the importance of macrophages in the pathogenesis of psoriasis. Research indicates that macrophages constitute 61.29% of the infiltrating inflammatory cells within psoriatic lesions, predominantly located in the transitional zone between the epidermis and dermis, and also in the dermal region [3,4]. Macrophages play a dual role in the context

of psoriasis. On one hand, pro-inflammatory M1 macrophages participate in pathogen engulfment and digestion through pattern recognition receptors, clear cellular debris, and contribute to the body's non-specific defense (innate immunity). These cells release pro-inflammatory signaling molecules including NF-κB, IL-6, IL-12, IFN-γ, and IL-23, which further drive the inflammatory response in the recurrent sites. On the other hand, as for the anti-inflammatory process, pro-repair M2 macrophages facilitate skin repair by secreting a range of growth factors, including epidermal growth factor (EGF), interleukin-10 (IL-10), platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), and vascular endothelial growth factor (VEGF). However, the skin lesions of individuals with psoriasis exhibit a marked predominance of M1 (CD68+ and iNOS+) macrophages and a notable deficiency of M2 (CD68+ and CD163+) macrophages, resulting in a significantly elevated M1/M2 macrophage polarization ratio [5]. This polarization state greatly promotes the chronic severity and recurrent symptoms of psoriasis. To ameliorate the symptoms of psoriasis, researchers have discovered that IL-35 can diminish the M1/M2 macrophage ratio and lower the overall macrophage count, thus easing the condition. Furthermore, macrophages, being a crucial element of the innate immune system, significantly contribute to the development of psoriasis by secreting inflammatory cytokines like IL-20, TNF-α, prokineticin (PK)2, and macrophage migration inhibitory factor (MIF). This secretion promotes immune dysregulation, aberrant proliferation of keratinocytes, and vascular endothelial cells, all of which are pivotal in the disease's pathogenesis (**Figure 1**) [6].

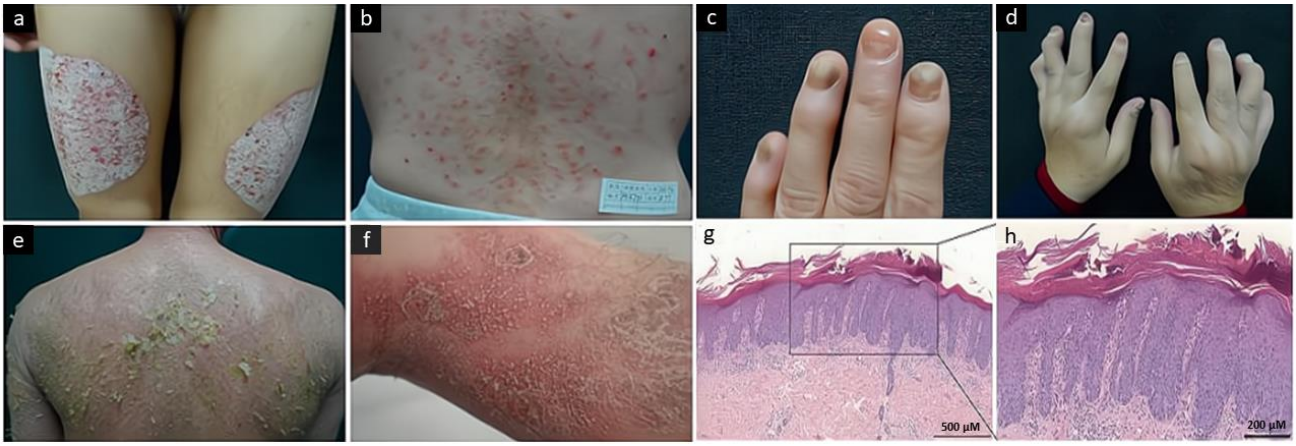

Figure 1. Picture and microslice plots of psoriasis patients. **(a–f)** Clinical diversity and histopathology features of psoriasis; **(g–h)** psoriatic histopathology images [6].

To improve the therapeutic effect, an increasing number of drug carriers are being applied in local skin drug delivery, significantly enhancing the therapeutic efficacy of drugs on skin diseases and reducing toxicity caused by drug entry into the systemic circulation. Nanomaterials, characterized by their extensive surface area, facile modifiability, superior biocompatibility, excellent biodegradability, and advantageous properties in terms of low drug solubility and systemic absorption rates, can significantly enhance the safety and efficacy of therapeutic treatments [7]. Nanostructured carriers can greatly improve the sensitivity of immunoassays, which solves the problem that traditional drug carriers have high density and complex modification steps, and poor reproducibility can produce large background signals.

This review delves into the mechanisms that encompass macrophage infiltration, the interactions between macrophages and other cells, and inflammatory pathways in the context of psoriasis. Subsequently, an overview of nanomedicines and nano delivery systems regulating skin macrophages for the treatment of psoriasis is provided. It is anticipated that this review will deepen the understanding of the specific mechanisms of macrophages in psoriasis and further assist in the development of potential therapeutic agents. We believe that nanomedicines and nanodelivery systems will become important tools for alleviating and treating inflammatory skin diseases.

2. Introduction of macrophages

Macrophages were first identified by Elie Metchnikoff in 1882, when he observed that macrophages play a crucial role in host resistance to infection, phagocytosis of debris cells, and participation in the processes of tissue repair [8]. Moreover, it has been demonstrated that macrophages are extremely important in regulating inflammation, initiating and shaping adaptive immunity, processing antigens and presenting them to T cells, as well as integrating signals from various pattern recognition receptors [9]. Over the past decades, the research on macrophages in psoriasis has received increasing attention. However, the specific mechanisms of their actions and the key molecules still need further study.

Macrophages are a group of cells with variability and multifunctionality, exhibiting different functions in a wide range of microenvironments both in vivo and in vitro. Based on their cell surface markers, secreted cytokines, and biological functions, macrophages can be classified into M1 type (classically activated macrophages) and M2 type (alternatively activated macrophages) [10]. The proportions of different macrophage subtypes (*e.g.*, M1/M2, M1/M2A, and M1/M2B) in the skin of psoriasis patients are closely related to the severity of skin inflammation.

Specifically, an increase in CD68 and iNOS-expressing M1 macrophages is observed [11–13]. LPS and IFN-γ induce macrophage polarization towards the M1 phenotype by activating Stat1 and the aerobic glycolysis pathway, resulting in a decrease in CD68 and CD163-expressing M2 macrophages [14]. M1 cells express biomarkers such as CD16, CD32, CD64, CD68, CD80, and MHCII, indicating their phenotype. Upon stimulation by polarized M1 macrophages, the secretion levels of pro-inflammatory cytokines (TNF-α, IL-12, IL-27, and IL-23), chemokines (*i.e.*, CXCL11, CXCL9, CXCL10), and matrix metalloproteinases (MMP-1, 2, 7, 9, 12) increase correspondingly. During this process, antigen presentation by M1 macrophages is enhanced, and there is an increase in reactive oxygen species generation [15]. IL-4 induces M2 polarization of macrophages by activating STAT6 and relying on fatty acid oxidation (FAO). The M2 macrophages can be further subdivided into M2a, M2b, M2c, and M2d subtypes [16]. Moreover, the M2 macrophages express surface markers such as CD206, CD163, CD209, and FIZZ1, Ym1/2. In contrast to the M1 subtype, M2 downregulates IL-12 and IL-23 expression, while upregulating levels of IL-10, IL-1RA, VEGF, TGF-β, CCL17, CCL18, and CCL22, among other cytokines [17,18]. These mediators promote tissue remodeling and repair by inducing fibroblast-mediated extracellular matrix production, cell proliferation, and angiogenesis. Additionally, M2 macrophages play crucial roles in

anti-inflammatory responses, metabolism, wound healing, and immune regulation [19,20]. The role of macrophages in the pathogenesis of psoriasis can be seen in **Figure 2**.

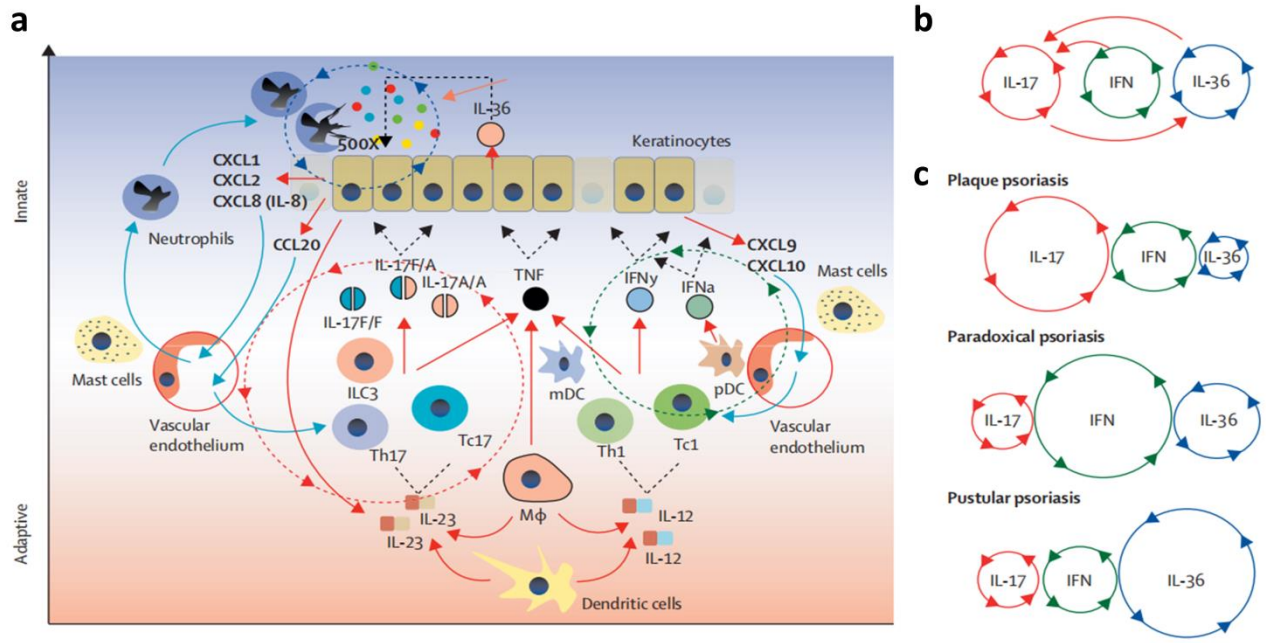

Figure 2. The role of macrophages in the pathogenesis of psoriasis. **(a)** Th17 and TC17 responses by the IL-17, IL-23, and CCL20 feedback loops (dotted red lines), and plasmacytoid dendritic cell-driven type I and type II interferon circuits, the CXCL10 feedback circuit (green dotted line), IL-36, and neutrophil axis secreted by IFN-γ through CXCL9 and CX1 and TC1 are driven by chemokines CXCL1, CXCL2, and CXCL8 (IL-8; blue dotted line). The neutrophils are shown in green (cathepsin G), blue (neutrophil elastase) and red (proteinase 3); **(b)** these three circuits are linked to the IL-36 and IFN-γ responses through a positive feedback mechanism, supporting a Th17 response that activates the IL-36 response as part of feedforward amplification; **(c)** the balance between these three inflammatory circuits may help explain some of the clinical heterogeneity of psoriasis, with IL-17 responses dominating in plaque psoriasis and shifting toward interferon responses in paradoxical psoriasis [6].

The balance between M1 and M2 macrophages and their specific role in the pathogenesis of psoriasis

Overactivation of M1 macrophages triggers inflammation. In psoriatic lesions, the number of M1-type macrophages significantly increases. They secrete pro-inflammatory factors (such as TNF-α, IL-1β, iNOS), activate the Th17 immune axis, and promote abnormal proliferation of keratinocytes. Studies have shown that clearing macrophages (e.g., using clodronate liposomes) can significantly improve inflammation and epidermal hyperplasia in psoriasis mouse models, confirming that M1 polarization is a key link in disease progression. Suppression of M2 macrophage function leads to repair disorders. In psoriasis, the number of anti-inflammatory M2-type macrophages decreases and their function is limited. They secrete insufficient repair factors such as IL-10, TGF-β, resulting in delayed skin barrier repair and uncontrolled angiogenesis. Experiments indicate that promoting M2 polarization (e.g., shikonin intervention) can downregulate inflammatory factors such as IL-20, TNF-α, and alleviate psoriasis-like lesions in mice [21,22]. The role of A2aR and the NF-κB

pathway—Adenosine A2a receptor (A2aR) is highly expressed in M1 polarization and enhances the release of pro-inflammatory factors by activating the NF-κB pathway. Inhibiting A2aR or using its agonists (e.g., CGS21680HCl) can regulate the level of M1 polarization and improve psoriasis inflammation [23]. Abnormal activation of the IL-23/STAT3 axis further exacerbates M1 polarization and is associated with the severity of psoriasis subtypes (e.g., pustular) [21]. Oxidative stress products (e.g., ROS) and a high-fat metabolic environment in psoriasis lesions promote M1 polarization through the TLR4/PPARγ pathway, while inhibiting IL-4/STAT6 signaling related to M2. Shikonin restores macrophage polarization balance by inhibiting M1-related inflammatory factors (TNF-α, iNOS) and promoting M2 marker (Arg1, IL-10) expression, and when combined with methotrexate, it can enhance efficacy and reduce toxicity. Developing small molecule inhibitors targeting A2aR or STAT3, or designing nanocarriers for delivering IL-4/IL-10, is expected to specifically regulate macrophage subset function. The occurrence of psoriasis is closely related to the imbalance of M1/M2 macrophages: M1 polarization drives the inflammatory cascade, while M2 functional defects hinder repair. Future research needs to combine single-cell sequencing and other technologies to analyze subtype-specific mechanisms and develop stratified treatment plans by targeting key molecules (e.g., A2aR) or combining active ingredients of traditional Chinese medicine. Inhibition of pro-inflammatory signaling pathways (M1 polarization regulation)—By blocking pro-inflammatory pathways such as NF-κB, STAT3, the activation of M1-type macrophages can be reduced [24,25]. For example, using STAT3 small molecule inhibitors (e.g., WP1066) or TLR4 antagonists (e.g., TAK-242) can significantly reduce the release of inflammatory factors such as TNF-α, IL-1β. Adenosine A2a receptor (A2aR) antagonists can inhibit M1 polarization, while A2aR agonists (e.g., CGS21680HCl) can promote anti-inflammatory responses in specific microenvironments. Activation of anti-inflammatory signaling pathways (M2 polarization induction)—The IL-4/IL-13-STAT6 pathway is the core mechanism driving M2 polarization. Using recombinant IL-4 or gene editing techniques (e.g., CRISPR activation of STAT6) can enhance the repair function of M2-type macrophages and promote the secretion of IL-10, TGF-β. Regulating lipid and oxidative stress metabolism—In diseases such as psoriasis and atherosclerosis, high levels of free fatty acids (FFAs) and ROS promote M1 polarization through the TLR4/PPARγ pathway. Using PPARγ agonists (e.g., rosiglitazone) can inhibit M1 and induce M2 polarization. Supplementing antioxidants (e.g., N-acetylcysteine) or targeted clearance of ROS nanodrugs can improve the oxidative stress microenvironment and restore the M1/M2 balance. Reprogramming of glucose metabolism, M1 macrophages rely on glycolysis for energy, while M2-type macrophages mainly use mitochondrial oxidative phosphorylation. Inhibiting key enzymes of glycolysis (e.g., HK2) or activating the AMPK pathway can inhibit M1 polarization and promote the M2 phenotype. Precision delivery systems achieve local regulation such as intelligent response-type nanocarriers. Design pH-sensitive or ROS-responsive nanoparticles for targeted drug release at inflammatory sites. For example, liposomes loaded with IL-10 release in an acidic microenvironment, promoting M2 polarization. Exosome carriers can deliver miRNA (e.g., miR-125b) or siRNA, silencing M1-related genes (e.g., iNOS), while upregulating M2 markers (e.g.,

Arg1) [26]. Dual-targeting ligand modification—Modify the surface of nanoparticles with bispecific antibodies for CD206 (M2 marker) and CD86 (M1 marker) to achieve simultaneous regulation of M1 clearance and M2 activation. Synergistic regulatory effects of traditional Chinese medicine active ingredients such as multi-target traditional Chinese medicine formulas. The formula for invigorating qi, resolving phlegm, and removing blood stasis inhibits M1 polarization by regulating the TLR4/MyD88/NF-κB pathway while activating the STAT6 pathway to promote M2 repair, significantly improving lung inflammation in a COPD model [27]. Monomer components such as shikonin, celastrol, etc., can inhibit M1-related factors (TNF-α, IL-6) and upregulate M2 markers (CD163, IL-10), achieving bidirectional regulation. Individualized stratified treatment strategies, such as precision intervention based on biomarkers. Identify patient macrophage polarization characteristics through single-cell sequencing: M1 high expressers preferentially use STAT3 inhibitors, and M2 defective individuals supplement IL-4/IL-13. Metabolomics analysis guides medication; for example, those with abnormal lipid metabolism combine PPARγ agonists with dietary interventions. Dynamic monitoring and combination therapy—Use live imaging techniques (e.g., PET-CT combined with M2-specific probe CD206) to assess polarization status in real-time and adjust drug doses. Combine traditional immunosuppressants (e.g., methotrexate) with new nanodrugs to achieve a synergistic effect of inflammation inhibition and tissue repair. Precision regulation of the M1/M2 balance requires the integration of molecular target intervention, metabolic microenvironment remodeling, delivery system optimization, and individualized treatment strategies. Future developments can combine single-cell multi-omics and artificial intelligence prediction models to develop dynamically adaptive precision treatment plans.

3. The pathogenesis of psoriasis involves macrophages

3.1. Macrophage infiltration in psoriasis

A prominent feature of psoriasis is the infiltration of macrophages, especially around the junction of the epidermis and dermis [28]. Recruitment and activation of macrophages in the lesional skin of psoriasis are key pathogenic factors. Research conducted on two distinct mouse models—the first being a T cell-dependent model with diminished CD18 expression, and the second an epidermis-specific IKK2 knockout model—has uncovered the pivotal role of macrophages in the development of psoriasis. This is evidenced by the substantial presence of macrophages within these models. Further studies have found that blocking the TNF-α signaling pathway can effectively reduce the number of macrophages and TNF-α production, leading to a significant improvement in psoriasis-like skin inflammation. After the removal of macrophages from damaged skin, the numbers of other cells remain normal, and inflammation at the lesion site is significantly improved [29,30]. The findings from these mouse models of psoriasis are consistent with observations in human psoriasis, indicating that activated macrophages play a critical role in the initiation and maintenance of psoriasis-like skin inflammation. Therefore, targeting macrophages and their related signaling pathways provides new potential targets for the treatment of psoriasis.

In a mouse model of psoriasis-like skin lesions induced by doxycycline-induced overexpression of human tumor necrosis factor, macrophages were once again confirmed as the main infiltrating inflammatory cells in the skin lesions. It is noteworthy that the infiltration of CD163-positive M2 macrophages in psoriatic lesions is significantly increased. However, the expression of IL-23p19, IL-12/23p40, and CCL20 genes within macrophages significantly increases, and the protein products also correspondingly increase, exacerbating the inflammatory response in psoriatic lesions. Fortunately, after effective treatment with TNF-α inhibitors, the number of macrophages decreases significantly to levels seen in non-lesional skin, providing new insights for the clinical treatment of psoriasis [31–33]. Further studies in mice have demonstrated that reducing the number of macrophages not only improves inflammation in psoriasis but also lowers the levels of Th1 cell cytokines (including IL-1α, IL-6, IL-23, and TNF-α) to normal levels [34]. Clinical observations have also found that psoriasis patients have a large number of macrophages in their skin lesions, and the peripheral blood monocyte content increases, tending towards the M1 phenotype [12,35,36]. Furthermore, the skin inflammation in psoriasis is closely related to macrophage polarization, characterized by an increase in CD68, iNOS+ M1 macrophages, and a decrease in CD68, CD163+ and M2 macrophages [11].

3.2. Macrophages in psoriasis by interacting with other cells

The role of macrophages in psoriasis is complex and crucial. Their interactions with other immune cells have a significant impact on the proliferation of keratinocytes, which in turn profoundly affects the development and persistence of psoriatic inflammation and immune reactions. In psoriatic lesions, macrophages will release various cytokines (e.g., IL-20, TNF-α, PK2, and MIF) when stimulated by specific signals. These inflammatory mediators not only exacerbate the imbalance of the immune system but also directly promote abnormal proliferation of keratinocytes, and further exacerbated the pathological process of psoriasis [37]. IL-20 stimulates keratinocytes, leading to excessive proliferation and abnormal differentiation, resulting in epidermal thickening. IL-20 also activates the Stat3 pathway, significantly increasing the expression of CK16 and S-100 proteins, exacerbating keratinocyte proliferation. This triggers the expression of proteins associated with skin transition and remodeling, driving the progression of psoriasis [38,39]. MIF helps activate the stress kinase pathway and RSK1 signaling pathway, promoting accelerated proliferation of keratinocytes, leading to their abnormal differentiation, worsening psoriasis [37]. Dermal macrophages express MCP-1 and its receptor CCR2, actively participating in the recruitment of monocytes. The serum levels of MCP-1 are significantly increased in psoriasis patients, playing a crucial role not only in the pathogenesis of psoriasis but also in recruiting Th1 inflammatory cells [4,40,41]. TNF-α, IL-6, and IL-1β can stimulate and assist T (Th) cells to differentiate into Th1, Th17, and Th22 cell subtypes. Increased levels of inflammatory factors such as IFN-γ, IL-17A/F, and IL-22 promote the proliferation and activation of keratinocytes. This leads to the production of IL-23, exacerbating inflammation and the progression of psoriasis [42,43].

Research has revealed the key pathogenic role of macrophages in psoriasis, and

this has been confirmed through selective depletion experiments of macrophages. Experimental results show that reducing the number of macrophages can significantly improve the PASI score (Psoriasis Area and Severity Index) of psoriasis patients and effectively inhibit Th1 signaling [44]. Research has revealed the key pathogenic role of macrophages in psoriasis, and this has been confirmed through selective depletion experiments of macrophages. In the TNF-induced adult ihTNFtg mouse model of psoriasis, researchers have also observed a significant infiltration of immune cells in the psoriatic skin, with macrophages being the main infiltrating cells. Additionally, exacerbation of macrophage infiltration into psoriatic skin and disease worsening occurs when Tregs (regulatory T cells) are depleted. However, when adoptive transfer of Tregs into RAG1 knockout mice or immunocompetent mice significantly reduced macrophage migration to TNF-damaged skin, it then reduced its harmful effect on IHTNF transgenic mice. These research findings indicate that macrophages are the main immune effector cells in TNF-mediated psoriasis, while Tregs can alleviate the severity of the disease by reducing the migration of macrophages to the lesioned skin.

3.3. Macrophage-immune cell network

Macrophages, especially the M1 type, activate Th17 cells through the secretion of IL-23 and TNF-α, which subsequently release IL-17, further promote the aberrant proliferation and inflammatory response of keratinocytes. IL-17 secreted by Th17 cells also feedback enhances the M1 polarization of macrophages and forms a positive feedback loop, thus aggravating psoriatic skin lesions. Macrophages release antigens by phagocytosing skin debris and coactivate T cells with DCs to drive the adaptive immune response. For example, in psoriasis, M1 type highly express MHC-II molecules, which enhances the recognition of the autoantigen by T cells [45]. M1 type macrophages activate Th 17 cells by secreted IL-23, which releases cytokines such as IL-17A and IL-17F, and further stimulate macrophages to produce proinflammatory factors such as TNF-α and IL-1β, forming a vicious cycle. New studies show that the IL-23 receptor (IL-23R) is highly expressed in psoriasis on the surface of macrophages, suggesting that Th17 cells may directly enhance the pro-inflammatory function of macrophages through paracrine IL-23. Macrophages and dendritic cells (DCs) jointly participate in antigen processing and presentation in psoriatic skin lesions. Macrophages release antigen fragments by phagocytizing apoptotic cells or pathogens and are presented to DCs by MHC-II molecules, which further activate CD4+ T cells. In psoriasis, M1 type macrophages highly express co-stimulatory molecules such as CD80/CD86, which bind to CD28 on the surface of DCs to enhance T cell activation and promote Th17 differentiation. DCs deliver exogenous antigens to the MHC-I pathway by cross-presentation (cross-presentation) to activate CD8+ T cells, while IL-12 secreted by macrophages can promote the maturation of DCs and form a pro-inflammatory microenvironment. IL-23 secreted by DCs activates Th 17 cells to produce IL-17, which stimulates macrophages to polarize into M1 type and release TNF-α, IL-1β, to further activate DCs to form a positive feedback loop. The finding that IL-23 levels in the skin lesions in psoriasis suggests that the DCs-macrophage-Th17 axis is a core mechanism of sustained inflammation [46,47]. TNF-α secreted by M1 macrophages enhances the migration ability of DCs and promotes

their homing to lymph nodes; meanwhile, type I interferon (IFN-α/β) produced by DCs enhances the proinflammatory phenotype of macrophages through the STAT1 pathway. Pro-inflammatory factors such as TNF-α and IL-1β secreted by M1 macrophages lead to uncontrolled proliferation and impaired differentiation by activating the NF-κB and STAT 3 pathways in keratinocytes. Thymic stromal lymphopoietin (TSLP) and IL-36 released by keratinocytes can further activate M1 polarization of macrophages and form an inflammatory amplification loop. Keratinocytes produce antimicrobial peptides (e.g., LL-37) and chemokines (CXCL 8, CXCL 10), recruiting more [48,49]. Studies show a tight interaction between neutrophils and macrophages, and neutrophils contribute to macrophage anti-inflammatory phenotypic differentiation via CSF1 secretion and inhibiting NF-κB activation. During the tissue repair stage, macrophages phagocytize apoptotic neutrophils and polarize to the M2c phenotype to support healing. However, in studies related to NETs, neutrophils have predominantly exhibited pro-inflammatory effects. The presence of NETs leads to active glycolysis and inflammasome pathways in macrophages, consistent with a pro-inflammatory phenotype. NETs act as regulators of macrophage function and enhance calcium flux and cytokine release. The cGAS-STING is the major DNA sensor in NETs, and activation of this pathway can cause BBB breakdown. Although the relationship between NETs and cGAS-STING was not explored in keratinocytes, STING/NF-κB activation led to the release of inflammatory mediators. We also found that TBK 1/NF-κB phosphorylation levels and inflammatory cytokine release were increased in macrophages after NET stimulation [50].

3.4. Inflammatory pathways

3.4.1. NF-κB signaling pathway

The NF-κB signaling pathway serves as a major control switch for the expression of various inflammatory factors and plays a crucial role in many important immune transcription processes, such as the inflammatory response of macrophages and other innate immune cells to microbes and viruses [51,52] as well as the development and activation of adaptive immune cells, and the formation of secondary lymphoid organs [53,54]. The NF-κB protein family consists of five members including NF-κB1p50, NF-κB2p52, RELA (p65), RELB, and c-REL. When stimulated by inflammatory factors, pattern recognition receptors (PRRs) or cytokine receptors recognize their ligands, triggering a series of reactions that lead to the phosphorylation of the IKK2 complex. Subsequently, phosphorylated IKK2 acts on IκBα, causing it to be ubiquitinated and degraded in the proteasome. The NF-κB dimer is thus released and binds to DNA in the nucleus to exert its function as a transcription factor, thereby promoting the transcription of target genes. Continuous stimulation by inflammatory factors forms a positive feedback loop, leading to periodic activation of NF-κB until the signal is terminated. This pathway is known as the classical pathway of NF-κB [55–57].

In the presence of LPS, pathogen recognition receptors (PRRs) in macrophages can activate the NF-κB pathway through the Toll-like receptor 4 (TLR4) signaling or the interferon regulatory factor (IRF) 3 pathway, which is connected to MyD88. Specific I-κB kinase degrades I-κB-α, then modifies it (phosphorylation,

ubiquitination), resulting in the translocation of the P65p50 complex into the nucleus, leading to nuclear translocation and regulation of M1 macrophage polarization [58,59]. This process promotes the transcription of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α, regulates the gene expression of inducible enzymes like iNOS and COX-2, thereby intensifying the inflammatory signals and exacerbating the inflammatory symptoms of psoriasis [60–62]. When PPL prevents the nuclear translocation of p65 and the histone deacetylase HDAC3, changes in macrophage infiltration occur, leading to a reduction in inflammation in psoriatic skin [63]. Treatment with GDF11 and Salubrinal can inhibit the activation of the NF-κB signaling pathway in macrophage nuclei, leading to a significant improvement in inflammation in psoriatic skin in mice [64,65].

Activating mutations in SHP2 can lead to the development of psoriasis [66]. Actually, high expression of SHP2 is observed on macrophages in lesional skin tissues of psoriasis patients. Treatment with SHP2 inhibitors or conditional knockout of SHP2 in macrophages significantly improves inflammation in psoriasis-like skin in mice. SHP2 recruits phosphorylated TLR7 at tyrosine 1024 in macrophages, leading to dephosphorylation and subsequent ubiquitination, trafficking to endosomes, and activation of the downstream NF-κB pathway. This promotes the transcription of inflammatory factors in the nucleus, exacerbating the progression of psoriasis [42]. SGK1 is a key negative regulatory factor in IMQ-induced psoriasis, regulating psoriasis through the SGK1\u2012BTK\u2012NF-κB signaling axis. SGK1 is downregulated in macrophages of psoriasis patients. Inhibition of SGK1 enhances NF-κB activity and promotes TNF-α production in IMQ-stimulated RAW264.7 cells. Systemic inhibition of SGK1 increases the production of pro-inflammatory cytokines and amplifies the severity of psoriasis inflammation [67].

In addition, NF-κB is closely related to the JAK/STAT signaling pathway. STAT1 can activate the transcriptional activity of NF-κB, regulate the M1/M2 balance, and influence the interaction between STAT3 and NF-κB. The coordinated regulation of NF-κB and the MAPK signaling pathway can inhibit inflammation [68].

3.4.2. JAK/STAT signaling pathway

The Janus kinase (JAK)-Signal Transducer and Activator of Transcription (STAT) signaling pathway is a common enzyme-linked receptor-mediated signaling pathway involved in the pathogenesis of inflammation and autoimmune diseases. The JAK/STAT pathway is composed of ligand (i.e., cytokine)-receptor complexes, JAKs, and STATs as its three main components. JAKs are non-receptor tyrosine kinases, including four types of JAK1, JAK2, JAK3, and Tyk2, while the STAT family consists of seven members [69]. Together, they maintain the precise operation of the pathway. When cytokines tightly bind to their receptors, it leads to receptor dimerization and activates the associated JAKs. The activation of these kinases triggers tyrosine phosphorylation within the receptor, providing binding sites for STATs. With the assistance of JAKs, STATs bind to the receptor through their SH2 domain and undergo phosphorylation activation. Eventually, activated STATs form dimers, enter the cell nucleus, bind to specific target gene promoters, and promote the transcription and expression of specific genes [69].

In the pathogenesis of psoriasis, the JAK-STAT pathway plays a crucial role. It

not only transmits signals of various key cytokines such as IL-12, IL-23, IL-22, and IFN-γ but also affects the IL-23/Th17 axis, Th1/Th2 imbalance, regulatory T cell dysfunction, and macrophage polarization. When IFN-γ and IL-12 bind to their receptors, JAK is activated, leading to phosphorylation of STAT1, which promotes the polarization of M1 macrophages and the production of pro-inflammatory factors. On the other hand, IL-4 and IL-13 increase the expression of STAT6, while IL-6 increases the expression of STAT3. Both STAT6 and STAT3 promote the polarization of M2 macrophages and the production of anti-inflammatory factors. These two pathways mutually constrain each other in cells and collectively maintain the balance of macrophage polarization [70–72]. The PSORI-CM02 formula reduces the infiltration of M1 macrophages and promotes the proliferation of M2 macrophages by controlling the expression of STAT1 and STAT6. This therapeutic mechanism plays a role in the treatment of psoriasis [73]. CMX reduces the production of pro-inflammatory cytokines by inhibiting the phosphorylation of JAK1/2 and STAT1/3 in macrophages induced by lipopolysaccharide (LPS). In an in vitro model of psoriasis, CMX demonstrates anti-inflammatory and anti-proliferative effects [74]. Ixekizumab inhibits the activation of the JAK/STAT3 signaling pathway in psoriasis mice, regulating macrophage polarization, thereby alleviating psoriasis in mice [75].

Hou et al. found that IL-23 induces undifferentiated macrophages to differentiate into a specific subset M(IL-23) through the JAK-STAT pathway. These cells do not secrete M1- or M2-related cytokines but produce IL-17A, IL-17F, and IL-22 through the STAT3-RORγt pathway, or produce IFN-γ through the T-bet pathway. This promotes inflammatory responses in psoriasis [76]. Currently, in clinical studies, drugs like Tildrakizumab, Risankizumab, Mirikizumab, and other JAK pathway inhibitors have shown significant efficacy and safety, further confirming the important role of the JAK-STAT pathway in the treatment of psoriasis. These medications reduce the production of M1 and M(IL-23) in psoriasis by inhibiting the JAK-STAT pathway downstream of IFN-γ and IL-23, bringing new treatment hopes to psoriasis patients [77].

3.4.3. PI3K-AKT signaling pathway

The PI3K/Akt signaling pathway plays a key role in various biological processes in the body, such as cell survival, migration, metabolism, angiogenesis, and recruitment of inflammatory factors. It is an important signaling pathway in the development of psoriasis [78]. PI3K, comprising two major domains, catalytic and regulatory, the PI3K enzyme can be activated by various receptors, leading to the phosphorylation of PIP2 to generate PIP3. This ultimately activates downstream serine/threonine kinase Akt [79]. Akt, also known as protein kinase B (PKB), exists in three isoforms in mammals: Akt1 (Aktα), Akt2 (Aktβ), and Akt3 (Aktγ). Through interactions with numerous downstream signaling molecules, they regulate various physiological functions of cells [80]. PI3K consists of a catalytic domain and a regulatory domain, and can be activated by G protein-coupled receptors, receptor tyrosine kinases (RTKs), insulin-like growth factor receptors (IGFRs), and B cell receptors. PI3K phosphorylates PIP2 to generate PIP3, which then recruits downstream signaling proteins, including Akt serine/threonine kinase. Akt can also be phosphorylated and activated at the serine 473 site by PDK2. Activated Akt interacts

with multiple downstream signaling molecules, such as p21, p27, transforming growth factor B (TGFB), ataxin-1, GABA receptors, NF-κB, and mTOR [79,81].

The PI3K/Akt pathway plays a central role in regulating the function of macrophages. It not only affects the survival, migration, and proliferation of macrophages, but also regulates their responses to various metabolic and inflammatory signals [82]. Studies have shown that activation or overexpression of PI3K or Akt kinase can attenuate the activation of macrophages by LPS. Conversely, non-specific chemical inhibition of PI3K signaling transduction in TLR-activated cells can enhance NF-κB activation and inducible nitric oxide synthase expression, promoting the M1-type macrophage response [83,84]. The different subtypes of AKT have different effects on the polarization state of macrophages. The absence of AKT1 fosters macrophage polarization towards the M1 phenotype, thereby enhancing the expression of pro-inflammatory mediators such as iNOS, TNF-α, and IL-6. Conversely, the loss of AKT2 leads to macrophage polarization towards the M2 phenotype, which is associated with an upregulation of the anti-inflammatory cytokine IL-10 [85,86]. Loss of AKT3 reduces the infiltration of M2 macrophages and affects the healing of skin wounds [87]. The mammalian target of rapamycin (mTOR) serine/threonine kinase targets two evolutionarily conserved signaling complexes as catalytic components. The mTOR signaling complex 1 (mTORC1) is a key regulator of growth factor and nutrient signals. The mTOR signaling complex 2 (mTORC2) regulates the actin cytoskeleton and activates Akt through phosphorylation at S473. Increased expression and phosphorylation levels of mTOR in psoriatic skin are associated with excessive phosphorylation of mTOR in the basal layer of lesional skin, which may lead to reduced transduction of PI3K/Akt signaling [88]. S6 kinase is the most characteristic downstream effector of mTORC1. Research has found that ribosomal protein S6 is activated in the basal ganglia and differentiates the lesional psoriatic skin layer. Phosphorylation of mTOR at Ser2448 in lesional psoriatic skin is mainly associated with the activation of mTORC1. Nonivamide inhibits the IL17A and Akt/mTOR pathways, promoting macrophage differentiation and autophagy, thereby alleviating IMQ-induced psoriasis symptoms [89]. Rosenberger et al. suggested that the thickening of the epidermis in psoriasis leads to insufficient oxygen supply, and hypoxia adaptation is achieved through hypoxia-inducible factors (HIF). Growth factors and inflammatory factors activate the PI3K pathway and enhance HIF activity through phosphorylation of Akt [82,90]. Therefore, in psoriatic skin, the main oxygen-dependent HIF subtypes are strongly upregulated, and the expression of phosphorylated Akt is significantly enhanced in dermal capillaries and macrophages around the epidermis [91].

Overall, the PI3K/Akt signaling pathway plays a crucial role in suppressing the pro-inflammatory response of macrophages induced by TLR stimulation, while also playing a key role in promoting the anti-inflammatory response. It is considered a negative regulator in the signal transduction of TLR and NF-κB in macrophages, and it also plays a role as a positive regulator in JAK-STAT signal transduction [92,93].

3.4.4. cGAS-STING signaling pathway

The cGAS protein is a member of the nucleotidyltransferase (NTase) superfamily, capable of recognizing exogenous or endogenously released nucleic

acids. The structure includes a positively charged N-terminal domain and a DNA-binding C-terminal catalytic domain containing the NTASE core and the Mab21 binding domain [94,95]. STING (Stimulator of Interferon Genes) is a transmembrane protein consisting of four transmembrane helices, a ligand binding domain (LBD), and a C-terminal tail containing a phosphorylation site for TBK1 (TANK-binding kinase 1) [96]. Once activated, STING interacts with adapter molecules, leading to the phosphorylation and nuclear translocation of IRFs. This triggers the production of interferons, initiating antiviral or antitumor immune responses. STING transmits downstream signals by recruiting and activating TBK1. The C-terminal tail of STING binds to TBK1 to form an interface that is crucial for the phosphorylation and dimerization of IRF3. Specific mutations, such as Pro371Gln and Gln581Ala, may disrupt this interaction, affecting interferon-I induction.

The cGAS-STING signaling pathway plays a crucial role in immune responses. When cytoplasmic double-stranded DNA is sensed by cGAS, it triggers the synthesis of cGAMP and activates STING, further promoting the activation and nuclear translocation of transcription factors such as NF-κB and IRF3. This process stimulates the cascade response of IRF3/1 type interferons and NF-κB/IL-6 signaling, leading to immune responses. However, in certain situations such as viral infections or multiple sclerosis treatment, the use of type I interferons may lead to the onset or exacerbation of psoriasis or psoriatic skin lesions [96–100]. Studies have shown that the STING pathway inhibitor H-151 can alleviate skin lesions in a psoriasis mouse model by inhibiting STING/NF-κB signaling, reducing the secretion of pro-inflammatory cytokines, and decreasing the infiltration of M1 macrophages and Th17 cells [101]. In fact, the mRNA levels of STING/TMEM173, TBK1, and NFKB1 are elevated in the lesional skin of patients with psoriasis [102]. MYSM1 can inhibit the cGAS-STING signaling pathway by blocking STING dimerization and aggregation, suppressing the recruitment of TBK1 and IRF3, and ultimately reducing inflammation in patients with psoriasis.

3.4.5. MAPK pathway

Mitogen-activated protein kinase (MAPK) plays a crucial role in the development of psoriasis, and it is a key molecule regulating cell proliferation, differentiation, gene expression, and apoptosis. The MAPK signaling pathway consists of multiple subtypes, with the three most common types being extracellular signal-regulated kinase (ERKMAPK), MAPK14 (p38MAPK), and stress-activated protein kinase or c-Jun N-terminal kinase (SAPK or JNK) subfamilies. These MAPK subtypes play important roles in the pathogenesis of psoriasis and may serve as potential therapeutic targets [103]. Previous studies have shown that activation of MAPK and NF-κB can trigger inflammatory responses, promote epidermal overproliferation, and exacerbate the development of psoriasis [104]. In particular, excessive phosphorylation of p38MAPK can disrupt skin homeostasis and induce cellular stress, which may be a triggering factor for psoriatic skin inflammation. According to research [105], p38MAPK, ERK1/2, and JNK play important roles in the development of psoriasis. Phosphorylated p38 protein is abundantly detected in pathological psoriatic skin tissues, with a significant nuclear distribution, suggesting its potential involvement in the activation of gene expression. Upregulated antimicrobial peptide S100A8 in

lesional psoriatic skin is found to be regulated by a p38-MAPK-dependent mechanism [106]. Lipopolysaccharide (LPS) is an endotoxin component released by Gram-negative bacteria, which stimulates macrophages to induce downstream signal cascades. MAPK can be activated in LPS-induced macrophages and regulate inflammatory and immune responses [107,108]. MKP-1, as a key negative regulator protein of the MAPK signaling pathway, is involved in the development of psoriasis, but its mechanism of action is not yet clear. Mice deficient in MKP-1 are highly sensitive to skin inflammation induced by imiquimod (IMQ), which is associated with increased production of inflammatory cytokines and chemokines. Therefore, the lack of MKP-1 exacerbates the severity of IMQ-induced psoriasis-like skin disease [109]. He et al. found in clinical studies that the expression levels of IL-36a, IL-36β, IL-36γ, phosphorylated p38MAPK, and NF-κBp65 were significantly elevated in psoriasis patients [110]. The expression levels of IL-36 were closely related to the expression levels of p38MAPK and NF-κBp65, and there was also a significant positive correlation between p38MAPK and NF-κBp65. Therefore, inhibiting the NF-κB and MAPK pathways may be helpful in treating psoriasis.

3.4.6. Other pathways

The macrophage-inducible C-type lectin (Mincle) induced by macrophages is crucial for maintaining the pro-inflammatory phenotype of M1 macrophages [111]. Macrophages mediate psoriasis through the Mincle-Syk-NF-κB pathway. Deletion of Mincle leads to significantly reduced expression of iNOS both in vivo and in vitro. Mincle maintains the M1 polarization of epidermal macrophages, promoting inflammation and skin damage in psoriasis through downstream signals Syk and NF-κB. Additionally, research has found that LPS induces M1 macrophage expression of Mincle through a PU.1-dependent mechanism. Anti-Mincle antibodies show potential therapeutic effects in inhibiting IMQ-induced psoriasis-like skin damage and inflammation, demonstrating a significant anti-psoriatic effect [112].

NLRP3 inflammasome-mediated IL-1β production is implicated as a cause of psoriasis development [113,114]. The activation of the NLRP3 inflammasome in macrophages typically requires two signals [115]. The priming signal is mediated by Toll-like receptor ligands (such as LPS) or cytokines (such as TNF-α), activating NF-κB, leading to upregulation of NLRP3 and/or pro-IL-1β. The activation signal is mediated by pathogen-associated molecular patterns or damage-associated molecular patterns (such as ATP), where the NLRP3 inflammasome cleaves pro-IL-1β and releases mature IL-1β by recruiting ASC and activating caspase-1, to regulate the immune response to infection and cellular stress [116,117]. Astragaloside IV inhibits caspase-1 activation-dependent NLRP3 inflammasome in macrophages, thereby suppressing the production of IL-1β and GasderminD-mediated pyroptosis, which helps improve IMQ-induced psoriasis-like skin inflammation in mice [118]. Clinical data from psoriasis patients indicate that enzymes affecting S1P receptors are positively correlated with the expression of NLRP3 inflammatory components, some of which are targets of the NF-κB signaling pathway. Other NF-κB target genes show differences between healthy and psoriatic skin, suggesting that the regulation of NLRP3 inflammasome components may involve other signaling pathways beyond NF-κB [119]. Lysophosphatidic acid receptor 5 (LPA5)-mediated signaling is a novel

pathogenic factor in psoriasis. TCLPA5 can attenuate the upregulation of macrophage NLRP3 in the damaged skin of IMQ-induced psoriatic mice. LPA exposure activates the NLRP3 inflammasome in cells triggered by lipopolysaccharide, achieving this through upregulation of NLRP3, activation of caspase-1, and maturation/secretion of IL-1β. The LPA5-driven NLRP3 inflammasome activation in lipopolysaccharide-induced cells is significantly reduced after LPA5 knockout [120].

This article discusses the role of macrophages in the pathogenesis of psoriasis and research on nanotherapy for psoriasis, involving the regulation of IL-4, AMPK, JAK/STAT, NF-κB, and PI3K-AKT signaling pathways. Specific topics include the influence of AMPK on M2 macrophage polarization, the role of the JAK/STAT signaling pathway in psoriasis pathogenesis, the importance of NF-κB in the expression of inflammatory factors, and the role of PI3K-AKT in macrophage regulation. The article reveals the significant role of macrophages in the pathogenesis of psoriasis, providing new insights and methods for psoriasis treatment and serving as a reference for the treatment of inflammatory diseases (**Figure 3**). Future research could explore the specific mechanisms of macrophages in psoriasis, seek more effective treatment strategies, and develop new nanotherapy approaches for psoriasis.

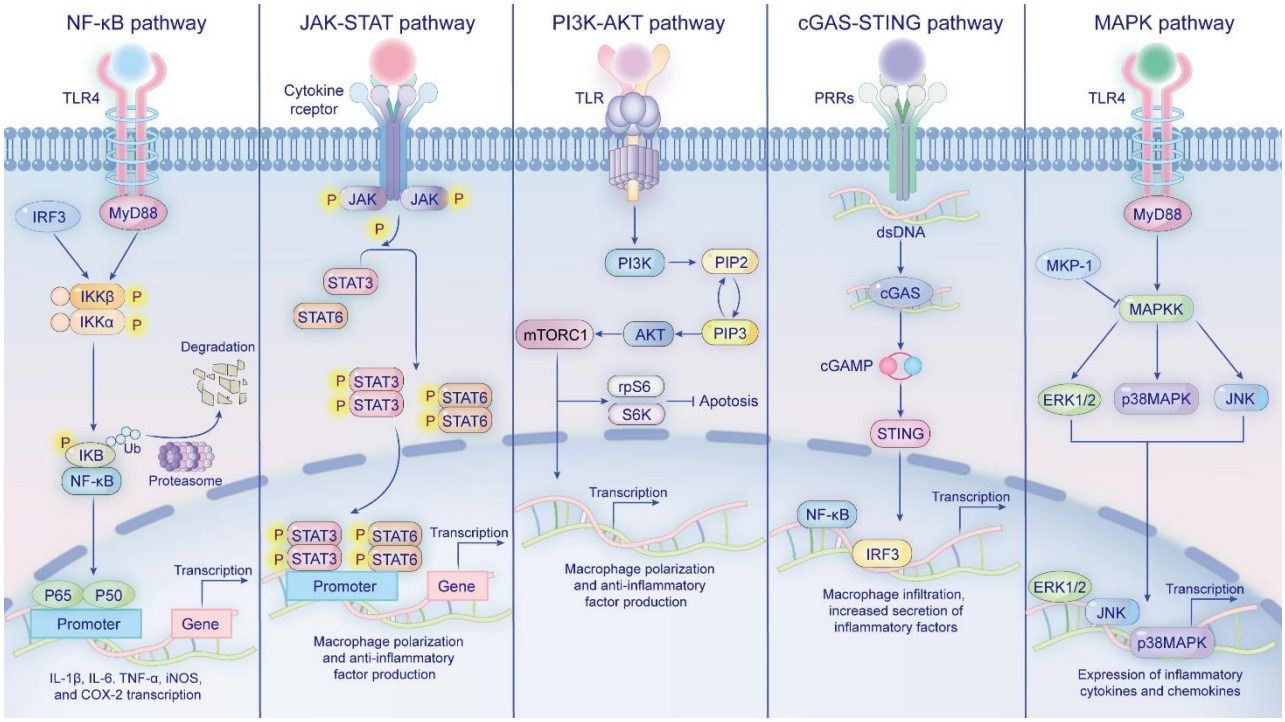

Figure 3. The pathogenesis of psoriasis involves macrophages.

4. Nanomaterials for the treatment of psoriasis through macrophages

Traditional treatments for psoriasis typically include anti-inflammatory medications, immunosuppressive therapy, biologic therapy, and phototherapy. Local treatment is considered the preferred method, so most researchers focus on this approach to improve efficacy and safety. Nanotechnology offers new possibilities for local treatment, allowing for the design of drug carriers to better target the skin,

enhancing treatment effectiveness while reducing adverse reactions. Nanomaterials play a crucial role in inhibiting macrophage infiltration, regulating inflammatory factors and pathways (such as NLRP3 inflammasome, NF-κB pathway, CGAS-STING pathway, STAT3-cyclinD1), modulating macrophage polarization, and regulating interactions between macrophages (**Figure 4** and **Table 1**).

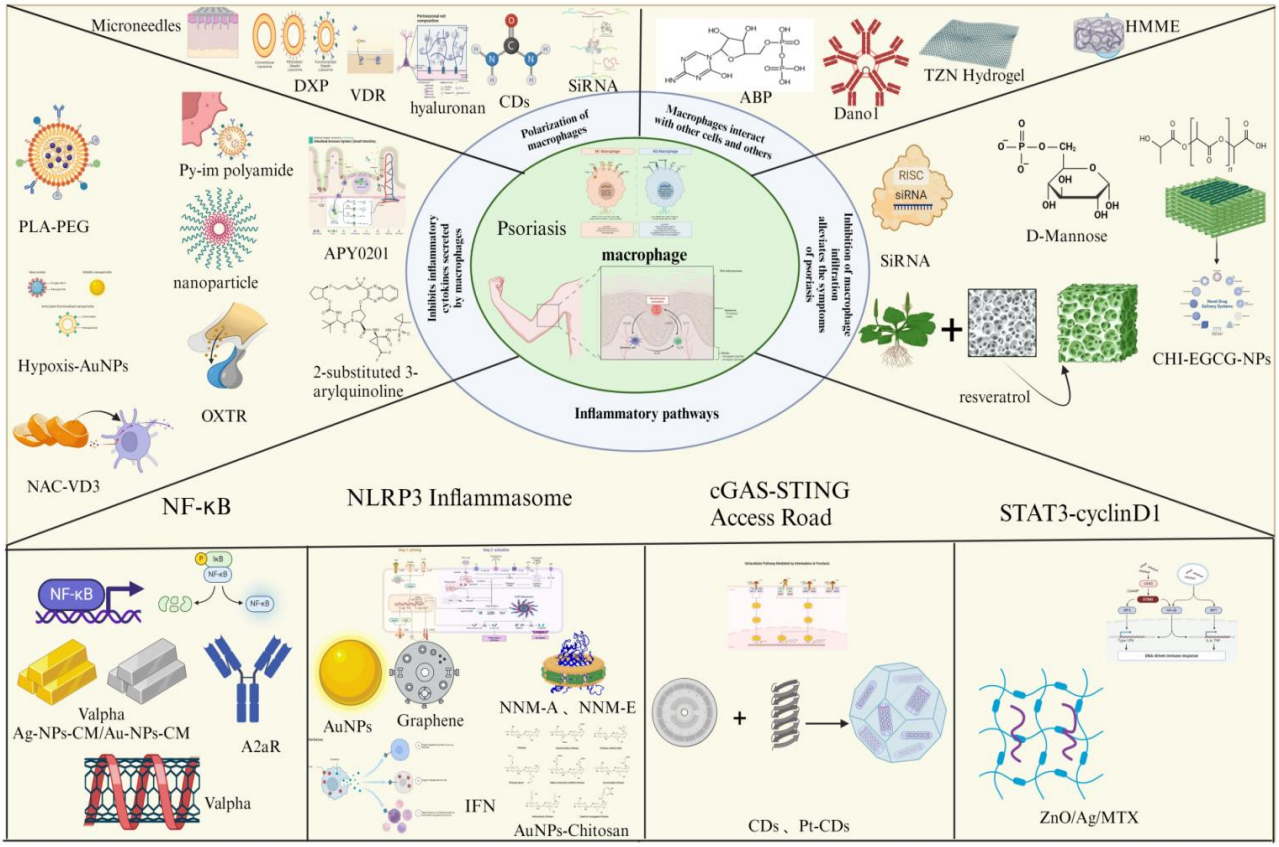

Figure 4. Nanomaterials are classified according to the mechanisms by which macrophages treat psoriasis.

4.1. Inhibiting macrophage infiltration reduces psoriasis symptoms

Macrophage infiltration is an inflammatory response that is particularly prominent in psoriatic skin lesions. The infiltration of macrophages and the secretion of cytokines are two of the mechanisms underlying the pathogenesis of psoriasis. Studies have found that resveratrol can reduce the infiltration of macrophages in psoriatic skin lesions and decrease the levels of macrophage-related pro-inflammatory cytokines (such as IL-6, IL-1β, and TNF-α) secretion. Additionally, resveratrol can also decrease the expression of M1 pro-inflammatory cytokines and increase the infiltration of regulatory T cells. Resveratrol alleviates psoriasis symptoms by inhibiting macrophage infiltration and suppressing glycolysis, providing a new approach for the treatment of psoriasis. Kakkar and Kaur have developed a novel surfactant-based nanovesicular drug carrier system (Span plastic), in which the surfactant consists of Span 60 as a nano-sized non-ionic surfactant and edge activator (EA). These surfactant molecules disrupt the stability of the lipid bilayer, thereby increasing the deformability of the vesicles. Incorporating drugs into suitable nano-carriers helps maintain the active form of the drug and enables it to penetrate deeper

layers through the stratum corneum, thereby maximizing its effectiveness. Studies have shown that a formulation containing 50% Span-60, 25% Birj35, and 25% Cremophor (F11) with resveratrol exhibits advantages in drug encapsulation, modified release, and penetration through the skin barrier. This is likely due to the combination of three different surfactants, each of which influences the formulation properties. In the Carbopol 934 gel formulation, F11 and F10 plastics were added. G1 and G5 showed the best drug release effects, with release rates of 40.13% ± 2.017% and 73.76% ± 2.46%, respectively. The rheological properties exhibited non-Newtonian shear-thinning (pseudoplastic) flow; at a shear stress of 500 s^{-1}, the viscosity of G1 was 1048.5 ± 2.12 cps, and that of G5 was 954 ± 2.15 cps. The group treated with G5 showed significant improvement in erythema and scaling symptoms, maintaining healthy skin, and exhibiting minimal changes in the expression of inflammatory cytokine mRNA genes. Therefore, the formulation containing resveratrol-loaded F11 plastics in G5 is the optimal formula for treating psoriasis induced by pyrimidine. Epigallocatechin gallate (EGCG), a polyphenol found in green tea, can alleviate inflammation, increase the expression of caspase-14, and promote epidermal differentiation and keratinization by treating keratinocyte and mouse skin. A chitosan-based EGCG polymer nanoparticle formulation (CHI-EGCG-NPs, hereinafter referred to as nano-EGCG) is suitable for the local treatment of psoriasis, addressing the limited effectiveness of EGCG therapy for psoriasis due to its limited bioavailability [121,122]. The nano-EGCG is stably released intracellularly and inhibits proliferation and inflammatory responses induced by various TPA and IL-22. It can alleviate skin inflammation parameters, improve various aspects of psoriasis-like disease in mice, including normalization of epidermal structure, inhibition of macrophage infiltration, and reduction of inflammatory reactions. Its efficacy is equivalent to using a dose of free EGCG more than 20 times higher. Nano-EGCG also reduces the proportion of infiltrating immune cells, suppresses the expression of Th1/Th2/Th17 inflammatory cytokines and monocyte activation factors, playing a crucial role in improving skin immune status [122,123]. Researchers have developed an siRNA delivery system based on poly (lactic-co-glycolic acid) (PLGA) nanoparticles for the local treatment of psoriasis. The system is combined with ablative laser to enhance siRNA absorption in the skin. The study results show that the nano-carrier has low cytotoxicity and is easily taken up by cells, leading to a reduction in IL-6 expression levels. The nano-carrier contains a cationic surfactant (Forestall) that can form ion pairs with siRNA, resulting in knockdown efficiencies of IL-6 in keratinocytes and macrophages reaching 66% and 77% respectively. Fraction-mediated nano-carrier delivery significantly alleviates erythema and scaling lesions in psoriasis-like dermatitis, reduces epidermal hyperplasia, and macrophage infiltration [124]. Research has found that oral D-mannose can reduce the expression of SPHK1 in the skin of psoriasis mice, with no significant difference in the expression of SPHK2. Additionally, D-mannose can inhibit the expression of genes related to inflammasomes and pyroptosis (such as AIM2, caspase-1, GSDMD, IL-1β) and reduce macrophage infiltration in the skin of mice. In the dermis of psoriasis patients, there is high expression of SPHK1 in nuclear cells. In vitro experiments show that D-mannose can reduce the inflammatory response of mouse macrophages to LPS stimulation. Transcriptomic data from patients show a positive correlation between high expression of AIM2 in skin lesions and PASI

scores. Finally, the study suggests that both D-mannose and PF-543 (an SPHK1 inhibitor) can inhibit macrophage apoptosis induced by AIM2 inflammasome activation [125].

4.2. Inhibition of inflammatory cytokine secretion by macrophages

Nanomaterials and natural products can improve psoriasis inflammation by inhibiting the factors secreted by macrophages. Oxytocin (OT), a neuropeptide, possesses anti-inflammatory properties and can promote wound healing. Studies have shown that in human macrophages, the oxytocin receptor (OXTR) is significantly upregulated under inflammatory stimulation. The NF-κB and NF-IL-6 binding sites are located in the promoter region of the OXTR gene. Research by Szeto et al. suggests that NF-κB plays a key role in the inflammatory process by activating the promoter region of the OXTR gene. OXTR is significantly upregulated under inflammatory stimulation, and its expression is correlated with changes in the inflammatory cytokine IL-6, which may contribute to the anti-inflammatory effects of oxytocin [126]. Yang et al. synthesized 2-substituted 3-phenylquinoline derivatives and studied their anti-inflammatory effects on LPS-activated mouse macrophages. The research results indicate that compounds 18a and 18b reduce the production of NO, TNF-α, and IL-6 in LPS-activated macrophages by inhibiting the NF-κB and MAPK signaling pathways. Of particular note, compound 18b can form a stable complex with TNF-α and bind to the TNF-α dimer through the central cleft of the dimer rather than through hydrogen bonding interactions. These research results suggest that compounds 18a and 18b may serve as candidate compounds for anti-inflammatory and immunosuppressive drugs [127].

IL-12 and IL-23 are pro-inflammatory cytokines that are associated with the development of inflammatory and autoimmune diseases. Research has found that APY0201 is a small molecule inhibitor of IL-12/23 production [128]. By interacting with the PIKfyve kinase and inhibiting the conversion of PtdIns3P to PtdIns(3,5)P2, APY0201 suppresses the production of IL-12/23. APY0201 may regulate the production of IL-12 and IL-23 in macrophages, thereby reducing the pathological production of the pro-inflammatory cytokines IL-12/23. A novel IL-23-targeting polyamide has been shown to specifically decrease IL-23 expression, improving the development of psoriasis and experimental autoimmune uveitis (EAU) in mice [129]. Compared to other peptides or chemical drugs, Py-Im polyamide has cell-penetrating properties and does not require a delivery agent. It inhibits the production of IL-23 in dendritic cells and macrophages, non-autonomously regulating Th17 cell differentiation, and reducing IL-23 expression in dendritic cells and macrophages may lead to impaired Th17 immune responses in mice treated with the polyamide [129–131]. TNF-α plays a key role in the signal transduction, activation, and amplification of the immune cascade reaction in psoriasis. IL-6 and IL-1β are associated with the IL-23/Th17 axis and regulate pro-inflammatory mediators, T cell differentiation, and epidermal proliferation [132,133]. Liquid crystal nanoparticles (LCNs) are a topical drug delivery system with high internal order, a large interfacial area, and a skin-like structure, among other advantages. LCNs are designed to encapsulate triptolide (TP) and complex small interfering RNA (siRNA) targeting TNF-α and IL-6 on their

surface to achieve local combined delivery and regulation of multiple targets for the treatment of psoriasis. Studies have shown that the multifunctional therapy of LCNs can significantly reduce the release of TNF-α, IL-1β, IL-6, and TGF-β1 from cells stimulated by LPS. TP can regulate multiple signaling pathways and inhibit Toll-like receptor activation, leading to a reduction in pro-inflammatory mediators in macrophages and other immune system cells [134]. When LCNs transport and bind with siTNF-α and siIL-6, these effects become more pronounced. Overall, using biocompatible lipids and polycyclic aromatic hydrocarbons to prepare LCNs is an ideal platform for overcoming the limitations of skin delivery of TP and free siRNA. The use of LCNs combining these two therapeutic agents represents a potential strategy for improving local treatment of psoriasis and other inflammatory diseases [135]. Researchers have constructed a nanoparticle library containing LXR agonists using biodegradable polymer derivatives, synthesized through a self-assembly process. Treatment with LXR-NPs effectively inhibits the expression of pro-inflammatory cytokines MCP-1 and TNFα in macrophages, and also significantly reduces protein secretion levels. After treatment with PpcPgGW, MCP-1 mRNA levels decreased by 70% and TNFα mRNA levels decreased by 80%. Additionally, the PpcPgGW formulation significantly inhibits the protein secretion of MCP-1 and TNFα, indicating its anti-inflammatory and resolving effects in vivo, with significant relief of inflammation [136,137]. NAC-VD3 is a nanostructured liposomal carrier containing vitamin D3 and the antioxidant C50 carotenoid. It has a small size (70 nm), good storage stability, and the ability to protect vitamin D3 from thermal degradation [138]. NAC-VD3 may play a significant role in macrophages through endocytosis, which is influenced by SRA1 mediated by PGP-Me. Experimental results indicate that activated macrophages may internalize a large amount of NAC-VD3 [139]. SRA1 also inhibits the response to LPS triggered by TLR4 by suppressing the NF-κB pathway [140,141]. The anti-inflammatory activity of the SRA1 ligand is demonstrated by NAC-VD3 effectively reducing IL-8 secretion in LPS-activated macrophages. Additionally, NAC-VD3 also decreases the production of reactive oxygen species (ROS). Gold nanoparticles (GNPs) are generally considered to be biologically inert and non-cytotoxic, making them one of the most ideal nanomaterials for medical applications. Gold nanoparticles (GNPs) are generally considered to be biologically inert and non-cytotoxic, making them one of the most ideal nanomaterials for medical applications. Hypoxis-AuNPs have been used in traditional medicine for treating immune-related diseases, and studies have shown that blood extracts have anti-inflammatory activity [142]. Studies have found that Hypoxis-AuNPs can reduce macrophage viability and decrease the levels of IL-1β and TNF-α secreted by macrophages, demonstrating anti-inflammatory effects. IL-10, as a multifunctional anti-inflammatory cytokine, can regulate the expression of various inflammatory mediators induced by various cells, such as bacterial inflammation [143], including Chlamydia and other inflammatory diseases [144]. However, the biological half-life of IL-10 is very short, which limits its potential application in therapy and necessitates frequent administration. Biodegradable nanoparticles are increasingly being recognized for their role as carriers and immune stimulants in therapeutic research. Polymer nanoparticles, prepared from biodegradable polymers, are widely studied as immune stimulants, especially for targeted delivery of vaccines, genes, drugs, and

other biomolecules. Currently, poly (lactic acid) and polyethylene glycol polymers are receiving significant attention for the development of nanoscale therapeutic materials due to the inherent advantages of sustained drug release [145,146]. Research has shown that encapsulating IL-10 in biodegradable PLA-PEG nanoparticles can effectively slow down the degradation rate of IL-10. These nanoparticles can extend the release time of IL-10 to 60 days, maintaining its anti-inflammatory properties in vitro. PLA-PEG nanoparticles have been widely used to increase the drug loading capacity of hydrophobic drugs, reduce burst effects, avoid macrophage phagocytosis, and improve the stability and bioavailability of drugs [146,147], Comprehensive research shows that PLA-PEG nanoparticles, as an effective delivery system for IL-10, can prolong the biological half-life of IL-10, achieve slow sustained release, maintain its anti-inflammatory properties, and regulate inflammatory mediators in vitro. Encapsulated IL-10 has been shown to have an impact on inflammatory responses in immunotherapy, providing a proof of concept for its application in bacterial infections, inflammatory conditions, and autoimmune diseases [148]. A peroxide scavenger, mannose-modified polymeric albumin manganese dioxide (mSPAM) nanoassembly, can inhibit the expression of HIF1α by clearing H_2O_2 in macrophages. In a localized endotoxemia animal model, mSPAM nanoassembly treatment significantly reduced free radicals, alleviated neutrophil and other white blood cell infiltration. This mSPAM nanoassembly system, as an effective anti-inflammatory agent, holds great potential value in the treatment of various inflammation-related diseases [149]. Keehoon Jung and his team have developed a novel fusion decoy receptor called Valpha, which can simultaneously inhibit VEGF-A and TNF-α associated with inflammatory angiogenesis. Valpha is created by fusing ligand-binding domains of different receptors, but its recombinant engineering product retains the same binding ability as the original receptors VEGF-A and TNF-α. Experimental results demonstrate that Valpha significantly blocks VEGF-A and TNF-α, showing potential in treating retinal diseases and psoriasis in mouse models. In cell experiments, Valpha effectively inhibits NF-κB nuclear translocation, indicating its potential as a decoy receptor in dealing with TNF-α. On the other hand, VEGF-A is another hot topic in the pathogenesis and treatment research of psoriasis. Psoriasis patients exhibit increased expression of VEGF-A in skin lesions and serum, and the polymorphisms of VEGF and VEGFR genes are correlated with susceptibility, severity, and prognosis of psoriasis [150,151]. Furthermore, the antagonistic effect of VEGF-A can lead to the reversal of disease phenotypes [152–155]. In order to evaluate the combined therapeutic effect of dual blockade of VEGF-A and TNF-α, a Th17-driven psoriasis-like inflammation model with elevated levels of VEGF-A and TNF-α in the skin was utilized [156].

4.3. Inhibiting inflammatory pathways

The inflammatory pathway is a natural immune response of the body to injury and infection, but in certain diseases, the inflammatory response can be excessively activated, leading to the development of the disease and pathological changes. We hope to provide new targets and treatment strategies for diseases such as psoriasis by gaining a deeper understanding of the regulatory mechanisms of these pathways.

(1) NF-κB pathway

Natural products have always been an important source for drug development due to their biocompatibility and efficacy. Particularly, polyphenols and flavonoids in natural products have garnered increasing attention for their antioxidant and antimicrobial properties. One simple method to prepare green bean-derived NPs (MBNs) can serve as a drug and vaccine delivery vehicle. MBNs have shown the potential to treat psoriatic skin inflammation. Bioactivity assessment of IMQ-induced mice revealed that MBNs have significant therapeutic effects. The skin symptoms in the MBN treatment group were notably reduced compared to the PBS group, and histological evaluation demonstrated that MBNs can inhibit the infiltration of inflammatory cells and abnormal thickening of epithelial cells. Additionally, MBNs can lower the expression levels of inflammatory mediators, reduce the infiltration of inflammatory cells, and thereby improve psoriatic skin inflammation. Following IMQ stimulation, mice treated with PBS exhibited significant scaling, hardening, erythema, and dorsal skin folds compared to the blank control group. Interestingly, the clinical severity index in the MBNs group was significantly reduced compared to the PBS group. Histological evaluation of skin samples showed reduced infiltration of inflammatory cells, thickening of the epidermis, and decreased expression of inflammatory factors, alleviating the inflammatory symptoms of psoriasis and maintaining immune microenvironment homeostasis in psoriatic skin tissue. Further evidence of the effects of MBNs on psoriatic skin treatment was obtained through intradermal injection, where IMQ-induced mice exhibited severe scaling, hardening, and erythema on the dorsal skin compared to normal mice (control group). H&E staining of skin tissues confirmed that MBNs significantly inhibited the infiltration of inflammatory cells and abnormal thickening of epithelial cells. The above-mentioned adverse symptoms in the MBN treatment group of mice skin were significantly alleviated. These results confirm the role of MBNs in improving psoriasis-like skin inflammation. Classically activated macrophages (M1) and selectively activated macrophages (M2) exhibit different phenotypes and functions. M1 macrophages accelerate inflammatory responses, while M2 macrophages attenuate inflammation. M1 polarization is induced by TNF-α and IFN-γ, leading to antigen presentation, while M2 polarization is induced by IL-4 and IL-13, and prevents inflammation. Confocal laser scanning microscopy (CLSM) images show that MBNs can be internalized by macrophages, and the number of internalized MBNs gradually increases with incubation time. Furthermore, stimulating macrophages with TNF-α, real-time polymerase chain reaction (PCR) results show that MBNs significantly reduce the mRNA expression levels of inflammatory mediators such as COX-2, IL-1β, and IL-6. Infiltration of inflammatory cells is a significant feature of IMQ-induced psoriasis skin. It has been reported that iNOS, Ptgs2, and TNF-α are key cytokines in the M1 polarization process and play harmful roles in inflammatory diseases. Conversely, Chil3, Retnia, and Arg1 have been reported as common biomarkers of M2 polarization, showing anti-inflammatory functions in various diseases. Real-time PCR analysis of total RNA extracted from macrophages reveals that the mRNA levels of Ptgs2, iNOS, and TNF-α are elevated compared to normal skin levels, while MBN treatment significantly downregulates mRNA expression levels. Additionally, after IMQ stimulation, the levels of Chil3, Retnia, and Arg1 decrease, but this change is

reversed after MBN treatment. MBNs can regulate the expression of M1/M2 macrophage marker molecules' mRNA, inhibit macrophage inflammatory responses, and maintain the stable polarization state of macrophages. By collecting and analyzing spleen tissue, further study on the systemic inflammatory response induced by IMQ was conducted. Representative images and spleen weight show that the spleen significantly swells after establishing a mouse model of IMQ-induced skin inflammation. As expected, spleen swelling is suppressed after MBN treatment. In addition, collecting splenocytes and analyzing them through flow cytometry shows that MBNs reverse the IMQ-mediated polarization of macrophages. The effects of MBNs on the polarization of skin and splenic macrophages indicate their regulatory role in both local and systemic immune responses. The NF-κB signaling pathway is a key pathway in inflammatory diseases, including psoriasis-like skin diseases. Immunostaining for p65 shows that MBNs significantly inhibit the nuclear translocation of p65 compared to the PBS-treated group. For in vivo comparison, skin samples are collected from the IMQ-induced skin inflammation mouse model (n = 6) after 7 days of treatment under different conditions. Following IMQ stimulation, the mRNA levels of NF-κB1 in the skin increase, indicating activation of the NF-κB signaling pathway, which is suppressed in the MBN treatment group. Furthermore, Western blot and immunohistochemistry tests show that the levels of p-IκBα in the skin lesions are reduced after the addition of MBNs following IMQ enhancement. These results suggest that MBNs can inhibit the activation of the NF-κB signaling pathway both in vitro and in vivo, thereby improving the clinical symptoms of psoriasis skin (**Figures 5**–**8**) [157].

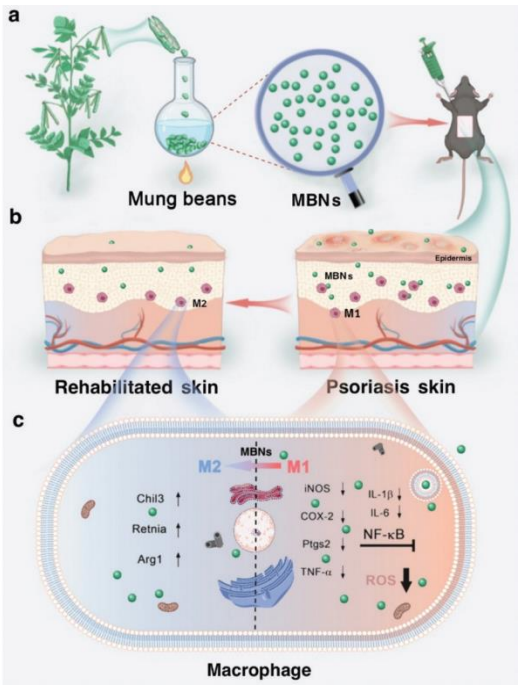

Figure 5. Schematic illustration of the role of MBNs in maintaining immune microenvironment homeostasis of skin with psoriasis. **(a)** Scheme for the preparation of MBNs and topical administration of MBNs on psoriasis-inflamed skin. **(b,c)** regulation of the macrophage polarization and inhibition of the activation of the NF-κB signaling pathway [157].

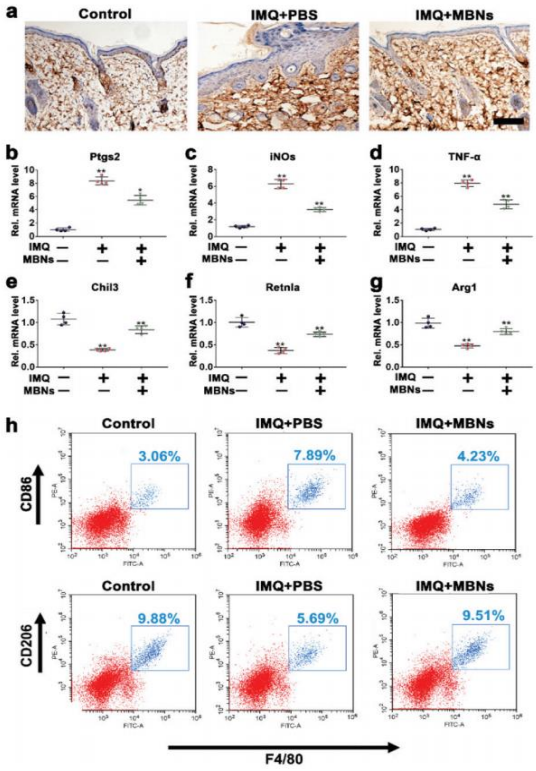

Figure 6. MBNs regulate macrophage polarization in an IMQ-induced psoriasis mice model. **(a)** Infiltration of macrophages in skin following IMQ stimulation as detected by immunohistochemistry of CD68. Scale bar is 300 μm. **(b–g)** Quantitative statistics of the Ptgs2, iNOS, TNF-α, Chil3, Retnia and Arg1 mRNA levels in macrophages. **(h)** Flow cytometry of macrophages in the skin samples of indicated groups. Data are represented as means ± SD (n = 3; *P < 0.05, **P < 0.01, ***P < 0.001) [157].

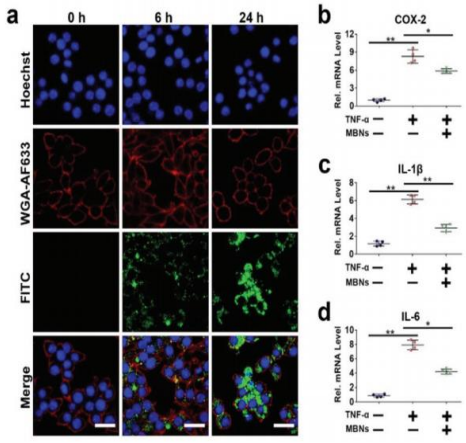

Figure 7. Macrophage uptake of MBNs, where MBNs reduce the mRNA levels of inflammatory factors in macrophages. **(a)** CLSM images of RAW264.7 cells after incubation with FITC-labelled MBNs for different times. Blue and red fluorescence indicate the cell nucleus and membrane, respectively. Green fluorescence indicates the FITC-labelled MBNs. Scale bars are 25 μm. **(b–d)** Quantitative statistics of COX-2, IL-1β, IL-6 mRNA levels in RAW264.7 cells (n = 3). Data are represented as means ± SD (*P < 0.05, **P < 0.01, ***P < 0.001) [157].

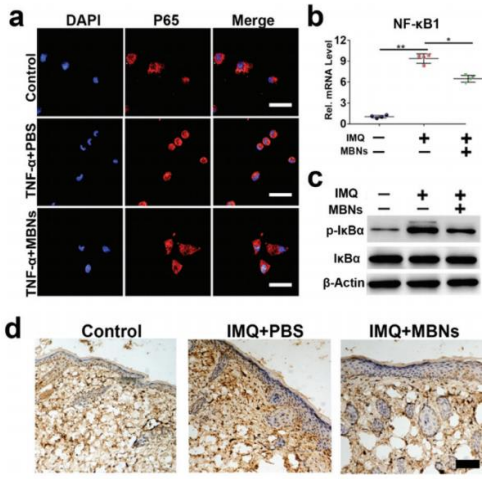

Figure 8. Inhibition of the activation of the NF-κB pathway. **(a)** CLSM images of RAW264.7 cells after p65 immunostaining. Blue and red represent the cell nuclei and P65 protein, respectively. The scale bar is 50 μm. **(b)** Quantitative statistics of the NF-κB1 mRNA levels in mouse dorsal skin. **(c)** Western blot and **(d)** immunohistochemistry of the p-IκBα protein in mouse dorsal skin. The scale bar is 150 μm. Data are represented as means ± SD (n = 3; *P < 0.05, **P < 0.01, ***P < 0.001) [157].

Gold nanoparticles (AuNPs) show promising applications in a wide range of biological applications. AuNPs synthesized using honey as a reducing agent exhibit cytotoxicity [158]. Honey itself possesses antioxidant and anti-inflammatory properties. Phenolic acids and flavonoid compounds in honey can synergistically interact to produce antioxidant and anti-inflammatory effects [159–161]. For example, the flavonoid galangin [159,162] can inhibit cytokine production stimulated by lipopolysaccharide [163] by reducing the expression of TLR4 and phosphorylated IκB [164,165]. These results indicated that the effect of honey gold nanoparticles on IL-6 secretion of LPS-activated macrophages was significant. First of all, honey gold nanoparticles had no obvious effect on the proliferation and toxicity of THP-1 cells, indicating their high safety. Second, in cytokine response assessment, honey gold nanoparticles significantly inhibited the secretion of IL-6 stimulated by LPS, but had no significant effect on the secretion of other cytokines such as IL-1β and TNF, showing its specificity. Finally, in Western blot analysis, honey gold nanoparticles were able to inhibit the phosphorylation of I-KB upon LPS stimulation, suggesting that it affects IL-6 secretion by inhibiting the NFKB signaling pathway. Taken together, these results support the potential of honey gold nanoparticles as a potential immunomodulator, providing strong evidence for their use in the treatment of diseases such as chronic inflammation [166].

Graphene exposure has a significant impact on macrophages. Studies have found that graphene may stimulate the secretion of Th1/Th2 cytokines (including IL-1a, IL-6, IL-10, TNF-a, and GM-CSF) as well as chemokines (such as MCP-1, MIP-1a, MIP-1b, and RANTES) by activating TLR-mediated and NF-κB-dependent transcription, thereby regulating macrophage function [167]. Furthermore, these graphene-induced factors reshape the assembly of actin, reducing their ability to adhere to the extracellular matrix and weakening their phagocytic capacity, thereby altering the

morphology of naive macrophages. Graphene plays a crucial role in modulating the immune response of macrophages through negative feedback, preventing excessive activation of macrophages [168]. In recent years, new metal nanoparticles (NPS) carrying polyphenol-rich extracts have shown good anti-inflammatory activity, but metal particles can cause toxicity through reactive oxygen species. However, the green method of synthesizing nanomaterials by extracting anthocyanin molecules from natural extracts can counteract these potential toxic effects and make the nanomaterials more stable. Polyphenol-rich Cornus officinalis extract (13–52 nm) Au-NPs-CM is more effective than (9–82 nm) Ag-NPs-CM in reducing the secretion of NO, TNF-α, and IL-12 to alleviate macrophage infiltration at the inflammatory site. Additionally, NPs-CM is more effective in inhibiting macrophage activation and cytokine production compared to hydrocortisone, possibly due to the better bioavailability of NPs-CM in inflammatory infiltrates in psoriatic plaques. Studies show a reduction in plaque thickness in psoriatic skin after treatment with NPs-CM, indicating a decrease in excessive epidermal proliferation and inflammatory skin components [169].

Research indicates that in psoriatic lesions of patients, the expression of A2aR on macrophages is higher than in adjacent skin lesion tissues, and it correlates positively with disease severity. Additionally, the expression of A2aR on M1 macrophages is also higher in lesions compared to adjacent skin lesion tissues. Experimental results show that the A2aR agonist CGS 21680 HCl can improve inflammatory symptoms in psoriatic mice, reduce skin lesions, and decrease the number of macrophages, M1 macrophages, and Th1/17 cells in the skin and spleen. In vitro experiments suggest that CGS 21680 HCl can inhibit the polarization of BMDM1 by regulating the NF-κB pathway. Further studies reveal that A2aR inhibits the expression of KRT16 through the NF-κB signaling pathway, thereby suppressing the polarization of BMDM1. Furthermore, A2AR agonists also regulate chemokines by inhibiting CXCL1011 expression, affecting dendritic cell/macrophage-T cell interactions, reducing $CD4^+$ T cell infiltration and Th1/17 cell differentiation. Lastly, the A2aR agonist can suppress the expression of KC inflammatory factors induced by BMDM1 [23].

(2) NLRP3 Inflammasome

NLRP3 is an inflammasome sensor protein that has been extensively studied in many diseases. Activation of NLRP3 leads to the formation of a protein complex oligomer, including ASC and Caspase-1. This oligomeric protein complex is referred to as the “inflammasome,” and when the sensor protein in the complex is NLRP3, it is called the NLRP3 inflammasome. The activation of the inflammasome is regulated by complex molecular interactions beyond the inflammasome sensor protein. AuNPs and their functionalized chitosan have low toxicity and high biocompatibility, making them considered non-toxic biocompatible molecules. Studies have found that Au_CHIT-L and Au_CHIT-H are involved in the activation of the NLRP3 inflammasome, inhibiting the secretion of factors such as CCL2, TNF-α, and IL-6 by macrophages. These findings suggest that the pro-inflammatory response of cells is largely influenced by the surface charge of nanoparticles, and this charge-dependent pro-inflammatory response is mainly driven by chitosan [170]. Research has found that nanoformulated mefloquine A (NNM-A) and nanoformulated mefloquine E (NNM-E) are two compounds that can inhibit the activation of the NLRP3 inflammasome. NNM-A can effectively inhibit NLRP3 inflammasome activation

induced by imidazoquinoline drugs, while NNM-E treatment significantly reduces the mRNA expression levels of inflammatory factors such as Il23a, Il17a, and Cxcl1 secreted by macrophages in IMQ-treated mice, as well as the elevated levels of mature IL-1β. Particularly, it shows high selectivity towards the NLRP3 inflammasome, indicating its potent inhibitory effect on psoriasis [171–174].

Type I interferons (IFNs) include IFN-α (IFNA) and IFN-β (IFNB), which possess anti-inflammatory properties and can be used to treat autoimmune and inflammatory diseases. IFNB can inhibit the activation of the human macrophage nucleotide-binding oligomerization domain-like receptor, pyrin domain-containing 3 (NLRP3) inflammasome through various pathways, effectively suppressing the secretion of the inflammatory cytokine interleukin (IL)-1β by macrophages [175,176]. At the same time, IFNτ significantly reduced the uptake of silica nanoparticles, indicating its inhibitory effect on phagocytosis [177–179].

The application of locally administered inflammasome inhibitors in phagocytic macrophages has shown significant potential for the treatment of psoriasis. Current research reveals the development of non-spherical lipid nanoparticles that mimic pathogen similarity, composed of anti-inflammatory inflammasome inhibitory lipids (dipalmitoyl pyridoxal), as a Trojan horse strategy. The nanorods exhibit an enhanced anti-inflammatory effect compared to nanocylinders and nanospheres, with a 3.8-fold and 4.5-fold increase respectively. Nanorods are capable of reducing the expression of apoptosis-associated speck-like protein, inhibiting lysosomal rupture, calcium influx, and mitochondrial reactive oxygen species. The synergistic inhibition rate of NLRP3/AIM-2-IN-3-loaded nanorods compared to free drugs and in combination with caspase-1 inhibitors reaches 21.5-fold and 59-fold respectively. When the nanorods are transformed into polymer scaffolds, they effectively inhibit NLRP3, AIM2, caspase-1, chemokine ligand-2, gas-d, interleukin-1β, toll-like receptor 7/8, and IL-17A, with inhibition effects in psoriatic skin reaching 13.0-fold, 4.2-fold, 24.4-fold, 4.3-fold, and 1.82-fold respectively [180].

(3) cGAS-STING Pathway

Cyclic GMP-AMP synthase (cGAS) is a cytosolic DNA sensor that activates the cGAS-STING pathway upon detecting pathogenic DNA. This pathway mediates the innate immune response to combat various DNA-containing pathogenic microbial infections, while aberrant activation of the self-DNA cGAS-STING pathway can lead to autoimmune and inflammatory diseases [181].

A nano-inhibitor targeting the cGAS-STING pathway can absorb extracellular cfDNA released by damaged or dead KCs, thereby activating the cGAS-STING pathway. Research results show that CDs and Pt-CDs can significantly reduce the levels of cytokines IL-17 and IL-23 in the skin. Additionally, the gene expression levels of representative cGAS-STING pathway markers such as CXCL10, CCL20, and IFN-β also decrease significantly, indicating pathway inhibition. Treatment with Cd and Pt-CDs can inhibit the overexpression of STING and pSTING, with the Pt-CD group even reversing this upregulation almost completely. This demonstrates that Pt-CDs can effectively inhibit the skin inflammatory response in IMQ-induced psoriasis in mice. On the 11th day, tangled chain-like structures of extracellular DNA appeared in the psoriatic lesions, and treatment with CDs or Pt-CDs reduced the levels of cfDNA, with the local cfDNA levels in the Pt-CD group significantly lower than those

in the model group and CDs group. Both CDs and Pt-CDs treatments could decrease the levels of cfDNA in the plasma, with Pt-CDs showing better efficacy. The levels of TNF-α in psoriatic skin significantly decreased after treatment, with Pt-CDs exhibiting a more pronounced inhibitory effect on TNF-α and IL-6. The research results indicate that Pt-CDs effectively cleared cfDNA and inflammatory cytokines in mice, thereby reducing psoriasis-like inflammation. Furthermore, Pt-CDs accumulated quickly in psoriatic skin, had a broader distribution, and were cleared rapidly from the liver and kidneys, demonstrating good biocompatibility [102].

(4) STAT3-cyclinD1

Signal transducers and activators of transcription (STATs) are important regulatory factors that function by regulating the transcription of downstream target genes. The key member of the signal transducers and activators of transcription family, signal transducer and activator of transcription 3 (STAT3), and its downstream gene CyclinD1 have been shown to play a role in psoriasis [182].

Methotrexate (MTX) is an immunosuppressive agent used to treat moderate to severe psoriasis. Currently, the introduction of nanocarriers such as hydrogels, liposomes, polymers, and microneedles has helped to achieve transdermal delivery of anti-psoriatic drugs like MTX, which can help to avoid the adverse reactions associated with traditional therapies [183]. Therefore, the development of multifunctional hydrogel nanocarriers for precise control of MTX release, inhibition of inflammatory pathways, enhancement of the efficacy of low-dose MTX, and inhibition of psoriasis worsening has become an alternative strategy. In this study, we prepared zinc oxide (Ag-$[Zn(OH)_4]^{2-}$) hybrid mesoporous microspheres by precisely controlling the content of silver nanoparticles (Ag NPs) and loading different proportions of Ag nanoparticles (0.01%, 0.1%, and 1 wt%). The research showed that zinc oxide hybrid mesoporous microspheres containing 0.1 wt% Ag may exhibit superior anti-inflammatory activity and no cell toxicity even at very low concentrations. It is hypothesized that the 0.1 wt% zinc oxide hybrid mesoporous microspheres may interfere with the induction of pro-inflammatory cytokines in macrophages by limiting p65. Cell studies demonstrated that the 0.01 wt% and 0.1 wt% zinc oxide hybrid mesoporous microspheres significantly suppressed the mRNA expression of psoriasis-related cytokines, including TNF-α, IL-23, IL-1β, and IL-6. The zinc oxide hybrid mesoporous microspheres could block IL-23-induced macrophage release of TNF-α and IL-17A. Additionally, through ELISA and Western blot analysis, it was found that the zinc oxide hybrid mesoporous microspheres significantly reduced the expression of innate cytokines in pro-inflammatory M1 cells and inhibited p65 phosphorylation.

The study revealed that N3 with a particle size of 200 nanometers exhibited greater dermal penetration depth in a time-dependent manner compared to F3. Even after 24 h, the deposition of MTX-ZA in N3 was still detectable in the dermal layer, while it was undetectable in F3, indicating enhanced penetration depth and prolonged retention time of the nanomicelles. Furthermore, Car@NMs@MTX-ZA hydrogel could effectively penetrate the stratum corneum and even reach the thickened epidermis of psoriatic lesions. Sensitization skin tests showed that the contact dermatitis induced by 1% DNCB had the highest irritation score in the DNCB group, with the F1 group exhibiting mild scaling symptoms. However, the other groups

showed negligible irritation. Skin tissue histology confirmed these results, with the DNCB group showing apoptotic keratinocytes and inflammatory changes, while the other groups showed no histological changes. The study concluded that the composite hydrogel demonstrated satisfactory biocompatibility, low allergenicity for skin applications, and suitability for local drug delivery. Through qRT-PCR and ELISA analysis, the impact of Car@NMs@MTX-ZA hydrogel on psoriasis cell cytokines in damaged skin was investigated. The results demonstrated that N3 significantly inhibited the expression of TNF-α, IL-23, IL-1β, and IL-6, showing superior anti-inflammatory effects. Further immunofluorescence analysis indicated that N3 could effectively reduce the expression of p65 in pro-inflammatory macrophages, confirming the anti-inflammatory function of ZA. Additionally, N3 exhibited a significant blocking effect on the K17 immune ring, further proving its potential in psoriatic skin inflammation. Toxicology studies indicated that the biological toxicity induced by Car@NMs@MTX-ZA hydrogel at therapeutic doses could be considered negligible. Analysis of Ag^+ distribution revealed that it was mainly present in skin tissues, with lower levels in visceral organs, and was excreted from the body by the 7th day. These results provide crucial support for the safety and therapeutic potential of the hydrogel. Therefore, this multifunctional hydrogel is considered a promising methotrexate transdermal drug delivery nano-platform with significant anti-psoriatic properties and clinical translational potential [184].

4.4. Regulating macrophage polarization

Macrophages are essential components of the immune system and can polarize into M1 or M2 macrophages depending on different external stimuli [185]. M1 macrophages are primarily involved in inflammatory responses and immune reactions, while M2 macrophages have anti-inflammatory and tissue repair functions. The ratio of different macrophage subtypes, such as M1/M2, M1/M2A, M1/M2B, in the skin of psoriasis patients significantly impacts the severity of skin inflammation. Therefore, regulating macrophage polarization is a strategy for the treatment of psoriasis.

Hyaluronic acid is a bioactive glycosaminoglycan biopolymer present in the extracellular matrix. It can regulate macrophage activation and modulate inflammatory responses by interacting with cell surface hyaluronic acid receptors [186–188]. Hyaluronic acid nanoparticles (HA-NP) are nano-carriers formed by the self-assembly of hyaluronic acid and hydrophobic group conjugates. They can be used for long-term and targeted drug delivery [189]. Wang Hee Lee and his team found that HACN can inhibit M1 polarization in LPS-induced BMDMs, PMs, and THP-1 cells. It also suppresses the activation of MAP kinases and NF-κB under LPS stimulation, as well as the expression of NLRP3 and IL-1β in BMDMs. HACN effectively penetrates the IMQ-induced inflammatory skin, targets skin macrophages, inhibits M1 polarization of macrophages, suppresses IMQ and IL-23-induced skin inflammation, and repairs damaged skin barrier, improving psoriatic skin inflammation. This provides a new approach for the treatment of psoriasis [4,22,41,190–194].

Carbon dots (CDs), as a novel nanomaterial, have low or no toxicity, a small size, solubility, and excellent biocompatibility in the field of biomedicine [195–197]. The study found that the model group treated with IMQ exhibited significant typical

symptoms of psoriasis, such as erythema, swelling, increased skin/ear thickness, and scales, compared to the control group. After treatment with methotrexate (MTX) or different doses of PCC-CDs, there was a noticeable improvement in the psoriatic appearance of the skin and right ear, indicating a protective effect of PCC-CDs against IMQ-induced psoriatic inflammation. Consistent with the skin and ear appearance, the Psoriasis Area Severity Index (PASI) scores of IMQ-treated mice gradually increased over seven consecutive days, including erythema, skin/ear thickness, grading scores, and cumulative scores ($P < 0.01$), as shown in **Figure 6a–h**. All drug treatment groups also exhibited typical psoriasis-like symptoms, but significant improvements were observed in the skin and ear tissues after methotrexate or PCC-CD treatment. Notably, the PASI scores of the middle-dose CDs treatment group were significantly lower than those of the high-dose and low-dose groups. Furthermore, MTX and PCC-CDs treatment significantly improved the levels of pro-inflammatory cytokines in M1 macrophages in skin tissues, including TNF-α, IL-6, and iNOS. The induction of M2 markers in cells by PCC-CDs was higher compared to cells incubated only with IL-4. Therefore, CDs alleviate psoriatic inflammation by inhibiting M1 activation and relatively promoting M2 polarization.

Over the past decade, targeted strategies using liposomal encapsulation of corticosteroids have shown significant therapeutic effects in animal models of inflammatory diseases such as rheumatoid arthritis (RA), multiple sclerosis (MS), cancer, and skin diseases. DXP is a phosphate derivative of dexamethasone, a potent anti-inflammatory corticosteroid. In the past decade, targeted strategies using liposomal corticosteroids have shown significant therapeutic effects in animal models of inflammatory diseases such as rheumatoid arthritis (RA), multiple sclerosis (MS), cancer, and skin diseases. DXP is a phosphate derivative of dexamethasone, a potent corticosteroid with strong anti-inflammatory properties. Dexmedetomidine (DXP) encapsulated in liposomes plays an important role in regulating macrophage polarization. Liposomal DXP can shift macrophage polarization towards M2 polarization, thereby regulating the inflammatory response [198–201]. Small interfering RNA (siRNA) drugs have significant advantages in treating autoimmune inflammatory diseases. Researchers have identified siRNA targeting the endoplasmic reticulum core signaling 1 (ERN1) gene (siERN1). Cationic polymers, such as polyethylenimine (PEI) and poly (beta-amino ester) (PBAA), can serve as carriers for siERN1, enhancing the transfection efficiency of siRNA. They have developed a nanodrug delivery system that targets macrophages for the treatment of autoimmune inflammatory diseases. IRE1α is an ER transmembrane sensor associated with ER function and secretion pathways. Previous studies have shown that Ca^{2+} concentration plays a regulatory role in polarization in macrophages [202,203]. SiERN1-nano prodrug interferes with the intracellular concentration of Ca^{2+} by regulating ERN1 and IP3R1/3, thereby affecting the polarization of M1 and M2 macrophages. The siERN1-nano prodrug promotes the polarization of M2 macrophages and the secretion of anti-inflammatory factors. Additionally, FA-PEG-R-NPs@siERN1, as a regulator of macrophage polarization, blocks the MyD88-dependent TLR signaling pathway [204].

DF-MN array is a dual-function microneedle system used to induce long-term local reprogramming of macrophages towards an anti-inflammatory immune pathway, thereby improving symptoms of psoriasis. In vitro experiments have shown that

targeted delivery of IL-13-carrying HA to M1 macrophages through HA's interaction with CD44 can inhibit expression and induce reprogramming. The research revealed that co-culturing cy5.5-labeled HA with LPS-activated RAW 264.7 cells resulted in higher expression of cy5.5 in M1-type RAW 264.7 cells, suggesting HA's targeting of M1 macrophages via CD44. Furthermore, immunofluorescence staining revealed that treatment with microneedles (MNs) significantly inhibited M1 polarization in M0 RAW 264.7 cells and increased the expression of the M2 phenotype. RNA and ELISA analyses confirmed this modulation, showing that the DF-MN array can inhibit M1 polarization and promote repolarization towards the M2 phenotype, thereby achieving an anti-inflammatory effect. Immunohistochemical staining was used to analyze the expression of inflammation-related proteins in psoriasis. Under external stimuli, Th17 cells produce abundant inflammatory factors such as IL-17A and TNF-α. Therefore, the IMQ-induced psoriasis model showed increased expression of inflammatory factors like IL-17A and TNF-α. Immunohistochemistry revealed a significant increase in the expression of TNF-α, IL-17A, and iNOS after IMQ stimulation. In both the model and MN groups, the levels of these inflammatory cytokines in the skin significantly increased after IMQ treatment but decreased significantly after treatment with DF-MNs. The reduction in serum levels of inflammatory cytokines, including TNF-α, IL-17A, and IL-23A, further supported these findings. These results suggest that the DF-MN array can inhibit M1 macrophage expression, thereby reducing the levels of inflammation-related cytokines in psoriasis, suppressing downstream pathways, alleviating abnormal proliferation of keratinocytes, and relieving psoriatic symptoms. Moreover, DF-MN treatment significantly improved splenomegaly, thereby reducing systemic inflammation. Blood routine analysis showed that DF-MNs could alleviate the increase in white blood cells (WBCs), lymphocytes, and neutrophils induced by IMQ stimulation, further validating the therapeutic effects of MNs on systemic inflammation. This effect may be attributed to the dual functionality of the MN array, which involves the rapid release of HA@IL-13 and the expansion and recruitment of macrophages by GelMA@M-CSF, regulating macrophage phenotypes in a dual-time-dependent manner. This novel therapeutic approach provides hope for breakthroughs in the treatment of immunological skin diseases in the future (**Figures 9–12**) [205].

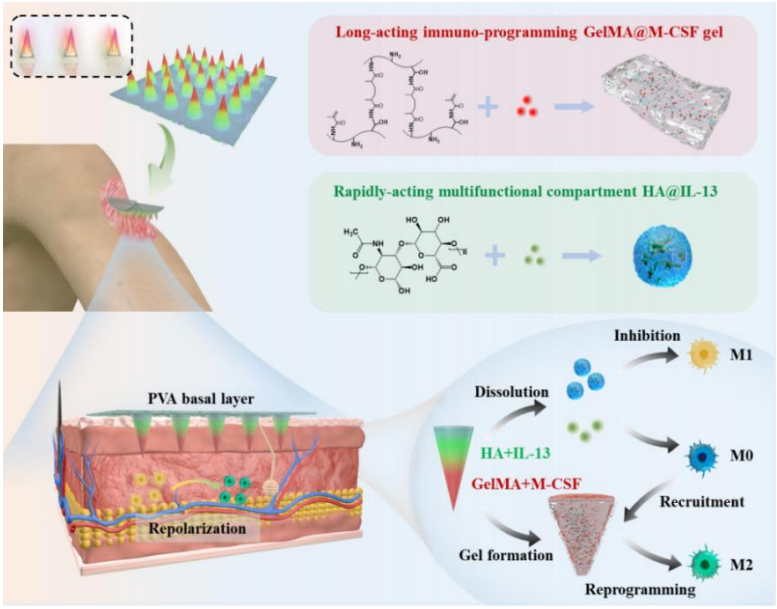

Figure 9. Schematic design of the application of dual-functional MN arrays for polarizing macrophages to psoriasis treatment [205].

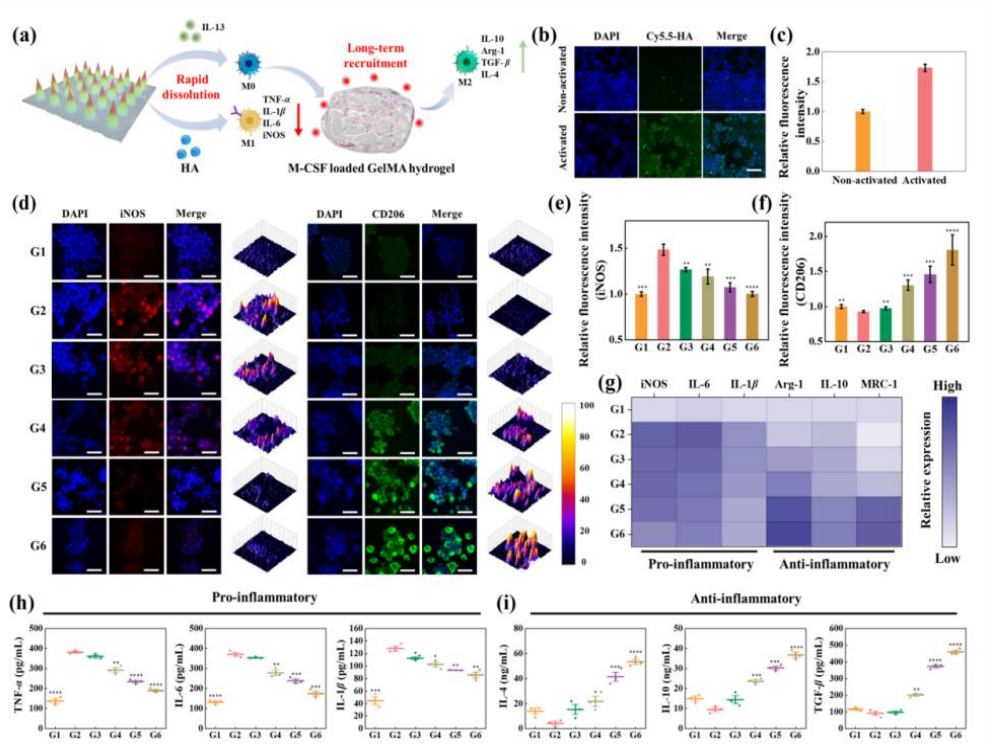

Figure 10. DF-MN arrays for modulating the polarization of the RAW 264.7 to M2 phenotype *in vitro*. **(a)** Mechanism of DF-MN arrays for regulating RAW 264.7 cell phenotype. **(b)** CD44 inactivation versus activation of RAW 264.7 on cy5.5-HA uptake (scale bar: 50 μm). **(c)** Relative fluorescence intensity of cy5.5-HA. **(d)** Immunofluorescence staining of the RAW 264.7 cells after being cocultured with different groups; iNOS (red): M1; CD206 (green): M2; blue: nuclei (scale bars: 20 μm). Relative fluorescence intensity of **(e)** iNOS and **(f)** CD206 in immunofluorescence staining images (n = 3). **(g)** Relative mRNA expression of the RAW 264.7 cells after being cocultured with different groups. ELISA assay of **(h)** pro-inflammatory cytokine: TNF-α, IL-6 and IL-1β, and **(i)** anti-inflammatory cytokine: IL-4, IL-10 and TGF-β (n = 3). G1: control; G2: LPS; G3: GelMA/HA MNs; G4: GelMA@M-CSF MNs; G5: HA@IL-13 MNs; G6: DF-MNs [205].

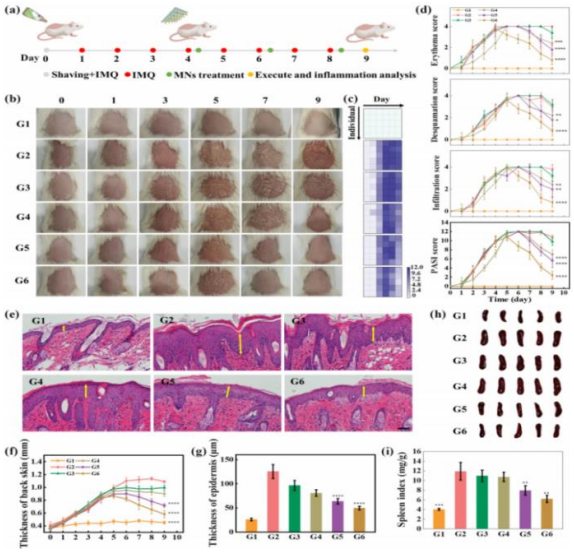

Figure 11. Assessment of the therapeutic efficacy of DF-MN arrays in a psoriasis-like mouse model. **(a)** Schematic representation of psoriasis mouse modeling and MNs treatment. **(b)** Representative images of the dorsal skin in different treatment groups from day 0 to 9. **(c)** Heatmap of PASI score (total) of each individual. **(d)** Changes in PASI scores (erythema, induration, desquamation, and total) in each group over time (n = 5). **(e)** H&E staining images of dorsal skin tissue in different treatment groups (scale bar: 50 μm, n = 5). Yellow arrows represent the thickness of the epidermis. **(f)** Changes in average dorsal skin thickness in each group over time (n = 5). **(g)** Statistical analysis of epidermal thickness in different mouse groups (n = 5). **(h)** Optical photographs of the spleen and **(i)** spleen index (spleen weight/mouse weight) of different treatment groups (n = 5). G1: control; G2: IMQ; G3: GelMA/HA MNs; G4: GelMA@M-CSF MNs; G5: HA@IL-13 MNs; G6: DF-MNs [205].

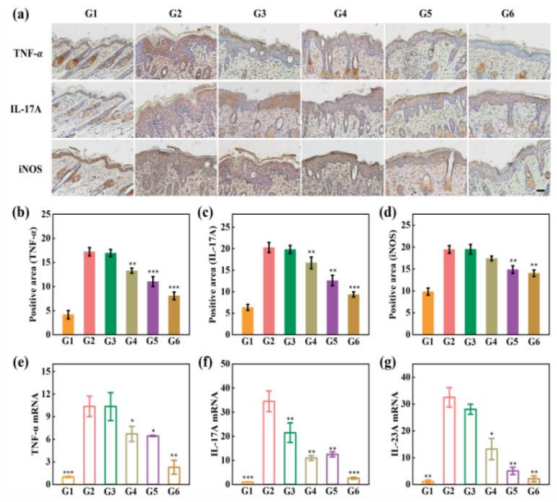

Figure 12. Modulation of psoriasis-associated cytokines using different DF-MN arrays. **(a)** Immunohistochemical staining images showing the expression of TNF-*α*, IL-17A, and iNOS (scale bar: 50 μm, n = 5). The quantification of positive areas in different treatment groups is presented for **(b)** TNF-*α*, **(c)** IL-17A, and **(d)** iNOS. Relative mRNA expression of psoriasis-related inflammatory factors: **(e)** TNF-*α*, **(f)** IL-17A, and **(g)** IL-23A (n = 5). G1: control; G2: IMQ; G3: GelMA/HA MNs; G4: GelMA@M-CSF MNs; G5: HA@IL-13 MNs; G6: DF-MNs [205].

Psoriasis is an immune-related skin disease in which the characteristics of keratinocytes (KCs) play a key role in its pathogenesis. Studies have shown that KCs in psoriasis patients typically exhibit low expression of the vitamin D receptor (VDR). Furthermore, extracellular vesicles derived from VDR-deficient HaCaT cells can stimulate macrophages, leading to polarization of macrophages towards the M1 type and simultaneously inhibiting apoptosis. This mechanism of extracellular vesicle transfer appears to involve the overexpression of miR-4505, which is highly expressed in psoriatic skin. Therefore, extracellular vesicles produced by VDR-deficient HaCaT cells influence the polarization state of macrophages and the inhibition of apoptosis through the transfer of miR-4505, further exacerbating the inflammatory process [206].

Tumor-derived extracellular vesicles as well as melanoma-derived extracellular vesicles exhibit high expression of PD-L1, which contributes to immune evasion in tumors. Jia et al. introduced a natural anti-inflammatory triterpenoid substance called pritimerin for extracting extracellular vesicles from melanoma cells. Through the interaction of PD-1/PD-L1 and the action of pritimerin, engineered melanoma-derived extracellular vesicles can more effectively suppress inflammation in the treatment of psoriatic skin. The immune infiltration activity in psoriatic skin is crucial for disease development, with macrophages playing a key role in psoriatic inflammation. Engineered extracellular vesicles derived from melanoma cells help reduce the infiltration of inflammatory macrophages and promote their polarization towards the M2 subset. Additionally, the interaction between PD-L1 on the surface of extracellular vesicles and PD-1 on the surface of immunesuppressive T cells leads to T cell dysfunction, thereby improving the inflammatory state of the affected skin [207].

Extracellular vesicles (Extracellular Vesicles, EVs) include exosomes (Exosomes, EXOs), microvesicles (Microvesicles, MVs), and apoptotic bodies (Apoptotic Bodies, APOs). Contain nucleic acids, proteins, and lipids that are essential for intercellular communication. Clinical trials have evaluated the potential of EVs in the treatment of multiple pathological states, including psoriasis. Studies have shown that subcutaneous injection of EXOs derived from MSCs attenuates psoriasis inflammation. Although EVs show low toxicity and high biocompatibility in clinical applications, the mechanism and effect of EVs still need further investigation. In this study, we investigated the fusion of T cell-derived EVs overexpressing ANXA 1 with the M2 type macrophage membrane, retained the properties of EVs and M2 type macrophages, and maintained the anti-inflammatory effect of ANXA 1 protein.

Studies demonstrate the first application of an engineered T cell-derived EV to the treatment of psoriasis by regulating macrophage polarization and reducing inflammatory cytokine secretion. T cells overexpressing ANXA 1 were selected as the source of EV to use their interaction with macrophages. ANXA 1 reduces inflammatory responses, promotes macrophage polarization to the M2 phenotype, and promotes EXOs generation. Studies have shown that the T cell-derived EV is enriched with ANXA 1. The M2 macrophage membrane was chosen as the EV fusion partner resulting in the deposition of EV in multiple organs. Local administration strategies confer high targeting ability of EV, and the uptake of EV by macrophages is regulated by multiple pathways. Fusion with M2 macrophages increases EV uptake. In vivo experiments showed that EV treatment improved skin inflammation and reduced

macrophage infiltration. In vitro experiments demonstrated reduced the number of macrophages after EAM treatment. The EV treatment downregulated the IL-1 β, IL-6, and TNF- α accumulation in the skin initiated by the IMQ, blocking the positive feedback loop of psoriatic inflammation. EV treatment restored the hepatic sinusoidal structure and alleviated the renal injury caused by the IMQ. Psoriasis is not limited to the skin, but arthritis is a common complication. The results suggest that engineering EV has potential therapeutic applications in a wider range of the immune system. Although the engineered EV overall components were not evaluated, the results support that the anti-inflammatory response depends on preloaded ANXA 1 protein in EV and M2 macrophage membranes, effectively modulating macrophage polarization. Studies to successfully establish a bridge between a confluent nanoparticle delivery system and psoriasis treatment [208].

Studies have shown that a drug delivery system utilizing zinc-doped mesoporous silica nanoparticles (Zn-MSN) and microneedles (MN) aims to enhance the utilization of drugs and prolong the effects of anti-inflammatory and anti-itching. The MN system facilitates the transdermal delivery of betamethasone dipropionate (BD), allowing for its slow release. The BD@Zn-MSN-MN system promotes the polarization of macrophages towards the anti-inflammatory M2 phenotype, achieving superior anti-inflammatory effects compared to the BD cream clinically used. Furthermore, this study indicates that BD@Zn-MSN-MN can reduce the excitability of transient receptor potential vanilloid 1 (TRPV1) ion channel-positive neurons, decrease the release of calcitonin gene-related peptide (CGRP) in the dorsal root ganglion (DRG), and further alleviate itching in psoriatic mice. These findings provide new insights and effective therapeutic options for the design of future transdermal drug delivery systems for psoriasis [209].

4.5. Factors influencing the interaction between macrophages and other cells

The development of psoriasis is mainly driven by the interaction between overproliferation of keratinocytes and activated immune cells. Although current drug therapies are limited in efficacy, alleviating psoriasis by inhibiting the abnormal proliferation of keratinocytes remains a challenging strategy. Acoustic phase-change nanodroplets can induce stable vaporization under ultrasound stimulation, thereby enhancing vascular permeability, tumor penetration, and transdermal delivery [210,211]. The experimental results indicate that under ultrasound stimulation, HMME-PFP-LPs can generate bubbles through acoustic rupture, leading to the production of reactive oxygen species in solution and HaCaT cells. Cell uptake experiments show that nanodroplets can be rapidly absorbed with ultrasound assistance. Additionally, the combined effect of nanodroplets and ultrasound can effectively induce apoptosis of keratinocytes, resulting in mitochondrial dysfunction. Moreover, due to the anti-inflammatory properties of POPG, blank nanodroplets significantly inhibit the release of inflammatory cytokines in vitro. PFP-encapsulated nanodroplets, acting as cavitation generators, can penetrate the epidermis and induce the production of reactive oxygen species. Therefore, in an IMQ-induced psoriasis mouse model, HMME-PFP-LPs combined with ultrasound stimulation induced

apoptosis of epidermal cells, effectively reducing psoriatic plaques. The inhibitory effect of SDT also suppressed the expression of pro-inflammatory cytokines, contributing to the treatment of inflammatory skin damage. Overall, these phase-change nanodroplets inducing apoptosis of keratinocytes through SDT demonstrate promising anti-psoriatic activity, indicating the potential of SDT as a safe and effective treatment for psoriasis for the first time [212].

4.6. Macrophages interact with other cells

In psoriatic arthritis (PsA), synovial cells and immune cells are sources of inflammation within the synovial space, including osteoblasts, osteoclasts, macrophages, neutrophils, mast cells, T cells, and B cells [213]. Targeting the IL-23-IL-17 pathway has been effective in the treatment of psoriatic arthritis (PsA) [214]. Nitrogen-phosphorus dendritic polymers (ABP) have a unique three-dimensional structure, with the N3P3 core in black, the polyphosphorhydrazone (PPH) branching monomer (including branching points) in blue, and the tyramine (blue) group in orange. These nanoscale dendritic macromolecules have been widely used in the field of biomedicine. Studies have shown that in vitro use of PPH dendritic polymers terminated with anionic nitrogen-phosphorus ester groups (ABP dendritic polymers) can inhibit human macrophages and possess anti-inflammatory properties. In animal models, anti-inflammatory ABP dendritic polymers have demonstrated therapeutic effects on acute and chronic inflammatory diseases [215,216]. Researchers have developed a novel in-situ gel suitable for delivering TZN molecules in the dermal layer. This in-situ gel exhibits favorable properties, including optimal gelation temperature and capacity, suitable pH value, and good appearance. In vitro release experiments showed that the solubility of TZN increased and sustained dissolution over a period extending up to 24 h. Both L929 and RAW264.7 cells exhibited strong cell viability, while the stimulation of cells by TZN was reduced. In-situ gels containing 5% and 10% TZN significantly inhibited nitrite production, demonstrating anti-inflammatory effects. Additionally, only the 10% concentration of TZN in-situ gel reduced PGE2 production, indicating an enhanced analgesic effect ($p < 0.01$). Therefore, this developed in-situ gel as a carrier for TZN in the dermal layer has great potential and can be safely used for psoriasis treatment [217].

Ion channels are ideal targets in the field of therapy, but the development of ion channel-selective drugs with high selectivity and low toxicity is essential. Nanobodies, composed of small single-domain antibody fragments, offer an effective solution to this challenge. P2X7 is a ligand-gated ion channel that initiates pro-inflammatory signaling cascades, including the release of cytokines such as interleukin-1b (IL1b), upon sensing the release of ATP from damaged cells. Researchers have developed and identified nanobodies targeting mouse P2X7, with nanobody 13A7 effectively modulating the gating of the channel. Systemic administration of nanobody 13A7 in mice can block the action of P2X7 on T cells and macrophages, leading to an improvement in inflammation. Furthermore, they have also developed a specific nanobody, Dano1, targeting human P2X7, which shows a 1000-fold stronger inhibition of IL-1b release in human blood treated with endotoxin compared to current clinically developed small molecule P2X7 antagonists [218].

Table 1. Classification of nanomaterials by macrophage therapy for psoriasis.

	Mechanisms	**Examples**	**Strategies**
Inhibition of macrophage infiltration alleviates the symptoms of psoriasis	(1) Decreased levels of macrophage-associated pro-inflammatory cytokines such as IL-6, il-1β and TNF-α; (2) Decreased expression of M1 Proinflammatory cytokine and increased infiltration of regulatory T cells.	Resveratrol-loaded vesicular elastic nanocarriers gel	Hydrogel
	(1) Decreased the ratio of infiltrating immune cells; (2) Inhibited the expression of Th1/Th2/TH17 inflammatory mediators and monocyte activators.	CHI-EGCG-NPs	Formulation of EGCG polymer nanoparticles based on chitosan
	Decreased epidermal proliferation and macrophage infiltration (IL-6 knockout efficiency in macrophages was 77%).	Polylactic acid-Hydroxyacetic Acid nanoparticles	siRNA Delivery system
	(1) Inhibit the expression of genes related to inflammasome and pyroptosis, such as AIM2, Caspase-1, GSDMD, il-1β; (2) Inhibit the macrophage infiltration in mouse skin.	D-Mannose	Polysaccharide nanocomposites
Inhibits inflammatory cytokines secreted by macrophages	Inhibiting IL-6 by activating the promoter region of the OXTR gene.	OXTR	Neuropeptide oxytocin
	(1) Inhibition of NF-κ B and MAPKs signaling pathway; (2) Reduced the production of NO, TNF-α and IL-6 in LPS-activated macrophages.	2-substituted 3-arylquinoline derivatives	Organic nanomaterials
	(1) Rregulates the production of Il-12 and Il-23 by macrophages; (2) Reduces the production of IL-1223, a pathological Proinflammatory cytokine.	APY0201	IL-12/23 Production of inhibitors
	Inhibiting the production of Il-23 by dendritic cell and macrophages, a non-autonomous mechanism regulates Th17 cell differentiation.	Py-im polyamide	Novel IL-23 targeting polyamide
	Inhibit the expression of Proinflammatory cytokine MCP-1 and TNF-α in macrophages.	LCNs	External drug delivery system
	The secretion of IL-8 in macrophages activated by LPS was decrease.	NAC-VD3	Nano-structured paleo-lipid carrier
	Il-1β and TNF-α secreted by macrophages were decreased.	Hypoxis-AuNPs	Gold nanoparticles
	(1)I ncrease the loading of hydrophobic drug, delay the degradation of IL −10; (2) reduce the drug burst effect; (3) avoid phagocytosis of macrophages; (4) improve the stability and bioavailability of the drug.	PLA-PEG	Biodegradable nanoparticles

Table 1. (*Continued*).

	Mechanisms		Examples	Strategies
Inflammatory pathways	NF-κB	Nuclear translocation of NF-κB was inhibited effectively.	Valpha	A novel fusion decoy receptor
		The secretion of NO, TNF-α and Il-12 and macrophage infiltration were decreased.	Ag-NPs-CM/Au-NPs-CM	nanoparticle
		Inhibition of KRT16 expression leads to inhibition of BMDM1 polarization.	A2aR	Adenosine A2A receptor
		(1) Regulating macrophage polarization; (2) Inhibiting the activation of the NF-κB signaling pathway.	MBNs	Bean-derived nanoparticles
	NLRP3 Inflammasome	IL-6 production is specifically reduced by modulating levels of pI κb, a component of the TLR4/NF-κB pathway.	AuNPs	Aunps synthesized from honey as a reducing agent
		By activating TLR-mediated and NF-κB-dependent transcription, the secretion of Th1/Th2 cytokines (including IL-1A, IL-6, IL-10, TNF-a and GM-CSF) and chemokines (such as MCP-1, MIP-1a, MIP-1b and RANTES) was significantly stimulated to regulate macrophage function.	Graphene	Inorganic nanomaterials
		CCL2, TNF-α and IL-6 secreted by macrophages were inhibited.	Aunps and their functionalized chitosan	Nano-compound, polysaccharide, Nanocomposite
		(1) Reduced mRNA expression levels of inflammatory factors secreted by macrophages, such as IL23A, IL17A and CXCL1, and increased levels of mature il-1β; (2) Showed high selectivity for NLRP3 inflammasome.	NNM-A and NNM-E	Nanoscale compounds
		(1) Inhibition of human macrophage glycosyl-binding oligomerization domain-like receptor, pyrin domain 3(NLRP3) inflammasome activation; (2) Inhibition of macrophage inflammatory cytokine interleukin (IL) −1 b secretion.	IFN	Anti-virus nanomaterials
		The NLRP3/AIM-2-IN-3 nanorod when transformed into a polymeric scaffold, simultaneously and effectively inhibits RNA levels of NLRP3, AIM2, caspase-1, chemokine ligand-2, gasdermin-D, interleukin-1β, toll-like receptor 7/ 8, and IL-17A by 6.4-, 1.6-, 2.0-, 13.0-, 4.2-, 24.4-, 4.3-, and1.82-fold, respectively in psoriatic skin in comparison to Imiquimod positive control group in an in-vivopsoriasis-like mice model.	NLRP3/AIM-2-IN-3	NLRP3/AIM2-IN-3; NA3
	cGAS-STING Access Road	Decreased the levels of Il-17, IL-23, CXCL10, CCL20 and IFN-β in skin.	CDs and Pt-CDs	Nano-inhibitors
	STAT3-cyclinD1	Downregulation of ROS-mediated STAT3-cyclinD1 signaling pathway inactivates p65 in proinflammatory macrophages and reduces adaptive cytokine secretion in KCS.	ZnO/Ag/MTX	Hydrogel

Table 1. (*Continued*).

	Mechanisms	Examples	Strategies
Polarization of macrophages	Inhibit macrophage M1 polarization, inhibit IMQ and IL-23-induced skin inflammation.	hyaluronan	Glycosaminoglycan biopolymer nanoparticles
	Inhibition of M1 activation and relative promotion of M2 polarization.	CDs	Nanomaterial
	Promote macrophage polarization to M2 polarization to regulate the inflammatory response.	DXP	Liposomes
	Promoted the polarization of M2 macrophages and the secretion of anti-inflammatory factors.	siRNA	Targeting endoplasmic reticulum core signaling
	Promote the polarization of macrophages to the M1 type.	VDR	Vitamin D receptor
	Promote the reprogramming of M1 macrophages to M2 macrophages.	DF-MN	Dual function microneedle system
	ANXA 1 protein in EV and M2 macrophage membranes, effectively modulating macrophage polarization.	Engineering EVs	EV
	The BD @ Zn-MSN-MN system promoted the polarization of macrophages to the anti-inflammatory M2 phenotype and achieved superior anti-inflammatory effects compared to the clinically used BD cream.	BD @ Zn-MSN-MN	Zn-MSN and MN
Macrophages interact with other cells	Induce apoptosis of macrophages.	HMME	Delivery of nanodroplets
	Inhibits macrophage activity and has anti-inflammatory properties.	ABP	Organic nanomaterials
	Inhibit the production of nitrite and PGE2.	Novel in situ gel	Hydrogel delivering TZN molecules
	Prevents P2X7 from acting on T cells and macrophages.	Dano1	Nanoantibodies initiate a cascade of pro-inflammatory signals

5. Clinical translation challenges of nanotherapy

Studies to successfully establish a bridge between a confluent nanoparticle delivery system and psoriasis treatment. In the field of psoriasis treatment, nanomaterials have shown great potential in targeted delivery and anti-inflammatory regulation. However, in clinical applications, nanomaterials still face several key challenges and limitations, as detailed below:

5.1. Toxicity risk and contradiction with skin barrier penetration

(1) Local cellular toxicity risk

Studies have shown that nanomaterials such as metal nanoparticles may induce keratinocyte damage by inducing reactive oxygen species (ROS), thereby exacerbating skin inflammation. Given that the skin barrier function of psoriasis patients is already compromised, further damage by nanomaterials may lead to secondary infections or long-term toxic reactions.

(2) Systemic metabolic burden

Some nanocarriers (such as carbon-based materials) are difficult to degrade due to their chemical inertness and may accumulate in organs such as the liver and spleen. Especially for psoriasis patients with cardiovascular diseases, this may increase systemic metabolic burden.

(3) Dose sensitivity

Psoriasis requires long-term medication, but the toxicity of nanomaterials may

dynamically change with surface modifications (such as charge, hydrophobicity). For example, cationic nanoparticles are more likely to penetrate the skin but have higher cytotoxicity, requiring precise balancing of efficacy and safety.

5.2. Immunogenicity and interaction with the disease microenvironment

(1) Abnormal activation of the immune system

Psoriasis is mainly mediated by Th17 cells, and nanomaterials may be recognized by immune cells as "danger signals", activating the complement system or pro-inflammatory factors (such as IL-17, TNF-α), exacerbating local immune responses.

(2) The double-edged sword effect of targeted modification

Antibody-coupled nanocarriers can target diseased skin, but overmodification may induce anti-drug antibodies (such as anti-PEG antibodies), reducing the efficiency of repeated dosing. For example, the PEG coating of lipid nanoparticles may trigger immune clearance.

(3) Risk of skin flora interference

The antibacterial properties of nanomaterials may disrupt the balance of skin microbiota, and the occurrence of psoriasis is closely related to flora imbalance, requiring assessment of its impact on symbiotic bacteria.

5.3. Drug delivery efficiency and lesion delivery bottleneck

(1) Insufficient skin permeability

The thickened stratum corneum and abnormal keratinization of psoriasis plaques hinder the penetration of nanoparticles. Studies have shown that the delivery efficiency of traditional nanocarriers in skin lesions is less than 5%, and flexible carriers (such as liposomes) with a size less than 30 nm or physical penetration enhancement technologies need to be developed.

(2) Limited targeting specificity

About 70% of systemically administered nanodrugs are captured by the liver and spleen, while the accumulation rate of locally administered drugs at the lesion site is low. It is necessary to combine dynamic targeting strategies (such as pH-responsive polymers) to improve skin enrichment.

(3) Uncontrollable drug release

The heterogeneity of the psoriasis inflammatory microenvironment (such as redox state, enzyme activity fluctuations) may cause nanocarriers to release drugs prematurely, and multiple response-type drug release systems need to be developed.

5.4. Other systemic challenges

(1) Lack of long-term safety evidence: Most existing studies are based on short-term animal models and lack assessment of the cumulative effects of nanomaterials in the chronic course of psoriasis.

(2) Production standardization difficulties: Parameters such as particle size and drug loading of nanodrugs need strict quality control, but existing processes (such as microfluidic technology) are costly and limit clinical translation.

(3) Conflicts with concomitant disease treatment: Psoriasis is often accompanied by cardiovascular diseases, and it is necessary to avoid the interference of systemic

distribution of nanodrugs with other organ functions.

5.5. Future optimization directions

(1) Biomimetic carrier design: Utilizing keratinocyte membrane coating of nanoparticles to enhance skin affinity and reduce immune recognition.

(2) Hierarchical toxicity assessment system: Combining organ-on-a-chip and AI models to predict the toxicity threshold of nanomaterials at specific pathological stages of psoriasis.

(3) Local-systemic synergistic delivery: Developing a combined regimen of transdermal nanogels and intravenous injection carriers, taking into account both local anti-inflammatory and systemic immune regulation.

Through interdisciplinary collaboration (materials science-immunology-clinical medicine) and technological innovation, nanomaterials are expected to achieve breakthroughs in safety and efficacy in psoriasis treatment, but still require large-scale clinical validation to clarify their risk-benefit ratio.

6. Recent research and future directions

6.1. The role of macrophage subsets in psoriasis subtypes

(1) Studies on the correlation between macrophage polarization phenotypes and psoriasis subtypes have revealed that in psoriatic lesions, macrophages mainly exhibit a pro-inflammatory M1-type polarization state. These cells significantly exacerbate the inflammatory response by secreting pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β). Further research indicates that different subtypes of psoriasis, such as plaque, pustular, and erythrodermic psoriasis, may exhibit significant differences in macrophage polarization due to differences in their microenvironments. For example, in erythrodermic psoriasis, M1-type macrophages may exhibit a more active state, which could further promote the occurrence and development of systemic inflammation. On the other hand, the function of anti-inflammatory M2-type macrophages in psoriasis seems to be suppressed, and the number of anti-inflammatory and repair factors they secrete, such as interleukin-10 (IL-10) and transforming growth factor-β (TGF-β), is reduced. This reduction may lead to abnormal proliferation of keratinocytes and uncontrolled angiogenesis, thus playing an important role in the pathological process of psoriasis.

(2) Signal pathway regulatory mechanisms play a crucial role in the polarization process of immune cells. In M1-type macrophage polarization, NF-κB, JAK-STAT3, cGAS-Sting, and MAPK pathways play key roles by activating and guiding macrophages towards a pro-inflammatory polarization through a series of complex signal transduction events. At the same time, the IL-4/STAT6 pathway promotes M2-type macrophage polarization by different signal transduction pathways, prompting macrophages towards an anti-inflammatory polarization. In the complex skin disease of psoriasis, different subtypes may be related to the activation degree of specific signal pathways. For example, in pustular psoriasis, the IL-17/STAT3 axis may be more pronounced, indicating

that in this subtype, the inflammatory response related to IL-17 may be stronger, leading to the formation of pustules. Understanding how these signal pathways function in different psoriasis subtypes is of significant importance for the development of targeted treatment strategies.

(3) The relationship between microenvironmental metabolites and subtype specificity is particularly important in psoriasis research. In the lesion areas of psoriasis, high levels of free fatty acids (FFAs) and oxidative stress products can be observed. These substances may exacerbate M1-type macrophage polarization by activating the TLR4/PPAR signaling pathway. For the metabolic characteristics of different psoriasis subtypes, such as abnormal lipid metabolism or disturbed glucose metabolism, researchers can deeply explore how specific metabolites regulate the macrophage polarization process. By understanding these mechanisms, it may be possible to develop treatment strategies targeted at specific subtypes in the future, thereby managing psoriasis more effectively.

6.2. Development directions for targeted nanotherapy

(1) Design of Nanocarriers Targeting Polarization Regulation-Utilizing nanoparticles (e.g., liposomes, polymer micelles) to load small molecule inhibitors (e.g., NF-κB inhibitors) or siRNA for precise regulation of macrophage polarization signaling pathways. For example, nanodrugs targeting STAT3 can inhibit M1-type polarization and alleviate inflammation in plaque psoriasis. Biomimetic nanoparticles (e.g., exosome carriers) can deliver cytokines such as IL-4 or IL-10 to promote M2-type polarization and accelerate skin repair.

(2) Microenvironment-Responsive Smart Nanosystems-Design pH-sensitive or ROS-responsive nanocarriers that release drugs in response to the acidic or high oxidative stress microenvironment of psoriasis lesions, improving local efficacy and reducing systemic side effects. For example, in pustular psoriasis, ROS-responsive carriers can preferentially release antioxidants (e.g., NAC) to inhibit M1-type polarization.

(3) Multi-target Synergistic Treatment Strategies-Through innovative applications of nanoplatforms, it is possible to effectively integrate immunomodulators (e.g., methotrexate) with anti-angiogenic drugs (e.g., VEGF inhibitors). This integrated approach can simultaneously exert the effects of both drugs, on one hand inhibiting the inflammatory response mediated by macrophages, and on the other hand inhibiting abnormal angiogenesis. This synergistic treatment strategy shows particular potential and advantages in treating refractory generalized psoriasis.

6.3. Potential value in promoting field research

(1) Mechanism analysis tools: Single-cell sequencing combined with nanoprobe technology can dynamically analyze the spatiotemporal distribution and functional evolution of macrophage subsets in psoriasis subtypes.

(2) Personalized treatment: Based on the patient's macrophage polarization characteristics, a stratified treatment plan can be formulated, such as prioritizing the use of TLR4 antagonist nanodrugs for those with high M1 expression.

Through the above research directions, not only can the understanding of the

heterogeneity mechanism of psoriasis be deepened, but the clinical translation of precise nanotherapy can also be promoted.

7. Summary

Macrophages are key innate immune cells, and their infiltration in the dermis and epidermis of psoriatic lesions in psoriasis patients is observed. This article discusses the role of macrophages in the pathogenesis of psoriasis and the research on nanotherapy for psoriasis. Macrophages play an important role in the pathogenesis of psoriasis by promoting inflammation, neovascularization, and hyperproliferation of keratinocytes caused by immune imbalance. Moreover, the infiltration and polarization of macrophages mediated by related inflammatory signaling pathways cannot be ignored in the pathogenesis of psoriasis. In recent years, there have been significant advances in understanding the role of macrophages in the inflammatory mechanisms of psoriasis, but further research is needed to elucidate the specific mechanisms of macrophages in psoriasis. This article also discusses the use of nanomedicine and other treatment approaches to treat psoriasis through macrophages. Researchers are currently seeking new treatment methods and targets to improve the quality of life for psoriasis patients. Additionally, the interactions between macrophages and other cells, as well as the effects of nanoparticles on cells, are crucial. These studies contribute to a better understanding of the pathogenesis of psoriasis and provide a theoretical basis for the development of new treatment methods.

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