Journal of Inflammation

REVIEW

Open Access

Advances in the study of macrophage polarization in inflammatory immune skin diseases

Tingting Xia[1,2], Shengping Fu[1], Ruilin Yang[1], Kang Yang[2], Wei Lei[2], Ying Yang[2], Qian Zhang[3], Yujie Zhao[4], Jiang Yu[1], Limei Yu[1] and Tao Zhang[1,2*]

Abstract

When exposed to various microenvironmental stimuli, macrophages are highly plastic and primarily polarized into the pro-inflammatory M1-type and the anti-inflammatory M2-type, both of which perform almost entirely opposing functions. Due to this characteristic, macrophages perform different functions at different stages of immunity and inflammation. Inflammatory immune skin diseases usually show an imbalance in the M1/M2 macrophage ratio, and altering the macrophage polarization phenotype can either make the symptoms worse or better. Therefore, this review presents the mechanisms of macrophage polarization, inflammation-related signaling pathways (JAK/STAT, NF-κB, and PI3K/Akt), and the role of both in inflammatory immune skin diseases (psoriasis, AD, SLE, BD, etc.) to provide new directions for basic and clinical research of related diseases.

Keywords Macrophage polarization, Signaling pathway, Inflammation, Immunity, Skin diseases

Introduction

The skin, the largest and most exposed organ of the body, must react appropriately to environmental stimuli through a variety of mechanisms to create an immunological and mechanical barrier to the environment. Skin inflammation is the body's response to different types of injuries, including infections. It involves a complex immune response that includes processes such as recruiting immune cells, responding to changes in blood vessels, and releasing inflammatory factors that aid in fighting pathogens, repairing damaged tissues, and maintaining balance within the body [1]. However, if the immune response becomes too intense, it can lead to chronic inflammation and autoimmune skin diseases. Macrophages are key players in the inflammatory immune response of the skin, and they have a vital role in maintaining the body's balance while also serving as the primary defense against foreign microorganisms and pathogens. Macrophages regulate skin homeostasis by responding to stimulation and creating polarization through various signaling pathways, which support both pro- and anti-inflammatory responses. In recent years, numerous research studies have identified a significant connection between the polarization of macrophages and the emergence and advancement of various inflammatory immune disorders. Consequently, this paper aims to compile information on macrophage polarization, associated signaling pathways, and their impact on

*Correspondence:
Tao Zhang
oceanzt@163.com
[1]Key Laboratory of Cell Engineering of Guizhou Province, Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou, China
[2]Department of Dermatology, Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou, China
[3]Department of Human Anatomy, Zunyi Medical University, Zunyi, Guizhou, China
[4]Department of Laboratory Medicine, Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou, China

inflammatory immune skin disease, hoping to offer valuable references for both fundamental research and clinical treatment of macrophage polarization-related skin diseases.

Origin, polarization types, and functions of macrophages

In response to danger signals, the immune system activates a protective inflammatory immune response that includes various processes such as destroying pathogens, removing cellular debris, repairing tissue, and maintaining body homeostasis [2]. As the body's first line of defense against diseases, macrophages are crucial because they phagocytose foreign microorganisms and regulate the immune system's reaction to different pathogens by processing and presenting antigens [3]. Macrophages are derived from circulating monocytes, which originate from hematopoietic stem cells in the bone marrow [4, 5]. It was previously believed that tissue-resident macrophages in both healthy and diseased areas come from circulating monocytes [6]. However, recent studies have shown that most tissue-resident macrophages actually originate from the yolk sac and fetal liver during embryonic development [7]. Macrophage populations differ greatly between tissues and perform important physiological functions specific to their residing tissues. Examples include microglia in the central nervous system, osteoclasts in the bone, Kupffer cells in the liver, alveolar macrophages in the lung, histiocytes in the spleen and connective tissue, tissue macrophages in the intestine, and Langerhans cells in the skin [8]. In general, resident macrophages maintain tissue homeostasis, while macrophages derived from monocytes primarily assist in host defense and pathological signaling [9].

Macrophages can adjust their phenotype and function in response to changes in their surroundings, which is known as macrophage polarization. This concept has been gaining a better understanding in the field of inflammation research. Depending on the expression of certain surface receptors and the secretion of specific molecules, macrophages can be polarized into two phenotypes, namely classically activated M1-type macrophages (pro-inflammatory) and alternative activated M2-type macrophages (anti-inflammatory) [10]. M1-type macrophages constitute the first line of defense against microorganisms or pathogens. They are mainly found in an inflammatory environment dominated by toll-like receptors (TLR) and interferon (IFN) signaling and are involved in promoting Th1 responses, promoting inflammatory responses in the early stages of inflammation, eliminating intracellularly infected pathogens, causing tissue damage through reactive oxygen species, and adversely affecting tissue regeneration and wound healing [11]. M1-type macrophages are typically induced by the combination of IFN-γ and bacterial lipopolysaccharide (LPS), which leads to the secretion of pro-inflammatory factors, such as tumor necrosis factor (TNF)-α, IL-1β, IL-6, nitric oxide synthase (iNOS), chemokines, and increased expression of certain cell surface markers like CD40, CD80, CD86 and major histocompatibility complex class II receptor (MHC-IIR) [12–14]. Among them, CD80/CD86 are cell surface glycoproteins expressed on various antigen-presenting cells, which induce inflammatory responses by binding to CD28 on naive T cells, enhancing proliferative responses and effector functions of T cells [15]. The CD40 receptor, a member of the TNF receptor superfamily found on different immune cells, stimulates the Th1 response when bound to the specific CD40L ligand expressed on the surface of activated CD4 T cells. This interaction is crucial for initiating and maintaining the inflammatory response. The CD40 receptor, a member of the TNF receptor superfamily found on a variety of immune cells, promotes the Th1 response when bound to the specific ligand CD40L expressed on the surface of activated CD4 T cell [16]. This interaction is crucial for initiating and maintaining the inflammatory response. MHC-IIR is found in macrophages, B cells, and dendritic cells, and its primary function is to present exogenously derived peptide antigens to CD4 T cells, playing an important role in initiating adaptive immune responses [17]. M2-type macrophages, also known as reparative macrophages, are involved in promoting Th2 responses with properties that help inhibit inflammatory responses and promote tissue repair and wound healing [11]. The induction of M2-type macrophages is primarily triggered by IL-4 or IL-13. These macrophages overexpress IL-10, transforming growth factor (TGF)-β, vascular endothelial growth factor, epidermal growth factor, and arginase1 (Arg1), as well as increasing the expression of cell surface markers CD163, CD204, and CD206 [12–14]. CD163, a transmembrane scavenger receptor expressed on the surface of monocytes and macrophages, is involved in the clearance of damaged cells and down-regulation of inflammation by directly stimulating the secretion of anti-inflammatory cytokines and facilitating hemoglobin to macrophages to trigger an anti-inflammatory response [18, 19]. CD204 is another scavenger receptor that participates in various pathophysiological processes such as inflammatory responses, innate immunity, host defense, and cancer in vivo by binding to its ligand [20, 21]. CD206, also known as the mannitol receptor, is a transmembrane protein primarily found in macrophages and dendritic cells that mediates phagocytosis and endocytosis uptake of bacterial, protozoan, fungal, and viral antigens and plays an important role in the regulation of innate immunity, inflammatory responses, and homeostasis in the body [22, 23]. Therefore, the polarization status of macrophages can be distinguished by examining

the secretion profile of macrophages and surface molecular markers (Fig. 1).

Macrophages are capable of adapting to different microenvironments and producing various bioactive substances that can either promote or suppress inflammation. During the acute phase of inflammation, macrophages polarize towards M1-type, inducing inflammatory response and the release of pro-inflammatory mediators that aid in the elimination of pathogens and damaged cells. Conversely, in the late phase of inflammation, macrophages transition to the M2 phenotype, producing anti-inflammatory cytokines that reduce the inflammatory response, facilitate tissue regeneration, and restore homeostasis in the body [24]. The polarization of T cells into Th1 or Th2 subsets is closely linked to the M1 or M2 phenotype of macrophages in humans, respectively, and together they work in coordination to maintain homeostasis. Any imbalance in this coordination can result in pathological inflammatory responses and associated diseases [25]. Consequently, modulating the ratio of M1 to M2 macrophages holds promise as a novel therapeutic approach for inflammatory immune disorders.

Signaling pathways involved in the regulation of inflammatory responses by macrophage polarization

Macrophage polarization is regulated through the activation of several interrelated cellular signaling pathways. The main polarization-related pathways involved in inflammation include janus kinases (JAK)/signal transducer and activator of transcription (STAT) signaling pathway, nuclear factor-κB (NF-κB) signaling pathway, phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway, etc.

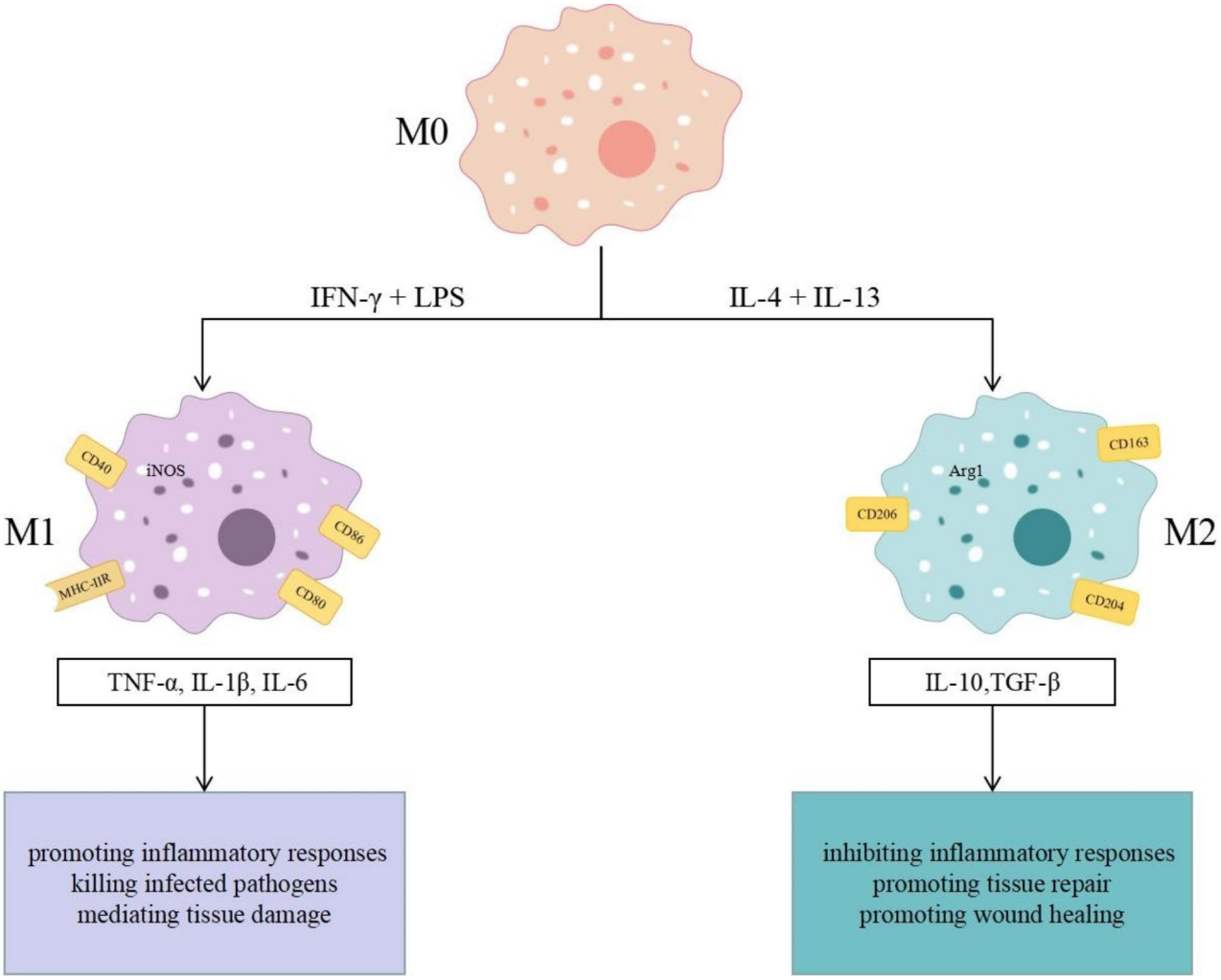

Fig. 1 M1-type and M2-type macrophage polarization. Under the influence of IFN-γ and LPS, M0 macrophages polarize into M1-type, leading to the activation of an inflammatory response, elimination of pathogens, and the initiation of tissue damage through the release of pro-inflammatory molecules like TNF-α, IL-1β, and IL-6. Conversely, when exposed to IL-4 and IL-13, M0 macrophages shift towards M2-type, resulting in the suppression of inflammation, promotion of tissue repair, and facilitation of wound healing through the secretion of anti-inflammatory molecules such as IL-10 and TGF-β

JAK/STAT signaling pathway

The scientific community now widely accepts that the development of many inflammatory immune diseases is connected to the JAK/STAT pathway [26]. JAK/STAT is a major signaling pathway utilized by more than 70 cytokines and is involved in vital biological processes such as cell proliferation, differentiation, apoptosis, and immune regulation [27]. Inflammatory factors are closely linked to the JAK/STAT signaling pathway. The pathway can be activated by inflammatory factors, and in turn, it can affect the expression of these factors. In this pathway, the STAT protein family is an important class of transcription factors, consisting of seven main members [28], among them, the relevant STAT members of macrophage polarization that regulate the inflammatory response include STAT1, STAT3, and STAT6. When IFN-γ and IL-12 bind to their receptors, JAK is activated, leading to the phosphorylation of STAT1. This promotes the polarization of M1-type macrophages and the production of pro-inflammatory factors [29]. 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-type macrophages and the production of anti-inflammatory factors [30, 31]. In summary, M1-type polarization is closely associated with STAT1, whereas M2-type macrophage polarization is influenced by the increased expression of STAT3 and STAT6.

NF-κB signaling pathway

NF-κB acts as a "master switch" for the expression of various pro-inflammatory molecules. When this pathway is dysregulated, it can contribute to the development of a wide range of autoimmune and inflammatory diseases [32]. Studies have shown that TLRs recognize conserved pathogenic microbial products, known as pathogen-associated molecular patterns, which trigger inflammatory immune responses and host defense mechanisms [33]. TLRs on the surface of macrophages bind to lipopolysaccharides (LPS) and activate the classical NF-κB pathway through either the MyD88-dependent pathway or the interferon regulatory factor (IRF) 3 pathway. As a result, NF-κB p65/p50 enters the nucleus and controls the polarization of M1-type macrophages [34]. This process leads to the transcription of pro-inflammatory factors such as IL-1β, IL-6, and TNF-α, thereby amplifying inflammatory signals [35]. In addition, there is a close relationship between NF-κB and JAK/STAT pathway, with STAT1 shown to activate the transcriptional activity of NF-κB [36] and mutual crosstalk between STAT3 and NF-κB regulating M1/M2 homeostasis [37–39].

PI3K/Akt signaling pathway

The PI3K/Akt signaling pathway is a crucial pathway that controls inflammatory reactions, regulates macrophage polarization, and is crucial for the inflammatory immune response [40]. In macrophages, stimuli such as growth factors and cytokines can be signaled through this pathway [41, 42]. The inhibition of M1-type macrophage polarization and the promotion of M2-type macrophage polarization were observed to occur upon activation of this signaling pathway [43]. This effect was supported by the finding that this signaling pathway negatively regulated TLR and NF-κB signaling and positively regulated STAT3 signaling in macrophages [44, 45]. However, in accordance with various Akt isoforms, the PI3K/Akt signaling pathway differentially promotes macrophage polarization. The three components of Akt, Akt1, Akt2, and Akt3, are 80% homologous and each performs a different regulatory task [46]. Akt1 deletion promotes macrophage polarization toward M1-type and increases the expression of pro-inflammatory factors iNOS, TNF-α, and IL-6, while Akt2 deletion promotes macrophage polarization toward M2-type and enhances the expression of anti-inflammatory factor IL-10; Akt3 deletion reduces M2-type macrophage infiltration and hinders skin wound healing [47, 48].

In summary, the JAK/STAT1, NF-κB, and PI3K/Akt2 signaling pathways promote macrophage M1 polarization, increase the production of pro-inflammatory factors IL-1β, IL-6, TNF-α and iNOS, etc., and initiate or exacerbate the inflammatory response; while the JAK/STAT3 or JAK/STAT6 and PI3K/Akt1 or PI3K/Akt3 signaling pathways promote macrophage M2 polarization, increase the production of anti-inflammatory factors such as IL-10 and TGF-β, and suppress the inflammatory response. In turn, these three types of signaling pathways interfere with one another and jointly determine the direction of macrophage polarization (Fig. 2).

Macrophage polarization regulates inflammatory immune skin diseases

Although inflammation plays a vital role in the body's defense against external invaders or the control of the immune system's response, it can also have a harmful effect on the body by impairing normal tissue function and even resulting in organ failure. This results in the emergence of numerous autoimmune and chronic inflammatory diseases. A group of systemic or organ-specific chronic inflammatory skin diseases known as "inflammatory immune skin diseases", whose pathogenesis is not fully understood, are caused by abnormal inflammatory responses and immune dysregulation [49]. Macrophages are key cells that coordinate chronic inflammation, and macrophage polarization takes place during the onset, development, progression, and

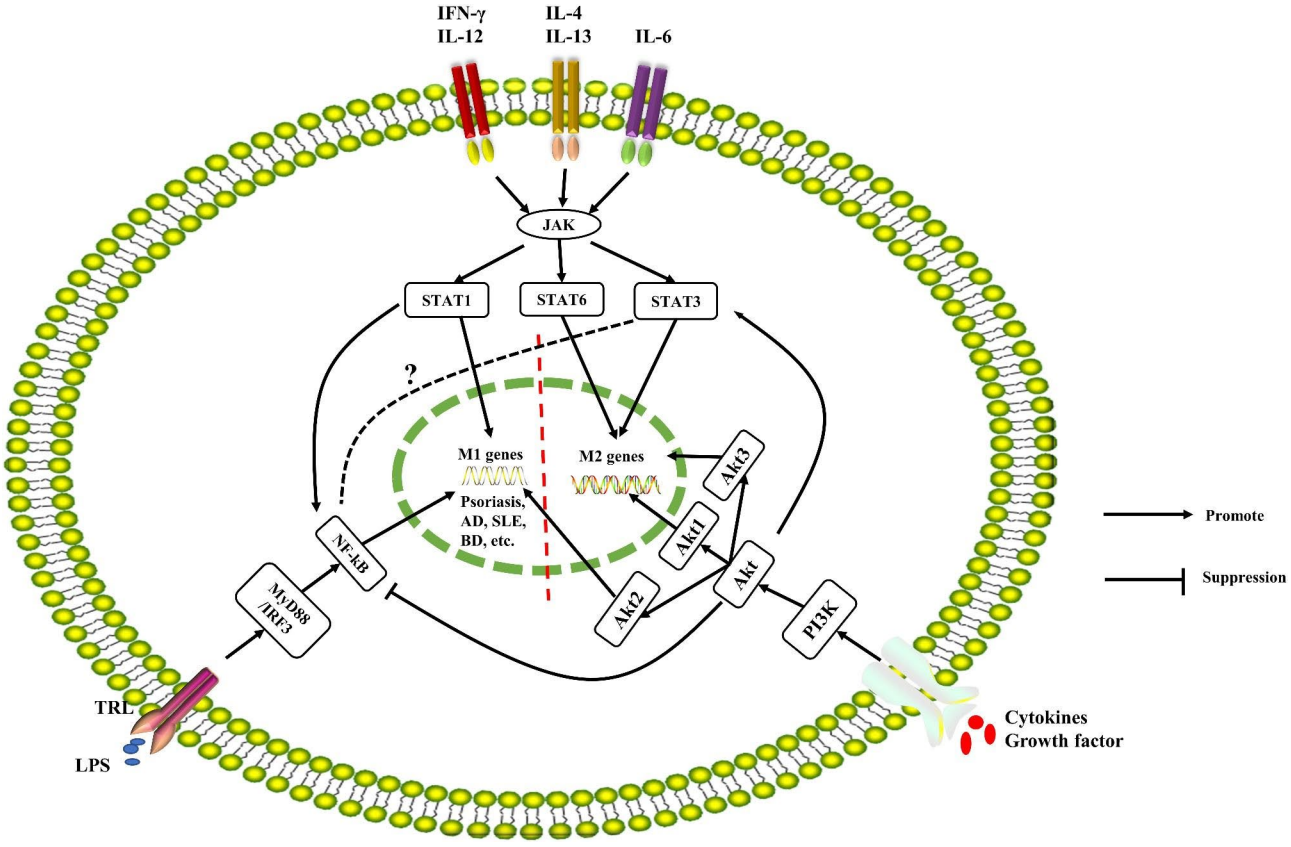

Fig. 2 Inflammation-related signaling pathways associated with macrophage polarization. The JAK/STAT1, NF-κB, and PI3K/Akt2 signaling pathways play a role in promoting M1 polarization of macrophages. On the other hand, the JAK/STAT3 or JAK/STAT6 and PI3K/Akt1 or PI3K/Akt3 signaling pathways are involved in promoting M2 polarization of macrophages. These signaling pathways can interact with each other, leading to a combined effect in determining the direction of macrophage polarization

remission of inflammatory diseases [50]. According to the studies listed below, macrophage polarization can regulate inflammatory immune skin diseases.

Psoriasis

With a global prevalence of about 2%, psoriasis is a chronic, relapsing immune inflammatory skin disease also known as the "cancer that never dies" [51]. Important cytokines like IL-17, IL-22, IL-23, and TNF-α are involved in the pathogenesis of psoriasis, as well as other crucial transduction pathways like the NF-κB and STAT signaling pathways. These pro-inflammatory factors are major drivers of psoriasis pathogenesis through signaling pathways [52, 53]. Kaempferia parviflora is a folk medicine widely used in Southeast Asia for its anti-inflammatory and anti-allergic effects [54]. Inhibiting the LPS-induced NF-κB pathway allows Kaempferia to prevent keratinocytes and macrophages from producing the pro-inflammatory factors TNF-α, IL-1, IL-6, IL-17, IL-22, and IL-23, indicating that this plant may be a promising candidate for the creation of anti-psoriasis medications [55]. This mechanism of reducing inflammation is closely connected to the polarization of macrophages. It is widely accepted that M1-type macrophages produce cytokines that promote inflammation, while M2-type macrophages produce cytokines that have anti-inflammatory properties. The balance between these two types of macrophages plays a crucial role in determining the progression of various inflammatory diseases, including psoriasis [56]. In one study, a circular RNA called hsa_circ_0004287 was found to inhibit the polarization of M1-type macrophages in vitro. Additionally, when a plasmid containing hsa_circ_0004287 was topically applied to mice with psoriasis-like symptoms, it resulted in a reduction of skin inflammation [57]. Traditional Chinese medicine has shown remarkable success in treating psoriasis in recent years, and figuring out how it works is a hot area of research right now. The herbal PSORI-CM02 formulation, which contains Rhizoma Curcumae, Radix Paeoniae rubra, Sarcandra glabra, Rhizoma Smilacis glabrae, and Fructus mume [58] has been shown to significantly improve imiquimod-induced skin lesions in psoriasis-like mice, and this process was accomplished by controlling STAT1 and STAT6 expression to lessen M1-type macrophage infiltration [59]. By preventing M1-type macrophage polarization in psoriasis and

lowering the production of psoriasis-related cytokines, purpurin plus methotrexate has also been shown to protect against psoriasis [60]. In addition to typical M1- and M2-type macrophages, Hou et al [61] identified a unique pathogenic macrophage subpopulation driven by IL-23, referred to as M(IL-23)-type macrophages, which highly expressed IL-17 A, IL-22 and IFN-γ. With the help of the STAT3 and retinoid-related orphan receptor-γT pathway, IL-23 induced the expression of IL-17 in macrophages, and the Th1-related key transcription factor T-bet mediated the production of IFN-γ, both of which significantly worsened skin lesions in mice with psoriasis-like symptoms. Based on these studies, it is suggested that treating psoriasis can be accomplished by decreasing the production of inflammatory factors and adjusting NF-κB and STAT signaling pathways to prevent the polarization of M1-type macrophages or infiltration of M(IL-23) cells.

Atopic dermatitis (AD)

Up to 20% of children and 5% of adults can develop AD, an immune-driven chronic pruritic inflammatory skin disease that is frequently accompanied by a personal or family history of food allergy, allergic rhinitis/conjunctivitis, or allergic asthma [62]. By controlling the immune response in the skin, macrophages play a direct role in the pathogenesis of AD, and atopic mice observed upregulation of M1-type macrophage markers and downregulation of M2-type markers [63]. Hsa_circ_0004287, which is overexpressed specifically in macrophages, suppressed M1-type macrophage polarization, which reduced skin inflammation in AD mice in addition to having an impact on psoriasis pathogenesis [57]. By activating the JAK2/STAT3 signaling pathway and encouraging M2-type macrophage polarization, Viola yedoensis Makin, a traditional Chinese medicine with anti-inflammatory properties [64], can significantly improve skin lesions and decrease levels of inflammatory factors IL-1β, TNF-α, and IL-18 while increasing levels of anti-inflammatory factor IL-10 in AD mice [65]. However, an intriguing study discovered that inhibiting both M1- and M2-type macrophages also alleviated AD symptoms [66]. It is still unclear how the inflammatory immune response in AD works because it is extremely complicated. To lay a more solid foundation for macrophage polarization in clinical translation, more in-depth investigation is required to clarify the mechanisms of the function of various macrophage subtypes in AD.

Systemic lupus erythematosus (SLE)

SLE is a chronic autoimmune inflammatory disease characterized by the presence of autoantibodies against nuclear antigens, immune complex deposits, and tissue damage in the skin, kidneys, heart, and lungs, and its pathogenesis has been shown to be associated with M1-type macrophage polarization [67]. Despite the fact that SLE has been the subject of extensive research, its pathogenesis is still unknown, and no effective medications have yet to be discovered [68]. According to Labonte et al.'s research [69], SLE patients' bone marrow contained more M1-type macrophages that expressed STAT1, SOCS3, and fewer M2-type macrophages that expressed STAT3, STAT6, and CD163. Exosomes derived from human umbilical cord mesenchymal stem cells decreased TNF-α and IL-1β levels, promoted M2-type macrophage polarization, and increased Treg cell production in the spleen in both in vitro and in vivo experiments, thereby improving nephritis and other serious organ damage and achieving the goal of treating SLE [70, 71]. Therefore, the immune inflammatory response to SLE can be improved by inhibiting M1-type macrophages and activating M2-type macrophages. According to one study, successive transplanting of M2-type macrophages into mice significantly lessened the severity of SLE [72]. Azithromycin has also been shown to inhibit the secretion of pro-inflammatory factors IL-1β, IL-6, and TNF-α, promote the production of anti-inflammatory factor IL-10, and stimulate macrophage M2 polarization through the PI3K/Akt signaling pathway, as well as suppress the immune inflammatory response in SLE [73]. Azithromycin has a good safety profile and is frequently used in clinical practice. A fresh approach to treating SLE patients may emerge from further investigation of its pharmacological effects and assessment of its therapeutic efficacy. These studies demonstrated that M1-type macrophages contribute to tissue injury while M2-type macrophages are involved in tissue healing in SLE, suggesting that restoring the balance between M1/M2 macrophages may be a novel therapeutic target for the disease.

Behcet's disease (BD)

Recurrent oral/genital ulcers, skin lesions, ocular damage, and other systemic manifestations are key features of BD, which is a chronic, multisystemic, inflammatory immune vasculitis [74]. BD patients have an overactive immune system and multisystem inflammatory damage, which is primarily shown by an increased inflammatory response and overexpression of pro-inflammatory cytokines like TNF-α, IL-1β, IL-6, IL-12, and IL-18 [75]. In addition, impaired secretion of the anti-inflammatory factor IL-10 is also associated with BD pathogenesis [76]. The ability of macrophages to polarize into different phenotypes, which is a result of their plasticity, allows them to play a significant role in both promoting and suppressing inflammatory processes. The M1/M2 macrophage ratio and the M1-type macrophage phenotype were found to be upregulated in BD mice when compared to normal mice in a study of herpes simplex virus-induced BD mice [77]. The inflammatory alterations in BD may

be brought on by BD serum factors [78]. A recent study showed that BD serum polarized macrophages toward M1-type by activating the NF-κB signaling pathway, driving Th1 differentiation, and promoting overexpression of IL-12 and TNF-α [79]. This dysregulation of M1/M2 macrophage homeostasis is associated with abnormal expression of the aryl hydrocarbon receptor (AHR) [80], the latter is a ligand-activated transcription factor. According to Palizgir et al.'s research, patients with BD had lower levels of monocyte-derived macrophages and in vitro-induced M1-type macrophage AHR mRNA expression than individuals without the condition [81]. There is an urgent need to comprehend the pathogenesis of BD and develop new therapeutic targets because the therapeutic effect of BD is still not satisfactory. As a new therapeutic target for BD, macrophage polarization may make significant strides in terms of BD prognosis improvement and disease burden reduction.

Others

Acne is a globally common chronic inflammatory immune skin disease that can occur at any age [82]. 5-Aminoketovaleric acid photodynamic therapy is clinically effective and safe in the treatment of patients with severe acne, but its exact mechanism is unknown. A very interesting study revealed that this therapy significantly upregulated the expression of various inflammation-related genes, triggered the polarization of macrophages to M1-type both in vitro and in vivo, and exerted its therapeutic effect by enhancing the intense inflammatory response and breaking chromaffin cells [83], providing new insights into the study of inflammatory-immune skin diseases.

Rosacea is another immune-mediated, chronic inflammatory skin disease that primarily affects the center of the face [84]. Although the exact cause of this condition is unknown, M1-type macrophages and their pro-inflammatory effects may play a role [85]. Zhou et al [86] found increased local infiltration of macrophages in rosacea mice and demonstrated that guanylate-binding protein 5 (GBP5) is an important gene controlling macrophage infiltration. They also proved that silencing GBP5 can achieve therapeutic effects by inhibiting M1-type macrophage polarization and the expression of pro-inflammatory factors IL-1, iNOS, and TNF-α through the NF-κB signaling pathway.

Overall, increased M1-type macrophages or increased M1/M2 macrophage ratio can contribute to or exacerbate inflammatory immune skin diseases like psoriasis, AD, SLE, and BD. Thus, it is anticipated that suppressing M1-type macrophages and achieving a balance in the M1/M2 macrophage ratio will prevent or treat these related diseases.

Summary and Outlook

In skin tissue, macrophages are key players in tissue homeostasis and immune surveillance, mobilizing immune activation in reaction to microbial invasion and supporting wound healing to restore damaged tissue. In terms of pathogenesis, macrophages, as essential mediators and coordinators of chronic inflammation, are crucial mediators in various diseases. The critical mechanism by which they exert these pathophysiological effects is macrophage polarization. Large amounts of pro- or anti-inflammatory cytokines and chemokines are produced by M1- and M2-type macrophages in response to their respective activators, activating numerous related signaling pathways and carrying out their regulatory functions. Existing research has demonstrated that macrophage polarization can contribute to the onset and development of several inflammatory immune skin diseases, such as psoriasis, AD, SLE, BD, etc. The proportion of M1/M2 type macrophages is elevated in these diseases, and M1-type macrophages dominate in the ongoing development and destructive cycle of the inflammatory response. By targeting molecules in signaling pathways like JAK/STAT, NF-κB, PI3K/Akt, and the local microenvironment, macrophages can be converted to the appropriate phenotype to regulate the onset, progression, and outcome of inflammatory diseases. The mechanisms underlying macrophage polarization in these inflammatory skin diseases, however, are still not yet fully elucidated, and therapies that target macrophage polarization are still in their infancy. Therefore, an in-depth study of macrophage polarization and its function in inflammatory immune dermatoses can provide us with a more thorough comprehension of the pathogenesis of associated dermatoses, which can then provide valuable references for the prevention and treatment of such diseases.

Abbreviations

AD	atopic dermatitis
Akt	protein kinase B
Arg1	arginase1
BD	Behcet's disease
IFN	interferon
IL	interleukin
iNOS	nitric oxide synthase
JAK	janus kinases
LPS	lipopolysaccharide
NF-κB	nuclear factor kappaB
PI3K	phosphoinositide 3-kinase
SLE	systemic lupus erythematosus
STAT	signal transducer and activator of transcription
TGF	transforming growth factor
TLR	toll-like receptor
TNF	tumor necrosis factor

Authors' contributions

TX wrote the original review and SP, KY and TZ reviewed edited and assisted with figures. All authors have read and agreed to the published version of the manuscript.

Funding
This work was supported by grants from the National Natural Science Foundation of China (No.82160599).

Data availability
Not applicable.

Declarations

Conflict of interest
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical approval
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 21 July 2023 / Accepted: 2 October 2023
Published online: 12 October 2023

References

1. Fioranelli M, Roccia MG, Flavin D, Cota L. Regulation of inflammatory reaction in health and disease. Int J Mol Sci. 2021;22(10)5277.
2. McComb S, Thiriot A, Akache B, Krishnan L, Stark F. Introduction to the immune system. Methods Mol Biol. 2019;2024:1–24.
3. Sheu KM, Hoffmann A. Functional hallmarks of healthy macrophage responses: their Regulatory basis and Disease Relevance. Annu Rev Immunol. 2022;40:295–321.
4. Arango Duque G, Descoteaux A. Macrophage cytokines: involvement in immunity and infectious diseases. Front Immunol. 2014;5:491.
5. Coillard A, Segura E. Vivo differentiation of human monocytes. Front Immunol. 2019;10:1907.
6. Yang J, Zhang L, Yu C, Yang XF, Wang H. Monocyte and macrophage differentiation: circulation inflammatory monocyte as biomarker for inflammatory diseases. Biomark Res. 2014;2(1):1.
7. Kurotaki D, Sasaki H, Tamura T. Transcriptional control of monocyte and macrophage development. Int Immunol. 2017;29(3):97–107.
8. Lee CZW, Ginhoux F. Biology of resident tissue macrophages. Development. 2022;149(8):dev200270.
9. Ruytinx P, Proost P, Van Damme J, Struyf S. Chemokine-Induced Macrophage polarization in inflammatory conditions. Front Immunol. 2018;9:1930.
10. Chen X, Liu Y, Gao Y, Shou S, Chai Y. The roles of macrophage polarization in the host immune response to sepsis. Int Immunopharmacol. 2021;96:107791.
11. Yadav S, Dwivedi A, Tripathi A. Biology of macrophage fate decision: implication in inflammatory disorders. Cell Biol Int. 2022;46(10):1539–56.
12. Viola A, Munari F, Sánchez-Rodríguez R, Scolaro T, Castegna A. The metabolic signature of macrophage responses. Front Immunol. 2019;10:1462.
13. Boutilier AJ, Elsawa SF. Macrophage polarization states in the tumor microenvironment. Int J Mol Sci. 2021;22(13):6995.
14. Cutolo M, Campitiello R, Gotelli E, Soldano S. The role of M1/M2 macrophage polarization in Rheumatoid Arthritis Synovitis. Front Immunol. 2022;13:867260.
15. Parker D. CD80/CD86 signaling contributes to the proinflammatory response of Staphylococcus aureus in the airway. Cytokine. 2018;107:130–6.
16. Tang T, Cheng X, Truong B, Sun L, Yang X, Wang H. Molecular basis and therapeutic implications of CD40/CD40L immune checkpoint. Pharmacol Ther. 2021;219:107709.
17. Drozina G, Kohoutek J, Jabrane-Ferrat N, Peterlin BM. Expression of MHC II genes. Curr Top Microbiol Immunol. 2005;290:147–70.
18. Etzerodt A, Moestrup SK. CD163 and inflammation: biological, diagnostic, and therapeutic aspects. Antioxid Redox Signal. 2013;18(17):2352–63.
19. Moestrup SK, Møller HJ. CD163: a regulated hemoglobin scavenger receptor with a role in the anti-inflammatory response. Ann Med. 2004;36(5):347–54.
20. Kelley JL, Ozment TR, Li C, Schweitzer JB, Williams DL. Scavenger receptor-A (CD204): a two-edged sword in health and disease. Crit Rev Immunol. 2014;34(3):241–61.
21. Gudgeon J, Marín-Rubio JL, Trost M. The role of macrophage scavenger receptor 1 (MSR1) in inflammatory disorders and cancer. Front Immunol. 2022;13:1012002.
22. van der Zande HJP, Nitsche D, Schlautmann L, Guigas B, Burgdorf S. The mannose receptor: from endocytic receptor and biomarker to Regulator of (Meta) inflammation. Front Immunol. 2021;12:765034.
23. Cummings RD. The mannose receptor ligands and the macrophage glycome. Curr Opin Struct Biol. 2022;75:102394.
24. Parisi L, Gini E, Baci D, Tremolati M, Fanuli M, Bassani B, et al. Macrophage polarization in Chronic Inflammatory Diseases: Killers or Builders? J Immunol Res. 2018;2018:8917804.
25. Murailles E, Leo O, Moser M. TH1/TH2 paradigm extended: macrophage polarization as an unappreciated pathogen-driven escape mechanism? Front Immunol. 2014;5:603.
26. Banerjee S, Biehl A, Gadina M, Hasni S, Schwartz DM. JAK-STAT signaling as a target for inflammatory and autoimmune Diseases: current and future prospects. Drugs. 2017;77(5):521–46.
27. O'Shea JJ, Schwartz DM, Villarino AV, Gadina M, McInnes IB, Laurence A. The JAK-STAT pathway: impact on human disease and therapeutic intervention. Annu Rev Med. 2015;66:311–28.
28. Hu X, Li J, Fu M, Zhao X, Wang W. The JAK/STAT signaling pathway: from bench to clinic. Signal Transduct Target Ther. 2021;6(1):402.
29. Liu Y, Liu Z, Tang H, Shen Y, Gong Z, Xie N, et al. The N(6)-methyladenosine (m(6)A)-forming enzyme METTL3 facilitates M1 macrophage polarization through the methylation of STAT1 mRNA. Am J Physiol Cell Physiol. 2019;317(4):C762–c75.
30. He Y, Gao Y, Zhang Q, Zhou G, Cao F, Yao S. IL-4 switches Microglia/macrophage M1/M2 polarization and alleviates neurological damage by modulating the JAK1/STAT6 pathway following ICH. Neuroscience. 2020;437:161–71.
31. Ren J, Han X, Lohner H, Liang R, Liang S, Wang H. Serum- and glucocorticoid-inducible kinase 1 promotes alternative macrophage polarization and restrains inflammation through FoxO1 and STAT3 signaling. J Immunol. 2021;207(1):268–80.
32. Sun SC. The non-canonical NF-κB pathway in immunity and inflammation. Nat Rev Immunol. 2017;17(9):545–58.
33. Fitzgerald KA, Kagan JC. Toll-like receptors and the control of immunity. Cell. 2020;180(6):1044–66.
34. Gao S, Mao F, Zhang B, Zhang L, Zhang X, Wang M, et al. Mouse bone marrow-derived mesenchymal stem cells induce macrophage M2 polarization through the nuclear factor-κB and signal transducer and activator of transcription 3 pathways. Exp Biol and Med (Maywood). 2014;239(3):366–75.
35. Chen XX, Tang L, Fu YM, Wang Y, Han ZH, Meng JG. Paralemmin-3 contributes to lipopolysaccharide-induced inflammatory response and is involved in lipopolysaccharide-toll-like receptor-4 signaling in alveolar macrophages. Int J Mol Med. 2017;40(6):1921–31.
36. Chen S, Ye J, Chen X, Shi J, Wu W, Lin W, et al. Valproic acid attenuates traumatic spinal cord injury-induced inflammation via STAT1 and NF-κB pathway dependent of HDAC3. J Neuroinflamm. 2018;15(1):150.
37. Ti D, Hao H, Tong C, Liu J, Dong L, Zheng J, et al. LPS-preconditioned mesenchymal stromal cells modify macrophage polarization for resolution of chronic inflammation via exosome-shuttled let-7b. J Translational Med. 2015;13:308.
38. Fan CS, Chen CC, Chen LL, Chua KV, Hung HC, Hsu JT et al. Extracellular HSP90α induces MyD88-IRAK complex-associated IKKα/β-NF-κB/IRF3 and JAK2/TYK2-STAT-3 signaling in macrophages for tumor-promoting M2-polarization. Cells. 2022;11(2):229.
39. Kanemaru H, Yamane F, Tanaka H, Maeda K, Satoh T, Akira S. BATF2 activates DUSP2 gene expression and up-regulates NF-κB activity via phospho-STAT3 dephosphorylation. Int Immunol. 2018;30(6):255–65.
40. Linton MF, Moslehi JJ, Babaev VR. Akt signaling in macrophage polarization, survival, and atherosclerosis. Int J Mol Sci. 2019;20(11):2703.
41. Acosta-Martinez M, Cabail MZ. The PI3K/Akt pathway in meta-inflammation. Int J Mol Sci. 2022;23(23):15330.
42. Long HZ, Cheng Y, Zhou ZW, Luo HY, Wen DD, Gao LC. PI3K/AKT Signal Pathway: a target of Natural Products in the Prevention and Treatment of Alzheimer's Disease and Parkinson's Disease. Front Pharmacol. 2021;12:648636.
43. Shen M, Yu H, Jin Y, Mo J, Sui J, Qian X, et al. Metformin facilitates osteoblastic differentiation and M2 macrophage polarization by PI3K/AKT/mTOR

pathway in human umbilical cord mesenchymal stem cells. Stem Cells Int. 2022;2022:9498876.
44. Jiang Z, Zhang Y, Zhang Y, Jia Z, Zhang Z, Yang J. Cancer derived exosomes induce macrophages immunosuppressive polarization to promote bladder cancer progression. Cell Commun Signal. 2021;19(1):93.
45. Jeon H, Oh S, Kum E, Seo S, Park Y, Kim G. Immunomodulatory effects of an aqueous extract of black radish on mouse macrophages via the TLR2/4-mediated signaling pathway. Pharmaceuticals (Basel). 2022;15(11):1376.
46. Lapi I, Daskalaki MG, Axarlis K, Paflioti E, Tsichlis PN, Vergadi E, et al. AKT Isoforms in Macrophage activation, polarization, and Survival. Curr Top Microbiol Immunol. 2022;436:165–96.
47. Arranz A, Doxaki C, Vergadi E, Martinez de la Torre Y, Vaporidi K, Lagoudaki ED, et al. Akt1 and Akt2 protein kinases differentially contribute to macrophage polarization. Proc Natl Acad Sci USA. 2012;109(24):9517–22.
48. Gu S, Dai H, Zhao X, Gui C, Gui J. AKT3 deficiency in M2 macrophages impairs cutaneous wound healing by disrupting tissue remodeling. Aging. 2020;12(8):6928–46.
49. Pezzolo E, Naldi L. Epidemiology of major chronic inflammatory immune-related skin diseases in 2019. Expert Rev Clin Immunol. 2020;16(2):155–66.
50. Liu YC, Zou XB, Chai YF, Yao YM. Macrophage polarization in inflammatory diseases. Int J Biol Sci. 2014;10(5):520–9.
51. Roszkiewicz M, Dopytalska K, Szymańska E, Jakimiuk A, Walecka I. Environmental risk factors and epigenetic alternations in psoriasis. Ann Agric Environ Med. 2020;27(3):335–42.
52. Griffiths CEM, Armstrong AW, Gudjonsson JE, Barker J, Psoriasis. Lancet. 2021;397(10281):1301–15.
53. Sun W, Gao Y, Yu X, Yuan Y, Yi J, Zhang Z, et al. Psoriasis 1′reduces psoriasis–like skin inflammation by inhibiting the VDR–mediated nuclear NF–κB and STAT signaling pathways. Mol Med Rep. 2018;18(3):2733–43.
54. Chen D, Li H, Li W, Feng S, Deng D. Kaempferia parviflora and its methoxyflavones: chemistry and biological activities. Evid Based Complementary Alternat Med. 2018;2018:4057456.
55. Takuathung MN, Potikanond S, Sookkhee S, Mungkornasawakul P, Jearanaikulvanich T, Chinda K, et al. Anti-psoriatic and anti-inflammatory effects of Kaempferia parviflora in keratinocytes and macrophage cells. Biomed pharmacotherapy; 2021;143:112229.
56. Lu CH, Lai CY, Yeh DW, Liu YL, Su YW, Hsu LC, et al. Involvement of M1 macrophage polarization in Endosomal Toll-Like receptors activated psoriatic inflammation. Mediat Inflamm. 2018;2018:3523642.
57. Yang L, Fu J, Han X, Zhang C, Xia L, Zhu R, et al. Hsa_circ_0004287 inhibits macrophage-mediated inflammation in an N(6)-methyladenosine-dependent manner in atopic dermatitis and psoriasis. J Allergy Clin Immunol. 2022;149(6):2021–33.
58. Lu Y, Yang Y, Zhang J, Zhang H, Ma C, Tang X, et al. Anti-angiogenic efficacy of PSORI-CM02 and the Associated mechanism in Psoriasis in Vitro and in vivo. Front Immunol. 2021;12:649591.
59. Li L, Zhang HY, Zhong XQ, Lu Y, Wei J, Li L, et al. PSORI-CM02 formula alleviates imiquimod-induced psoriasis via affecting macrophage infiltration and polarization. Life Sci. 2020;243:117231.
60. Tao T, Chen Y, Lai B, Wang J, Wang W, Xiao W, et al. Shikonin combined with methotrexate regulate macrophage polarization to treat psoriasis. Bioengineered. 2022;13(4):11146–55.
61. Hou Y, Zhu L, Tian H, Sun HX, Wang R, Zhang L, et al. IL-23-induced macrophage polarization and its pathological roles in mice with imiquimod-induced psoriasis. Protein Cell. 2018;9(12):1027–38.
62. Bieber T. Atopic dermatitis: an expanding therapeutic pipeline for a complex disease. Nat Rev Drug Discovery. 2022;21(1):21–40.
63. Yamasaki R, Fujii T, Wang B, Masaki K, Kido MA, Yoshida M, et al. Allergic inflammation leads to Neuropathic Pain via Glial Cell activation. J Neuroscience: Official J Soc Neurosci. 2016;36(47):11929–45.
64. Zeng HR, Wang B, Zhao Z, Zhang Q, Liang MY, Yao YQ, et al. Effects of Viola yedoensis Makino anti-itching compound on degranulation and cytokine generation in RBL-2H3 mast cells. J Ethnopharmacol. 2016;189:132–8.
65. Zeng H, Zhao B, Zhang D, Rui X, Hou X, Chen X, et al. Viola yedoensis Makino formula alleviates DNCB-induced atopic dermatitis by activating JAK2/STAT3 signaling pathway and promoting M2 macrophages polarization. Phytomedicine. 2022;103:154228.
66. Zeng L, Liu Y, Xing C, Huang Y, Sun X, Sun G. Saponin from Periploca forrestii Schltr mitigates Oxazolone-Induced atopic dermatitis via modulating macrophage activation. Mediat Inflamm. 2020;2020:4346367.
67. Ma C, Xia Y, Yang Q, Zhao Y. The contribution of macrophages to systemic lupus erythematosus. Clin Immunol (Orlando Fla). 2019;207:1–9.
68. Parra Sánchez AR, Voskuyl AE, van Vollenhoven RF. Treat-to-target in systemic lupus erythematosus: advancing towards its implementation. Nat Rev Rheumatol. 2022;18(3):146–57.
69. Labonte AC, Kegerreis B, Geraci NS, Bachali P, Madamanchi S, Robl R, et al. Identification of alterations in macrophage activation associated with disease activity in systemic lupus erythematosus. PLoS ONE. 2018;13(12):e0208132.
70. Sun W, Yan S, Yang C, Yang J, Wang H, Li C, et al. Mesenchymal stem cells-derived Exosomes Ameliorate Lupus by inducing M2 macrophage polarization and Regulatory T cell expansion in MRL/lpr mice. Immunol Investig. 2022;51(6):1785–803.
71. Dou R, Zhang X, Xu X, Wang P, Yan B. Mesenchymal stem cell exosomal tsRNA-21109 alleviate systemic lupus erythematosus by inhibiting macrophage M1 polarization. Mol Immunol. 2021;139:106–14.
72. Li F, Yang Y, Zhu X, Huang L, Xu J. Macrophage polarization modulates development of systemic lupus erythematosus. Cell Physiol Biochem. 2015;37(4):1279–88.
73. Wang J, Xie L, Wang S, Lin J, Liang J, Xu J. Azithromycin promotes alternatively activated macrophage phenotype in systematic lupus erythematosus via PI3K/Akt signaling pathway. Cell Death Dis. 2018;9(11):1080.
74. Alibaz-Oner F, Direskeneli H. Advances in the treatment of Behcet's Disease. Curr Rheumatol Rep. 2021;23(6):47.
75. Tong B, Liu X, Xiao J, Su G. Immunopathogenesis of Behcet's Disease. Front Immunol. 2019;10:665.
76. Hirahara L, Takase-Minegishi K, Kirino Y, Iizuka-Iribe Y, Soejima Y, Yoshimi R, et al. The roles of Monocytes and Macrophages in Behçet's Disease with Focus on M1 and M2 polarization. Front Immunol. 2022;13:852297.
77. Anower AK, Shim JA, Choi B, Kwon HJ, Sohn S. The role of classical and alternative macrophages in the immunopathogenesis of herpes simplex virus-induced inflammation in a mouse model. J Dermatol Sci. 2014;73(3):198–208.
78. Gholijani N, Ataollahi MR, Samiei A, Aflaki E, Shenavandeh S, Kamali-Sarvestani E. An elevated pro-inflammatory cytokines profile in Behcet's disease: a multiplex analysis. Immunol Lett. 2017;186:46–51.
79. Wu X, Wang Z, Shi J, Yu X, Li C, Liu J, et al. Macrophage polarization toward M1 phenotype through NF-κB signaling in patients with Behçet's disease. Arthritis Res Therapy. 2022;24(1):249.
80. Climaco-Arvizu S, Domínguez-Acosta O, Cabañas-Cortés MA, Rodríguez-Sosa M, Gonzalez FJ, Vega L, et al. Aryl hydrocarbon receptor influences nitric oxide and arginine production and alters M1/M2 macrophage polarization. Life Sci. 2016;155:76–84.
81. Palizgir MT, Akhtari M, Mahmoudi M, Mostafaei S, Rezaeimanesh A, Akhlaghi M, et al. Macrophages from Behcet's Disease Patients Express decreased level of Aryl Hydrocarbon receptor (AHR) mRNA. Iran J Allergy Asthma Immunol. 2017;16(5):418–24.
82. Kutlu Ö, Karadağ AS, Wollina U. Adult acne versus adolescent acne: a narrative review with a focus on epidemiology to treatment. An Bras Dermatol. 2023;98(1):75–83.
83. Liu P, Liu X, Zhang L, Yan G, Zhang H, Xu D, et al. ALA-PDT augments intense inflammation in the treatment of acne vulgaris by COX2/TREM1 mediated M1 macrophage polarization. Biochem Pharmacol. 2023;208:115403.
84. van Zuuren EJ, Arents BWM, van der Linden MMD, Vermeulen S, Fedorowicz Z, Tan J. Rosacea: New Concepts in classification and treatment. Am J Clin Dermatol. 2021;22(4):457–65.
85. Liu T, Deng Z, Xie H, Chen M, Xu S, Peng Q, et al. ADAMDEC1 promotes skin inflammation in rosacea via modulating the polarization of M1 macrophages. Biochem Biophys Res Commun. 2020;521(1):64–71.
86. Zhou L, Zhao H, Zhao H, Meng X, Zhao Z, Xie H et al. GBP5 exacerbates rosacea-like skin inflammation by skewing macrophage polarization towards M1 phenotype through the NF-KB signalling pathway. J Eur Acad Dermatol Venereol. 2023;37(4):796–809.

Publisher's Note