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

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Abstract

In response 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. This characteristic determines that macrophages carry out various tasks during various stages of immunity and inflammation. An imbalance in the M1/M2 macrophage ratio is often observed in inflammatory immune skin diseases, and modulation of the macrophage polarization phenotype exacerbates or alleviates the associated symptoms. Therefore, this review presents the mechanisms of macrophage polarization, inflammation-related signaling pathways (JAK/STAT, NF-ϰB, PI3K/Akt) and the role of both in inflammatory immune skin diseases (psoriasis, AD, SLE, BD, etc.) with the aim of providing new directions for basic and clinical research of related diseases.

Introduction

As the body's outermost organ, the skin must respond appropriately to external environmental stimuli via numerous mechanisms in order to provide a mechanical and immunological barrier to the environment. Skin inflammation is the body's response to a variety of injuries, including infections. It is typically accompanied by a complex immune response, which includes events like immune cell recruitment, vascular response, and the release of inflammatory factors that help the body fight pathogens, repair damaged tissues, and maintain homeostasis(1). Chronic inflammation and autoimmune skin diseases, however, may develop if the immune response is overly intense. Macrophages are involved in the inflammatory immune response of the skin and play a crucial role in the homeostasis of the body, as well as being the primary defense force against foreign microorganisms and pathogens. Macrophages regulate skin homeostasis in response to stimulation by creating polarization via various signaling pathways that support both pro- and anti-inflammatory responses. In recent years, many studies have found an important link between macrophage polarization and the development and progression of various different inflammatory immune diseases. Therefore, this paper will summarize the macrophage polarization, related signaling pathways and their effects on inflammatory immune skin diseases, hoping to provide some useful references for basic research and clinical treatment of macrophage polarization-related skin diseases.

1 Origin, polarization types and functions of macrophages

In response to danger signals, the immune system initiates a protective inflammatory immune response that includes a variety of processes ranging from pathogen destruction and cellular debris removal to tissue repair and body homeostasis maintenance(2). As the body's first line of defense against disease, macrophages are crucial because they phagocytose foreign microorganisms and control the immune system's reaction to different pathogens by processing and presenting antigens(3). Macrophages are derived from circulating

monocytes, which are derived from hematopoietic stem cells in bone marrow(4, 5). It has long been accepted that tissue-resident macrophages in both healthy and diseased sites originate from circulating monocytes(6). However, recent studies have found that most tissue-resident macrophages are derived from the yolk sac and fetal liver during embryonic development(7). Macrophage populations vary widely between tissues and maintain the basic physiological functions of the tissues in which they reside, including 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 promote tissue homeostasis, whereas monocyte-derived macrophages primarily assist in host defense and pathological signaling(9).

Macrophages are highly plastic and can adjust their phenotype and function in response to changes in the local microenvironment, called macrophage polarization. The idea of macrophage polarization and its function in inflammation are becoming better understood as research develops. Depending on the surface receptor expression and secretion profile, 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 present 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, killing intracellularly infected pathogens, mediating reactive oxygen species (ROS)-induced tissue damage, and adversely affecting tissue regeneration and wound healing(11). M1-type macrophages are usually induced by the combination of IFN-γ and bacterial lipopolysaccharide (LPS), which in turn secrete pro-inflammatory factors, including tumour necrosis factor (TNF)-α, IL-1β, IL-6, nitric oxide synthase (iNOS), as well as a variety of chemokines, and increased expression of cell surface markers CD40, CD80, CD86 and major histocompatibility complex class II receptor (MHC-IIR)(12-14). M2-type macrophages, also known as reparative macrophages, are involved in promoting Th2 responses with properties that inhibit inflammatory responses and promote tissue repair and wound healing(11). M2-type macrophages are mainly induced by IL-4 or IL-13 and secrete IL-10, transforming growth factor (TGF)-β, vascular endothelial growth factor, epidermal growth factor and other cytokines, as well as increasing the expression of Arginase1 (Arg1) and cell surface markers CD163, CD204, and CD206(12-14). Therefore, the polarization status of macrophages can be distinguished by combining the secretion profile of macrophages and surface molecular markers (Figure 1).

Due to their plasticity, macrophages produce different bioactive mediators in different microenvironments and exert pro- or anti-inflammatory biological effects during inflammation. In the acute phase of inflammation, macrophages polarize towards M1-type, inducing inflammatory response and releasing pro-inflammatory mediators that help to kill/clear pathogens and damaged cells; in the late phase of inflammation, macrophages polarize towards M2-type, producing anti-inflammatory cytokine mediators that reduce inflammatory response, promote regeneration of damaged tissues and restore homeostasis in the body(15). The Th1/Th2 response of T cells is closely linked to human M1/M2 macrophages, and the two coordinate to maintain body homeostasis, while imbalance induces pathological inflammatory responses and related diseases(16). Therefore, by regulating the ratio of M1/M2 macrophages is expected to be a new therapeutic idea for inflammatory immune diseases.

2 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.

2.1 JAK/STAT signaling pathway

It is now generally accepted that the pathogenesis of many inflammatory immune diseases is linked to the

JAK/STAT pathway(17). JAK/STAT is a major signaling pathway utilized by more than 70 cytokines and is involved in many important biological processes such as cell proliferation, differentiation, apoptosis and immune regulation(18). Inflammatory factors are closely related to the JAK/STAT signaling pathway, which can activate the JAK/STAT pathway, and the JAK/STAT pathway can in turn affect the expression of inflammatory factors. In this pathway, the STAT protein family is an important class of transcription factors, consisting of seven main members(19), among them, the relevant STAT members of macrophage polarization that regulate the inflammatory response include STAT1, STAT3 and STAT6. Binding of IFN-γ and IL-12 to their receptors activates JAK, which induces phosphorylation of STAT1, promotes M1-type macrophage polarization, and facilitates the production of pro-inflammatory factors(20). While IL-4 and IL-13 upregulate STAT6 expression, IL-6 upregulates STAT3 expression, both of which promote M2-type macrophage polarization and favor anti-inflammatory factor production(21, 22). In summary, M1-type polarization was closely associated with STAT1 phosphorylation, whereas M2-type macrophage polarization was influenced by the increased expression of STAT3 and STAT6.

2.2 NΦ-κB σιγναλινγ πατηωαψ

NF-κB is the "master switch" for the expression of various pro-inflammatory mediators, and dysregulated activation of this pathway leads to the development of a wide range of autoimmune and inflammatory diseases(23). Studies have shown that TLRs recognize conserved pathogenic microbial products, i.e. pathogen-associated molecular patterns, which induce activities that stimulate inflammatory immunity and host defense(24). TLR on the macrophage surface binds to LPS and activates the classical NF-κB pathway via the myeloid differentiation factor 88 (MyD88)-dependent pathway or interferon regulatory factor (IRF) 3, with NF-κB p65/p50 enters the nucleus, regulates the polarization of M1-type macrophage(25) , mediates the transcription of pro-inflammatory factors such as IL-1β, IL-6 and TNF-α, and amplifies inflammatory signals(26). In addition, there is a close link between NF-κB and JAK/STAT, with STAT1 shown to activate the transcriptional activity of NF-κB(27) and mutual crosstalk between STAT3 and NF-κB regulating M1/M2 homeostasis(28-30)。

2.3 PI3K/Akt signaling pathway

The PI3K/Akt signaling pathway is an important pathway involved in the regulation of inflammatory responses and macrophage polarization and plays a important role in the inflammatory immune response(31). In macrophages, stimuli such as growth factors and cytokines can be signaled through this pathway(32, 33). It was found that activation of this signaling pathway inhibited M1-type macrophage polarization and promoted M2-type macrophage polarization(34). Consistent with this effect, this signaling pathway was proved to be a negative regulator of TLR and NF-κB signaling and a positive regulator of STAT3 signaling in macrophages(35, 36). In fact, however, the PI3K/Akt signaling pathway differentially promotes macrophage polarization according to different isoforms of Akt. Akt is composed of three members, Akt1, Akt2 and Akt3, which are 80% homologous and have different regulatory functions(37). 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 increases the expression of anti-inflammatory factor IL-10; Akt3 deletion reduces M2-type macrophage infiltration and hinders skin wound healing(38, 39).

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 each other and jointly determine the direction of macrophage polarization (Figure 2).

3 Macrophage polarization regulates inflammatory immune skin diseases

Inflammation is an essential defense of the body against exogenous invaders or regulation of the body's

immune response and has a protective effect on the body, but an excessive inflammatory response can instead impair normal tissue function and even lead to organ failure, causing the development of many chronic inflammatory and autoimmune diseases. Inflammatory immune skin diseases are a group of systemic or organ-specific chronic inflammatory skin diseases caused by abnormal inflammatory responses and immune dysregulation(40), the pathogenesis of which is not fully understood. Macrophages are key cells that coordinate chronic inflammation, and macrophage polarization occurs throughout the development, progression, and regression of inflammatory diseases(41). The following studies have shown that macrophage polarization plays a regulatory role in inflammatory immune skin diseases.

3.1 psoriasis

Psoriasis is a chronic, relapsing immune inflammatory skin disease known as the "cancer that never dies", with a global prevalence of about 2%(42). The pathogenesis of psoriasis involves key cytokines such as IL-17, IL-22, IL-23, TNF-α and other important transduction pathways such as NF-κB and STAT signaling pathways, and these pro-inflammatory factors are key drivers of psoriasis pathogenesis through signaling pathways(43, 44). Kaempferia parviflora is a folk medicine widely used in Southeast Asia for its anti-inflammatory and anti-allergic effects(45). It was found that Kaempferia can inhibit the production of pro-inflammatory factors TNF-α, IL-1, IL-6, IL-17, IL-22 and IL-23 by keratinocytes and macrophages through inhibition of the LPS-induced NF-κB pathway, suggesting that this plant could be a promising candidate for the development of anti-psoriasis drugs(46). This anti-inflammatory mechanism is closely related to macrophage polarization, and it is now generally accepted that M1-type macrophages produce pro-inflammatory cytokines and M2-type macrophages produce anti-inflammatory cytokines, and that the balance between these two types of macrophages determines the progression of various inflammatory diseases such as psoriasis(47). For example, the circular RNA (circRNA) hsa_circ_0004287 inhibited M1-type macrophage polarization in vitro, and topical application of macrophage-specific overexpression of the hsa_circ_0004287 plasmid reduced skin inflammation in psoriasis-like mice(48). In recent years, traditional Chinese medicine has remarkable efficacy in the treatment of psoriasis, and exploring its specific mechanism is a hot topic of current research. The herbal PSORI-CM02 formulation (consists of Rhizoma Curcumae, Radix Paeoniae rubra, Sarcandra glabra, Rhizoma Smilacis glabrae and Fructus mume)(49) was shown to significantly improve imiquimod-induced skin lesions in psoriasis-like mice by regulating STAT1 and STAT6 expression to reduce M1-type macrophage infiltration(50). Purpurin plus methotrexate has also been shown to protect against psoriasis by inhibiting M1-type macrophage polarization in psoriasis and reducing the production of cytokines associated with psoriasis(51). In addition to typical M1- and M2-type macrophages, Hou et al(52) identified a unique pathogenic macrophage subpopulation driven by IL-23, referred to as M(IL-23)-type macrophages, which highly expressed IL-17A, IL-22 and IFN-γ. IL-23 induced IL-17 expression in macrophages via STAT3 and retinoid-related orphan receptor-γT pathway, and Th1-related key transcription factor T-bet mediated IFN-γ production, which significantly exacerbated skin lesions in psoriasis-like mice. These studies suggest that the treatment of psoriasis can be achieved by reducing the production of inflammatory factors and modulating NF-κB and STAT signaling pathways to inhibit macrophage M1-type polarization or M(IL-23)-type infiltration.

3.2 Atopic dermatitis (AD)

AD is an immune-driven recurrent chronic pruritic inflammatory skin disease that affects up to 20% of children and 5% of adults, often with a personal and family history of food allergy, allergic rhinitis/conjunctivitis and allergic asthma(53). Macrophages are directly involved in the pathogenesis of AD by regulating the immune response in the skin, and upregulation of M1-type macrophage markers and downregulation of M2-type markers were observed in atopic mice(54). In addition to affecting psoriasis pathogenesis, macrophage-specific overexpression of hsa_circ_0004287 also attenuated skin inflammation in AD mice by inhibiting M1-type macrophage polarization(48). Viola yedoensis Makin, a traditional Chinese medicine with reported anti-inflammatory properties(55), 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 by activating the JAK2/STAT3 signaling pathway and promoting M2-type macrophage polarization (56). In-

terestingly, however, one study found that inhibition of both M1- and M2-type macrophages also alleviated AD symptoms(57). The inflammatory immune response in AD is extremely complex and not yet fully understood. More in-depth exploration is needed to clarify the mechanisms of the role of different macrophage subtypes in AD in order to lay a more solid foundation for macrophage polarization in clinical translation.

3.3 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(58). Although a lot of research has been done on SLE, its pathogenesis is still unclear, and no specific drugs have been found so far(59). Labonte et al(60) found that more M1-type macrophages expressing STAT1, SOCS3 and fewer M2-type macrophages expressing STAT3, STAT6, CD163 were present in the bone marrow of SLE patients compared to healthy individual. In both in vitro and in vivo experiments, human umbilical cord mesenchymal stem cells -derived exosomes inhibited macrophage polarization to M1-type, reduced TNF-α and IL-1β levels, and promoted M2-type macrophage polarization and increased Tregs cell production in the spleen, ultimately improving nephritis and other key organ damage and achieving the goal of treating SLE(61, 62). Therefore, by inhibiting M1-type macrophages and activating M2-type macrophages, the immune inflammatory response to SLE can be improved. One study significantly reduced the severity of SLE in mice by successive transplantation of M2-type macrophages(63). In addition, the antibiotic azithromycin was shown to stimulate macrophage M2 polarization through the PI3K/Akt signaling pathway, promote the production of anti-inflammatory factor IL-10 while inhibiting the secretion of pro-inflammatory factors IL-1β, IL-6, and TNF-α, and suppress the immune inflammatory response in SLE(64). Azithromycin is widely used in clinical practice and has a good safety profile. Further exploration of its pharmacological effects and evaluation of its therapeutic efficacy may provide a new treatment strategy for SLE patients. These studies showed that M1-type macrophages promote tissue injury, while M2-type macrophages are involved in tissue healing in SLE, and targeting to restore the balance between M1/M2 macrophages may be a novel therapeutic target for SLE.

3.4 Behcet's disease (BD)

BD is a chronic, multisystemic, inflammatory immune vasculitis characterized by recurrent oral/genital ulcers, skin lesions, ocular damage, and other systemic manifestations(65). BD patients have an over-activated immune system and multi-system inflammatory damage, mainly manifested by an enhanced inflammatory response and overexpression of pro-inflammatory cytokines, which include TNF-α, IL-1β, IL-6, IL-12 and IL-18(66). In addition, impaired secretion of the anti-inflammatory factor IL-10 is also associated with BD pathogenesis(67). Due to their plasticity, macrophages play a key role in both promoting and suppressing inflammatory processes by polarizing into different phenotypes. In a study of herpes simplex virus-induced BD mice, it was found that the M1-type macrophage phenotype was upregulated and the M1/M2 macrophage ratio was increased in BD mice compared to normal mice(68). BD serum factors may be responsible for inflammatory changes in BD(69). A recent study showed that BD serum polarized macrophages toward M1-type by activating the NF-ϰB signaling pathway, drived Th1 differentiation, and promoted overexpression of IL-12 and TNF-α(70). This dysregulation of M1/M2 macrophage homeostasis is associated with abnormal expression of the aryl hydrocarbon receptor (AHR)(71), the latter is a ligand-activated transcription factor. Palizgir et al(72) found that both monocyte-derived macrophages and in vitro-induced M1-type macrophage AHR mRNA expression were reduced in BD patients compared to normal subjects. The current therapeutic effect of BD is still unsatisfactory, therefore, there is an urgent need to understand the pathogenesis of BD and develop new therapeutic targets, and macrophage polarization may make significant progress as a new therapeutic target in improving the prognosis and reducing the disease burden of BD.

3.5 Others

Acne is a globally common chronic inflammatory immune skin disease that can occur at any age(73). 5-Aminoketovaleric acid photodynamic therapy is clinically effective and safe in the treatment of patients with

severe acne, but its exact mechanism is unknown, and a very interesting study showed 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 increasing the intense inflammatory response and breaking chronic inflammation(74), providing new insights into the study of inflammatory-immune skin diseases.

Rosacea is also an immune-mediated chronic inflammatory skin disease that primarily affects the central area of the face(75). The exact etiology of this disease is unknown and may be related to M1-type macrophages and their pro-inflammatory effects(76). Zhou et al(77) found increased local infiltration of macrophages in rosacea mice and demonstrated that guanylate-binding protein 5 (GBP5) is an important gene controlling macrophage infiltration, further proving that silencing GBP5 can achieve therapeutic effects by inhibiting M1-type macrophage polarization and 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 cause or exacerbate inflammatory immune skin diseases such as psoriasis, AD, SLE and AD, therefore, prevention or treatment of these related diseases by suppressing M1-type macrophages and balancing M1/M2 macrophage ratio is expected.

4 Summary and Outlook

In skin tissue, macrophages play an important role in tissue homeostasis and immune surveillance, mobilizing immune activation in reaction to microbial invasion and supporting wound healing to repair damaged tissue. In terms of pathogenesis, macrophages, as essential mediators and coordinators of chronic inflammation, are major players in various diseases. Macrophage polarization is the critical pathway through which they exert these pathophysiological effects. Macrophages are mainly polarized into two phenotypes, namely pro-inflammatory M1-type and anti-inflammatory M2-type. M1- and M2-type macrophages are induced by their respective activators to produce large amounts of pro- or anti-inflammatory cytokines and chemokines, which activate multiple related signaling pathways and exert their regulatory functions. Existing studies have shown that macrophage polarization can be involved in the development of several inflammatory immune skin diseases including psoriasis, AD, SLE, BD, etc. In these diseases, the proportion of M1/M2 type macrophages is increased and M1-type macrophages play a dominant role in the ongoing development and vicious cycle of inflammatory response. By targeting molecules in signaling pathways such as 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. However, the mechanisms of macrophage polarization in these inflammatory skin diseases are not yet fully elucidated, and therapies targeting macrophage polarization are still in their infancy. Therefore, an in-depth study of macrophage polarization and its role in inflammatory immune dermatoses can provide us with a more thorough understanding of the pathogenesis of related dermatoses, which can then provide valuable references for the prevention and treatment of such diseases.

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.

Author 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.

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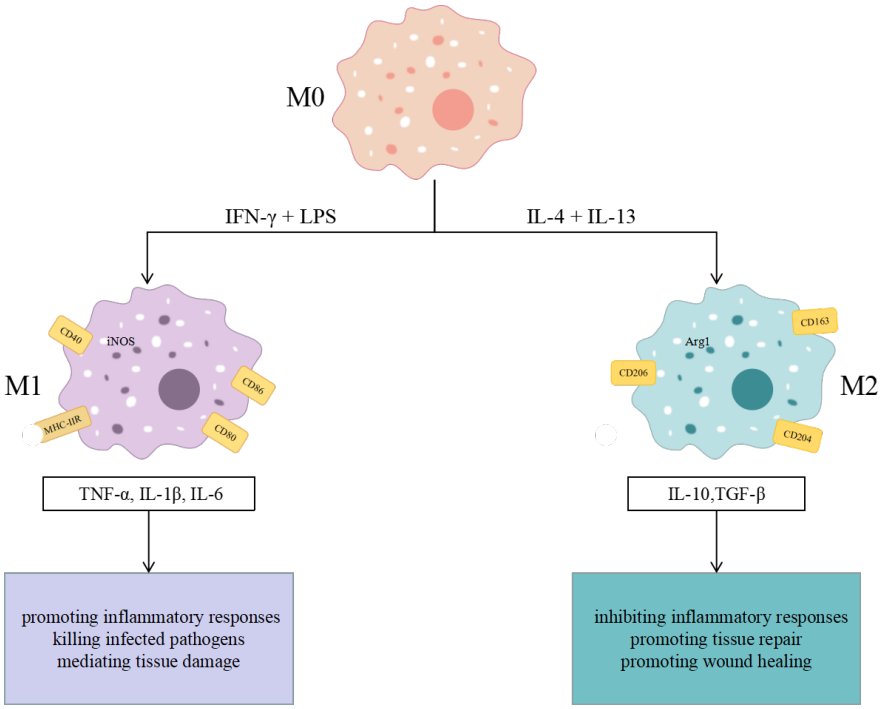

Figure 1

M1-type and M2-type macrophage polarization. Under the induction of IFN-γ and LPS, M0 macrophages polarize into M1-type, which in turn promotes inflammatory response, kills pathogens and mediates tissue injury by secreting pro-inflammatory factors such as TNF-α, IL-1β and IL-6; under the induction of IL-4 and IL-13, M0 macrophages polarize into M2-type, which in turn suppresses inflammatory response, promotes tissue repair and wound healing by secreting anti-inflammatory factors such as IL-10 and TGF-β.

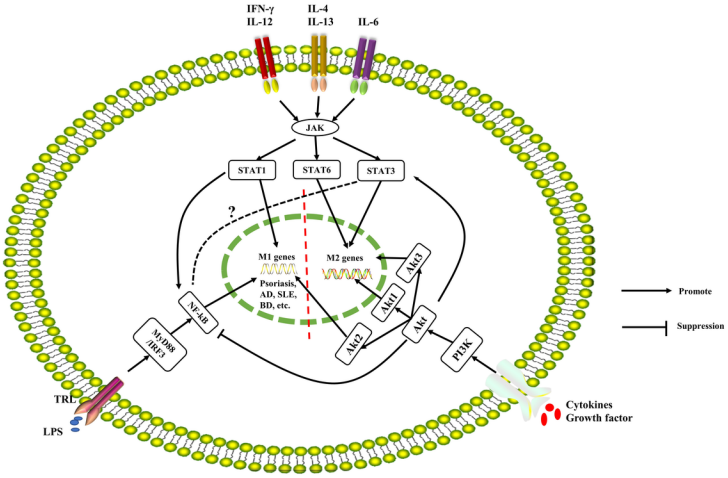

Figure 2

Inflammation-related signaling pathways associated with macrophage polarization. The

JAK/STAT1, NF-κB and PI3K/Akt2 signaling pathways promote macrophage M1 polarization, while the JAK/STAT3 or JAK/STAT6 and PI3K/Akt1 or PI3K/Akt3 signaling pathways promote macrophage M2 polarization. In turn, these three types of signaling pathways interfere with each other and jointly determine the direction of macrophage polarization.

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