Unfulfilled Inflammatory Resolution: 
A Key Factor in the Pathogenesis of Psoriasis

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ABSTRACT

Recent literature has highlighted the importance of chronic inflammation in psoriasis pathogenesis. Non-resolving inflammation can trigger progressive tissue damage and inflammatory mediator release which in turn perpetuate the inflammatory cycle. Under normal conditions, inflammatory responses are tightly controlled through several mechanisms that restore normal tissue function and structure. Defects in regulatory mechanisms of the inflammatory response can result in persistent unresolved inflammation and further increases of inflammation. Therefore, this review focuses on defects in regulatory mechanisms of inflammatory responses that lead to uncontrolled chronic inflammation in psoriasis. Databases such as Pubmed Embase, ISI, and Iranian databases including Iranmedex, and SID were researched to identify relevant literature. The results of this review indicate that dysregulation of the inflammatory response may be a likely cause of various immune-mediated inflammatory disorders such as psoriasis. Based on current findings, advances in understanding the cellular and molecular mechanisms involved in inflammation resolution are not only improving our knowledge of the pathogenesis of chronic inflammatory diseases but also supporting the development of new therapeutic strategies.

Keywords: Autoimmunity; Inflammation; Psoriasis; Skin

INTRODUCTION

Psoriasis encompasses a group of chronic inflammatory skin diseases and can be classified based on clinical phenotypes, pathogenic causes, the age at onset and severity. This common skin disorder has a varied spectrum of clinical presentations that may be associated with different etiologies.

At one end of this spectrum, there is the most common form of psoriasis, plaque psoriasis characterized by an autoimmune inflammatory process. On the opposite end, there is generalized pustular psoriasis with autoinflammatory characteristics. Therefore, psoriasis is considered as a unique disorder due to the proposed role of the autoimmune and autoinflammatory reactions in the pathogenesis of disease and shaping its clinical manifestations.1

Different studies have indicated that the psoriasis-associated inflammatory status can be the consequence of the abnormalities of innate and adaptive immune function.2,3

Moreover, it is known that aberrant activation of innate and adaptive immunity, are involved in the pathogenesis of autoinflammatory and autoimmune diseases, respectively.4 These findings help to provide a
more comprehensive picture of the relationship between the variables in the etiology of psoriasis and different subtypes of the disease. Regardless of the etiology, the resulting chronic inflammation drives psoriatic pathology and contributes to immunological changes that affect disease progression and perpetuation.

The role of inflammation in psoriasis has been subject to numerous recent publications and discussions. Nonetheless, most of the literature has focused on the initiation and amplification of the inflammatory responses and little attention has been given to defects in regulatory mechanisms that limit or terminate inflammation. Therefore, the present study will focus on the mechanisms that lead to inadequate or insufficient resolution of inflammatory reactions in patients with psoriasis.

**Inclusion and Exclusion Criteria**

No limitation was imposed with respect to the recruitment of cases (human subjects and animals). A number of studies were excluded as a result of insufficient clarity and lack of scientific assessment of data.

**Inflammation and Resolution**

Inflammation is an important defense mechanism and is essential for efficient immunity. It is initiated when the receptors of the innate immune system (pattern recognition receptors) recognize microbial components (pathogen-associated molecular patterns) or molecules from tissue injury (danger-associated molecular patterns) that are actively released in response to cellular stress. Interactions between receptors and ligands result in the activation of multiple signaling pathways that induce the production of pro- and anti-inflammatory mediators. Therefore, like other biological response mechanisms, the inflammatory response is a tightly regulated process and its activation can be counter-regulated by anti-inflammatory responses.

The onset of inflammation is accompanied by increased blood flow and permeability of the microvasculature that is mediated, in part, by vasoactive amines and lipid mediators. Then polymorphonuclear neutrophils (PMNs) migrate towards the site of inflammation. This migration is critically dependent on proinflammatory lipid mediators (eg, leukotriene B4 (LTB4) and chemokines) and is necessary to eliminate harmful stimuli. Later in inflammation, recruited neutrophils are replaced by monocytes, which can subsequently differentiate into M1 or inflammatory macrophages (MØs) (also called classically activated MØs). These cells with potent immune-stimulating activity produce high levels of proinflammatory cytokines and reactive oxygen species (ROS). These coordinated physiological responses (also known as acute inflammation) are necessary to combat harmful initiators of the inflammatory response. Acute inflammation has a rapid onset, lasting for hours or a few days and usually promotes healing. But, if it is left unchecked it can become chronic and eventually cause several chronic inflammatory diseases. Therefore, the development of mechanisms to control the inflammatory responses is of prime importance. These mechanisms are crucial for fine-tuning of inflammation and act through a highly organized network of many cell types, cytokines, chemokines, adhesion molecules, growth factors, and their corresponding receptors.

The basic mechanisms that are actively involved in the resolution of inflammation include:

- preventing and limiting the extent of leukocyte extravasation, regulation of inflammatory chemokines and cytokines, the switching off of signaling pathways that play a role in leukocyte survival, induction of leukocyte apoptosis and clearance (efferocytosis) by MØs, the polarization of pro-inflammatory M1-MØs to the anti-inflammatory/M2 phenotype, remigration of cells that have not undergone apoptosis to the vasculature or lymph and beginning of healing process.

To date, there have been several specialized articles about the defects in resolution mechanisms for inflammation, while there is not enough data on this issue and psoriasis. Therefore, this review aims to focus briefly on the particular importance of aberrant regulation of inflammatory response in patients with psoriasis (Figure 1).

**Classic versus Alternative MØ Activation**

MØs are polarized to either an M1 or M2 subtype depending on the immune responses and their microenvironment. M1 MØs have pro-inflammatory functions and constitute the first line of defense against invading pathogens. They are characterized by the production of pro-inflammatory cytokines such as interleukin (IL)-12 and IL-23, and reactive oxygen and nitrogen species. They also
express a high level of major histocompatibility complex (MHC) class II molecules and exhibit enhanced antigen-presenting capacity.

In contrast, M2 MØs (alternatively activated MØs) have anti-inflammatory effects and participate in the biological tissue healing without the prevalence of infection. They also generate an array of an anti-inflammatory cytokine such as IL-10 and IL-4.\textsuperscript{12-15} Phenotype shift between M1 and M2 MØ play important roles in the regulation of inflammatory responses and the imbalance of M1/M2 polarization is closely associated with various pathological processes or inflammatory conditions.\textsuperscript{16}

Currently, there is limited literature on MØ polarization status in psoriasis. Nonetheless, these research studies provide a worthy understanding of some aspects of MØ polarization and its role in disease pathogenesis. Emerging evidence from this literature highlights the importance of M1 MØs in psoriasis. For instance, studies in a mouse model of imiquimod (IMQ)-induced skin inflammation which is a useful experimental model of psoriasis, showed enhanced M1/M2 MØ ratio and increased expression of M1 MØ signature genes.\textsuperscript{17} In another study, Zhang et al have shown that IL-35 can relieve psoriatic inflammation by a significant reduction in the total number of MØs and M1/M2 ratio.\textsuperscript{18}

Figure 1. Schematic representation of mechanisms affecting the development of chronic inflammation in psoriasis.

Many factors can modify the course of the resolution phase of the inflammatory response. A combination of cells (such as neutrophils and macrophages) and mediators may provide the signals for the induction of persistent, unresolved inflammation in patients with psoriasis.

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The reduction of M1 MØs in psoriatic skin lesions after treatment with TNF-α inhibitors also highlights the potential involvement of M1/M2 polarity of MØs in disease pathogenesis. Several studies have strongly corroborated this notion. For instance, Lin et al observed a parallel decrease in the M1/M2a ratio and Psoriasis Area and Severity Index (PASI) score after treatment with adalimumab. Furthermore, the increased infiltration of M1/M2 MØ in the skin was returned to baseline after successful treatment with TNF-α inhibitor. This observation was consistent with previous reports showing that infliximab decreases the infiltration of inflammatory cells such as M1 MØs and neutrophils in the lesional skin of a patient with generalized pustular psoriasis.

Although the above-mentioned observations point toward a potential role for the exaggerated M1 polarization in disease pathogenesis, controversy still exists over the role of M1 MØs in the pathogenesis of psoriasis. For instance, the study by Hou et al reported that a unique MØ subpopulation M(IL-23) is involved in the pathogenesis of psoriasis. These MØs are induced by IL-23 and have a unique pattern of gene expression in contrast to M1 and M2 MØs. Moreover, a mixed M1/M2 phenotype has been detected in biopsies from psoriatic lesional skin. Therefore, future experimental studies will be needed to explore the potential role of MØ polarization and the underlying molecular mechanisms in the pathogenesis of psoriasis.

Polymorphonuclear Neutrophils

Neutrophils are the most abundant circulating white blood cells and contain an arsenal of toxic chemicals that are responsible for microbial killing. They constitute the first line of defense for the innate immune response and are the first innate cells that can be recruited to sites of infection or inflammation. Neutrophils have been shown to play an important role in the pathogenesis of psoriasis. Examples of evidence could include epidermal infiltration of neutrophils and microabscesses formation (called Munro abscesses), greater numbers of neutrophils in the circulation of patients, increased neutrophil activation and neutrophil markers in patients with psoriasis, the beneficial effects of neutrophil depletion on clinical and histopathological outcomes of disease. Neutrophils appear to be essential in the induction phase of psoriasis and initiating the inflammatory process. Moreover, their longevity increases under inflammatory conditions. Although, increased lifespan permit neutrophils to do more complex activities, but their persistence can also lead to the development of inflammation and inflammation-associated comorbidities.

Under normal conditions, neutrophils are programmed to die by apoptosis after performing their action at the inflamed site. Apoptosis is essential for the shutdown of neutrophil function, tissue clearance of extravasated neutrophils, and successful resolution of inflammation. Inhibition or delay of neutrophil apoptosis increases their lifespan and thereby contributes to the prolongation of inflammation. In this context, overproduction or unregulated release of cytotoxic mediators such as ROS and proteases can lead to amplification of systemic inflammation and tissue injury.

The molecular mechanisms behind the increased neutrophil lifespan in psoriasis are currently not well understood but multiple studies have demonstrated that the cytokine granulocyte macrophage-colony stimulating factor (GM-CSF) can prolong the survival of neutrophils by inhibiting their apoptosis. This cytokine is also important in the initiation and maintenance of chronic inflammatory processes. In line with this, several studies have been undertaken to investigate the potential role of GM-CSF in psoriasis. Some of these studies indicate that individuals with psoriasis have detectable concentrations of GM-CSF in their serum and suction blister fluid. In addition, increased expression of GM-CSF have been observed in psoriatic lesions.

Additional evidence for a pathogenic role of GM-CSF has been provided by the study of an animal model of psoriasis-like skin inflammation. For instance, it was reported that skin psoriasiform features in a flaky skin mouse model of psoriasis can be alleviated by neutralization of GM-CSF. Additionally, maculopapular eruptions, and disease exacerbation have been observed in neutropenic patients with psoriasis treated with GM-CSF.

Similar to GM-CSF, IL-17, Interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α) are crucial cytokines in the inflammatory process of psoriasis, and their circulating levels are directly correlated with the severity of psoriasis. Although the exact mechanism of action of these cytokines are complex and still not fully understand, but it has been demonstrated that all of them can reduce the induction
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of apoptosis and extend the lifespan of the neutrophils.39-41

In summary, the above-mentioned studies suggest a possible association between the increased survival of neutrophils and psoriasis. These results also indicate the importance of neutrophil apoptosis and the mechanisms that control the accumulation of neutrophils at sites of inflammation. Therefore, more research is needed to further elucidate the underlying reasons for ineffective regulatory mechanisms of neutrophil apoptosis in psoriasis, the mechanisms that could contribute to the chronicity of inflammation.

Counter-regulatory Cytokines and Regulation of Inflammatory Processes

Anti-inflammatory cytokines are thought to be one of the most valuable groups of compounds that control the pro-inflammatory cytokine response. Indeed, the balance between pro- and anti-inflammatory cytokinesis an important mechanism to prevent the undesirable consequences of an excessive inflammatory process.

IL-10 and TGF-β, are two prominent anti-inflammatory cytokines and are well known for their immunosuppressive functions. They have multiple cellular sources and targets, can act synergistically, and exert their suppressive effects via several different mechanisms.42,43 Three isoforms of TGF-β (TGF-β1, -β2 and -β3) have been identified. Among them, TGF-β1 has potent immunosuppressive effects and is principally expressed in the immune system. TGF-β1-deficient mice develop autoimmune inflammatory disease which affects multiple organ systems.44 Additionally, unregulated expression of TGF-β or unresponsiveness to TGF-β signaling plays a pivotal role in the pathogenesis of autoimmune diseases and chronic inflammatory conditions.45 It has been also indicated that mutations in the TGF-β gene lead to phenotype characteristic for autoimmune disorders.46

The mechanisms of regulation proposed for TGF-β are 1. suppressive effects on the differentiation of effector Th cell; 2. conversion of naive T cells into highly suppressor Treg cells; 3. inhibition of T and B lymphocyte proliferation; 4. inhibitory effects on the production of effector cytokines, such as IL-2, IFN-γ, and IL-4; 5. suppression the activities of MOs, dendritic cells (DCs) and natural killer (NK) cells.47

Based on the above-mentioned concerns, a decreased level of TGF-β would be expected to contribute to the pathological TGF-β effects. However, controversial findings have been reported about this issue. For instance, several studies indicate that the increased level of TGF-β may harm psoriasis. TGF-β1 levels have been reported to be increased in the epidermis and sera of patients with psoriasis and correlated with PASI score.48-50 In addition, the successful treatment of patients with psoriasis can lead to a reduction of TGF-β1 in the serum.51 It has also been demonstrated that elevated expression of TGF-β1 in the epidermis of transgenic mice resulting in the development of psoriasis-like skin lesions.52

TGF-β is a negative regulator of keratinocyte proliferation and despite its increased level, psoriatic keratinocytes continue to hyperproliferative. Abnormal signaling of TGF-β may explains, in part, the enhanced keratinocyte proliferation that occurs in patients with psoriasis. It must be mentioned that deregulation of TGF-β signaling has been reported in psoriasis and findings by Litvinov et al indicated that signaling abnormalities are accompanied by a clear downregulation of the TGF-β type I and II receptors in the psoriatic skin. This process involves the participation of CD109 that downregulates TGF-β signaling by enhancing TGF-β receptor internalization and degradation.53

Despite the above-mentioned findings, there is no consensus in the literature on the TGF-β changes in patients with psoriasis. For instance, Antiga et al did not observe any significant differences in the serum levels of TGF-β between patients and healthy controls.54 This result is consistent with the finding from Zaher et al which found no significant differences in the serum and tissue levels of TGF-β between psoriasis patients and controls.55

Altogether, the evidence presented here suggests that alterations of TGF-β levels in patients with psoriasis reflect the disturbance of regulatory mechanisms that control the production of this important cytokine. Nonetheless, the current evidence is insufficient to determine the exact molecular mechanisms of TGF-β in disease pathogenesis. Therefore, more studies are needed to reveal how this cytokine contribute to the initiation or perpetuation of inflammatory responses.

IL-10 is another anti-inflammatory cytokine that can suppress a broad range of inflammatory responses. It plays a vital role in the regulation of immune homeostasis and its activity needs to be tightly
regulated. The abnormal production or regulation of IL-10 has pathogenic consequences. Relative or absolute IL-10 overproduction can induce undesired immunosuppressive effects and inhibit the resolution of associated tissue damage. In contrast, a relative or absolute IL-10 deficiency can lead to a persistent immune activation and development of autoimmune disease.

The immunosuppressive activities of IL-10 depend on its ability to inactivate MØs by suppressing the production of proinflammatory cytokine (including IL-1, IL-6, IFN-γ, and TNF-α). IL-10 also reduces the expression of co-stimulatory molecules and MHC class II molecules that are critical in shaping the extent and nature of the immune response. It can control both proinflammatory Th1 and Th17 cell immune responses and promotes Treg population growth that has potent immune-suppressive activities.

Some clinical observations have revealed the existence of a relationship between altered IL-10 responses, and an elevated risk for psoriasis morbidity and severity. Decreased serum and lesional levels of IL-10 have been observed in patients with psoriasis. Moreover, it has been shown that upon stimulation with IL-8 and TNF, psoriatic fibroblasts are not able to produce IL-10, but neutrophils produced a small amount of this cytokine.

Another evidence for the role of IL-10 in psoriasis has been provided by the beneficial effects of IL-10 therapy in these patients. Indeed, IL-10 therapy has been associated with a decrease in the incidence of relapse and prolongs the disease-free interval. The researchers also discovered reduced numbers of IL-10-producing regulatory B (Breg) cells in patients with psoriasis whereas progenitor B cells are readily detectable. These findings imply the impaired function of Breg cells that are the essential negative regulators of immune responses. Another study in the same area showed a significant decrease in IL-10+B cells and a negative correlation with PASI, IL-17A+CD3+, and IFNγ+CD3+ T cells.

Analysis of associations between IL-10 polymorphisms and the occurrence of psoriasis is another research area that attempts to explore the role of IL-10 in the disease process. Some research results have demonstrated that IL-10 polymorphisms are related to disease susceptibility, although these results have not always replicated.

Despite the apparent importance of IL-10, its role in disease pathogenesis is still controversial. Several comparative studies have shown that there is no significant difference between IL-10 serum levels in patients with psoriasis compared to healthy controls. In contrast, Borska et al and Roussaki-Schulze et al indicated elevated circulating levels of IL-10 in psoriasis patients versus healthy subjects.

Taken together, the above-mentioned findings underscore the complexity of the associations between IL-10 and psoriasis. Therefore, more studies are needed to clarify the role of this cytokine in the pathogenesis of the disease.

Bioactive Lipid Mediators in Human Psoriasis

Bioactive lipids are a general term for a family of lipid mediators that are important in metabolic and physiological pathways. They are important in the regulation of the cutaneous immune system and expert coordinating actions with peptides, neurotransmitters, amines, hormones, etc. They are produced by the enzymes when required and are inactivated after completing their allocated task.

Bioactive lipids perform a wide array of functions necessary for the cellular activities including structure and organization of membranes, structure, and function of proteins, production of energy, signal transduction pathways and gene regulation.

Based on their biochemical functions, bioactive lipids have been divided into four categories: classical eicosanoids, specialized pro-resolving mediators (SPMs), lyso glycerophospholipids/sphingolipids and endocannabinoids.

Eicosanoids represent one of the major classes of bioactive lipid mediators that play a vital role in regulating the physiological and pathophysiological responses and often demonstrate potent inflammatory activities. Arachidonic acid (AA) in cell membrane phospholipids is a common substrate for the biosynthesis of eicosanoids. This 20-carbon polyunsaturated fatty acids released by phospholipase A2 (PLA2) activity and is then metabolized by cyclooxygenase (COX), lipooxygenase, and epoxygenases that are responsible for the catalysis of AA into prostaglandins, leukotrienes, and endoperoxides, respectively.

Excessive and uncontrolled production of pro-inflammatory eicosanoids, including the series-2 prostaglandins or the series-4 leukotrienes, is associated with a detrimental transition from acute to
chronic inflammation. The pattern of eicosanoids observed in psoriatic skin lesions shows an increased level of PLA2, lipooxygenase activity, 5-hydroxyeicosatetraenoic acids (HETE), 12-(HETE) and LTB4, that point to the role and relevance of eicosanoid species in psoriatic inflammation.78,80

Sphingolipids such as ceramide (Cer) and sphingosine1-phosphate are another class of bioactive lipid mediators containing a backbone of sphingoid bases. Like eicosanoids, abnormal sphingolipid metabolism is associated with the pathogenesis of psoriasis. Altered sphingolipid levels and malfunctions of the necessary enzyme for their proper formation have been found to correlate with disease presence or severity.76,81

Similar to eicosanoids, the classic endocannabinoids are metabolites of AA that can serve as endogenous ligands for the cannabinoid receptors (CB), CB1, and CB2. They are regulators of homeostasis within the body and are involved in a large number of physiological processes in most human organs including the skin. Endocannabinoids, their specialized receptors, and their metabolizing enzymes are present in healthy and diseased skin. They are not only involved in immune and inflammatory responses or sensory phenomena but also the regulation of cell growth, differentiation, and survival.

Evidence indicates that the endocannabinoids are dysregulated in psoriasis, suggesting that these lipid mediators may contribute to disease development.82,83

Specialized pro-resolving mediators (SPMs) make up the fourth class of bioactive lipids derived from essential fatty acids and contribute to the resolution of inflammation. They include resolvins, lipoxin, protectin, and maresins and their biological activities encompass different cells and molecules involved in inflammation. Lipoxins exhibit potent anti-inflammatory and resolution actions and exert their biological effects by binding to G-protein coupled receptors. They are derived from AA and can actively participate in the resolution of inflammation. Lipoxins can retard the entry of new neutrophils to sites of inflammation and reperfusion injury. They decrease vascular permeability, stimulate non phlogistic monocytes infiltration that appears to be essential for wound healing and promotes phagocytosis of apoptotic cells byMØs.84

Resolvins are another family of pro-resolution mediators that are generated during the resolution phase of acute inflammation. They are categorized as either E-series or D-series, derived chemically from eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), respectively. They possess potent immunoregulatory actions, reducing tissue trafficking of inflammatory leukocytes, reduce inflammatory pain and stimulate nonphlogistic phagocytosis of apoptotic neutrophils by MØs.85

Two other known members of the SPM, protectin, and maresins, are derived from the omega-3 fatty acid DHA. They have proven effective in controlling inflammatory conditions via a complex network of interactions. They reduce neutrophil recruitment, regulates chemokine/cytokine production, and promote clearance of apoptotic neutrophils byMØs.86,87

Considering the various anti-inflammatory effects of the SPMs during the resolution phase of inflammation, it has become apparent that dysregulation of their production can result in aberrant inflammatory responses. Literature has reported an imbalance between locally produced pro-resolution and proinflammatory SPMs in psoriatic skin and blood compartments.88,89

Research has also shown that polyunsaturated fatty acids (PUFAs) are beneficial to health, and decrease the risk of immune-related disorders such as psoriasis.90 These fatty acids serve as substrates for the biosynthesis of SPMs which in turn reduces inflammation through different mechanisms. They prevent transendothelial migration of neutrophils, production of proinflammatory cytokines such as IL-12, IL-23, IL-6 and TNF-α, hyperproliferation of keratinocytes and stop the production of LTB4 and PGs.91

In summary, cutaneous fatty acids and bioactive lipid mediators play an important role in maintaining the integrity of the skin and maintenance of the epidermal barrier. Deregulation of fatty acid composition and metabolism has been implicated in the skin barrier dysfunction. To date, it is not clear to what extent these SPMs are the important drivers of psoriasis pathology. Therefore, further studies will be required to determine the exact role of bioactive lipids in disease pathogenesis. These findings also provide a powerful approach to discover valuable diagnostic and therapeutic biomarkers in psoriasis.

**CONCLUSION**

The available preclinical and clinical data support the hypothesis that chronic, systemic inflammation...
plays an essential role in the development and progression of psoriasis.

It is now clear that the resolution of inflammation is a coordinated and active process and any disturbance in this process could lead to a systemic inflammatory response. In another word, the altered balance between the pro-inflammatory and anti-inflammatory events is considered a major determinant of progression to chronic inflammatory disorders.

Although the pathogenesis of psoriasis involves many pro-inflammatory mediators, it is clear that dysregulation of inflammatory resolution pathways plays a central role in the maintenance and perpetuation of chronic inflammation.

Despite the growing understanding of the cellular and molecular basis of inflammation in psoriasis, little is known about the molecular mechanisms involved in the dynamic control of inflammation. Tight regulation of inflammation is critical to avoid severe inflammation and unwanted tissue damage. This process involves several cell types and mediators, which interact to provide suitable conditions for the resolution phase to take place. Therefore, understanding the events that occur during the resolution of inflammation can greatly increase our knowledge of the disease pathogenesis. Comprehensive knowledge in this field may also provide new avenues for intervention strategies and the development of drugs that could potentially improve inflammatory processes in directed and controlled conditions.

**CONFLICT OF INTEREST**

The authors declare no conflicts of interest.

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