

# Cellular Mechanisms of Psoriasis Pathogenesis: A Systemic Review

Mengjun Wu<sup>1</sup>, Chan Dai<sup>2</sup>, Fanfan Zeng<sup>3</sup>

<sup>1</sup>Department of Otorhinolaryngology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, People's Republic of China; <sup>2</sup>Department of Immunology, School of Basic Medicine, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, People's Republic of China; <sup>3</sup>Department of Clinical Laboratory, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, People's Republic of China

Correspondence: Fanfan Zeng, Department of Clinical Laboratory, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, People's Republic of China, Email [zengfanfan@126.com](mailto:zengfanfan@126.com)

**Abstract:** Psoriasis is a common inflammatory skin disease characterized by abnormal proliferation of epidermal keratinocytes and massive infiltration of inflammatory cells. Many kinds of cells, including keratinocytes, T lymphocytes, dendritic cells, neutrophils, and macrophages, are reported to play critical roles in the pathogenesis and progression of psoriasis. However, to date, the role of each kind of cell in the pathogenesis and development of psoriasis has not been systematically reviewed. In addition, although antibodies developed targeting cytokines (e.g. IL-23, IL-17A, and TNF- $\alpha$ ) released by these cells have shown promising results in the treatment of psoriasis patients, these targeted antibodies still do not cure psoriasis and only provide short-term relief of symptoms. Furthermore, long-term use of these antibodies has been reported to have adverse physical and psychological effects on psoriasis patients. Therefore, gaining a deeper understanding of the cellular and molecular pathogenesis of psoriasis and providing new thoughts on the development of psoriasis therapeutic drugs is of great necessity. In this review, we summarize the roles of various cells involved in psoriasis, aiming to provide new insights into the pathogenesis and development of psoriasis at the cellular level and hoping to provide new ideas for exploring new and effective psoriasis treatments.

**Keywords:** psoriasis, cellular pathogenesis, keratinocytes, immune cells

## Introduction

Psoriasis is a chronic inflammatory skin disease that clinically presents as well-defined erythematous papules or plaques covered with silvery-white scales.<sup>1</sup> The prevalence of psoriasis varies widely among different populations, ranging from 0.24% in Taiwan, China to 8.5% in Norway, affecting more than 60 million children and adults worldwide.<sup>1,2</sup> There is no significant difference in the prevalence of psoriasis between men and women, and it occurs mainly in adults aged between 20 and 60 years old.<sup>3</sup> Psoriasis is often accompanied by the onset of other diseases, and 73% of psoriasis patients, especially those with severe psoriasis, have at least one comorbidity.<sup>4</sup> The most common comorbidities are psoriatic arthritis and Crohn's disease, which share a similar mechanism of pathogenesis with psoriasis.<sup>5</sup> In addition, there is also an increased risk of metabolic syndrome,<sup>6</sup> nonalcoholic fatty liver,<sup>6</sup> cardiovascular disease,<sup>7</sup> respiratory disease,<sup>8,9</sup> autoimmune diseases such as Hashimoto's thyroiditis, autoimmune hepatitis, multiple sclerosis,<sup>10</sup> and psychiatric disorders.<sup>5,11</sup> Compared to individuals without psoriasis, severe psoriasis increases overall mortality and reduces life expectancy by 3.5 and 4.4 years in men and women, respectively.<sup>12</sup> Psoriasis seriously affects patients' daily lives and work and imposes heavy psychological, physical, and economic burdens on psoriasis patients.

Psoriasis is characterized by hyperproliferation and abnormal differentiation of keratinocytes, and massive infiltration of inflammatory immune cells.<sup>13</sup> Although the pathogenesis of psoriasis is intricate, the pathogenesis of psoriasis has been gradually revealed with the deepening of basic and clinical research. Psoriasis is now considered to be caused by immune abnormalities, which are triggered by genetic and environmental factors.<sup>1,14</sup> There are many types of cells involved in psoriasis. Keratinocytes, as well as a variety of immune cells, including T cells, plasmacytoid dendritic cells

(pDCs), myeloid dendritic cells (mDCs), neutrophils, and macrophages, work together to form an inflammatory circuit to contribute to the pathogenesis and development of psoriasis.<sup>15</sup> However, each type of cell involved in psoriasis has its unique role in psoriasis. This article reviews the role of these cells in the pathogenesis and development of psoriasis, aiming to provide a deeper insight into psoriasis.

## Cellular Pathogenesis

### Keratinocytes

Keratinocytes are the major constituent cells of the skin epidermis. In addition to forming a mechanical barrier, they play key roles in the initiation, maintenance, and regulation of the skin immune response.<sup>16</sup> Keratinocytes are involved in the innate immune response by responding to antigenic stimuli in a rapid and nonspecific manner.<sup>17</sup> Although keratinocytes are not classical antigen-presenting cells, they can also process antigens and present them to T cells.<sup>18</sup> The function of keratinocytes is mainly determined by their activation and differentiation status. In the steady state, cell differentiation is normal, and the layers are constantly renewed. Keratinocytes in the basal layer are constantly transformed into spiny and granular layers, and eventually the nucleus disappears, forming the stratum corneum. In psoriatic lesions, the terminal differentiation of keratinocytes is incomplete, and cell proliferation is abnormal. Due to the rapid proliferation of cells, the keratinization of keratinocytes is incomplete, resulting in the nucleus remaining in epidermal keratinocytes,<sup>19</sup> which is pathologically known as parakeratosis.

During the development of psoriasis, a close relationship is established between keratinocytes, T cells, and dendritic cells (DCs). In response to environmental stimuli, bacteria, or some drugs, keratinocytes are stimulated and release a variety of cytokines. Simultaneously, stimulated keratinocytes release antimicrobial peptides (AMPs), such as LL37, which bind to nucleic acid DNA or RNA to form a complex. In addition to LL37, ADAMTS-like protein 5 (ADAMTSL5), which is selectively expressed by melanocytes in epidermis, has been reported to be another important autoantigen in psoriasis by stimulating CD8<sup>+</sup> cells. The LL-37-nucleic acid complex acts as an antigen to stimulate plasmacytoid DCs to release IFN- $\alpha/\gamma$ ,<sup>20</sup> which activates and transforms myeloid DCs into mature DCs.<sup>21</sup> Mature DCs circulate to draining lymph nodes and deliver antigens to T cells, and stimulate naive T cells differentiate into various effector cells, such as Th17, Th1, and Th22 cells, and express skin-resident receptors, such as CCR4, CCR6, and CCR10, which eventually migrate to specific sites in skin tissue and exert immune effects.<sup>22</sup>

In psoriatic lesions, a positive feedback loop is formed between keratinocytes and immune cells in response to inflammatory stimuli, which potently promotes the development of psoriasis. On the one hand, effector T cells release cytokines such as IL-23, IL-17, IL-22, and IFN- $\gamma$ , which act directly or indirectly on keratinocytes to promote the proliferation and abnormal differentiation of keratinocytes; on the other hand, stimulated keratinocytes actively release large amounts of antimicrobial peptides, cytokines, and chemokines to recruit more immune cells to the lesional skin, thereby maintaining and amplifying the inflammatory response in the local skin.<sup>23</sup> Such interactions create a positive feedback loop between immune cells and keratinocytes. Keratinocytes also release factors, such as vascular endothelial growth factor (VEGF), that promote the development of a typical pathological feature: angiogenesis.<sup>24</sup> Keratinocytes have also been found to secrete some cytokines that not only interact with other immune cells, but also act on themselves in an autocrine manner, such as IL-25 and IL-33, which promote inflammatory response in a positive feedback manner.<sup>25,26</sup> Keratinocytes mutations in Card14 gene amplify IL-17A signaling and promote the development of psoriatic dermatitis.<sup>27</sup> Moos et al reported that keratinocytes deletion of IL-17 receptor resulted in greatly reduced neutrophils recruitment and dermatitis development.<sup>28</sup> Lou et al reported that keratinocytes excessive polyamine generation promotes psoriatic skin inflammation.<sup>29</sup> Chen et al reported that keratinocytes Galectin-7 downregulation contributes to enhanced IL-17A signaling and skin pathology in psoriasis.<sup>30</sup> In addition, keratinocytes-derived miRNA and exosomes are also reported to regulate psoriasis pathogenesis and enhance psoriatic skin inflammation.<sup>31,32</sup> The roles of these molecules and signaling pathways in keratinocytes support the crucial role of keratinocytes in the development of psoriasis. Collectively, these studies indicate that keratinocytes play a key role in the pathogenesis and development of psoriasis.

## pDCs

pDCs are a small subpopulation of cells that predominantly reside in the local tissues. pDCs express Toll-like receptor 7 (TLR7) and TLR9, which recognize single-stranded RNA and DNA, respectively, and are involved in the antiviral response by producing large amounts of type I interferon.<sup>33</sup> Although pDCs are generally absent in the skin of healthy individuals, they have been found in the non-lesional skin and lesional skin of patients with psoriasis.<sup>34</sup> In addition, the number of pDCs is increased in psoriatic skin.<sup>35</sup> In the mouse model of imiquimod-induced psoriasis, pDCs promote psoriasis-like dermatitis by releasing large amounts of IFN- $\alpha/\beta$ .<sup>36–38</sup> Cristina et al showed that the increase of localized pDCs in psoriasis may be caused by fibroblasts-derived Chemerin, which promotes pDCs recruitment from high endothelial venules (HEV) to the dermis.<sup>39</sup>

Under normal homeostatic conditions, pDCs are tolerant to the DNA or RNA released by dead or stressed cells. While in psoriatic inflammatory conditions, AMP binds to nucleic acids to form complexes that serve as an autoantigen. This autoantigen stimulates pDCs activation through receptors TLR9/TLR7 and produces type I interferon, thereby activating T cells and promoting psoriasis initiation.<sup>40–42</sup> Another study in a xenograft mouse model showed that the activation and proliferation of T cells and the development of psoriasis were significantly inhibited by blocking type I interferon signaling or inhibiting the production of IFN- $\alpha$  from pDCs.<sup>34</sup> In addition, unregulated self-nucleic acid sensing by DCs facilitates psoriasis pathogenesis and progression.<sup>29</sup> Yin et al found that obstructing DC-sensory neuron communication mediated by pathogenic CGRP signaling ameliorated psoriasis.<sup>43</sup> Taken together, these studies suggest that pDCs play an important role in the initiation of psoriasis, as well as in the development of psoriasis.

## mDCs

mDCs were significantly increased in the psoriatic lesions. Zaba et al found an approximately 30-fold increase of CD11c<sup>+</sup> mDCs in psoriatic lesional skin compared to non-lesional skin of psoriasis patients and non-psoriatic normal skin.<sup>44</sup> The large amount of mDCs infiltration in psoriatic skin lesions suggests that mDCs play an important role in the pathogenesis of psoriasis.<sup>45</sup> On the one hand, mDCs in the psoriatic lesions could be activated by the pro-inflammatory cytokines IFN- $\alpha$  and IL-6 released by pDCs; and on the other hand, mDCs could be activated by the nucleic acid-LL-37 complex via TLR8, thus leading to TNF- $\alpha$  and IL-6 production and mDCs maturation.<sup>40</sup> Once mature, mDCs transform into mature antigen-presenting cells and secrete multiple cytokines, such as IL-12, IL-23, IFN- $\gamma$ , TNF- $\alpha$ , IL-1 $\beta$ , and IL-6, which interact with and activate naive T cells. In the stimuli of different cytokines, naive T cells differentiate into subpopulations such as Th-1, Th-17, and Th22.<sup>46,47</sup>

In addition to the classical DCs population, an inflammatory DCs subpopulation has also been identified in psoriatic skin.<sup>48,49</sup> The inflammatory subpopulation has been revealed to exhibit high heterogeneity and secrete multiple cytokines. This subpopulation includes TNF-secreting DC,<sup>50</sup> IL-20-secreting DC,<sup>51</sup> and IL-23-secreting DC.<sup>44,52</sup> TNF- secreted by mDCs in the skin acts on keratinocytes to promote the expression of adhesion molecules, chemokines, and some cytokines, such as IL-1, IL-6, and IL-8. mDCs can also release IL-20, which is a potent cytokine inducing the over-proliferation of keratinocytes.<sup>53</sup> In addition, mDCs are one of the major source cells producing IL-23 in psoriatic lesional skin.<sup>52,54</sup> Collectively, mDCs play an important role in the initiation and development of psoriasis.

## Th1 Cells

Th1 cells are a group of CD4<sup>+</sup> T cells that secrete mainly IFN- $\gamma$ , IL-2, and TNF- $\alpha$ . In the stimuli of IL-12, naive T cells differentiate into Th1 cells and thus increasing IFN- $\gamma$  secretion.<sup>55</sup> Th1 cells were once thought to be the predominant subpopulation of T cells that are involved in the local psoriatic inflammation.<sup>56,57</sup> Arican et al found that serum levels of IFN- $\gamma$ , TNF- $\alpha$ , and IL-12 were increased in patients with active psoriasis, and the serum levels were correlated with disease severity.<sup>58–61</sup> Besides, the number of Th1 cells in psoriatic lesions was found to be significantly increased.<sup>62</sup> In the early stages of psoriasis, Th1-secreted IFN- $\gamma$  activates antigen-presenting cells and stimulates antigen-presenting cells to produce and secrete chemokine CCL20.<sup>63</sup> Under the chemotaxis of CCL20, IL-17A<sup>+</sup> T cells are recruited to lesional skin to aggregate local skin inflammation. Additionally, IFN- $\gamma$ , synergizing with IL-17A, also promotes the production of substantial antimicrobial peptides by keratinocytes, thereby promoting the innate immune response.<sup>63,64</sup> Upon interaction with Th1 cells, stimulated keratinocytes release IL-1 family cytokines, including IL-18 and IL-1 $\beta$ , both of which play

important roles in Th1 cells function and early differentiation of Th17 cells.<sup>65,66</sup> Lin et al reported that the increased differentiation of Th1 cells contributes to the pathogenesis of psoriasis.<sup>67</sup> Taken together, these studies suggest that Th1 cells play a promotive role in the pathogenesis of psoriasis.

## Th17 Cells

Th17 cells play a predominant role in the pathogenesis and development of psoriasis. Th17 cells are a group of CD4<sup>+</sup> T cells that mainly secrete IL-17A. The differentiation of Th17 cells is dependent on the transcription factor ROR $\gamma$ t. Under the stimulation of cytokines IL-1 $\beta$ , TGF- $\beta$ , IL-6, and IL-23, ROR $\gamma$ t is induced and activated in naive T cells, which then differentiate into Th17 cells.<sup>68,69</sup> Th17 cells have been implicated in the pathogenesis of multiple inflammatory diseases, including psoriasis. Th17 cells differentiated by IL-6, IL-1 $\beta$ , and IL-23 stimulation are mostly involved in chronic inflammatory and autoimmune diseases, and Th17 cells differentiated by TGF- $\beta$  and IL-6 stimulation are less pathogenic and are mainly involved in maintaining tissue homeostasis and immune defense.<sup>70,71</sup> Most of the Th17 cells in psoriatic lesions are pathogenic and directly contribute to the pathogenesis and development of psoriasis.

An increasing number of studies have shown that Th17 cells play key roles in both psoriatic model mice and psoriasis patients. In psoriatic model mice, topical application of imiquimod induces psoriasis-like pathological features and skin inflammation mediated by the IL-23/Th-17 signaling axis.<sup>72</sup> Topical dermal injection of recombinant IL-23 causes psoriasis-like dermatitis in mice by promoting Th17 differentiation.<sup>73</sup> Blockading IL-17 signaling with anti-IL-17A antibodies or knockout of IL-17A or IL-23 significantly alleviates psoriatic disease manifestations and severity.<sup>72,73</sup> Th17 cells have been found to be essential for the development of psoriasis not only in mouse model, but also in clinical studies. Fujishima and Carlo et al found that the number of IL-17A-producing CD4<sup>+</sup> T cells was significantly higher in psoriatic lesional skin compared to non-psoriatic normal skin.<sup>74,75</sup> Treatment with anti-IL-17A monoclonal antibodies resulted in significant attenuation in patients with psoriasis.<sup>76,77</sup> In addition, inhibition of Th17 cell differentiation by using anti-IL-23 antibodies has shown promising clinical efficacy.<sup>78</sup> In psoriatic lesions, Th17 cells secrete cytokines, such as IL-17A, IL-12, IL-22, and IL-9, which act directly or indirectly on keratinocytes to promote keratinocytes abnormal proliferation and induce the release of cytokines and chemokines, such as IL-6, IL-8, TNF- $\alpha$ , CCL20, and CXCL1/2/3/5/8. These cytokines, in return, recruit Th17 cells or neutrophils to the local skin of psoriatic lesions, further amplifying the inflammatory response.<sup>64,79–81</sup>

Currently, a number of antibodies targeting IL-17 signaling have been developed and used in the clinical treatment of psoriasis, including secukinumab, ixekizumab, and brodalumab. All of these targeting antibodies have been shown to significantly alleviate psoriatic severity after months of treatment,<sup>82–84</sup> indicating the key role of Th17 cells in the development of psoriasis. In addition to anti-IL-17a antibody, inhibition of Th17 cells differentiation by some small compounds are also reported to ameliorate IMQ-induced psoriasis-like dermatitis.<sup>85</sup> Therefore, considering the key roles of IL-17A, the treatment of psoriasis by targeting Th17 cells and IL-17 signaling has now become one of the key focuses of psoriatic research.<sup>13</sup> In summary, Th17 cells play a predominant role in the pathogenesis, development, and maintenance of psoriasis.

## Th22 Cells

IL-22 is a cytokine produced by Th22 cells and has been reported to be a potent inducer of keratinocyte hyperproliferation.<sup>86</sup> Luan et al found that the number of Th22 cells and plasma levels of IL-22 increased in patients with psoriasis and were positively correlated with disease severity.<sup>62,87</sup> High levels of IL-22 induce the expression and release of antimicrobial peptides (AMPs), such as S100A7, S100A8, S100A9, and  $\beta$ -defensin, as well as neutrophil chemokines, including CXCL8, CXCL5, and CXCL1, in the epidermis.<sup>88</sup> All these upregulated molecules contribute directly or indirectly to facilitating the development of psoriasis.

IL-22 also inhibits the normal differentiation of keratinocytes and interferes with skin healing processes.<sup>89</sup> Ekman et al reported that IL-22 acts directly on keratinocytes to promote cell stemness and hyperproliferation.<sup>85</sup> Zheng et al found that IL-22 induces psoriatic dermatitis and epidermal acanthosis by activating the IL-23 signaling pathway mediated by STAT3.<sup>90</sup> IL-22 deficiency markedly attenuates IL-23-induced epidermal hyperplasia and skin inflammation.<sup>90</sup> In addition, Van Belle et al found that in a mouse model of psoriasis, knockout IL-22 gene or treatment

with IL-22-neutralizing antibody significantly reduced antimicrobial peptide levels and inhibited psoriatic progression.<sup>91</sup> During active psoriasis, Th22 cells in the epidermis express increased levels of IL-22, which activates keratinocytes and leads to acanthosis. In addition, Th22 cells in the epidermis of clinically healed psoriatic skin continue to produce IL-22 after six years of remission,<sup>92</sup> indicating that Th22 may be also involved in the relapse of psoriasis. Taken together, these studies indicate that Th22 cells play an important role in the development and relapse of psoriasis.

## $\gamma\delta$ T Cells

The role of  $\gamma\delta$ T cells in psoriasis is considered to depend mainly on the production of IL-17A, which amplifies IL-17A signaling in psoriasis.<sup>93,94</sup> In response to IL-23, IL-1 $\beta$ , or some other stimuli,  $\gamma\delta$ T cells are rapidly activated and produce IL-17A, thereby promoting the Th17 immune response.<sup>95</sup> In murine study, deficiency of  $\gamma\delta$ T cells by knockout of the T cell receptor delta gene (Tcrd<sup>-/-</sup>) in mice significantly reduced disease manifestations and IL-17A levels compared to those in wild-type (WT) mice upon psoriatic model induction.<sup>96,97</sup> In addition, Cai et al found that after intradermal injection of recombinant IL-23, Tcrd<sup>-/-</sup> mice exhibited significantly attenuated psoriasis-like skin inflammation and epidermal thickening compared with WT mice, suggesting an important role of  $\gamma\delta$ T cells in the development of psoriasis.<sup>96</sup> In a clinical study, a large amount of IL-17A-producing  $\gamma\delta$ T cells was found in the lesional skin of psoriasis patients, and dermal  $\gamma\delta$ T cells increased the expression of IL-17A and CCR6 upon IL-23 stimulation.<sup>96</sup>  $\gamma\delta$ T cells in human blood are usually V $\gamma$ 9V $\delta$ 2 T cells, and the number of V $\gamma$ 9V $\delta$ 2 T cells increases in the lesional skin and decreases in the peripheral blood of patients with psoriasis, indicating that  $\gamma\delta$ T cells may migrate from the blood to the local skin to promote the pathogenesis and development of psoriasis. Ute et al found that V $\gamma$ 9V $\delta$ 2 T cells contribute to the development of psoriasis by releasing large amounts of psoriasis-related cytokines, IFN- $\gamma$ , TNF- $\alpha$ , and IL-9, as well as chemokines CCL3, CCL4, and CCL5.<sup>98</sup>

In addition to pathogenesis and development, a recent study revealed that  $\gamma\delta$ T cells may contribute to psoriasis relapse. The relapse of psoriasis around the primary lesions suggests an “immune memory” for psoriasis recurrence. In the IMQ-induced psoriasis mice model, dermal V $\gamma$ 4<sup>+</sup> T cells aggravate the psoriatic skin inflammation in IMQ-re-challenged mice.<sup>99</sup> Besides, dermal IL-17-producing  $\gamma\delta$ T cells have been reported to establish a long-lived memory phenotype in the skin, which may be associated with the relapse of psoriasis. Taken together,  $\gamma\delta$ T cells increase in psoriatic lesions and play an important role in the pathogenesis, development, and relapse of psoriasis.

## Regulatory T (Treg) Cells

The dysfunction of Treg cells is closely associated with the pathogenesis and development of psoriasis.<sup>100</sup> Treg cells belong to a group of regulatory T lymphocytes. Treg cells are characterized by high expression of the CD25 receptor, transcription factor FOXP3, and the production of immunosuppressive factors, such as IL-10.<sup>101</sup> Normally, Treg cells serve as an immunosuppressive member and play an important role in immune homeostasis by suppressing excessive immune responses.<sup>102</sup> Under normal conditions, Treg cells secrete multiple suppressive cytokines, thereby downregulating the expression and release of inflammatory cytokines, chemokines, and adhesion molecules.<sup>103</sup> In contrast, in psoriatic inflammation, Treg cells are found to lose their immunosuppressive function and are associated with psoriatic skin inflammation. Yan et al reported that the number of FOXP3<sup>+</sup> Treg cells is increased in the peripheral blood and the skin lesions of psoriasis patients, and the number of FOXP3<sup>+</sup> Treg cells is positively correlated with the severity of psoriasis,<sup>104–106</sup> suggesting that Treg cells may play a promotive role in the development of psoriasis. In addition to the dysfunction of Treg cells in peripheral blood, studies have also revealed the dysfunction of Treg cells in the skin lesions of psoriasis patients.<sup>107</sup> A study by Soler et al showed that Treg cells in psoriatic lesions had abnormalities in terms of cell number, function, and chemotaxis and therefore failed to suppress the inflammatory response in psoriasis.<sup>108</sup>

Treg cells also showed high plasticity under the influence of the local inflammatory microenvironment.<sup>109</sup> A study by Jorn et al showed that FOXP3-positive Treg cells in psoriatic lesions could transform into triple-positive IL-17A<sup>+</sup>FOXP3<sup>+</sup>CD4<sup>+</sup> Th-17 cells, which have a strong pro-inflammatory effect and thus aggravate psoriatic inflammation.<sup>110</sup> Taken together, Treg cells are dysfunctional in psoriatic lesions and play a promotive role in the development of psoriasis, suggesting that restoring the normal function of Treg cells may be a potential strategy for psoriatic therapy.



## Neutrophils

Neutrophils are found to play an important role in the development of psoriasis. In murine study, Shao et al found that activation of neutrophils exacerbated disease manifestations in IMQ-induced psoriatic model mice.<sup>111</sup> In clinical study, a previous study indicated that the neutrophil-to-lymphocyte ratio was significantly increased in psoriatic patients,<sup>112</sup> and that the neutrophils-to-lymphocytes ratio was associated with the severity of psoriasis.<sup>113</sup> In addition, the neutrophil-to-lymphocyte ratio decreased after psoriasis patients received treatment, which further indicated the role of neutrophils in the progression of the disease.<sup>114</sup> Reich et al reported that clinical application of anti-IL-17A antibodies probably initially targets neutrophil-derived IL-17A to interrupt the loop between keratinocytes and neutrophils, thus achieving a good therapeutic effect.<sup>115</sup>

Neutrophil chemokines such as CXCL1, CXCL2, and CXCL8/IL-8 are abundantly expressed in the skin lesions of psoriatic model mice and recruit neutrophils from the peripheral blood into the lesional skin. Under the chemotaxis of these chemokines, neutrophils gradually accumulate in the stratum corneum of the epidermis in psoriatic lesions, forming a typical histopathological hallmark of psoriasis: Munro's microabscess.<sup>116</sup> In addition to chemokines, neutrophils also release some inflammatory mediators, such as protease 3, to accelerate the progression of psoriasis. Protease 3 cleaves pro-IL-36 into mature IL-36 cytokine, which, along with TNF- $\alpha$  and IFN- $\gamma$ , amplify the response of mDCs.<sup>117</sup> In addition, neutrophils closely interact with Th17 cells in the stimuli of psoriatic inflammation. IL-17A and IL-17F released by Th17 cells in the psoriatic lesions can also effectively induce chemotaxis and activate neutrophils, thus linking adaptive and innate immunity.<sup>118</sup>

Neutrophils are an important subpopulation of innate immune cells and could participate in immune defense via phagocytosis or formation of extracellular bactericidal networks (NETs). NETs are meshwork structures that are composed of extruded sticky chromatin covered with many antimicrobial components, including histones, MPO, cathepsin G, high mobility group protein B1, and antimicrobial peptides such as LL-37.<sup>119</sup> In patients with psoriasis, neutrophils are pre-activated and generate NETs in the psoriatic lesions.<sup>120</sup> Studies have shown that NETs are increased in the peripheral blood of patients with psoriasis and are associated with the severity of psoriasis.<sup>119,121</sup> Except from peripheral blood, researchers have also found elevated levels of NETs in psoriatic lesions by staining for nucleic acids and neutrophil elastase.<sup>121–123</sup> NETs-derived proteins may act as self-antigens and mediate tissue damage in psoriasis.<sup>124</sup> Studies have also shown that NETs may be involved in extracellular DNA production in the epidermis, thereby mediating the formation of nucleic acid-antimicrobial peptide complexes, suggesting that NETs contribute to the pathogenesis of psoriasis.<sup>125</sup>

In addition to psoriatic pathogenesis, NETs are also involved in the development of psoriasis.<sup>126</sup> NETs stimulate epidermal keratinocytes to release inflammatory cytokines by activating crosstalk between TLR4 and IL-36R.<sup>120</sup> Besides, NETs also promote the synthesis of inflammatory mediators, such as IFN- $\alpha$  and IFN- $\beta$  in plasmacytoid dendritic cells.<sup>127</sup> Myeloid dendritic cells are subsequently activated to release a variety of pro-inflammatory mediators, such as IL-6, IL-12, IL-23, and TNF- $\alpha$ ,<sup>128</sup> which play an important role in initiating Th1, Th17, and Th22 cellular immune responses.<sup>129</sup> Neutrophils are also one of the major sources producing IL-17A through forming NETs in psoriasis.<sup>123,130</sup> Activation of NETs is closely associated with Th17 responses in psoriasis patients.<sup>131</sup> Moreover, NETs can also contribute to the progression of psoriasis by facilitating the link between innate and adaptive immune responses through priming of T cells.<sup>132</sup> Altogether, these studies indicate that neutrophils play a crucial role in the pathogenesis and development of psoriasis.

## Macrophages

An increasing number of studies have reported that macrophages are closely associated with psoriasis. In murine study, Leite Dantas et al showed that TNF transgenic mice showed psoriasis-like manifestations, and the number of macrophages was significantly increased compared to the control mice. Importantly, depletion of macrophages in mice decreased psoriatic inflammation and disease severity.<sup>133</sup> Besides, Morimura et al found that decreasing the number of macrophages alleviated psoriasis-like inflammation by decreasing the expression of psoriasis-related cytokines.<sup>134</sup> Macrophages polarization induced by IL-23 promoted the development of disease in imiquimod-induced psoriasis-like

dermatitis in mice.<sup>135</sup> In clinical study, psoriasis patients had elevated levels of circulating monocytes in the peripheral blood,<sup>136</sup> and they were mainly M1 macrophages.<sup>137</sup> Marble et al found that the number of macrophages increased in the lesions of psoriasis patients and decreased to non-lesional skin levels after effective treatment with TNF- $\alpha$  inhibitors.<sup>44,138</sup> In another study, Koh et al reported that the activity of macrophages were increased in the lesional skin of patients with psoriasis,<sup>139</sup> suggesting the involvement of macrophages in psoriasis.

Macrophages are highly plastic and heterogeneous, and the diversity of macrophages population facilitates the contribution of macrophages in psoriasis.<sup>140</sup> Some macrophages in the skin are skin-resident cells and play an important role in tissue repair and regeneration.<sup>141,142</sup> There is also a subpopulation of macrophages belonging to inflammatory macrophages, which are involved in the innate immune response and play a dual role in immune response as phagocytes and antigen-presenting cells. In the local inflammatory microenvironment of psoriatic lesions, macrophages are recruited to the lesions by chemokines, such as CCL2 and MCP-1,<sup>143,144</sup> and contribute to the development of psoriasis by producing a variety of cytokines and chemokines, including IL-23, IL-6, IL-8, TNF- $\alpha$ , IFN- $\gamma$ , CXCL1, CXCL5, and CCL5.<sup>144–146</sup> In addition, activated macrophages are also crucial in maintaining tissue homeostasis by phagocytosis and in regulating psoriatic blood vessel hyperplasia by releasing vascular endothelial growth factor (VEGF).<sup>147</sup> In conclusion, macrophages play an important role in facilitating the development and maintenance of psoriasis.

## Discussion

Psoriasis seriously affects the quality of individual's life and brings economic burdens on individuals as well as the whole society.<sup>1</sup> Psoriasis pathogenesis implicates many types of cells, and the key role of T cells, especially Th17 cells, in the pathogenesis of psoriasis is now increasingly being recognized. However, an increasing number of basic studies and clinical findings have shown that in addition to Th17 cells, some other cells also play a crucial role in the pathogenesis and development of psoriasis.<sup>13</sup> Previous studies on psoriasis showed that the underlying pathogenesis involves an intense and intertwined inflammatory network mediated by keratinocytes, T lymphocytes, dendritic cells, macrophages, neutrophils, and gamma T cells. In the presence of complex genetic and environmental factors, these cells work together to induce the pathogenesis and development of psoriasis.<sup>14</sup>

Advances in the understanding of the immune pathogenesis of psoriasis have led to the successful development of new targeted biologic agents, including anti-IL-23 antibodies, anti-IL-17A antibodies, and anti-TNF- $\alpha$  antibodies.<sup>128</sup> All of these antibodies are found to control or alleviate clinical manifestations and symptoms in most of the psoriasis patients, significantly improving the clinical situation and patients' lives. However, most of these targeted molecules are involved in normal physiological processes, such as antiviral, bacterial, or fungal infections. Long-term use of targeted antibodies often leads to negative consequences, such as depression and suicidal ideation, which should not be neglected.<sup>148</sup> Therefore, we should try to explore more effective targets and therapeutic options with fewer side effects to benefit psoriasis patients. For example, enhancing the immunosuppressive function of Treg cells and inhibiting the activation of Th cells, pDCs, and keratinocytes may deserve further investigation. The development of topical small molecule drugs that can penetrate the skin barrier is of particular interest, as these drugs may be effective topical therapeutic strategies that can reduce systemic side effects in patients with psoriasis. In addition, interdisciplinary collaboration could not only address issues such as the systemic effects of psoriatic inflammation, but also further provide the possibility of personalized targeted therapies. Altogether, by providing a deep review of psoriasis pathogenesis at the cellular level, we hope that new therapeutic strategies for restoring immune homeostasis by regulating cell immune response or immune tolerance appear in the near future.

## Conclusion

Great progress has been made in recent years in the understanding of the pathogenesis of psoriasis, which includes the identification of the key cytokines IL-17A and IL-23 and the development and clinical application of targeting antibodies against these cytokines. Th17 cells is considered to play a crucial role in the pathogenesis of psoriasis. However, the development of psoriasis cannot be fully explained by the response of Th17 lymphocytes. Targeting cytokine IL-17A or IL-23 does not completely cure psoriasis. Now, an increasing number of studies show that the interaction of various cytokines and different cells, including DCs, neutrophils, macrophages, keratinocytes, and Th17 cells, constitutes

a complex cascade of events that ultimately leads to the pathogenesis and development of psoriasis. Therefore, researchers should spare more focus on multiple cells, multiple targets, and interdisciplinary collaboration in the development of psoriasis therapeutic strategies. However, our present understanding of the pathogenesis and progression of psoriasis is still incomplete and much remains to be uncovered. Hence, it is of great necessity to delve deeper into the pathogenic mechanisms of each type of cell in psoriasis and provide new insights into the pathogenesis of psoriasis. As our understanding of the pathogenesis of psoriasis deepens, we will be able to develop new therapeutic strategies and provide patients with other options that have good efficacy and fewer side effects.

## Data Sharing Statement

This is a review article. All data generated or analyzed during this study are included in this published article.

## Author Contributions

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

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## Disclosure

The authors report no conflicts of interest in this work.

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