

# Cellular Mechanisms of Psoriasis Pathogenesis: A Systemic Review

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**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.

## References

1. Griffiths CEM, Armstrong AW, Gudjonsson JE, Barker J. Psoriasis. *Lancet*. 2021;397(10281):1301–1315. doi:10.1016/S0140-6736(20)32549-6
2. Michalek IM, Loring B, John SM. A systematic review of worldwide epidemiology of psoriasis. *J Eur Acad Dermatol Venereol*. 2017;31(2):205–212. doi:10.1111/jdv.13854
3. Pezzolo E, Naldi L. Epidemiology of major chronic inflammatory immune-related skin diseases in 2019. *Expert Rev Clin Immunol*. 2020;16(2):155–166. doi:10.1080/17446666X.2020.1719833
4. Machado-Pinto J, Diniz Mdos S, Bavoso NC. Psoriasis: new comorbidities. *An Bras Dermatol*. 2016;91(1):8–14. doi:10.1590/abd1806-4841.20164169
5. Takeshita J, Grewal S, Langan SM, et al. Psoriasis and comorbid diseases: epidemiology. *J Am Acad Dermatol*. 2017;76(3):377–390. doi:10.1016/j.jaad.2016.07.064
6. Ferdinando LB, Fukumoto PK, Sanches S, Fabricio LHZ, Skare TL. Metabolic syndrome and psoriasis: a study in 97 patients. *Rev Assoc Med Bras*. 2018;64(4):368–373. doi:10.1590/1806-9282.64.04.368
7. Masson W, Lobo M, Molinero G. Psoriasis and cardiovascular risk: a comprehensive review. *Adv Ther*. 2020;37(5):2017–2033. doi:10.1007/s12325-020-01346-6
8. Santus P, Rizzi M, Radovanovic D, et al. Psoriasis and respiratory comorbidities: the added value of fraction of exhaled nitric oxide as a new method to detect, evaluate, and monitor psoriatic systemic involvement and therapeutic efficacy. *Biomed Res Int*. 2018;2018:3140682. doi:10.1155/2018/3140682
9. Damiani G, Radaeli A, Olivini A, Calvara-Pinton P, Malerba M. Increased airway inflammation in patients with psoriasis. *Br J Dermatol*. 2016;175(4):797–799. doi:10.1111/bjd.14546
10. Furue M, Kadono T. “Inflammatory skin march” in atopic dermatitis and psoriasis. *Inflamm Res*. 2017;66(10):833–842. doi:10.1007/s00011-017-1065-z
11. Rousset L, Halioua B. Stress and psoriasis. *Int J Dermatol*. 2018;57(10):1165–1172. doi:10.1111/ijd.14032
12. Springate DA, Parisi R, Kontopantelis E, Reeves D, Griffiths CE, Ashcroft DM. Incidence, prevalence and mortality of patients with psoriasis: a UK population-based cohort study. *Br J Dermatol*. 2017;176(3):650–658. doi:10.1111/bjd.15021
13. Armstrong AW, Read C. Pathophysiology, clinical presentation, and treatment of psoriasis: a review. *JAMA*. 2020;323(19):1945–1960. doi:10.1001/jama.2020.4006
14. Uppala R, Tsoi LC, Harms PW, et al. “Autoinflammatory psoriasis”—genetics and biology of pustular psoriasis. *Cell Mol Immunol*. 2021;18(2):307–317. doi:10.1038/s41423-020-0519-3
15. Ogawa E, Sato Y, Minagawa A, Okuyama R. Pathogenesis of psoriasis and development of treatment. *J Dermatol*. 2018;45(3):264–272. doi:10.1111/1346-8138.14139
16. Barker JNWN, Griffiths CEM, Nickoloff BJ, Mitra RS, Dixit VM, Nickoloff BJ. Keratinocytes as initiators of inflammation. *Lancet*. 1991;337(8735):211–214. doi:10.1016/0140-6736(91)92168-2
17. Nestle FO, Di Meglio P, Qin JZ, Nickoloff BJ. Skin immune sentinels in health and disease. *Nat Rev Immunol*. 2009;9(10):679–691. doi:10.1038/nri2622



18. Michael M, Amel T, Evelyn G, et al. Self-antigen presentation by keratinocytes in the inflamed adult skin modulates T-cell auto-reactivity. *J Invest Dermatol.* 2015;135(8):1996–2004. doi:10.1038/jid.2015.130
19. Griffiths CEM, Barker JNWN. Pathogenesis and clinical features of psoriasis. *Lancet.* 2007;370(9583):263–271. doi:10.1016/S0140-6736(07)61128-3
20. Lande R, Botti E, Jandus C, et al. The antimicrobial peptide LL37 is a T-cell autoantigen in psoriasis. *Nat Commun.* 2014;5(1):5621. doi:10.1038/ncomms6621
21. Kim TG, Kim SH, Lee MG. The origin of skin dendritic cell network and its role in psoriasis. *Int J Mol Sci.* 2017;19(1):42. doi:10.3390/ijms19010042
22. Diani M, Altomare G, Realì E. T cell responses in psoriasis and psoriatic arthritis. *Autoimmun Rev.* 2015;14(4):286–292. doi:10.1016/j.autrev.2014.11.012
23. Cai Y, Fleming C, Yan J. New insights of T cells in the pathogenesis of psoriasis. *Cell Mol Immunol.* 2012;9(4):302–309. doi:10.1038/cmi.2012.15
24. Benhadou F, Gritzner E, Brisebarre A, et al. Epidermal autonomous VEGFA/Flt1/Nrp1 functions mediate psoriasis-like disease. *Sci Adv.* 2020;6(2):eaax5849. doi:10.1126/sciadv.aax5849
25. Xu M, Lu H, Lee YH, et al. An interleukin-25-mediated autoregulatory circuit in keratinocytes plays a pivotal role in psoriatic skin inflammation. *Immunity.* 2018;48(4):787–798.e784. doi:10.1016/j.immuni.2018.03.019
26. Zeng F, Chen H, Chen L, et al. An autocrine circuit of IL-33 in keratinocytes is involved in the progression of psoriasis. *J Invest Dermatol.* 2021;141(3):596–606.e597. doi:10.1016/j.jid.2020.07.027
27. Wang MC, Zhang SS, Zheng GX, et al. Gain-of-function mutation of card14 leads to spontaneous psoriasis-like skin inflammation through enhanced keratinocyte response to IL-17A. *Immunity.* 2018;49(1):66–+. doi:10.1016/j.immuni.2018.05.012
28. Moos S, Mohebiany AN, Waisman A, Kurschus FC. Imiquimod-induced psoriasis in mice depends on the IL-17 signaling of keratinocytes. *J Invest Dermatol.* 2019;139(5):1110–1117. doi:10.1016/j.jid.2019.01.006
29. Lou F, Sun Y, Xu Z, et al. Excessive polyamine generation in keratinocytes promotes self-RNA sensing by dendritic cells in psoriasis. *Immunity.* 2020;53(1):204–216.e210. doi:10.1016/j.immuni.2020.06.004
30. Chen HL, Lo CH, Huang CC, et al. Galectin-7 downregulation in lesional keratinocytes contributes to enhanced IL-17A signaling and skin pathology in psoriasis. *J Clin Invest.* 2021;131(1). doi:10.1172/JCI130740
31. Jiang M, Fang H, Shao S, et al. Keratinocyte exosomes activate neutrophils and enhance skin inflammation in psoriasis. *FASEB J.* 2019;33(12):13241–13253. doi:10.1096/fj.201900642R
32. Huang C, Zhong W, Ren X, et al. MiR-193b-3p-ERBB4 axis regulates psoriasis pathogenesis via modulating cellular proliferation and inflammatory-mediator production of keratinocytes. *Cell Death Dis.* 2021;12(11):963. doi:10.1038/s41419-021-04230-5
33. Michel G, Wei C, Yong-Jun L. Plasmacytoid dendritic cells: sensing nucleic acids in viral infection and autoimmune diseases. *Nat Rev Immunol.* 2008;8(8):594. doi:10.1038/nri2358
34. Nestle FO, Curdin C, Adrian TK, et al. Plasmacytoid dendritic cells initiate psoriasis through interferon-alpha production. *J Exp Med.* 2005;202(1):135–143. doi:10.1084/jem.20050500
35. Wollenberg A, Günther S, Moderer M, et al. Plasmacytoid dendritic cells: a new cutaneous dendritic cell subset with distinct role in inflammatory skin diseases. *J Invest Dermatol.* 2002;119(5):1096–1102. doi:10.1046/j.1523-1747.2002.19515.x
36. Michel G, Curdin C, Michael G, et al. Psoriasis triggered by toll-like receptor 7 agonist imiquimod in the presence of dermal plasmacytoid dendritic cell precursors. *Arch Dermatol.* 2004;140(12):1490. doi:10.1001/archderm.140.12.1490
37. Schmid P, Itin P, Cox D, McMaster GK, Horisberger MA. The type I interferon system is locally activated in psoriatic lesions. *J Interferon Res.* 1994;14(5):229–234. doi:10.1089/jir.1994.14.229
38. Walter A, Schäfer M, Cecconi V, et al. Aldara activates TLR7-independent immune defence. *Nat Commun.* 2013;4(3):1560. doi:10.1038/ncomms2566
39. Cristina A, Claudia S, Sabatino P, et al. Chemerin expression marks early psoriatic skin lesions and correlates with plasmacytoid dendritic cell recruitment. *J Exp Med.* 2009;206(1):249. doi:10.1084/jem.20080129
40. Ganguly D, Chamilos G, Lande R, et al. Self-RNA-antimicrobial peptide complexes activate human dendritic cells through TLR7 and TLR8. *J Exp Med.* 2009;206(9):1983–1994. doi:10.1084/jem.20090480
41. Roberto L, Josh G, Valeria F, et al. Plasmacytoid dendritic cells sense self-DNA coupled with antimicrobial peptide. *Nature.* 2007;449(7162):564–569. doi:10.1038/nature06116
42. Shin M, Kenshi Y, Beda M, et al. Cathelicidin antimicrobial peptide LL-37 in psoriasis enables keratinocyte reactivity against TLR9 ligands. *J Invest Dermatol.* 2012;132(1):135–143. doi:10.1038/jid.2011.259
43. Yin Q, Sun L, Cai X, et al. Lidocaine ameliorates psoriasis by obstructing pathogenic CGRP signaling-mediated sensory neuron-dendritic cell communication. *J Invest Dermatol.* 2022;142(8):2173–2183.e2176. doi:10.1016/j.jid.2022.01.002
44. Zaba LC, Irma C, Patricia G, et al. Amelioration of epidermal hyperplasia by TNF inhibition is associated with reduced Th17 responses. *J Exp Med.* 2007;204(13):3183–3194. doi:10.1084/jem.20071094
45. Nestle FO, Turka LA, Nickoloff BJ. Characterization of dermal dendritic cells in psoriasis. Autostimulation of T lymphocytes and induction of Th1 type cytokines. *J Clin Invest.* 1994;94(1):202–209. doi:10.1172/JCI117308
46. Kim J, Krueger JG. The immunopathogenesis of psoriasis. *Dermatol Clin.* 2015;33(1):13–23. doi:10.1016/j.det.2014.09.002
47. Greb JE, Goldminz AM, Elder JT, et al. Psoriasis. *Nat Rev Dis Primers.* 2016;2:16082. doi:10.1038/nrdp.2016.82
48. Zaba LC, Krueger JG, Lowes MA. Resident and “inflammatory” dendritic cells in human skin. *J Invest Dermatol.* 2009;129(2):302–308. doi:10.1038/jid.2008.225
49. Zaba LC, Judilyn FD, Narat John E, et al. Psoriasis is characterized by accumulation of immunostimulatory and Th1/Th17 cell-polarizing myeloid dendritic cells. *J Invest Dermatol.* 2009;129(1):79. doi:10.1038/jid.2008.194
50. Lowes MA, Chamian F, Abello MV, et al. Increase in TNF- $\alpha$  and inducible nitric oxide synthase-expressing dendritic cells in psoriasis and reduction with efalizumab (anti-CD11a). *Proc Natl Acad Sci.* 2005;102(52):19057–19062. doi:10.1073/pnas.0509736102
51. Frank W, Edmund L, Lowes MA, et al. Prominent production of IL-20 by CD68+/CD11c+ myeloid-derived cells in psoriasis: gene regulation and cellular effects. *Digest World Core Med J.* 2006;126(7):1590–1599.
52. Lee E, Trepicchio WL, Oestreicher JL, et al. Increased expression of interleukin 23 p19 and p40 in lesional skin of patients with psoriasis vulgaris. *J Exp Med.* 2004;199(1):125–130. doi:10.1084/jem.20030451
53. Sa SM, Valdez PA, Jianfeng W, et al. The effects of IL-20 subfamily cytokines on reconstituted human epidermis suggest potential roles in cutaneous innate defense and pathogenic adaptive immunity in psoriasis. *J Immunol.* 2007;178(4):2229. doi:10.4049/jimmunol.178.4.2229

54. Gamze P, Sylva-Steenland RMR, Bos JD, Teunissen MBM. In vitro and in situ expression of IL-23 by keratinocytes in healthy skin and psoriasis lesions: enhanced expression in psoriatic skin. *J Immunol.* 2006;176(3):1908–1915. doi:10.4049/jimmunol.176.3.1908
55. Bing S. *T Helper Cell Differentiation and Their Function*. Springer; 2014.
56. Schlaak JF, Buslau M, Jochum W, et al. T cells involved in psoriasis vulgaris belong to the Th1 subset. *J Invest Dermatol.* 1994;102(2):145–149. doi:10.1111/1523-1747.ep12371752
57. Austin LM, Ozawa M, Kikuchi T, Walters IB, Krueger JG. The majority of epidermal T cells in psoriasis vulgaris lesions can produce type 1 cytokines, interferon- $\gamma$ , interleukin-2, and tumor necrosis factor- $\alpha$ , defining TC1 (Cytotoxic T Lymphocyte) and TH1 effector populations: 1 a type 1 differentiation bias is. *J Invest Dermatol.* 1999;113(5):752–759. doi:10.1046/j.1523-1747.1999.00749.x
58. Kenan A, Okan T, Sevim A, et al. Effects of malassezia yeasts on serum Th1 and Th2 cytokines in patients with guttate psoriasis. *Int J Dermatol.* 2013;52(1):46–52. doi:10.1111/j.1365-4632.2011.05280.x
59. Szabo SK, Hammerberg C, Yoshida Y, Bata-Csorgo Z, Cooper KD. Identification and quantitation of interferon-gamma producing T cells in psoriatic lesions: localization to both CD4+ and CD8+ subsets. *J Invest Dermatol.* 1998;111(6):1072–1078. doi:10.1046/j.1523-1747.1998.00419.x
60. Uyemura K, Yamamura M, Fivenson DF, Modlin RL, Nickoloff BJ. The cytokine network in lesional and lesion-free psoriatic skin is characterized by a T-helper type 1 cell-mediated response. *J Invest Dermatol.* 1993;101(5):701. doi:10.1111/1523-1747.ep12371679
61. Arican O, Aral M, Sasmaz S, Ciragil P. Serum levels of TNF- $\alpha$ , IFN- $\gamma$ , IL-6, IL-8, IL-12, IL-17, and IL-18 in patients with active psoriasis and correlation with disease severity. *Mediators Inflamm.* 2005;2005(5):273–279.
62. Kagami S, Rizzo HL, Lee JJ, Koguchi Y, Blauvelt A. Circulating Th17, Th22, and Th1 cells are increased in psoriasis. *J Invest Dermatol.* 2010;130(5):1373–1383. doi:10.1038/jid.2009.399
63. Ilona K, Bruce AT, Gudjonsson JE, et al. Induction of IL-17+ T cell trafficking and development by IFN- $\gamma$ : mechanism and pathological relevance in psoriasis. *J Immunol.* 2008;181(7):4733. doi:10.4049/jimmunol.181.7.4733
64. Hawkes JE, Chan TC, Krueger JG. Psoriasis pathogenesis and the development of novel targeted immune therapies. *J Allergy Clin Immunol.* 2017;140(3):645–653. doi:10.1016/j.jaci.2017.07.004
65. Dinarello CA. IL-18: a TH1-inducing, proinflammatory cytokine and new member of the IL-1 family. *J Allergy Clin Immunol.* 1999;103(1):11–24. doi:10.1016/S0091-6749(99)70518-X
66. Chung Y, Chang SH, Martinez GJ, et al. Critical regulation of early Th17 cell differentiation by interleukin-1 signaling. *Immunity.* 2009;30(4):576–587. doi:10.1016/j.immuni.2009.02.007
67. Lin Y, Xue K, Li Q, et al. Cyclin-dependent kinase 7 promotes Th17/Th1 cell differentiation in psoriasis by modulating glycolytic metabolism. *J Invest Dermatol.* 2021;141(11):2656–2667.e2611. doi:10.1016/j.jid.2021.04.018
68. Ivanov II, McKenzie BS, Zhou L, et al. The orphan nuclear receptor ROR $\gamma$  directs the differentiation program of proinflammatory IL-17 + T helper cells. *Cell.* 2006;126(6):1121–1133. doi:10.1016/j.cell.2006.07.035
69. Yang XO, Pappu BP, Nurieva R, et al. T helper 17 lineage differentiation is programmed by orphan nuclear receptors ROR $\alpha$  and ROR $\gamma$ . *Immunity.* 2008;28(1):29–39. doi:10.1016/j.immuni.2007.11.016
70. Gaffen SL, Jain R, Garg AV, Cua DJ. The IL-23-IL-17 immune axis: from mechanisms to therapeutic testing. *Nat Rev Immunol.* 2014;14(9):585–600. doi:10.1038/nri3707
71. Patel DD, Kuchroo VK. Th17 cell pathway in human immunity: lessons from genetics and therapeutic interventions. *Immunity.* 2015;43(6):1040–1051. doi:10.1016/j.immuni.2015.12.003
72. van der Fits L, Mourits S, Voerman JS, et al. Imiquimod-induced psoriasis-like skin inflammation in mice is mediated via the IL-23/IL-17 axis. *J Immunol.* 2009;182(9):5836–5845. doi:10.4049/jimmunol.0802999
73. Chan JR, Wendy B, Erin M, et al. IL-23 stimulates epidermal hyperplasia via TNF and IL-20R2-dependent mechanisms with implications for psoriasis pathogenesis. *J Exp Med.* 2006;203(12):2577–2587. doi:10.1084/jem.20060244
74. Fujishima S, Watanabe H, Kawaguchi M, et al. Involvement of IL-17F via the induction of IL-6 in psoriasis. *Arch Dermatol Res.* 2010;302(7):499–505. doi:10.1007/s00403-010-1033-8
75. Carlo C, Rachel C, Montserrat A, et al. Prostaglandin E2 synergistically with interleukin-23 favors human Th17 expansion. *Blood.* 2008;112(9):3696. doi:10.1182/blood-2008-05-155408
76. Gordon KB, Blauvelt A, Papp KA, et al. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. *N Engl J Med.* 2016;375(4):345–356. doi:10.1056/NEJMoa1512711
77. Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis — results of two phase 3 trials. *N Engl J Med.* 2014;371(4):326–338. doi:10.1056/NEJMoa1314258
78. Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (Phoenix 2). *Lancet.* 2008;371(9625):1675–1684. doi:10.1016/S0140-6736(08)60726-6
79. Chiara O, Francesca N, Chiara B, Ornella DP, Giampiero G, Andrea C. CD56brightCD16(-) NK cells accumulate in psoriatic skin in response to CXCL10 and CCL5 and exacerbate skin inflammation. *Eur J Immunol.* 2010;36(1):118–128.
80. Kastelan M, Massari L, Gruber F, et al. Perforin expression is upregulated in the epidermis of psoriatic lesions. *Br J Dermatol.* 2004;151(4):831–836. doi:10.1111/j.1365-2133.2004.06168.x
81. Büchau AS, Gallo RL. Innate immunity and antimicrobial defense systems in psoriasis. *Clin Dermatol.* 2007;25(6):616–624. doi:10.1016/j.clindermatol.2007.08.016
82. Blauvelt A, Papp KA, Griffiths CEM, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: results from the Phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. *J Am Acad Dermatol.* 2017;76(3):405–417. doi:10.1016/j.jaad.2016.11.041
83. Gordon KB, Strober B, Lebwohl M, et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. *Lancet.* 2018;392(10148):650–661. doi:10.1016/S0140-6736(18)31713-6
84. Reich K, Papp KA, Blauvelt A, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. *Lancet.* 2017;390(10091):276–288. doi:10.1016/S0140-6736(17)31279-5

85. Ekman A.K., Bivik Eding C., Rundquist I., et al. IL-17 and IL-22 Promote Keratinocyte Stemness in the Germinative Compartment in Psoriasis. *The Journal of investigative dermatology*. 2019;139 7 :1564–1573.e8. doi:10.1016/j.jid.2019.01.014
86. Ekman AK, Bivik Eding C, Rundquist I, Enerbäck C. IL-17 and IL-22 promote keratinocyte stemness in the germinative compartment in psoriasis. *J Invest Dermatol*. 2019;139(7):1564–1573.e1568. doi:10.1016/j.jid.2019.01.014
87. Luan L, Ding Y, Han S, Zhang Z, Liu X. An increased proportion of circulating Th22 and Tc22 cells in psoriasis. *Cell Immunol*. 2014;290(2):196–200. doi:10.1016/j.cellimm.2014.06.007
88. Guilloteau K, Paris I, Pedretti N, et al. Skin inflammation induced by the synergistic action of IL-17A, IL-22, oncostatin M, IL-1 $\alpha$ , and TNF- $\alpha$  recapitulates some features of psoriasis. *J Immunol*. 2010;184(9):5263–5270. doi:10.4049/jimmunol.0902464
89. Pan Y, Du D, Wang L, Wang X, He G, Jiang X. The role of T helper 22 cells in dermatological disorders. *Front Immunol*. 2022;13:911546. doi:10.3389/fimmu.2022.911546
90. Zheng Y, Danilenko DM, Valdez P, et al. Interleukin-22, a T(H)17 cytokine, mediates IL-23-induced dermal inflammation and acanthosis. *Nature*. 2007;445(7128):648–651. doi:10.1038/nature05505
91. Van Belle AB, de Heusch M, Lemaire MM, et al. IL-22 is required for imiquimod-induced psoriasiform skin inflammation in mice. *J Immunol*. 2012;188(1):462–469. doi:10.4049/jimmunol.1102224
92. Cheuk S, Wiken M, Blomqvist L, et al. Epidermal Th22 and Tc17 cells form a localized disease memory in clinically healed psoriasis. *J Immunol*. 2014;192(7):3111–3120. doi:10.4049/jimmunol.1302313
93. Cai Y, Fleming C, Yan J. Dermal  $\gamma\delta$  T cells — a new player in the pathogenesis of psoriasis. *Int Immunopharmacol*. 2013;16(3):388–391. doi:10.1016/j.intimp.2013.02.018
94. Tomotaka M, Tomonori T, Hwang ST. Epidermal CCR6+  $\gamma\delta$  T cells are major producers of IL-22 and IL-17 in a murine model of psoriasiform dermatitis. *J Immunol*. 2011;187(10):5026–5031. doi:10.4049/jimmunol.1101817
95. Martin B, Hirota K, Cua DJ, Stockinger B, Veldhoen M. Interleukin-17-producing  $\gamma\delta$  T cells selectively expand in response to pathogen products and environmental signals. *Immunity*. 2009;31(2):321–330. doi:10.1016/j.immuni.2009.06.020
96. Cai Y, Shen X, Ding C, et al. Pivotal role of dermal IL-17-producing gammadelta T cells in skin inflammation. *Immunity*. 2011;35(4):596–610. doi:10.1016/j.immuni.2011.08.001
97. Stanislav P, Stefan H, Barbara I, et al. Ror $\gamma$ t+ innate lymphocytes and  $\gamma\delta$  T cells initiate psoriasiform plaque formation in mice. *J Clin Invest*. 2012;122(6):2252–2256. doi:10.1172/JCI61862
98. Ute L, Paola DM, Perera GK, et al. Identification of a novel proinflammatory human skin-homing V $\gamma$ 9V $\delta$ 2 T cell subset with a potential role in psoriasis. *J Immunol*. 2011;187(5):2783–2793. doi:10.4049/jimmunol.1100804
99. Zhu R, Cai X, Zhou C, et al. Dermal V $\gamma$ (4)(+)T cells enhance the IMQ-induced psoriasis-like skin inflammation in re-challenged mice. *Am J Transl Res*. 2017;9(12):5347–5360.
100. Owczarczyk-Saczonek A, Czerwińska J, Placek W. The role of regulatory T cells and anti-inflammatory cytokines in psoriasis. *Acta Dermatovenerol Alp Pannonica Adriat*. 2018;27(1). doi:10.15570/actaapa.2018.4
101. Joseph B, Drew P, Fan P. Treg functional stability and its responsiveness to the microenvironment. *Immunol Rev*. 2014;259(1):115–139. doi:10.1111/imr.12172
102. Nedoszytko B, Lange M, Sokolowska-Wojdylo M, et al. The role of regulatory T cells and genes involved in their differentiation in pathogenesis of selected inflammatory and neoplastic skin diseases. Part II: the treg role in skin diseases pathogenesis. *Postepy Dermatol Alergol*. 2017;34(5):405–417. doi:10.5114/ada.2017.71105
103. Yun WJ, Lee DW, Chang SE, et al. Role of CD4+CD25high+FOXP3+ regulatory T cells in psoriasis. *Ann Dermatol*. 2010;22(4):397. doi:10.5021/ad.2010.22.4.397
104. Yan KX, Fang X, Han L, et al. Foxp3+ regulatory T cells and related cytokines differentially expressed in plaque vs. guttate psoriasis vulgaris. *Br J Dermatol*. 2010;163(1):48–56. doi:10.1111/j.1365-2133.2010.09742.x
105. Li Z, Xue-Qin Y, Juan C, Rang-Song H, Tian-Wen G. Increased Th17 cells are accompanied by FoxP3(+) Treg cell accumulation and correlated with psoriasis disease severity. *Clin Immunol*. 2010;135(1):108–117. doi:10.1016/j.clim.2009.11.008
106. Fujimura T, Okuyama R, Ito Y, Aiba S. Profiles of Foxp3+ regulatory T cells in eczematous dermatitis, psoriasis vulgaris and mycosis fungoides. *Br J Dermatol*. 2010;158(6):1256–1263. doi:10.1111/j.1365-2133.2008.08504.x
107. Hideaki S, Rolland G, Eiko T, et al. Dysfunctional blood and target tissue CD4+CD25high regulatory T cells in psoriasis: mechanism underlying unrestrained pathogenic effector T cell proliferation. *J Immunol*. 2005;174(1):164–173. doi:10.4049/jimmunol.174.1.164
108. Soler DC, Sugiyama H, Young AB, Massari JV, McCormick TS, Cooper KD. Psoriasis patients exhibit impairment of the high potency CCR5 + T regulatory cell subset. *Clin Immunol*. 2013;149(1):111–118. doi:10.1016/j.clim.2013.06.007
109. Kleiweinfeld M, Hafler DA. The plasticity of human Treg and Th17 cells and its role in autoimmunity. *Semin Immunol*. 2013;25(4):305–312. doi:10.1016/j.smim.2013.10.009
110. Jorn H, Kerkhof B, van Erp PE, et al. Foxp3+ regulatory T cells of psoriasis patients easily differentiate into IL-17A-producing cells and are found in lesional skin. *J Invest Dermatol*. 2011;131(9):1853–1860. doi:10.1038/jid.2011.139
111. Shao S, Cao T, Jin L, et al. Increased lipocalin-2 contributes to the pathogenesis of psoriasis by modulating neutrophil chemotaxis and cytokine secretion. *J Invest Dermatol*. 2016;136(7):1418–1428. doi:10.1016/j.jid.2016.03.002
112. Polat M, Bugdayci G, Kaya H, Oğuzman H. Evaluation of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in Turkish patients with chronic plaque psoriasis. *Acta Dermatovenerol Alp Pannonica Adriat*. 2017;26(4):97–100. doi:10.15570/actaapa.2017.28
113. Paliogiannis P, Satta R, Deligia G, et al. Associations between the neutrophil-to-lymphocyte and the platelet-to-lymphocyte ratios and the presence and severity of psoriasis: a systematic review and meta-analysis. *Clin Exp Med*. 2019;19(1):37–45. doi:10.1007/s10238-018-0538-x
114. Balevi A, Olmuşçelik O, Ustuner P, Özdemir M. Is there any correlation between red cell distribution width, mean platelet volume neutrophil count, lymphocyte count, and psoriasis area severity index in patients under treatment for psoriasis? *Acta Dermatovenerol Croat*. 2018;26(3):199–205.
115. Reich K, Papp KA, Matheson RT, et al. Evidence that a neutrophil-keratinocyte crosstalk is an early target of IL-17A inhibition in psoriasis. *Exp Dermatol*. 2015;24(7):529–535. doi:10.1111/exd.12710
116. Lowes MA, Suarez-Farinas M, Krueger JG. Immunology of psoriasis. *Annu Rev Immunol*. 2014;32(1):227–255. doi:10.1146/annurev-immunol-032713-120225

117. Henry CM, Sullivan GP, Clancy DM, Afonina IS, Kulms D, Martin SJ. Neutrophil-derived proteases escalate inflammation through activation of IL-36 family cytokines. *Cell Rep.* 2016;14(4):708–722. doi:10.1016/j.celrep.2015.12.072
118. Weaver C, Hatton R, Mangan PR, Harrington LE. IL-17 family cytokines and the expanding diversity of effector T cell lineages. *Annu Rev Immunol.* 2007;25(1):821–852. doi:10.1146/annurev.immunol.25.022106.141557
119. Lee KH, Kronbichler A, Park DD, et al. Neutrophil extracellular traps (NETs) in autoimmune diseases: a comprehensive review. *Autoimmun Rev.* 2017;16(11):1160–1173. doi:10.1016/j.autrev.2017.09.012
120. Shao S, Fang H, Dang E, et al. Neutrophil extracellular traps promote inflammatory responses in psoriasis via activating epidermal TLR4/IL-36R crosstalk. *Front Immunol.* 2019;10:746. doi:10.3389/fimmu.2019.00746
121. Hu SC, Yu HS, Yen FL, Lin CL, Chen GS, Lan CC. Neutrophil extracellular trap formation is increased in psoriasis and induces human  $\beta$ -defensin-2 production in epidermal keratinocytes. *Sci Rep.* 2016;6:31119.
122. Aubert P, Suarez-Farinas M, Mitsui H, et al. Homeostatic tissue responses in skin biopsies from NOMID patients with constitutive overproduction of IL-1 $\beta$ . *PLoS One.* 2012;7(11):e49408. doi:10.1371/journal.pone.0049408
123. Lin AM, Rubin CJ, Khandpur R, et al. Mast cells and neutrophils release IL-17 through extracellular trap formation in psoriasis. *J Immunol.* 2011;187(1):490–500. doi:10.4049/jimmunol.1100123
124. Knight JS, Carmona-Rivera C, Kaplan MJ. Proteins derived from neutrophil extracellular traps may serve as self-antigens and mediate organ damage in autoimmune diseases. *Front Immunol.* 2012;3(Supplement):380. doi:10.3389/fimmu.2012.00380
125. Kumar V, Sharma A. Neutrophils: Cinderella of innate immune system. *Int Immunopharmacol.* 2010;10(11):1325–1334. doi:10.1016/j.intimp.2010.08.012
126. Pinegin B, Vorobjeva N, Pinegin V. Neutrophil extracellular traps and their role in the development of chronic inflammation and autoimmunity. *Autoimmun Rev.* 2015;14(7):633–640. doi:10.1016/j.autrev.2015.03.002
127. Skrzeczynska-Moncznik J, Zabieglo K, Bossowski JP, et al. Eosinophils regulate interferon alpha production in plasmacytoid dendritic cells stimulated with components of neutrophil extracellular traps. *J Interferon Cytokine Res.* 2017;37(3):119–128. doi:10.1089/jir.2016.0036
128. Lebowitz M. Psoriasis. *Ann Intern Med.* 2018;168(7):Itc49–Itc64. doi:10.7326/AITC201804030
129. Chan TC, Hawkes JE, Krueger JG. Interleukin 23 in the skin: role in psoriasis pathogenesis and selective interleukin 23 blockade as treatment. *Ther Adv Chronic Dis.* 2018;9(5):111–119. doi:10.1177/2040622318759282
130. Blauvelt A, Chiricozzi A. The immunologic role of IL-17 in psoriasis and psoriatic arthritis pathogenesis. *Clin Rev Allergy Immunol.* 2018;55(3):379–390. doi:10.1007/s12016-018-8702-3
131. Di Domizio J, Gilliet M. Psoriasis caught in the NET. *J Invest Dermatol.* 2019;139(7):1426–1429. doi:10.1016/j.jid.2019.04.020
132. Tillack K, Breiden P, Martin R, Sospedra M. T lymphocyte priming by neutrophil extracellular traps links innate and adaptive immune responses. *J Immunol.* 2012;188(7):3150–3159. doi:10.4049/jimmunol.1103414
133. Leite Dantas R, Masemann D, Schied T, et al. Macrophage-mediated psoriasis can be suppressed by regulatory T lymphocytes. *J Pathol.* 2016;240(3):366–377. doi:10.1002/path.4786
134. Morimura S, Oka T, Sugaya M, Sato S. CX3CR1 deficiency attenuates imiquimod-induced psoriasis-like skin inflammation with decreased M1 macrophages. *J Dermatol Sci.* 2016;82(3):175–188. doi:10.1016/j.jdermsci.2016.03.004
135. Hou Y, Zhu L, Tian H, et al. IL-23-induced macrophage polarization and its pathological roles in mice with imiquimod-induced psoriasis. *Protein Cell.* 2018;9(12):1027–1038. doi:10.1007/s13238-018-0505-z
136. Nguyen CTH, Kambe N, Yamazaki F, Ueda-Hayakawa I, Kishimoto I, Okamoto H. Up-regulated expression of CD86 on circulating intermediate monocytes correlated with disease severity in psoriasis. *J Dermatol Sci.* 2018;90(2):135–143. doi:10.1016/j.jdermsci.2018.01.005
137. Lin SH, Chuang HY, Ho JC, Lee CH, Hsiao CC. Treatment with TNF- $\alpha$  inhibitor rectifies M1 macrophage polarization from blood CD14+ monocytes in patients with psoriasis independent of STAT1 and IRF-1 activation. *J Dermatol Sci.* 2018;91(3):276–284. doi:10.1016/j.jdermsci.2018.05.009
138. Marble DJ, Gordon KB, Nickoloff BJ. Targeting TNF $\alpha$  rapidly reduces density of dendritic cells and macrophages in psoriatic plaques with restoration of epidermal keratinocyte differentiation. *J Dermatol Sci.* 2007;48(2):87–101. doi:10.1016/j.jdermsci.2007.06.006
139. Koh MS, Majewski BB, Rhodes EL. Increased macrophage activity in psoriasis. *Acta Derm Venereol.* 1985;65(3):194–198. doi:10.2340/0001555565194198
140. Das A, Sinha M, Datta S, et al. Monocyte and macrophage plasticity in tissue repair and regeneration. *Am J Pathol.* 2015;185(10):2596–2606. doi:10.1016/j.ajpath.2015.06.001
141. Wynn TA, Vannella KM. Macrophages in tissue repair, regeneration, and fibrosis. *Immunity.* 2016;44(3):450–462. doi:10.1016/j.immuni.2016.02.015
142. Vannella KM, Wynn TA. Mechanisms of organ injury and repair by macrophages. *Annu Rev Physiol.* 2017;79(1):593–617. doi:10.1146/annurev-physiol-022516-034356
143. Perera GK, Di Meglio P, Nestle FO. Psoriasis. *Annu Rev Pathol.* 2012;7(1):385–422. doi:10.1146/annurev-pathol-011811-132448
144. Schultze JL, Schmieder A, Goerdt S. Macrophage activation in human diseases. *Semin Immunol.* 2015;27(4):249–256. doi:10.1016/j.smim.2015.07.003
145. Judilyn FD, Mayte SFA, Zaba LC, et al. A subpopulation of CD163-positive macrophages is classically activated in psoriasis. *J Invest Dermatol.* 2010;130(10):2412. doi:10.1038/jid.2010.165
146. Lorthois I, Asselineau D, Seyler N, Pouliot R. Contribution of in vivo and organotypic 3D models to understanding the role of macrophages and neutrophils in the pathogenesis of psoriasis. *Mediators Inflamm.* 2017;2017:7215072. doi:10.1155/2017/7215072
147. Mantsounga CS, Lee C, Neverson J, et al. Macrophage IL-1 $\beta$  promotes arteriogenesis by autocrine STAT3- and NF- $\kappa$ B-mediated transcription of pro-angiogenic VEGF-A. *Cell Rep.* 2022;38(5):110309.
148. Ataseven A, Temiz SA, Eren G, Özer İ, Dursun R. Comparison of anti-TNF and IL-inhibitors treatments in patients with psoriasis in terms of response to routine laboratory parameter dynamics. *J Dermatolog Treat.* 2022;33(2):1091–1096. doi:10.1080/09546634.2020.1801975

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