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Immune Markers in Psoriasis

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Abstract

Psoriasis is a chronic inflammatory skin disorder with high immunological background caused by a complex interplay between an altered immune system, genetic factors, autoantigens, lifestyle, and environmental factors. Extensive literature in recent years highlighted the crucial role played by the immune system in the pathogenesis of this pathology. Although it is unequivocally accepted that psoriasis is a T-cell mediated autoimmune condition, both innate and specific immune cells are highly involved in the pathogenesis of psoriasis. The aberrant interactions between immune cells and resident hyper-proliferative keratinocytes are mediated by immune and non-immune related molecules which lead to amplification of the local immune responses, that maintain the chronic inflammatory status. In this chapter, we will highlight the immune molecules resident in the psoriatic tissue or appending to the blood circulation that can indicate the prognosis of this systemic autoimmune disease. Moreover, we will focus on immune cells resident or circulating ones that can pinpoint the clinical evolution of the psoriatic disease. All these data can be developed in immune markers patterns that aid psoriasis diagnosis and/or future (immune) therapies.

Keywords: psoriasis, autoimmunity, inflammation, immune markers, cytokines

1. Introduction

Psoriasis (Ps) is a chronic inflammatory T-cell mediated disease, that is manifested mainly as skin lesions and extracutaneous comorbidities, the overall symptomatology of the disease having a strong impact on the patients' life quality [1].

Worldwide, the prevalence of this disease is increasing for both adults and children, and varies between 0.09% and 11.4%, respectively between 1.5% and 5% in most developed countries. The disease incidence depends on age, sex, ethnicity, geographical regions, and environmental factors [2]. Ps especially affects Caucasians as compared to other ethnic groups and is more common in high-income countries. In children, the incidence increases with age, the median age at diagnosis being 10.6 years, with a higher prevalence in girls compared to boys [3].

The exact causes of Ps onset are still unknown. Ps is a complex and multifactorial skin condition that occurs on an altered genetic and immunologic background, favored by environmental factors [4] and aggravated by extrinsic risk factors and intrinsic risk factors [5].

Its complexity rides also on the fact that Ps presents a wide spectrum of skin lesions therefore, the specific clinical type of Ps is important in choosing the adequate treatment protocol. Ps is histologically characterized by keratinocytes (KCs) hyperproliferation which induces acanthosis, elongation of the rete ridges, hyperkeratosis, and parakeratosis, and an inflammatory infiltrate consisting mainly of dendritic cells (DCs) and T cells [6].

For many years, Ps was classified as an immune-mediated inflammatory disorder and less as an autoimmune condition due to the fact that the autoantigens causing T cell activation remain unknown. Recent studies reported the identification of four possible autoantigens involved in Ps' pathogenesis: KCs – derived antimicrobial peptide LL-37 (cathelicidin) [7], ADAMTS-like-protein 5 (a disintegrin- and metalloprotease domain-containing thrombospondin type 1 motif-like 5) produced by melanocytes, lipid antigens generated by phospholipase A2 group IVD (PLA2G4D) [8] and keratin 17 derived from hair follicles [9]. Studies regarding the autoimmune character of Ps have also focused on the existence of specific autoantibodies, the most common being anti-stratum corneum antibodies [10] and anti-heat shock protein 65 [11]. However, the clinical significance of these autoantibodies remains still evasive.

Although Ps is recognized as one of the most prevalent T-cell mediated chronic inflammatory skin conditions, its pathogenesis involved both innate and adaptive immune cells. Pathogenic crosstalk between hyper-proliferative resident KCs and immune cells mediated by immune and non-immune molecules are responsible for the development and maintenance of Ps' inflammatory state [12].

Two phases were described in the Ps' pathogenesis: initiation of psoriatic events, in which the cells belonging to the innate immunity (DCs, NK cells, M ϕ -macrophages) play an important role, and the phase of maintaining inflammatory status, in which the key players belong to the adaptive immunity (T helper (h)-cell subsets). In earlier stages of the disease, under the action of triggering factors (genetic, environmental, physical injury, infections, stress), KCs and cells belonging to innate immunity (plasmacytoid (P) DCs, NK cells, M ϕ) produce tumor necrosis factor (TNF)- α , interferon (IFN)- α , IFN- β , IFN- γ , interleukin (IL)-1 β , IL-6 thus activating the myeloid (M)DCs. In the initiation of psoriatic events, a starting key is represented by the activation of PDCs, secreting two type I IFNs (IFN- α , IFN- β), further promoting MDCs activation. Activated MDCs, by secreting IL-12 and IL-23, will determine the differentiation of naïve T-cells into Th1, Th17, and Th22 subpopulations. TNF- α , IFN- γ , IL-17, and IL-22 secreted by these effector subsets, will be able to activate KCs, which will produce a variety of cytokines (TNF- α , IL-1 β , IL-6, IL-8, IL-19, IL-36), chemokines (CXCL1/2/3/5/8), antimicrobial peptides (LL-37) and S100 proteins, thus propagating and maintaining the inflammatory status [13–15]. A general outline of the initiation and propagation stages of Ps is depicted in **Figure 1**.

Ps is not only a skin disease, it also has significant disabling systemic manifestations [13]. The disease is frequently associated with arthritic, metabolic, cardiovascular, and psychological comorbidities, which can lead to increased mortality among affected persons [16]. Knowing and understanding the relationship between Ps and other associated pathologies is particularly important for optimal clinical management of patients.

Depending on the Ps severity, there is a wide range of therapeutic options, from the traditional topical treatment, phototherapy, and systemic treatments, to new biological therapies. Despite various treatment options available, Ps still remains an incurable and undertreated disease [17], and finding an adjuvant treatment [18] to help existing ones remains a challenge for researchers.

Figure 1.
Immune mechanisms are associated with the onset of psoriatic events and the maintenance of the inflammatory status. KCs and innate immune cells are activated by triggers that secrete cytokines, leading to the differentiation in Th1, Th17, and Th22 cells via IL-12, IL-23, and TNF-α secreted by activated MDCs. These effectors promote KCs activation through TNF-α, IFN-γ, IL17, and IL22, leading to the perpetuation of the inflammatory cycle by generating AMP (LL-37, β-defensins, S100 proteins) and by secreting of cytokines (TNF-α, IL-6, IL-1β) and chemokines (CXCL1, CXCL2, CXCL3, CXCL5, CXCL8, CXCL9, CXCL10, CXCL20). Created with BioRender.com.

Although it is unequivocally accepted that Ps is a T-cell mediated condition, both innate and specific immune cells are highly involved in the pathogenesis of Ps. The aberrant interactions between immune cells and resident hyper-proliferative KCs are mediated by immune and non-immune related molecules which lead to amplification of the local immune responses, that maintain the chronic inflammatory status. In this chapter, we will highlight the immune molecules resident in the psoriatic tissue or appending to the blood circulation that can indicate the prognosis of this systemic autoimmune disease. Moreover, we will focus on immune cells resident or circulating ones that can pinpoint the clinical evolution of the psoriatic disease. All these data can be developed in immune markers patterns that aid Ps' diagnosis and/or future (immune)therapies development.

2. Immune cells in the development of psoriasis

As already stated, Ps is an immune-mediated inflammatory skin disorder based on the pathological crosstalk between KCs and immune cells sustained by a complex array of pro-inflammatory cytokines/chemokines. Disturbances in both innate and adaptive immune responses, as well as hyper-proliferative KCs, have important roles in triggering the early psoriatic events and in sustaining the chronic inflammation that follows. Immune cells are highly involved in both phases of Ps pathogenesis: innate immune cells (PDCs, MDCs, NK cells, Mφ, neutrophils) play a major role in the initiation of the psoriatic events, while adaptive immune cells (Th-cell subsets: Th17, Th22, Th1) are the main actors in maintaining the inflammatory status of the disease.

2.1 Tissue resident immune cells

Dendritic cells, professional antigen-presenting cells (APCs), are crucial in the early stages of the disease due to their ability to recognize the antimicrobial peptides (AMP) (LL-37, β-defensins, S100 proteins) released by damaged KCs in response to

various triggering factors [19]. LL-37, recognized as an autoantigen in Ps, binds to self-DNA and RNA from other damaged cells and stimulates toll-like receptor (TLR) 9, respectively TLR8 in PDCs. Activated PDCs will secrete IFN- α thus promoting MDCs activation. These activated cells will migrate into draining lymph nodes and by secreting high amounts of IL-12, IL-23 and TNF- α will further guide the differentiation of naïve T-cells in Th1, Th17, and Th22 populations [15]. These effector subsets will produce TNF- α , IFN- α , IL-17, IL-22 thus promoting KCs proliferation. Activated KCs will perpetuate the inflammatory cycle by generating AMP (LL-37, β -defensins, S100 proteins) and by secreting cytokines (TNF- α , IL-6, IL-1 β) and chemokines (CXCL1, CXCL2, CXCL3, CXCL5, CXCL8, CXCL9, CXCL10, CXCL20) [14]. LL-37 secreted by KCs will be recognized by LL-37-activated PDCs which will perpetuate the pathogenic mechanism. IL-17, CXCL1, CXCL2, and CXCL8 released by Th17 and KCs mediate the recruitment of neutrophils which will migrate to the psoriatic lesions, release large amounts of reactive oxygen species (ROS), granules and form neutrophil extracellular traps (NETs) [20].

MDCs can be also PDCs-independent activated, by CCL20 released by KCs in response to the skin microbiome, drugs, and injury [21]. Once activated, MDCs will initiate the inflammatory state in Ps. Two subpopulations of dermal MDCs have been described in psoriatic lesions: CD11c⁺BDCA-1⁺ cells, which are also found in normal skin, and CD11c⁺BDCA-1⁻ cells, characterized by the ability to produce inflammatory cytokines. CD11c⁺BDCA-1⁺ cells are comparable in number to those found in normal skin, while CD11c⁺BDCA-1⁻ cells, named “inflammatory MDCs”, are increased 30-fold in psoriatic lesions. Both subpopulations of MDCs induce T cell proliferation and cause differentiation into Th1 cells. In addition, inflammatory MDCs are responsible for the IL-23-induced Th17 stimulation [22].

Neutrophils, important representatives of innate immune cells, are considered to be regulators between innate and adaptive immune systems. Neutrophils are attracted to the psoriatic plaque by chemokines (CXCL1, CXCL2) and cytokines (IL-8) released by activated KCs, forming Munro microabscesses, an important histopathological feature of Ps [23]. Respiratory burst, degranulation, and NETs formation, the main offensive function of neutrophils, are correlated with Ps' development and progression.

During activation, neutrophils mobilize and release granular components thus inducing their own migration and activating their antimicrobial activities. NE (neutrophil elastase), MPO (myeloperoxidase), and LL-37 (recognized as an autoantigen in Ps) were reported to be highly involved in Ps. NE and cathepsin G activate IL-36 leading to an exacerbated tissue inflammation [24]. In Ps patients' circulatory neutrophils have increased MPO and NOX2 (reduced nicotinamide adenine dinucleotide phosphate-NADPH oxidase) activities and enhanced respiratory burst, releasing more ROS compared to healthy individuals [25]. Overproduction of ROS induces proliferation and differentiation of Th1, Th17, and Th22 cells, and inhibits regulatory T cells (Tregs). Inflammatory cytokines secreted by these T cell subsets along with VEGF, stimulate KCs proliferation and angiogenesis [26, 27]. In psoriatic plaque and pustules, NETs are overexpressed and IL-17 releasing cells will be activated. Accordingly, the synthesis of inflammatory mediators will be stimulated, leading to auto-amplification of neutrophil's overall activities [20]. Inhibition of neutrophils degranulation and suppression of respiratory burst can become new therapeutical targets for alleviating Ps symptoms.

Macrophages, cells with phagocytic and antigen-presenting properties, are important innate immune sentinels. M ϕ is abundant in psoriatic lesions and are involved in

the inflammatory process due to their ability to produce cytokines and inflammatory mediators. The most representative monokines are IL-23, responsible for the differentiation of Th17 [28], and TNF- α responsible for Th22 differentiation [29].

NK cells, recognized for their ability to kill virally infected cells and cancer cells, appear to be involved in the pathogenesis of Ps, but their role still remains controversial. Thus, Ottaviani et al. identified a subpopulation of NK cells with the CD56^{bright}CD16⁻CD158⁺ phenotype able to produce large amounts of IFN- γ , and these cells are recruited by KC activated through chemokine secretion (CXCL10, CCL5) [30]. Thus recruited, NK cells can contribute to the inflammatory environment of the skin. On the other hand, Dunphy et al. noted the presence of NK cells in skin lesions of Ps patients, but these cells were characterized by poor degranulation potency and reduced secretion of proinflammatory cytokines (IFN- γ and TNF- α) [31].

NKT cells are a distinct cellular subset that exhibits both T-cell receptor (TCR) and NK cells lineage markers and can produce large amounts of cytokines in response to various stimuli, such as lipids and cytokines. NKT cells have been identified in psoriatic lesions and were reported a decreased following treatment [32]. Bonish et al. have shown that NKT cells (CD161⁺) can produce large amounts of IFN- γ that induce CD1d overexpression on KCs in psoriatic lesions. These KCs subsequently activate NKT cells to produce IFN- γ . Bonish et al. also suggested that the interactions between NKT and KCs could provide a relevant mechanism in the pathogenesis of Ps [33]. Several NKT cells can secrete IL-17 and IL-22 after IL-1 β and IL-23 stimulation. These cells, named NKT17, express high levels of ROR γ T, and were found in the lung, liver, marginal lymph nodes, and skin [34], but their role in the skin is not yet well defined.

Other innate immune cells involved in Ps pathogenesis are innate lymphoid cells (ILCs) and $\gamma\delta$ T cells, which are activated in Ps and may represent important sources of IL-22 and IL-17.

ILCs are members of lymphoid lineage and are involved in the early response to infections in the skin, lung, and gastrointestinal tract. In the absence of an antigen-specific receptor, they are activated through signals from cytokine and NK receptors and secrete high levels of cytokines. Within the three types of known ILCs, ILC3 type seems to be involved in Ps due to its ability to produce IL-17 and IL-22. Depending on the presence or absence of natural cytotoxicity receptor (NCR), ILC3 were classified into NCR⁺ILC3 (increased in psoriatic lesions), NCR⁻ILC3 (commonly in normal skin), and lymphoid tissue inducer cells (LTi). When they are activated, NCR⁺ILC3 secrete IL-22, NCR⁻ILC3 produce IL-17, IL-22 and IFN- γ , LTi-lymphotoxin, IL-17, and IL-22 [35]. Vilanova et al. reported an increased amount of IL-22 and IL-17 producing ILC3 in psoriatic skin, correlated with disease severity [36]. Another study showed that NCR⁺ILC3 isolated from psoriatic skin, stimulated by IL-2, IL-23, and IL-1 β , produce large amounts of IL-22, but not IL-17 [37], thus suggesting that ILC3 contribute to the development of Ps via IL-22.

$\gamma\delta$ T cells are involved in the pathology of allergic and autoimmune diseases in mice and humans and contribute to the development of Ps by IL-17 production. Unlike $\alpha\beta$ T cells, $\gamma\delta$ T cells express TCR that consists of γ and δ chains. They interact with both innate and adaptive immune cells, and with non-immune tissue cells, and can promote tissue repair and wound healing [38]. $\gamma\delta$ T cells are able to recruit inflammatory myeloid cells and modulate classical T cells functions by increasing Th17 inflammatory responses and/or by reducing the activity of Treg cells [39]. In addition to IL-17, they also secrete IFN- γ , IL-22, and GM-CSF. Cai et al. reported that both human and murine dermal innate $\gamma\delta$ T cells are an important source of IL-17 in the skin upon IL-23 stimulation, and may represent a novel target for the Ps' treatment [40].

However, recent studies have shown that $\gamma\delta$ T cells account for up to 1% of T cells in Ps, the majority of IL-17-producing T cells being $\alpha\beta$ T cells and not $\gamma\delta$ T emphasizing that human Ps is mainly driven by $\alpha\beta$ T cells [41]. However, more studies are needed to accurately determine the involvement of $\gamma\delta$ T cells in Ps.

T lymphocytes, cellular exponents of the adaptive immune system, are the key players in the phase of maintaining the inflammatory status in Ps. The pathogenic interactions between T-cells subsets (T-CD8⁺, autoreactive T cells Th1, Th17, Th22, DCs, and KCs, result in a self-maintaining inflammatory status with TNF α /IL-23/IL17 axis as a key point [42]. Although the involvement of T cells in Ps has been extensively studied, the gradual scaling of T-cell mediated events is not yet fully elucidated. Casciano et al. pointed out the four T-dependent stages consisting of a skin T cell activation phase, the onset of chronic inflammation, the maintenance of the inflammatory status, and the migration of specific subsets of T cells outside the skin possibly involved in Ps extra-cutaneous manifestations [43]. Various T cell sub-populations have been recognized as involved in Ps pathogenesis.

T-CD8 cells have a crucial role in Ps plaque formation and strongly sustain the autoimmune nature of the disease. DCs recognize and present epidermal autoantigens (LL-37, ADAMTS-like-protein 5, keratin 17) to IL-17-producing T-CD8 cells, in an MHC-restricted manner. Human leukocyte antigen (HLA)-C*06:02, a specific MHC allele is involved in the autoimmune T-cell response in Ps [44]. Recent studies have shown that T-CD8 cells accumulate in active and resolved psoriatic lesions as tissue-resident memory T cells (TRM) with $\alpha\beta$ TCR [41] and have an IFN- γ /IL-17/IL-22 cytokine profile (thus maintaining the inflammatory status) [45]. Autoantigens recognition by Tc1/Tc17 cells induces the secretion of cytokines that will cause the onset of KCs hyper-proliferation. Activated KCs will contribute to the propagation and maintenance of inflammation through the secretion of antimicrobial peptides, cytokines, and chemokines [46].

Activated DCs also secrete IL-12 and IL-23, inducing the differentiation in Th1 and Th17 subsets of naive T lymphocytes. In response, these effector subsets will produce TNF- α , IFN- α , IL-17, IL-22 thus promoting KCs proliferation.

Initially, Ps was considered a predominantly Th1-mediated disease, being reported as an imbalance between Th1 and Th2 cells. This imbalance was due to the increasing of IFN- γ expressions as compared to low levels obtained for IL-4, IL-5, or IL-10, which are specific Th2 cytokines [47]. Th1 cells, a subset of T-CD4⁺ cells, are defined by activation of transcription factors STAT4 and T-bet and the secretion of proinflammatory cytokines (IFN- γ , IL-2, and TNF). Th1 cells and IFN- γ levels were found elevated in psoriatic lesions [48]. IFN- γ , along with TNF- α , IFN- α , IFN- β , IL-1 β , and IL-6 activate IL-12 and IL-23 – producing MDCs in the initial phase of the disease, and under the influence of Th1 cells, KCs secrete pro-inflammatory mediators (IL-1 β and IL-18) that are further involved in the differentiation of Th1 and Th17 cells [49]. Although the involvement of IFN- γ -producing Th1 cells has been extensively studied, the results of clinical trials based on anti-IFN- γ antibodies did not have the expected results [50].

Extensive literature in recent years has proven the clinical efficacy of IL-17 inhibitors, highlighting the important role of IL-17-secreting lymphocytes—Th17 and Tc17 cells—in Ps. Th17 cells are a T-CD4⁺ subset defined by mainly IL-17A, IL-17F, IL-22, IL-21, and IL-26 secretion, and express retinoic acid receptor-related orphan receptor- γ t (ROR- γ t) and IL-23 receptor (R) [51]. Th17-derived proinflammatory cytokines have a critical role in the pathogenesis of many autoimmune and inflammatory diseases, including Ps. Th17 cells activated by IL-1 β and IL-23, trigger

inflammation and autoimmunity, while activation through IL-6 and transforming growth factor (TGF)- β is involved in tissue defense and homeostasis [52]. Although NK and $\gamma\delta$ T cells also synthesize IL-17, Th17 remains the main source of IL-17.

IL-12 and IL-23 secreted by activated MDCs cause differentiation into Th1, Th17, and Th22 effector cells. IL-23 secreted by MDCs induces the differentiation of Th17 cells, and by activation of IL-23R expressed on Th17 cell, maintain the local inflammation [53]. IL-17A released by Th17 cells will promote the KCs activation, which will maintain the chronic inflammatory status through the secretion of antimicrobial peptides, cytokines, and chemokines. Activated Th17 cells are present in psoriatic lesions [54], and elevated levels of IL-23, a Th17-driving cytokine, were reported in lesional skin [55]. These data sustain the importance of IL-23/Th17 axis in the development of Ps.

Although it is recognized that Th17 cells play a critical role in the Ps pathogenesis, and the secreted cytokines are strongly involved not only in the onset and development of the disease but can cause complications of other associated diseases, more research is needed regarding the pathogenicity of Th17 cells in Ps.

Another subset of T-CD4⁺ lymphocytes involved in Ps pathogenesis is represented by Th22 cells. Th22 differentiate from naive T cells in the presence of IL-23, IL-6, and TNF- α , and upon activation, these cells will produce IL-22, TNF- α , IL-13, and IL-26, but not IFN- γ or IL-17. IL-22 can induce specific chemokines that will increase specific effector responses mediated by the IL-23 / Th17 axis [56], the network leading to epidermal hyperplasia and hypergranulosis. In a recent study, Cheuk et al. demonstrated that epidermal Th22 and Th17 cells are retained in healed psoriatic skin and can induce the recurrence of the disease in previously affected areas through the secretion of specific cytokines [57].

Another significant role in Ps' pathogenesis is played by Tregs lymphocytes, cells that suppress the autoimmune responses and other aberrant or excessive immune responses against non-self-antigens [58]. Tregs play an important role in maintaining homeostasis and can cause local suppression of the activity of other immune cells, including Th1 and Th17 cells. In Ps, the suppressive function of Tregs is altered, resulting in a Th17/Tregs imbalance and an upregulation of pro-inflammatory cytokines [59]. The decreased suppression function of Tregs can be a result of elevated levels of IL-6 produced by DCs, Th17, and endothelial cells, which inhibit per se Tregs' activity. Furthermore, Tregs cells can differentiate into a Th17 phenotype in Ps. IL-17A⁺Foxp3⁺CD4⁺ cells were found in psoriatic lesions from patients with severe Ps, thus highlighting Tregs' potential to differentiate into an IL-17A-producing phenotype [60]. Thus, in Ps Tregs behave in a Th17 cells manner and hence are unable to exert their suppressor functions. Nussbaum et al. suggested several ways of restoring Th17/Tregs balance: induction of Tregs (using anti-TNF- α , folic acid analogs, phototherapy, vitamin D, retinoids, anti-IL-17, and anti-IL-23), downregulation of Th17 cells (using phototherapy, folic acid analogs, retinoids, and anti-IL-17) and inhibition of Tregs plasticity (using pan-PKC inhibitor and anti-IL-23) [59]. Although the involvement of B lymphocytes in Ps pathogenesis has been not as much studied compared to T lymphocytes, recent years' research has highlighted the possible role of IL-10-secreting regulatory B cells (Bregs) in disease's attenuation. Bregs are a subset with regulatory properties exerted mainly by the production of cytokines like IL-10, TGF- β . These subpopulations are associated with the regulation and control of excessive inflammatory responses. Recently was underlined the heterogeneity of Bregs cells, suggests that this population may develop from any subset of B cells in the context of adequate stimulation [61]. IL-10-secreting B cells seem to have an inhibitory effect in Ps development. Thus, Yanaba et al. have shown that Bregs cells suppress Ps-like skin

inflammation induced by imiquimod (IMQ), a potent agonist for TLR7 and – 8 in a murine experimental model [62]. Although recombinant IL-10 was one of the first biologic agents used in Ps, the clinical trials have not been completed to be introduced in the clinical management of Ps patients, thus more studies are needed to determine Bregs involvement in the course of Ps.

2.2 Circulatory immune cells

Although the distribution of peripheral blood cell populations can be a valuable indicator for establishing the patient's immune status and ability to develop an effective defense against pathogenic factors, circulatory immune cells have been less studied in Ps as compared to tissue-resident immune cells. Due to their important role in the pathogenesis of Ps, lymphocyte populations and subpopulations have been the most studied circulating immune cells. Tissue immune cells are mirrored by the circulatory ones as there is a constant circulation between these sites (Figure 2).

In the peripheral blood of Ps' patients, an increased T-CD4⁺ cells activation and an imbalance in the Th1/Th2 ratio, with high Th1 and low Th2 phenotypes have been reported [63]. Also, higher levels of IFN- γ , IL-2, and IL-10, decreased concentration of IL-4, and increased expression of T-bet mRNA (Th1-specific transcription factor) sustain that Ps is predominantly a Th1-mediated disease [64]. In the early stages of Ps, the patients have increased IFN- γ expression, while patients in the chronic stage have high levels of IL-10. All these findings suggest a possible shift from Th1 to Th2 response in order to down-regulate the inflammatory response [65].

In a recent study regarding the immunophenotyping of T cells in Ps' peripheral blood, increased Th1/Th17 cells and decreased Th2/Tregs cells were reported. The percentages

Figure 2. Immune cells like activated dermal DCs can circulate through the lymphatic system into lymph nodes where DCs activate various T cell subpopulations that can travel into the skin and contribute to the activation of PDCs; the activation of cells within the skin would trigger the chemotaxis of monocytes and neutrophils into the skin and increase the inflammatory status of the psoriatic lesion. Created with BioRender.com.

of Th1/Th17 cells were positively correlated with disease severity (PASI score) [63]. A positive correlation has also been reported between elevated levels of IL-21⁺ Th17 cells and IL-21 found in peripheral blood of Ps patients with the severity of the disease. The study also has shown that IL-21 can promote the differentiation into the Th17 subset, and recommends IL-21 as a potential immune marker [66].

Another T-CD4⁺ cell subset involved in Ps' pathogenesis is Th22. Luan et al. reported elevated levels of circulating Th22, Tc22, and IL-22 in patients showing a positive correlation between Th22, IL-22, and PASI score. Nevertheless, no correlation was observed between circulating Tc22 and PASI score [67].

The studies regarding Tregs cells distribution in peripheral blood are controversial. Thus, some authors report a low frequency of circulating Tregs in Ps [68], others observed high percentages of Tregs correlated with PASI scores in moderate to severe Ps [69], and others show no differences compared to healthy volunteers [70]. Although the relevance of Tregs distribution in the periphery remains unclear, the decreased suppressive function and an altered Th17/Tregs balance contribute to the exacerbation of Ps.

T follicular helper (Tfh) cells are a specialized subset of T-CD4⁺ cells expressing increased levels of CXCR5, inducible T cell costimulatory (ICOS), programmed death protein-1 (PD-1), and the transcription factors B cell lymphoma 6 (Bcl-6). This sub-population actively secretes high levels of IL-21, IL-17, and IFN- γ [71]. Tfh cells are activated in Ps and identifying a higher percentage of circulating Tfh17 (CXCR3-CCR6⁺ phenotype) correlates with disease' severity. Thus, the frequency of circulating Tfh cells and the secretion of cytokines are significantly decreased after one month of treatment. All these findings indicate that activated circulating Tfh cells are involved in Ps pathogenesis and can constitute a potential therapeutic target for psoriatic disease [72].

In contrast to T-CD4⁺ cells, considered the key subset of pathogenic T lymphocytes, circulating T-CD8⁺ cells have been less studied and characterized. The frequency of circulating T-CD8⁺ cells which express cutaneous lymphocyte antigen (CLA) is higher in Ps patients compared to healthy individuals and is strongly correlated with PASI score [73]. Colombo et al. evaluated circulating IL17⁺/IFN- γ ⁺/IL-17/IL-22⁺ T-CD8 cells in Ps, psoriatic arthritis (PsA), and rheumatoid arthritis (RA), and reported high levels of IFN- γ ⁺ T-CD8 cells in PsA compared to Ps. A significant correlation between the extent and severity of Ps and the frequency of circulating IL-17⁺ T-CD8 cells was as well reported [74].

Although B cells play also an important role in skin inflammation, their distribution in peripheral blood has been poorly studied in Ps. Lu et al. found upregulated percentages of CD19⁺ B cells in peripheral blood mononuclear cells (PBMCs) of Ps patients, which were positively correlated with PASI score. The authors also investigated the expression of CD40, CD44, CD80, CD86, and CD11b on B cells in 4 clinical types of Ps and showed that the expressions of these activation markers are different in various types of Ps [75]. Other studies reported decreased circulating IL-10-producing Bregs cells in Ps, negatively correlated with Th1, Th17 cells, and IFN γ ⁺ and IL-17⁺ NKT cells. During apremilast treatment, these values increased and were correlated with the clinical response [76, 77].

NK cells, known for their anti-viral and anti-tumoral functions, were found in the inflammatory infiltrate of the psoriatic lesions. Even though Ps is a skin disorder, there have been reported changes in circulating NK cells. The number of circulating NK cells is reduced in Ps patients. The levels of circulating IFN- γ and TNF- α are similar to healthy controls [78]. The low levels of NK cells in Ps patients peripheral blood, correlated with a lower frequency of cells expressing NK specific markers (CD56, CD16, CD94, CD158a) but no correlation with the severity of the disease [79]. NK cells had

increased expression of the apoptosis-associated Fas receptor and lower expression of CD94 and NKG2A. In addition to its ability to induce apoptosis, Fas receptor is also able to induce the production of proinflammatory cytokines, including TNF- α , a key cytokine in Ps. No differences between Ps patients and controls were reported for CD56^{dim}CD16⁺ and CD56^{bright}CD16⁻ in peripheral blood [80]. Significantly decreased circulating CD3⁻CD16⁺CD56⁺ NK cells correlated with increased B lymphocytes in Ps patients were also reported [81]. The role of circulating NK cells in Ps pathogenesis remains still unclear and a subject for further investigation.

In our studies, we identified several phenotypic changes in lymphocyte main populations in the IMQ-mice model. We reported decreased percentages of circulating T-CD4⁺ and B-CD19⁺ cells, and elevated levels of T-CD8⁺ and NK1.1⁺ cells in IMQ-treated mice as compared to healthy animals [82]. For NK cells phenotypic characterization we used a large panel of surface markers including activation, maturation, and markers for cytokine receptors. The results showed important differences in IMQ-treated mouse NK cell phenotype as compared to controls [83]. Taking into account the recently found relation between gut microbiota and Ps initiation, we have demonstrated that oral ingestion of IgY raised against pathological gut bacteria resistant to antibiotics can alleviate psoriatic lesions and restore immune parameters [18].

In Ps innate immune cells have been less studied in the peripheral circulation compared to lymphocytes. Besides KCs and T cells, neutrophils are an important cellular source of IL-17 via NETs formation in psoriatic lesions. NETs are increased in blood samples and were correlated with the severity of Ps [84]. Lambert et al. demonstrated that NETs promote Th17 cells induction from PBMCs in Ps. They also suggested that Th17 cells and neutrophils have a cross-talk because this effector helper subset produces cytokines that promote the development, recruitment, and lifespan of neutrophils [85].

Nguyen et al. observed a high expression of the co-stimulatory molecule CD86 on intermediate monocytes (CD14⁺⁺CD16⁺) in Ps patients, along with high serum beta defensin-2 levels, these parameters positively correlated with PASI score [86]. Recent studies reported that low levels of monocytic myeloid-derived suppressor cells (Mo-MDSCs) are present in the peripheral blood of Ps patients; these cells secrete different pro-inflammatory cytokines (e.g. matrix metalloproteinases 9 and 1, IL-8) moderately suppressing T-CD8⁺ cell proliferation. According to Soler et al., the immune system is unable to self-regulate due to the capability of Mo-MDSCs to induce aberrant Tregs cell conversion from naive T effector cells, in presence of pro-inflammatory molecules [87].

ILCs has a significantly increased frequency in the skin, but Villanova and al. observed in the blood of healthy individuals and Ps patients a large amount of CD3 negative (CD3⁻) ILC who produce IL-17A and IL-22 (20% of IL-17 producing cells, respectively 40% of IL-22) [88]. NKp44⁺ ILC3 group is the most frequent subset of ILCs in the peripheral blood and in the skin of Ps patients as compared to healthy individuals. The frequency of circulating NKp44⁺ ILC3 could reflect the disease severity and/or the response to anti-TNF treatment (adalimumab), highlighting the role of TNF in NKp44⁺ ILC3 human differentiation [89].

Depending on the δ chain, $\gamma\delta$ T cells are classified into V δ 1–V δ 3 subsets. In the peripheral blood are present V δ 2 and V δ 3 groups, with the major subset V γ 9V δ 2 which produce a large range of pro-inflammatory mediators (e.g. IL-17A) and activate KCs in a TNF- α and IFN- γ dependent manner. Laggner et al. ha shown in peripheral blood a distinct subset of pro-inflammatory CLA and CCR6 positive V γ 9V δ 2 T cells, which are rapidly recruited into the injured skin [90]. These cells secrete IL-17A,

IL-22 and activate KCs upon TNF- α , IFN- γ , and IL-23 stimulation [65]. Ps patients present low numbers of V γ 9V δ 2⁺ T cells in peripheral blood and concomitant high levels in psoriatic lesions, both suggesting the pathogenic role of the V γ 9V δ 2⁺ T subset [90]. The decreased concentration of circulating V γ 9V δ 2⁺ T cells is normalized after successful Ps treatment. All the data suggest a redistribution of these subsets of $\gamma\delta$ T cells from blood to the skin [65].

3. Immune molecules as biomarkers in psoriasis

Ps is a polygenic skin disease with immunological etiology. The immune system interacts with KC and a complex network of cells is generated, where dendritic cells, T-lymphocytes, neutrophils, and mast cells communicate through immune-related molecules inducing the complex pathology of Ps. The main immune molecules involved in the development of this disease are IL-23, IL-17, IL-12, IL-22, IL-23, IL-6, IL-10, IFN, TNF, TGF- β 1 [91]. All these molecules have cellular sources mainly Th17, Th22, and Tregs cells [92]. The presence of these molecules induces an inflammatory process that sustains the proliferation of epidermal cells, neo-angiogenesis, and infiltration of DCs in the skin. Recently, new players were identified in the Ps development, such as the skin microbiome [18] and the skin's serotonergic system [93]. For example, it was recently reported that the microbiome variations are associated with the level of inflammatory cytokines receptors, especially with the IL-2 receptor [94, 95].

A recent study has shown that Ps deregulated genes were found. These genes are involving cytokine-cytokine receptor interaction, cell cycle and cell adhesion molecules and these candidate genes regulating important immune pathways can be new therapeutic targets in Ps [96]. There are more than 50 genetic susceptible biomarkers associated with the risk of Ps. The strongest association is with the presence of the HLA-C*06 gene and HLA-B27 [97]. The other genetic Ps risk, single nucleotide polymorphisms (SNPs) are near the genes encoding molecules functioning in the adaptive and innate immunity [98].

3.1 Tissue immune molecules as biomarkers in psoriasis

The first cellular line of skin's defense is KCs that upon injury secrete an array of alarmins. These are molecules that induce a rapid innate immune response against danger signals. Any deregulation in the physiology of KCs can lead to chronic inflammation, hyper-proliferation, and eventually a psoriatic lesion. Keratins (KRTs), major structural intermediate filament proteins of KCs were shown to be involved in Ps. Hence, up-regulation of KRT6/16/17 induces hyper-proliferation and innate immune activation followed by autoimmune T cells activation [99]. Transcriptomic studies have shown that KCs from Ps skin harvested from patient's skin have a high expression of mRNA encoding for SERPINB [100]. Moreover, SERPINB is regulated by TEA domain family member 4 (TEAD4) and affects the secretion of chemokines in Ps, hindering the normal cross-talk between KCs and T cells [101]. Other important cells within the skin are dermal fibroblasts that are in close contact with immune cells. A recent proteomic study has shown that Ps fibroblasts have upregulated proinflammatory factors and downregulated other factors that are involved in transcription/translation processes, glycolysis/adenosine triphosphate synthesis. All these deregulations contribute to the promotion of epidermal cell hyper-proliferation [102]. Another major cell involved in Ps is the Langerhans cell (LCs), the only DCs residing

in the epidermis that is physically linked to KCs through E-cadherin. A recent study has shown that in Ps E-cadherin does not regulate LCs maturation, migration, and function [103].

There are a series of surface molecules appending to immune cells that are highly involved in Ps' appearance and maintenance of immune tolerance. Therefore, neuropilin-1 (NRP1), PD-1, and HLA-G are the main tissue players in Ps. These molecules were found significantly lower in Ps compared to normal skin and were similar in Ps variants like PsA and Ps vulgaris patients [104]. Another tissue immune marker relevant for Ps is the TLR superfamily. When TLRs become aberrantly activated, T cell-mediated autoimmune activation will take place, leading to several diseases including Ps [105]. In Ps' skin samples low levels of thrombospondin-1 (TSP-1) and CD47 were found inversely correlated with disease severity. The TSP-1/CD47 signaling pathway impacts Th17 and Tregs differentiation, favoring disease initiation [106]. Recently in an IMQ-induced psoriatic animal model, it was shown that IL-17A, IL-23, TNF- α , and STRA6 levels were found significantly increased in tissue along with their circulatory counterparts. RBP4 and STRA6 were found upregulated and involved in the experimental Ps [107]. The inflammatory Th17 response in Ps was reported to be modulated by IL-33 produced by the inflamed skin tissue, adding to the chronic status of Ps [108]. CDC6 is an essential regulator of the complex (pre-RC) assembly on chromatin. CDC6 expression was found upregulated in Ps lesions and probably the main route is induced by IL-22/STAT3 signaling, a key signaling pathway in Ps [109]. In a genetic mouse model, it was demonstrated that IL-23 produced by KCs induces chronic skin inflammation displaying an IL-17 pattern. In KCs from Ps' lesions, a decrease in H3K9 demethylation is correlated with IL-23 increased expression [110]. In a mouse experimental model harboring mutations in the gene encoding for CARD14 (KCs signaling molecule) it was shown that the animals spontaneously develop Ps, their skin has increased expression of anti-microbial peptides, chemokines, and cytokines, therefore Ps' pathogenesis in this model being driven by the IL-23/IL-17 axis. A diagram of the main immune molecules involved in Ps' pathogenesis is depicted in **Figure 3** [111].

In the IL-23/IL-17 axis, T lymphocytes, namely the Th17 subpopulation are the main cells that secrete IL-17A, IL-17F, and IL-22 [112], but also mast cells and neutrophils were shown to produce IL-17 in Ps' lesions [113].

3.2 Circulatory immune markers

Cytokines/chemokines that appear in the psoriatic lesion are essential for KCs activation. In immune homeostasis, if genetic and/or non-genetic factors interfere in the KC-T cell cross-talk the relation between resident T cells and KCs will be altered and a chronic inflammatory response will sustain the Ps lesions [114, 115]. All these alterations in terms of immune and non-immune molecules will be mirrored by the circulatory pattern of cytokines, chemokines, and various other molecules that can become biomarkers in Ps. A proteomic approach of Ps patients' plasma has shown that several proteins are decreased while others are increased. Hence apolipoprotein M, and proteins involved in vitamin D metabolism were found to decrease, while proteins involved in signaling molecule secretion were found to increase favoring cellular proliferation [116].

The complement system is essential in host defense against various pathogens, but in the last years, it was shown that due to its regulation properties of inflammation is involved in Ps development. As autoantibodies can activate the complement system, any deficiency of this system induces an impaired immune complex clearance and would sustain Ps lesions [117].

Figure 3.
IL-23/Th17 axis in Ps. DC are activated by various cells (KCs, Mφ, PDC, NKT cells) and stimuli. When activated DC will secrete IL-23 activating Th17 lymphocytes that will activate KCs through IL-17, IL-22, IL-21. Activated KCs will express specific Ps' genes (DEFB4 gene which encoded human β-defensin 2) and secrete an array of molecules (S100 protein, lipocalin (LCN), CCL20, CXCL1-3, 5, 6, 8, IL-1β) that will induce chronic inflammation of the skin. Created with BioRender.com.

As already stated, the main deregulated axis in Ps is IL-22/IL-23/IL-17 axis. Memory Tregs are the main source of IL-17 in Ps [118]. IL-17A and F, when highly abundant, strongly induce S100-alarmins expression during KCs maturation [119]. IL-17A and IL-22 were found elevated in the serum of Ps patients, in accordance with increased IL-17 mRNA levels in the skin [120, 121]. IL-17A would further stimulate KCs to secrete chemokine CCL20, IL-8, and AMP, promoting inflammation [122]. Additionally, in Ps IL-17A synergizes with TNF and IL-22 and this cytokine cocktail upregulates IL-36 contributing to the inflammatory status [123]. IL-17F is found elevated in the serum of Ps [124] and is promoted by IL-23 [125], inducing further IL-6 and IL-8 secretion by KCs [126].

CD100-plexins were found elevated in Ps serum and were reported to increase the production of chemokines (CXCL1, CCL20) and cytokines (IL-1β, IL-18) when KCs activate NLRP3 inflammasome [127].

A recent study has shown that surviving, a protein belonging to the apoptosis inhibitor family was found to significantly increase in Ps patients suggesting its role in the pathogenesis of Ps [128].

4. Immune therapeutical outlines in Ps

Although diagnosis and therapy in skin pathologies have benefited from novel investigation assays [129, 130] and new therapies are emerging [18], there are still many immune niches that can be explored in the quest to find the best biomarker in diagnostic and therapy efficacy improvement [131].

A recent meta-analysis of biologics treatment in Ps has shown that the biological treatments that target IL-17, IL-12, IL-23, and TNF- α were significantly more effective in comparison to small molecules/conventional systemic agents [132]. Slowing down the pro-inflammatory biological processes using early intervention with anti-IL-17 and anti-IL-23 agents might positively change the course of Ps, especially in the current pandemic era, where chronic patients can reduce their hospital visits [133].

IL-17 inhibitors, namely secukinumab, ixekizumab, brodalumab and IL-23 inhibitors, namely guselkumab, tildrakizumab, risankizumab show increased effectiveness compared to other biologics [134]. A recent meta-analysis has shown that these are the best choices in order to achieve PASI 90 in patients with moderate-to-severe psoriasis. The authors point out that future trials are needed to evaluate directly the biological agents in order to establish the best choice in terms of type and timing. Therefore, trials on anti-IL-17 versus anti-IL-23, anti-IL-23 versus anti-IL-12/-23, anti-TNF- α versus anti-IL-12/-23, and so on are to be expected (Cohrane skin group, 2021). Despite the therapeutical success of recent drugs, there are still a reactive patients to these treatments. Therefore, the combination of multiple immune-modulatory drugs can be an appropriate alternative strategy to improve the quality of life in Ps [135, 136]. Moreover, new biomarkers should personalize treatment with IL-17 inhibitors and IL-23 inhibitors and should stratify patients in Ps subgroups that could best benefit from these new biologics [137].

Historically, TNF- α inhibitors were the first biologics approved in PsA. Now, targeting IL-12/IL-23 p40 common subunit, IL-17A, T cells co-stimulation, is proving an increased efficacy in Ps therapy. Moreover, additional drugs targeting phosphodiesterase-4 and JAK/STAT pathways are recently being developed [138]. Many cytokines are related to the pathways controlled by JAK/signal transducers and activators of transcription (STATs). JAK inhibitors have been approved in PsA [139]. In 2020, data from the Phase II trial of several selective TYK2 inhibitors in Ps were published [140] and new drugs targeting the JAK/STAT3 axis in Ps treatment are awaited [141]. Berberine was reported to inhibit CDK4/6-RB-CDC6 signaling in KCs, reducing their proliferation. This alkaloid extracted from Berberis plants represses JAK1, JAK2, and TYK2, inhibiting STAT3 activation [109].

Drug	Target	Stage	Reference
Anti-TNF	TNF- α	Approved	[132]
Secukinumab, ixekizumab, brodalumab	IL-17	Approved	[132, 133]
Guselkumab, tildrakizumab, risankizumab	IL-23		[134]
TYK2 inhibitors	TYK2	Phase II trial	[140]
Berberine	CDK4/6-RB-CDC6 signaling	In vitro experiments	[109]
Prostaglandin D2	Th2 cells	In vitro experiments	[144]
Luteolin	Proinflammatory cytokines	In vitro experiments	[146]

Table 1.
Main drugs approved in Ps and/or that are in various testing stages.

Co-stimulatory molecules (CD28, CD40, OX40, CD27, DR3, LFA-1, LFA-3) and co-inhibitory molecules (CTLA-4, PD-1, TIM-3) regulate T cells functions, including cytokines production and Tregs differentiation. In 2021 it was shown that co-signaling molecules targeting can be developed in future Ps' drugs [142].

Biologics targeting TNF, IL-17s, and IL-23 in Ps are associated with adverse immune effects. In a recent study, high antinuclear antibodies (ANA), high eosinophils, and high IgE were reported. Therefore, in Ps, careful observation is required when patients are subjected to these new biologics [143]. Due to these adverse effects, several other compounds are tested in Ps, like prostaglandin D2 inhibiting Th2 cells [144]. Vitamin D3 analogs, corticosteroids, or a combination of these compounds are tested as future drugs in Ps [145]. Flavonoids like luteolin can suppress proinflammatory cytokines (e.g., IL-1 β , IL-6, IL-8, IL-17, IL-22, TNF- α) and regulate the signaling pathways that are highly involved in Ps [146].

Table 1 summarizes the main drugs that are already approved and/or are in various development stages in Ps.

5. Conclusion

Ps management is constantly evolving in parallel with new insights in the immune pathogenesis. In spite of extensive studies, Ps remains a complex and enigmatic disease as still, its clear etiology is a matter of intense research. New drugs that are targeting the immune pathways using biologics and small molecules have significantly improved life quality in Ps. Biomarkers from the area of cytokines, various soluble mediators, cell-surface molecules or receptors, intracellular signaling pathways molecules, encompass the panel of tools that can improve diagnosis and prognosis in Ps. The most recent image of Ps within the immunological system highlights the importance of immune cells involved in Ps.

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Conflict of interest

The authors declare no conflict of interest.

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