Review

A Multifaced Approach on Psoriasis Pathogenesis

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A Multifaced Approach on Psoriasis Pathogenesis

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Abstract: Psoriasis is a chronic recurrent inflammatory autoimmune pathology, with a major genetic component and several interferences of immunological cells and their cytokines. The complex orchestration of psoriasis pathogenesis is related to the synergic effect of immune cells, polygenic alterations, the presence of autoantigens and several external factors. The major act of IL-23/IL-17 axis, strongly influencing the inflammatory pattern established during the disease activity, is visible as a continuous perpetuation of the pro-inflammatory response and keratinocyte activation and proliferation leading to the development of psoriatic lesions. Genome wide association studies (GWAS) along offered a better view of psoriasis pathogenic pathways, with approximately one third of psoriasis genetic impact on psoriasis development is associated to MHC region, with genetic loci located on chromosome 6. The most eloquent genetic factor of psoriasis, PSORS1, was identified in the MHC I site. Between the several factors involved in its complex etiology, dysbiosis, due to genetic or external stimulus, exhibiting less variety and the involvement of pathogenic bacteria, cand induce a burst of proinflammatory consequences, both cutaneous and gut microbiome being involved in psoriasis pathogenic process. A complex understanding of the major pathways that interplay in order to initiate and perpetuate psoriatic diseases and its associated comorbidities can help the current clinical practice by properly evaluating completely and individualized each patient and establish the proper therapeutic management.

Keywords: psoriasis; microbiome; genetics; cytokines; signaling pathways

1. Introduction

Psoriasis is a chronic recurrent inflammatory autoimmune pathology, with a major genetic component and several interferences of immune cells and their cytokines [1,2]. It has a worldwide prevalence of about 2-3% of the general population, with variabilities depending on the skin phenotype, lower in Asia or Africa, higher in Scandinavian populations [3,4]. It shows an increased incidence in adults and equal distribution between men and women, with an onset in early ages for female patients, especially in case of positive family history [5]. Clinically, it is expressed by several types, most of the cases corresponding to psoriasis vulgaris or plaque-type psoriasis, pathologically characterized by an abnormal proliferation and differentiation of keratinocytes [6].

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The severity and of the psoriatic disease arises not only from its progressive evolution and association in about one third of the cases with development of psoriatic arthritis, but also throughout its several comorbidities, that share a common pathogenesis [7].

During the past decades studies based on unrevealing the current knowledge of psoriasis pathogenesis have enabled the development of fundamental insights that allow a targeted therapy, highly efficient, with a major impact on quality of life of these patients [8].

The complex orchestration of psoriasis pathogenesis is related to the synergic effect of immune cells, polygenic alterations, the presence of autoantigens and several external factors [9]. Over the past years the scientific researches clearly stated that psoriasis is a T-cell mediated pathology, with an excessive production of IL-17 as a consequence of IL-23 stimulation. The major act of IL-23/IL-17 axis, strongly influencing the inflammatory pattern established during the disease activity, is visible as a continuous perpetuation of the pro-inflammatory response and keratinocyte activation and proliferation leading to the development of psoriatic lesions [9,10].

Between the several factors involved in its complex etiology, dysbiosis, due to genetic or external stimulus, exhibiting less variety and the involvement of pathogenic bacteria, cand induce a burst of proinflammatory consequences, both cutaneous and gut microbiome being involved in psoriasis pathogenic process [11]. With its role of both physical and immune barrier towards external injuries, the skin has an extensive microbiome that can constitute the target of multiple factors, leading to its dysregulation and gaps in immunoregulatory processes [12]. The relevance of gut microbiome is established by the interrelation between different components of both innate and adaptive immune systems, with the major role of T cells [13].

We aimed to describe the main components of psoriasis pathogenesis and their crosstalk mechanisms in initiation and progression of psoriasis. A complex understanding of the major pathways that interplay in order to initiate and perpetuate psoriatic diseases and its associated comorbidities can help the current clinical practice by properly evaluating completely and individualized each patient and establish the proper therapeutic management, in order to obtain not only the remission of the disease and decrease its psychosocial impact, but to prevent future organ damage and improve the quality of life for our patients.

2. Genetic Disturbances in Psoriasis

Genome wide association studies (GWAS) along with next generation sequencing (NSG) analysis offered a better view of psoriasis pathogenic pathways, strongly impacted by genomic alterations (Single nucleotide polymorphisms (SNPs), copy number variations (CNVs), and epigenetic changes) and further possible therapeutic options [14]. For the past years, a paramount amount of data related to genetic characterization of a specific pathologies was generated using GWAS approach [14–18]. GWAS have identified 10 loci, with the most proven association, from PSORS1 to PSORS10. The reported data show an extensive interference of several genes, from the ones associated with the functionality of skin barrier, adaptive immunity related genes, especially CD8+ T and CD4+ T lymphocytes, or genes that belong to the histocompatibility complex (MHC) region on chromosome 6 [18]. Approximately one third of psoriasis genetic impact on psoriasis development is associated to MHC region, with genetic loci located on chromosome 6. The most eloquent genetic factor of psoriasis, PSORS1, was identified in the MHC I site, where human leukocyte antigen (HLA)-Cw-6 was considered the PSORS1 risk variant. PSORS1 is bounded by a 300-kb critical region in MHC where about fifteen genes have been identified, strongly related to psoriasis. Between these, data shows HLA-C to be the most likely PSORS1 gene [29]. The risk allele HLACw0602*, present in up to 10-15% of the general population, inputs a 20 fold higher risk for developing psoriasis and in proven to be present in about 60% of psoriasis patients. It has been identified especially in young subjects, with familial history of psoriasis, where various infections, predominantly *Streptococccal* ones, trigger the first lesions [20]. Moreover, there has been shown the presence of a five times higher psoriasis risk in subjects with homozygous HLA-Cw0602* allele compared to heterozygous ones [22]. A recent study, published in 2021, that included 124 patients with psoriasis and aimed to establish the possible correlation between HLA-Cw0602* positivity and response to treatment, showed a lower response for the cases with this risk allele [22]. PSORS2 was identified on chromosome 17q, where CARD14 (caspase recruitment domain-containing protein 14) was described to be associated to psoriasis. CARD14 was detected in a highly expressed manner in

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keratinocytes, with a subsequent activating action on NF-κB and an increased release of pro-inflammatory cytokines [23–25]. Other two genes, SLC9A3R1 and NAT9, associated to psoriasis, where found on chromosome 17q and are responsible for RUNX1 transcription factor binding, directly correlated to T cells functionality [26–29]. PSORS4 resides on chromosome 1q21 and it has been associated to the presence of LCE genes (l ate cornified envelope genes) as the deletion of LCE3B and LCE3C is highly related to psoriasis, and the expression of this protein is significantly increased in psoriatic lesions [30,31]. A major impact on the development of both psoriasis and psoriatic arthritis is attributed to rs4349859 SNP located in HLA-B gene, linked to HLA-B27 [32]. The presence of HLA-B27 predict the development of certain future PsA characteristics, as dactylitis, axial involvement and also o more severe evolution of the disease, especially in early onset cases; in an opposite manner identifying the presence of HLA-B57 inputs a decreased risk of developing psoriasis [33]. Although the genetic impact on psoriasis is clearly demonstrated, there is no evidence of a single genetic variant to initiate the disease appearance as there is required an interference of several genetic mutations, along with other pathogenic pathways.

3. Microbiome

With its role of both physical and immune barrier towards external injuries, the skin has an extensive microbiome that can constitute the target of multiple factors, leading to its dysregulation and gaps in immunoregulatory processes [34–36]. The largest organ in the human body plays a host to several bacteria, viruses and fungi, all contributing to maintaining a balance for the immune system. The range and distribution of skin microbiota is highly different depending on the site and unique for each individual, dependent of external conditions, associated comorbidities, sex, age or hygiene level, with marked importance to different pathologies development [37]. Multiple studies have reported changes in skin microbiome for different pathologies, including psoriasis, and the analysis of specimens from both lesions and regular areas, along with probes from controls, have enlightened important data. In 2008, *Gao et al.*, reported that *Firmicutes* was the most plentiful phylum populating psoriatic skin and *Actinobacteria* both in unaltered samples from psoriasis patients and healthy individuals [38]. A study published by *Fahlén et al.* revealed that there were three major microorganisms present both in normal and psoriatic skin, *Firmicutes*, *Proteobacteria* and *Actinobacteria*, as well as a significant higher level of *Proteobacteria* in psoriasis compared to controls. Another important observation of the report is represented by the lower level of *Staphylococci* and *Propionibacteria* in psoriasis patients compared to healthy individuals [39]. In 2013, *Alekseyenko et al*, analyzed the of lesional and non-lesional skin samples of 75 psoriasis patients and 124 controls and stated the relationship between *Firmicutes* and *Actinobacteria*-rich cutaneotype to psoriasis. Also, an important conclusion of the report that underlines the importance of skin microbiome analysis and establishing certain biomarkers, was that the presence of major skin genra, *Corynebacterium*, *Proponibacterium*, *Staphylococcus* and *Streptococcus*, both in lesions as well as in healthy skin samples of patients with psoriasis, along with a decrease of other taxa, *Cupriavidus*, *Methylobacterium* and *Schlegella* [40]. In 2018, *Fyhrquist et al.*, performed an analysis of skin microbial population related to patterns of cutaneous gene expression in patients with atopic dermatitis or psoriasis, discovered only weak relationships between potential pathogens and the expression of host transcripts in patients with psoriasis, with an important role attributed to *Corynebacterium*, which can perform a regulatory role, potentially protective [41]. Later, *Quan C et al.*, in a report published in 2020, showed that there is a certainly increased difference between samples from lesions and unaffected skin, as well as controls, with *Propionibacterium* and *Corynebacterium* dominating the probes with psoriasis. The results also showed a positive correlation between the severity of the lesions and the presence of *Corynebacterium* species. The severity of the lesions, quantified using PASI (Psoriasis Disease Activity Index), was confirmed to be directly related to the presence of *Corynebacterium* species by several other scientific reports [42]. *Chang et al.* performed an analysis of skin bacterial species that revealed significant inequalities between the psoriasis-associated and healthy skin microbiota, sustaining that a decrease of certain regulatory species, as *Staphylococcus epidermidis* and *Propionibacterium acnes* may prompt an increase settlement of *Staphylococcus aureus*, event that subsequently leads to an enhanced cutaneous inflammatory process via Th17 axis [43]. Another relevant study, published by *Tett et al.*, using high-resolution shotgun metagenomics to characterize the microbiome of psoriatic and unaltered skin from 28 patients, demonstrated that members of the genus *Staphylococcus* are

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significantly more abundant on diseased skin compared to unaffected skin. The results also showed the presence of different other bacteria, as well as *Malassezia spp*., an abundant fungal type of the skin [44]. Although the part of *Malassezia*, a lipophilic and lipid-dependent commensal fungus, in psoriasis is not completely understood, it was first described by *Rivolta et al.* in 1873, from a psoriasis lesion [45], and T-cells reactive to *Malassezia* yeast [46] and antibodies against *Malassezia* [47] have been found in lesional skin but not in normal subjects; also, *M. globosa* was the most commonly isolated species during psoriasis exacerbation [48]. It is also of utmost importance that the increase of LL-37, a cathelicidin antimicrobial peptide with major role in IFN-α production, initiation and perpetuation of psoriatic lesions, can be subsequent to *Malassezia* colonization of the skin [49]. An additional supporting part when analyzing skin microbiome in patients with psoriasis is represented by smoking, a well known promoter of several inflammatory autoimmune conditions [50]. The colon is the leading site of micro-organism distribution, followed by the skin, with a diversity of microbiome settled from the first years of life, influenced by genetics, lifestyle or use of certain medication [41,51,52]. Disruptions in gut microbiome may promote an increased risk of metabolic and autoimmune conditions, with a potential on initiating or sustaining an inflammatory status, including psoriasis and its well described comorbidities [53,54]. Although there are several published studies, supported by advancements in sequencing technologies, the limited number of patients included lead to slight differences in the reported reports, with the benefit of providing important up to date data and outlining future researches directions. Gut microbiome integrates an extensive number of bacterial types, mostly represented by *Actynobacteria*, *Bacteroides, Firmicutes*, *Fusobacteria*, *Proteobacteria* and *Verrucomicrobia*, as well as viruses, fungi, protozoa or Archaea, maintaining a symbiotic status with the host, highly influenced by age, genetics, dietary manners or environmental external factors [13,55–57]. Changes in local intestinal microbiome can interact with skin homeostasis by influencing systemic immunomodulatory mechanisms [56]. Several reports have concluded that the changes seen in patients with psoriasis are relative semblable to those identified in patients with inflammatory bowel diseases, with an exuberance of *Actinobacteria* and *Firmicutes*, conjunctively to *Firmicutes-to Bacteroides* ratio, model of altered gut epithelial barrier [53,57–60]. The study of intestinal microbiota profiling, reported by *Chen et al* in 2018, observed that *Ruminococcus* and *Megasphaera*, of the phylum *Firmicutes*, were the top-two genera of discriminant abundance in psoriasis, and decreased abundance of phylum Bacteroidetes. Analyzing the samples from 35 patients with psoriasis and 27 controls [57], *Huang et al* reported that the relative abundances of *Firmicutes* and *Bacteroidetes* were inverted at the phylum level, and 16 kinds of phylotype at the genus level were detected with important distinctions. In addition to them, *Proteobacteria* and *Actinobacteria* were also found to be underrepresented in psoriasis patients [59]. *Shapiro et al.* documented a significant increase in the *Firmicutes* and *Actinobacteria* phyla as compared with controls. At the species level, the psoriatic patients presented significant increases of *Ruminoccocus gnavus*, *Dorea formicigenerans* and *Collinsella aerofaciens*, while *Prevotella copri* and *Parabacteroides distasonis* were significantly lower as compared to controls [58]. The study of *Masallat et al.* reported statistically significant differences in *Firmicutes* and *Bacteroidetes* ratio, directly associated to PASI score. *Actinobacteria* was found in a high level for controls. The results suggest that the differences in gut microbiome are the source for counteracting and inducing inflammation respectively, and therefore inducing psoriasis [57]. Another study, performed on 52 patients with psoriasis, revealed that the microbiome obtained was marked by an increased *Faecalibacterium* and a decrease of *Bacteroides*, with higher values of *Akkermansia* and *Ruminococcus genra* compared to controls [61]. Discordant to these results, *Scher et al.* obtained a significant reduction in *Akkermansia*, *Ruminococcus*, and *Pseudobutyrivibrio* in the analyzed samples [60]. Several scientific publications have reported other types of bacteria found with increased levels in patients with psoriasis, mentioning *Bacillus*, *Subdoligranum*, *Slackia*, *Christensenella*, *Dorea*, *Coprococcus*, *Collinsella*, *Blautia*, *Enterococcus* or *Lactococococcus*, as well as others were determined in relatively low concentrations, *Allobaculum*, *Alistipes*, *Barnsiella*, *Gordonibacter* or *Paraprevotella* [52,60,62]. Regarding individual species, there are studies that report an increased level for *Escherichia coli*, *Clostridium citroniae*, *Collinsella aerofaciens*, *Dorea formicigenerans* [58,59,63]. Besides the stated role of different bacterial species, viral infections, including human papiloma virus, or fungus, such as *Candida albicans*, or *Malassezia*, have been interrelated to psoriasis. The presence of *Candida albicans* activate dendritic cells, via its ligand, beta-glucan, inducing the production of IL-36α with a further development of psoriasis phenotype [64]. The relevance of gut microbiome on the pathogenesis of

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psoriasis is settled by the interrelation between different components of both innate and adaptive immune systems [56,65–70]. The main role of gut-skin axis in psoriasis is endorsed by T cells, by the imbalance between Treg and Th17 cells [71,72]. There are data suggesting that the absence of microbiota, or its change, decreases the pro-inflammatory T cell response and further decreases the severity of cutaneous inflammation. This is further supported by several studies describing the ability of commensal bacteria to modulate T cell development. An increased epithelial permeability, subsequent to chronic inflammation derived from gut dysbiosis, is one of the underlying mechanisms of skin impairment. Another pathway for systemic inflammatory state is represented by metabolic disturbances, with activation of several pattern recognition receptors, located on epithelial cells. As a result of the altered integrity of the mucosal cells and the increased permeability, effector T cells are activated. The bidirectional relationship between gut microbiota and mucosal epithelial cells, directly impacting the protective and functional status, is driven by the specific metabolites or immune modulating factors, between which it is worth mentioning short chain fatty acids (SCFAs), retinoic acid or polysaccharide A, as a result of the fermentation of non-digestible substrates, complex polysaccharides and indigestible oligosaccharides by colonic microorganisms [58,67,73,74]. SCFAs modulate glucose and lipid metabolism [75], maintain gut mucosal integrity [76], and regulate the immune system and inflammatory responses [77]. All these actions are mediated through different mechanisms, including specific G protein coupled receptor family (GPCR) and epigenetic effects [78–81]. Disruptions in gut microbiome balance and the further, activation of T- cells via interactions with pattern recognition receptors and Toll-like receptors triggers an inflammatory process and induces autoimmune conditions such as rheumatoid arthritis [82], inflammatory bowel disease [83], systemic lupus erythematosus [84], multiple sclerosis [85], psoriasis [56,65–72], as well as other skin alterations, such as atopic dermatitis [86] and vitiligo [87].

4. Immune Cells

4.1. Keratinocytes (KCs)

Psoriasis is a pathology characterized by hyperproliferation and disturbed differentiation of KCs, cells with both structural and immune role that interfere in early stages of the disease, as well as in maintaining chronic inflammation [88]. They constitute the main cellular population altered in psoriasis as they express receptors for all types of cytokines involved in the complex pathogenesis of the disease [89–91]. Consequent to dermal injury there can be observed an increased secretion of antimicrobial peptides, cathelicidin, LL-37, S100 proteins, and β-defensins from keratinocytes, promoting the activation of pDCs and release of IFN-α, IFN-γ, TNF-α, and IL-1β [92–94]. Besides the stated role in early stages of the disease, they continue to perpetuate the inflammatory process during disease evolution. After activation, they continuously produce chemokines, in high amounts (CXCL1/2/3, CXCL8, CXCL9/10/11, CCL2, and CCL20), recruit leucocytes or antimicrobial peptides and stimulate the inflammatory process. In addition, along with fibroblasts and endothelial cells have a major contribution to tissue restructuring, consecutive to their interaction with Th17 cells [95–97].

4.2. T Cells

It is well-established that psoriasis is a T-cell mediated disease, as it is assumed that effector T cells transmigrate form the lymph nodes into systemic circulation, as well as they derive from the injured skin sites [98,99]. All types of T cells, CD4+ T cells (Th), CD8+ T cells (Tc), and Treg cells, are involved in the initiation and perpetuation of psoriatic lesions [100]. Proinflammatory cytokines, IL-12, IL-23 and TNF, released by dendritic cells (DC) and activated macrophages, prompt the activity of Th cells (Th1, Th17, Th22) and promote epidermal hyperproliferation with an inhibition of apoptosis [100,101]. Concomitant, IL-17 and TNFα stimulate keratinocytes to release pro-inflammatory cytokines. Psoriasis patients in the early course of disease express high levels of IFN-γ, which shifted towards IL-10 secretion in chronic patients suggesting a possible shift from Th1 to Th2 response as an adaptation of the immune system to down regulate inflammatory Th1 response [101]. Another cytokine with contribution in psoriasis pathogenesis is represented by Th9, a majority of the memory Th9 cells being either skin-tropic or skin-resident. IL-9, released by Th9, is essential for production of IFN-γ, IL-17, and IL-13 by skin tropic T cells to maximal level [102]. Treg cells, known to conserve immune stability, are found in a low level in psoriasis, and in the context of an increased

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pro-inflammatory cytokine environment, psoriatic Tregs behave like Th17 cells and are unable to suppress the T effector activation [103,104].

4.3. B Cells

Known to be regulators of the pathogenesis in several autoimmune diseases, by producing autoantibodies and antigen presentation, they haven't been as extensively studied as lymphocytes T in patients with psoriasis and their input on psoriasis genesis and perpetuation is not completely clear [105]. Resident cutaneous B cells contribute not only to skin homeostasis, but also to regulating reparatory processes and local microbiome. Also, experimental studies proved that in areas of inflamed skin there is a high quantity of Il-6, IL-4, GM-CSF or IFN-γ [105–108].

4.4. Dendritic Cells (DCs)

Several types of DCs (plasmacytoid DCs-pDCs, conventional DCs-cDCs, and Langerhans cells-LCs) are involved in the pathogenesis of psoriasis, with numerous reports demonstrating the presence of pDCs and cDCs in the lesional skin samples of these patients [109,110]. Consecutive to different external stimulus DCs are activated, commuted to professional antigen-presenting cells (APCs), with subsequent interaction with naive T cells and production of proinflammatory cytokines, TNF-α, IL-23, IL-12, and IL-6, that furthermore activate inflammatory reaction, keratinocyte proliferation and recruitment of neutrophils [111,112]. A subset of inflammatory Dcs, TIP-DCs, secrete TNF and inducible nitric oxide synthase (iNOS), with a pro-inflammatory response in patients with psoriasis [113–115]. LCs, cells with an important contribution to local immunity of the skin, showed a debatable role in psoriasis pathogenesis. Experimental studies have shown divergent results, with reports revealing that they stimulate the secretion of multiple inflammatory cytokines and induce the proliferation of IL-17A-producing γδ T cells, or others suggesting they may exert an anti-inflammatory role in psoriasis, by increasing the production of IL-10, or IL-23 in case of LCs depletion [116–120]. *4.5 Neutrophils.* Excessive storage of neutrophils in psoriatic lesions is a typical feature of the disease as they infiltrate the dermis in early stages and subsequently migrate to the epidermis [121,122]. Subsequently to neutrophils activation, increased levels of reactive oxygen species (ROS) are released into circulation, with DCs stimulation, T cells stimulation and an altered balance between Th1 and Th2, the final result being represented by keratinocyte proliferation and increased angiogenesis [122–126]. Secondary to excessive ROS production, LL-37 is released, with a production of IFN-alfa by pDCs or ILP6, IL-12 and IL-23 by mDCs [127,128]. In addition to Th17 cells, neutrophils represent a category of cells that can contribute to IL-17A production and perpetuation of psoriasis development. Moreover, neutrophils are activated by keratinocytes in order to produce pro-inflammatory cytokines and augment dermal inflammation [129,130].

4.6. Macrophages

Antigen presenting cells, derived from monocytes, are shown to be present in psoriatic lesions, with TNF secretion upon activation and regulation of angiogenesis by releasing VEGF [131,132].

4.7. Natural Killer (NK) Cells

Natural killer (NK) cells are present in the lesional skin of psoriasis patients and exhibited reduced degranulation and produced lower levels of the pro-inflammatory cytokines IFN-γ and TNF-α [73].

5. Citokines

5.1. Th17 Cytokines

One of the first studies describing cytokines in the dermal samples of psoriasis patients, published in 1994 by *Schlaak et al*, revealed that Th1-related cytokines prevailed in the analyzed probes, with a few Th cells releasing Th-2 relate cytokines [133], results that were confirmed by others several further reports and rised the hypothesis that psoriasis can be defined as a Th1 mediated disease. Currently, it is very well established that the pathophysiology of the disease comprises a wide network of immune cells that, along with their cytokines, initiate the inflammatory response [134,135]. The Th17 cytokine family is the major effector in the pathogenesis of psoriatic disease and

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strongly influences the inflammatory pattern established during the disease activity [136,137]. In addition, the vast network of cells that orchestrates the pathophysiology makes psoriasis complex to study. *IL-23,* part of IL-12 family, IL-23 is produced by both resident [blood dendritic cell antigen (BDCA-1)/CD1c+] and inflammatory myeloid DCs (CD11c+ BDCA-1/CD1c–), as well as macrophages (CD163+) in psoriasis. It is responsible for the activation, differentiation and proliferation of Th17 cells that further initiate the release of acting cytokines IL-17A or IL-21, with effects on neutrophils draft [138–144].In psoriasis patients, the IL-23 pathway is activated and characterized by high level production of IL-23 by DCs and keratinocytes and increased numbers of Th17 cells [145]. *IL-17*is an acknowledged cytokine produced mainly, but in exclusively, by Th17 cells [146]. Besides Th1 cells, mast cells, γδ T cells, αβ T cells, and innate lymphoid cells represent major sources for IL-17 production [147,148]. From the six subtypes of IL-17 family, IL-17A and IL-17F have been proven to be found both in psoriasis plauqes, as well as in unaltered skin, with IL-17A playing a central part in the pathogenesis of the disease [146]. The aforementioned cytokines are expressed together and act in a synergist manner on upregulation of inflammatory markers. There are several mechanisms with intricate casting in psoriasis induction by which IL-17 exerts their action on immune cells, keratinocytes, and fibroblasts, inducing the release of inflammatory mediators including cytokines, IL-6, IL-1β, TNF, and granulocyte–macrophage colony-stimulating factor (GM-CSF), chemokines (CXCL1, CXCL2, CCL20, and CXCL8), matrix metalloproteinases (MMPs), antimicrobial peptides (AMPs; LL37, S100s, β-defensin), and complement [149–151]. Thus, initiates recruitment and activation of neutrophils, lymphocytes, and myeloid cells, with local dermal inflammation, effect developed by the synergic effects of IL-23 and possibly IL-36. Increased IL-17, produced by CD4+ Th17 cells, can also be detected in synovial fluid of patients with psoriasis. The effect of IL-17 goes beyond epithelial cells, being identified also in endothelial cells, with a pro-coagulant activation [151,152]. *IL-21* is a cytokine still under current investigations regarding its entire part in psoriasis, with high amounts of IL-21 receptor (IL-21R) revealed in keratinocytes. It represents a future therapeutic target as it has been stated as a major effect on Th17 proliferation, mediated by regulatory T cells (Treg) [153,154].

5.2. Th1 Cytokines

IL-12 is an activator for Th1 differentiation and proliferation, with consequent production of TNF-β, IFN-γ and IL-2, found to be increased in patients with psoriasis [155,156]. A major implication has been reported in psoriatic arthritis (PsA), where high levels of its soluble receptor (IL-12R) are directly correlated with the degree of cutaneous involvement [157,158]. IL-12 inhibitory agents proved their efficacy as they diminish the expression of IFN-γ and inhibits the release of IL-8 by keratinocytes; additionally experimental studies have shown a protective role of this cytokine in IL-23'Th17 pathway [143].

IL-8, a cytokine with marker role in inflammation throughout neutrophils attraction, is released by macrophages, epithelial cells, endothelial cells or respiratory smooth muscles. Keratinocytes production of IL-8 is stimulated by visfatin, an adipokine produced by leukocytes and adipose tissue, under TNF-α stimulation [159–161].

IL-22, a member of IL-10 family, that impairs keratinocytes proliferation, is associated with psoriasis progression when detected in high levels. It is secreted by NK cells, Th17 or Th22, with a marked input on keratinocytes cycle during regenerative processes [162]. It is notably that the study of *Kagami et al.* showed that IL-22 deficiency caused a significant decrease in epidermal acanthosis and dermal inflammation induced by IL-23 [163]. In addition, the study published by *Van Belle et al.* showed that IL-22 has not only a major part in the development of pustules and acanthosis but also in neutrophil infiltration in a mouse model triggered by the Toll-like receptor (TLR) 7/8 agonist imiquimod [164].

IL-1β is a cytokine highly expressed in psoriasis samples, and two genetic variants, rs16944 and rs2853550, were proven to be associated with late initiation of the disease and a slower progression [165].

IL-6 is expressed in high levels in the psoriatic lesion. It is a pleiotropic proinflammatory cytokine that is produced by a variety of cells such as fibroblasts, macrophages, endothelial cells, and KCs in response to a variety of stimuli, which include other cytokines such as IL-1, TNF-α, and PDGF [166]. IL-6 stimulates the proliferation of human KCs. Anti–IL-6 therapies, which are effective for

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rheumatoid arthritis, are either ineffective for psoriasis or can induce new-onset psoriasis-like disease [167].

TNF-α has been identified as a key cytokine mediating cutaneous inflammation in the pathogenesis of psoriasis [168]. TNF is a homotrimer cytokine mostly released by immune and epithelial cells and exerts its effects by binding to two different receptors: TNFR1/p55 (expressed ubiquitously and constitutively) and TNFR2/p75 (expressed only on immune, endothelial and neuronal cells, being inducible). Over the years, several studies have reported increased levels of TNF, TNFR1 and TNFR2 are observed in psoriatic lesions, being produced by various cellular populations involved in the pathophysiology of psoriasis, such as keratinocytes, dendritic cells (DCs), and NKT, Th1, Th17 and Th22 cells [169]. TNF induces not only immune and inflammatory responses orchestrated by keratinocytes but also tissue remodeling, cell motility, cell cycling, and apoptosis [170,171]. Additionally, activated keratinocytes also produce many chemokines responsible for recruitment of neutrophils, macrophages and skin-specific memory T cells, observations that underlines the fact that TNF might be involved in both the initial phase and the chronic phase of psoriasis [172].

T reg cells that express FOXP3 constitute major regulators of the immune system and inflammatory response. They inhibit the action of various immune cellular populations either directly or by releasing cytokines as IL-10 or TGF-β that act in a suppressing manner. The activity of T reg cells is probable to be impaired in psoriasis, as there are data sustaining that STAT3, activated by pro-inflammatory cytokines, inhibits T reg. IL-10, an anti-inflammatory cytokine, produced by regulatory T cells, has been stated as a major mediator in psoriasis and proved to be an important inhibitor for both pro-inflammatory T cell responses and keratinocyte inflammatory markers. The report of *Asadullah et al.* showed that the levels of mRNA along with the cytokine itself were decreased significantly in patients with psoriasis compared to other dermatologic disorders. An additional reported information was that the administration of recombinant IL-10 for 30 days diminished PASI score as well as Th-1 cytokines levels [173].

6. Intracellular Signaling Pathways

6.1. Janus Kinase-Signal Transducer and Activator of Transcription (JAK/STAT Pathway).

JAK is a member of tyrosine kinase (TYK) family, which comprises four members: JAK1, JAK2, JAK3 and TYK2, with various expression depending on the cellular type [174]. The development of various inflammatory autoimmune diseases is dependent on JAKs activation and phosphorylation of STATs, throughout several proinflammatory cytokines. Although the pathogenesis of psoriasis comprises multiple types of cytokines, the major role is attributed to IL-23 and Th17, directly linked to JAK/STAT pathway [175]. An increased expression of STAT1, directly related to JAK1/JAK2, determines an activation of IFN-α/β and IFN-γ. IFN-γ and IL-12 by a TYK2-dependent mechanism have a major input on keratinocytes stimulation and promote psoriatic inflammation [176]. An important observation was made by the study published by *Nada et al.* that reported a positive correlation between JAK1 and PASI score, as well as a significantly higher level compared to controls [177]. Other reports, performed on mouse models of psoriasis, concluded that TYK2 is able to slow the progression of psoriasis. STAT3, a major regulator for Th17 differentiation, via IL-23 activation, has been shown to be overexpressed in psoriasis skin samples and it constitutes a key regulator for keratinocytes [176]. In a similar manner, IL-22 stimulates keratinocytes proliferation and inhibits their differentiation, consecutive to STAT3 activation [178,179].

6.2. A3 Adenosine Signaling Pathway

Adenosine generated by ATP catabolism, acts as a supressive metabolite with immunomodulatory and anti-inflammatory functions enabled through four receptor subtypes A1, A2A, A2B and A3 [180]. A3 receptors are expressed on all types of immune cells and exert a pro-inflammatory effect in the respiratory system, while also having an anti-inflammatory action against LPS-induced cytokine release. This has enabled the development of various selective A3 receptor ligands [181]. Evidence of the role of A3Ars in modulating immune cell function and also positive results obtained in rheumatoid arthritis studies, has led to the development of a specific inhibitor CF10 (piclidenoson) for the treatment of psoriasis. It has shown positive results in vitro on cell growth

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and a reduction of PASI score. In addition, it lowers the expression of pro-inflammatory markers, like TNF- α, IL-17, IL-23 and phosphoinositide-3-kinase (PI3K) [182].

6.3. WNT

WNT signaling pathway plays an important role in cell growth, differentiation and migration. In psoriasis, WNT signaling generates an overexpression of WNT5A, with studies showing increased levels in affected areas, together with increased expression of its receptor proteins FZD2 and FZD5 [183]. Data suggests that the epidermis is one of the main sources of WNT5A in psoriatic lesions, with effects on inflammatory responses of human mononuclear cells and blood vessel proliferation [184,185].

6.4. NF-κB Signaling

The transcription factor NF-κB direct several processes including inflammation, proliferation, immunological actions, apoptosis and differentiation. Ccompared to normal samples, psoriatic derma presents high levels of active phosphorylated NF-κB. It influences psoriasis pathogenesis by stimulating TGF expression, VEGF induction and angiogenesis; also, binds to keratinocytes, with consequent cytokine production and chemokines activation [186].

7. Conclusions

Psoriasis etiology and extensive pathogenic pathways are not yet completely described with several hypotheses being proposed. Understanding the immunologic, genetic and autoimmune hallmarks of psoriasis has known an extensive development in the last decades and elucidating the underlying mechanism of the complex pathologic process associated to psoriatic disease enabled a tremendous progress in new and individualized therapeutic approaches, further to be extend by future characterization of the disease.

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