Pathophysiology of Psoriasis

Subjects: Dermatology | Medicine, General & Internal
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Psoriasis is an immune-mediated inflammatory disease, with a chronic relapsing-remitting course, which affects 2–3% of the worldwide population. Psoriasis vulgaris is a common inflammatory, immune-mediated, chronic, and recurrent dermatosis, caused by the interplay between multiple genetic and environmental risk factors. The clinical feature of psoriasis is dominated by erythematous-squamous plaques which usually, but non-exclusively arise symmetrically on the extensor surfaces of the elbows and knees, scalp, lumbosacral area, and it reflects some pathogenetic mechanisms underlying psoriasis, i.e., inflammation, hyperproliferation, angiogenesis.

Keywords: psoriasis ; pathophysiology 1. Introduction

1. Pathophysiology of Psoriasis

A key feature of psoriasis is sustained inflammation leading to altered keratinocyte proliferation and differentiation. What triggers and maintains this inflammation is dysregulation of the immune system, both in its innate and in adaptive components, caused by the interplay between multiple genetic and environmental risk factors [1][2]. Numerous cells and molecules are involved. Among these Th1, Th17, Th9, follicular Th (Tfh) and Th22 lymphocytes and their respective cytotoxic lymphocytes, Treg, γδT cells, dendritic cells, neutrophils, mast cells, NK and NKT cells, lymphoid innate cells (ILCs), keratinocytes, and IFN-α, INF-γ, IL-17, IL-22, IL-23, TNF-α, and numerous other dendritic cell-activating molecules, autoantigens, cytokines, chemokines play a role. An exhaustive discussion about all of them is beyond the scope of this section: the most crucial for “systematic repercussion” according to current evidence, will be described.

Following a chronologic line of discussion, dendritic cells are known to play a crucial role in the early stages of the disease. Although their mechanism of activation is still unclear, data show that antimicrobial peptides (AMPs), such as LL37, -defensins, S100 proteins, and cathelicidins, secreted by keratinocytes in response to damage, activate Toll-like receptors (TLRs) expressed by plasmacytoid dendritic cells (pDC), a particular type of dendritic cells that links innate and adaptive immunity [1][3]. The activation of pDc is crucial. Triggered, they produce IFN-, which promotes the maturation of myeloid dendritic cells (mDC): a specific population of them (CD11c + CD1c- cells), under this stimulus, begins to produce molecules that have become new therapeutic targets: TNF-α, IL-23, and IL-12 [4][5][6][7][8].

TNF-α is a pleiotropic molecule, meaning it is produced by a multitude of cells in addition to the DCs, and exerts its action on a multitude of cell types. It mainly induces in these the expression of adhesion molecules and secondary mediators. Noteworthy is that it stimulates the proliferation and differentiation of T lymphocytes, Th1, Th17, and Th22, which in turn will produce TNF-α, IL-17, IL-22, favoring initiation of a self-propelled cycle of inflammation. Essentially, this cytokine plays an indirect role in disease pathogenesis by promoting adaptive immune effects of the IL-23/IL-17 axis [9][10][11][12][13].

Activation of the IL-23/IL-1 axis, the focus on which has led to revolutionary targeted therapies, determines the amplification phase of the process and the tissue cellular response. Activated dendritic cells lead to massive lymphocyte infiltration and formation of DCs/T cell clusters, that facilitate the T-mediated response. The myeloid dendritic cells that infiltrate the dermis at this stage secrete IL-23, although, like TNF-α, it is not the only cell capable of doing so [7]. IL-23 production stimulates IL-17 producing cells, which include Th17, Tc17, γδ T cells, ILC3, mast cells, and neutrophils. Noteworthy is that recent studies have revealed that most IL-17-producing cells consist of γδ T cells [7][14]. The IL-17 cytokine family consists of 6 members, A–F, but only two have a pathogenetic role in psoriasis, IL17-A, and IL-17F. The former appears to have a stronger effect than the latter [15].

IL-17, in cooperation with other cytokines such as TNF-α and IL-22, induces the development of the psoriasis phenotype through tissue cell activation. The most relevant tissue response is provided by keratinocytes that, releasing chemokines and other pro-inflammatory molecules, such as CCL20 and IL-1 F9, sustain skin inflammation. Activation of the IL-23/17 axis is thus amplified by numerous mediators, and this determines the typical gene expression profile and histopathological picture of psoriasis [7][16][17].

An inflammatory cascade begins with IFN-γ and continues with TNF-α and IL-23 to end with IL-17, with progressive “disease-specificity”, so that IL-17 inhibitors, acting further downstream, have a more rapid onset of action [18][19]. Next to these “main” mediators, we find some “collateral” ones. IL-22, for example, would be pathogenically more relevant in vitro than in vivo. The “IL-2/IFN-γ” axis, which was considered essential before the “IL-17-centric” model, deserves mention. Th1 lymphocytes activated by various mediators, including IL-12, produce IFN-γ which probably plays a role as an upstream cytokine in the IL-23/IL-17 axis, but its pharmacological inhibition has not produced satisfactory results [20]. Other cells, such as neutrophils, vascular endothelium, and macrophages, also contribute to the pathogenesis of psoriasis, through the production of molecules such as VEGF, IL-17, IL-23 [17][21][22][23]. For what concerns psoriasis as immune-mediated systemic disease some questions still are pending: What do these processes occurring in the skin microenvironment have in common, and possibly connect, with the “systemic” ones? Which are the main pathogenetic drivers in psoriasis considered as a systemic inflammatory disease? Probably the best way to find answers is starting from the inflammatory pathway analysis rather than from the canonical point of view of clinical comorbidities.

2. Relevance of IL-23/IL-17 Axis in Systemic Involvement of Psoriasis

2.1. IL-23/IL-17 Axis and Psoriatic Arthritis

Psoriatic arthritis (PsA) is the most prevalent coexisting condition in PsO. In most cases, psoriasis precedes psoriatic arthritis [24]. Clinically, it can affect both axial and peripheral skeletons, with a wide range of clinical presentations including sacroiliitis, enthesitis, osteitis, and dactylitis.

Numerous pieces of evidence support the hypothesis that the IL-23/IL-17 axis plays a key role in the pathogenesis of PsA. High levels of Th17 cells have been found in psoriatic synovial fluid compared to rheumatic synovial fluid [25], similarly, high levels of IL-17A have been found in the synovial fluid and synovial membrane of patients with psoriatic arthritis [26]. Enthesitis, synovitis, and altered bone remodeling were observed in a mouse model after IL-23 administration. Inflammation and bone remodeling were mediated by TNF-α and IL-17 in this model [27]. Other studies have been reported in the literature on murine models with psoriasiform skin lesions, enthesitis, and arthritis were observed, and all of these models were linked to IL-23 [28].

A pathophysiologic model of psoriatic arthritis makes it resemble that of cutaneous psoriasis. A high ratio of myeloid to plasmacytoid dendritic cells was found in psoriatic synovial fluid. Inappropriate activation of dendritic cells triggers IL-23 production that activates IL-17-producing cells [29]. A second model, instead, supported by recent studies such as those mentioned above, attributes a fundamental role to the entheses, which have been proposed to be the site where the disease starts: IL-23 is released following biomechanical stress or trauma and activates IL-17 producing cells [24].

IL-17, acting in concert with other molecules produced in the process such as IL-22, IL-23, and TNF-α results in inflammation and pathological bone resorption and formation. Mesenchymal cells differentiate into osteoblasts in response to IL-22 and other signaling pathways, forming enthesophytes and syndesmophytes, involved in pathological bone formation [24]. IL-17 does not appear to directly activate osteoclasts, but stimulates osteoblasts to produce RANKL, which results, by binding to the RANK receptor on the surface of osteoclast precursors, in osteoclastogenesis [30].

We infer from current scientific evidence that both IL-17 and IL-23 play a key role in the pathogenesis of PsO and PsA, which might instead differ between skin and joints. is the “expression of the IL-23/IL-17 axis”.

For example, Belasco et al. [31] reported that gene expression patterns in skin and synovium are distinct, showing a stronger IL-17 signature in the skin than in synovium, while is an equivalent TNF-α signal across both tissues. Nerviani et al. [32] demonstrated that PsA synovial tissue shows a heterogeneous IL-23 axis profile when compared with matched skin. They reported that, while IL23A, IL12B, and IL23R are expressed at a high level in lesional skin, their expression in the synovium is hugely heterogeneous [32]. This could be the pathophysiological premise of the divergent skin-joints response, with less efficacy on the joint side, that is observed on a clinical base in patients under biological therapy. Recently, the existence of IL-23 producing cells in the axial involvement of PsA is gaining importance: the fact that IL-17 can be produced independently of IL-23, “outside the axis”, has relevant therapeutic consequences [33]. The relationship between osteoporosis, psoriasis, and psoriatic arthritis is still debated. Although these pathological conditions have common inflammatory pathways, such as TNF-α, INF-γ, IL-6, and although treatments used for PsO and PsA, such as methotrexate and cyclosporine, may induce bone rarefaction, studies on this subject are contradictory, and screening and management of osteoporosis in the psoriatic patient are still under debate [34]. A further link between osteoporosis and psoriasis could be IL-23, since this molecule induces osteoclastogenesis and receptor activator of kappa B ligand

(RANKL) expression in T cells. Recent studies support the idea of a protective effect of anti-IL23 therapy, but further confirmatory studies are needed [35].

2.2. IL-23/IL-17 Axis and Cardiovascular and Metabolic Comorbidities

The association between psoriasis and cardiovascular disease has been known for a long time, but the cause-and-effect relationship is still not well established. Robust data show that patients with severe psoriasis have an increased cardiovascular risk and reduced life expectancy. On the other hand, psoriatic patients are more likely to have a high BMI, metabolic syndrome, and type 2 diabetes mellitus. Although the contribution of cardiovascular risk factors to an increased rate of cardiovascular disease cannot be excluded, large studies show an independent relationship between PsO and cardiovascular disease [36][37][38][39].

IL-17, according to current scientific evidence, appears to be more central than IL-23 in the genesis of cardiometabolic complications in psoriatic disease.

IL-17 overexpressing mouse models had shorter life expectancy, and hypertrophic cardiomyopathy, and altered vascular endothelium compatible with increased cardiovascular risk [40]. IL-17 could have potentially opposite effects at the level of atherogenesis. IL-17 may promote the recruitment of neutrophils and monocytes to the plaque and their transformation into foam cells; at the same time, it may inhibit the expression of adhesion molecules and promote smooth muscle proliferation [41][42]. From a therapeutic point of view, instead, the CARIMA study showed that the administration of the IL-17 inhibitor secukinumab leads to a significant improvement in flow-mediated dilatation (FMD), an index of endothelial function [43]. Elnabawi et al. demonstrated that the IL-17 inhibitor was superior to biologics of other classes in reducing non-calcified plaques burden, through angiographic studies [44]. Although there are studies supporting the anti-atherogenic action of IL-17 [45][46], and the relationship between atherosclerosis and psoriasis is far from clear, overall, many authors believe it is pro-atherogenic, and, generally, the key molecule in the cardiovascular involvement of psoriasis, and as such, although still lacking controlled studies, the most promising “target” [39][47]. However, there is also a role for IL-23 in the cardiometabolic comorbidities of psoriasis, although, according to current evidence, less crucial than IL-17. The increased carotid intima-media thickness (IMT) could be considered to be a marker of generalized arteriosclerosis. Studies suggest that the carotid IMT may benefit from treatment with biological drugs, particularly anti-IL-12/23, in patients suffering from moderate-to-severe psoriasis. However, larger longitudinal studies should be performed to fully confirm these results [48].

Obesity, diabetes, and metabolic syndrome also seem to be linked to psoriasis via IL-17.

Studies show that IL-17 and cytokines secreted in response to its stimulus are relevant in the pathogenesis of obesity [49]. Obesity is associated with elevated serum levels of free fatty acids, which sensitize DCs to amplify the Th17 response [50]. In both visceral adipose tissue and other peripheral tissues of obese individuals, increased IL-17-producing T cells were detected, and elevated levels of IL-17 were found in serum [51][52].

Supporting the implication of IL-17 in the metabolic syndrome is the finding that IL-17R levels in the liver and muscle correlate with insulin resistance [53], and that blockade of IL-17 leads to decreased hepatic inflammation in non-alcoholic steatohepatitis syndrome [54].

Worthy of mention is that IL-17 interferes at the molecular level with insulin signaling. Since IL-17 activates the IκB kinase (IKK)/NFκB pathway, inhibitory phosphorylation of IRS-1 directly by IKK and indirectly by JNK activation in response to other proinflammatory cytokines is able to attenuate insulin sensitivity [55]. The opposite is also true, as shown by epidemiological studies mentioned earlier, namely that insulin resistance can worsen psoriasis. From a molecular point of view, we know that, under conditions of hyperinsulinemia, adipocytes secrete large amounts of VEGF. VEGF has been shown to activate keratinocyte inflammation, in interaction with IL-17 [56].

2.3. IL-23/1L-17 Axis: Psoriasis between Nervous and Gastrointestinal Systems

The complex pathogenesis of psoriasis is intertwined with that of inflammatory bowel and neurodegenerative diseases, with important therapeutic implications. Psoriasis and Chron’s Disease, or Ulcerative Colitis, for example, show similarities from a pathogenesis perspective, and a higher rate of co-occurrence [57][58][59]. Again, the IL-23/IL-17 axis plays a crucial role and, again, is expressed differently than in other body sites. In “intestinal comorbidity” of psoriasis IL-23 has a decisive pathogenic role compared with IL-17.

Increased levels of IL-17 and IL-23 are found in the intestinal lamina propria of patients with Crohn’s disease. A growing body of literature demonstrates that IL-17, as opposed to IL-23, in the intestine has a role in maintaining homeostasis rather than as a driver of inflammation [60]. In murine models of intestinal disease, treatment with IL-23 inhibitors improved

colic symptoms, increased the Treg/Th17 ratio, and improved epithelial barrier integrity, whereas treatment with IL-17 increased the number of proinflammatory cytokines, decreased the Treg/Th17 ratio, and worsened epithelial barrier integrity [61][62]. Manasson et al. demonstrated that in patients with psoriatic arthritis pharmacological blockade of IL-17 induced subclinical intestinal inflammation and dysbiosis [63]. Finally, gut dysbiosis could trigger IL-23-mediated inflammation, although a recent systematic review concludes that the relationship between psoriasis and the gut microbiome is still far from being understood and brought into clinical practice [24][64][65].

Court studies also report a statistically significant association between multiple sclerosis and psoriasis, an association that is denied by a few other studies [66][67][68]. The pathogenetic mechanism is unclear; however, a recent study attributing a key role to IL-17 in the genesis of neurodegenerative diseases is worthy of mention. It is able to activate microglia, astrocytes, oligodendrocyte precursors. What results is an inflammatory cascade that causes loss of dopaminergic neurons, glutamate excitotoxicity, and apoptosis of oligodendrocytes [69].

3. TNA-α in Systemic Involvement in Psoriasis: And “Old but Gold” Pathogenetic Driver

TNF-α, is the historic molecule investigated first as a pathogenic driver in psoriasis, it has demonstrated an indirect role in skin pathophysiology, promoting the effects of the IL-23/IL-17 axis.

We can state that TNF-α is a less “skin-specific” molecule, than the IL-23/IL-17 axis, but that, according to the current evidence, in psoriasis considered as a systemic inflammatory disease remains a “hallmark”.

In psoriatic arthritis, for example, its expression is stimulated by IL-17, and thus TNF-α is located “downstream” of it. TNF-α promotes pathological bone resorption by inhibiting osteoblastogenesis via Dkk-1 and promoting osteoclastogenesis via RANKL [70][71]. However, as is the case of pure cutaneous psoriasis, also the “IL-12/IFN-” axis has a pathogenic role in PsA, and TNF-α secretion, by Th1 cells, could be stimulated also in this sense. Thus, TNF-α could be located in the inflammatory cascade on the same level and upstream of IL-17 [24][70]. Although its position may seem collateral, “around” the IL-23/IL-17 axis, in reality, its role is crucial. TNF-α is equally expressed in the synovial tissue of psoriatic arthritis and rheumatoid arthritis [25]. According to Belasco et al. IL-17 is expressed proportionally more in psoriatic skin than in the joint, whereas TNF-α expression is equivalent in the two [31]. A question arises: can we consider IL-17 a “more cutaneous” molecule and TNF-α a “more arthropathic” molecule, in the context of psoriasis considered as a systemic disease, as suggested by the brilliant efficacy of TNF-α inhibitors in joint symptomatology and their superiority over IL-17/23 inhibitor, highlighted by studies?

The same is true for cardiometabolic involvement. In the process of atherosclerotic plaque formation, TNF-α plays a fundamental role. Armstrong et al. [71], noted how there might be two links between inflammation in psoriasis and atherogenesis. The first, mentioned above, is driven by the IL-23/17 axis, with a prominent role of IL-17, which is, according to the authors, involved in plaque instability. The second is, again, driven by the IL-12/INF-γ axis, with activation of Th1 cells producing TNF-α, which is more involved in plaque development. A study has demonstrated, through an interesting bioinformatics approach, that the dominant pro-inflammatory signals linking atherosclerosis and psoriasis are that of TNF-α and INF-γ [72]. Globally, apart from psoriatic disease, TNF-α is known to induce insulin resistance both in vitro and in vivo, by reducing tyrosine kinase activity of the insulin receptor, and endothelial dysfunction, and it may contribute to altered cardiac remodeling after myocardial infarction. TNF-α exacerbates hepatic insulin resistance, resulting in increased FFA synthesis and decreased FFA oxidation, thereby promoting hepatic steatosis. It contributes to the pro-inflammatory state of obesity [73][74].

Numerous pieces of evidence estimate that in inflammatory bowel diseases (IBD), local TNF-α secretion induces not only tissue damage but also activation of the adaptive immune system, which perpetuates the inflammatory state resulting in systemic inflammation [75]. Although clinical trials with nonselective anti-TNF-α antibodies completely failed, the role of TNF-α in the pathogenesis of multiple sclerosis is still widely debated [76].

4. Other Molecules, Other Cells: A Currently Collateral Role in Systemic Involvement of PsO

Studies have highlighted the role of other molecules and cells in the pathogenesis of psoriasis as an immune-mediated systemic inflammatory disease. According to the current evidence, however, they appear collateral or dependent on the systems considered above.

IL-22 has a role in the joint and cardiometabolic involvement of psoriasis, but is essentially dependent on the IL-23/IL-17 axis, since it has a primarily cooperative action with IL-17 [24][71]. Moreover, the strategy of blocking IL-22 has proven to be not effective in treating psoriasis [7]. L-1β induces dermal γδ T cell proliferation and IL-17 production in mice. In addition, IL-1β stimulates keratinocytes to secrete chemokines that preferentially chemoattract peripheral CD27- CCR6 + IL-17 capable of producing γδ T cells (γδT17) [77].

Adipokines are cytokines produced by adipose tissue, which have functions in the regulation of metabolic functions, such as glucose and lipid metabolism, inflammation, and vascular homeostasis. They have been implicated in cardiovascular involvement in psoriasis. According to a recent review on the subject by Lynch et al. [78], studies on adiponectin are contradictory regarding its pattern in PsO, and prospective controlled studies are needed to clarify their relationship. High levels of pro-inflammatory cytokines resistin and leptin have been detected and correlate with disease severity, but rather than a pathogenic role they may constitute markers of disease.

Vitamin D is a regulator of keratinocyte differentiation, and low levels of vitamin D have been associated with metabolic syndrome and increased cardiovascular risk. However, studies in this regard suggest a need to treat low serum levels of vitamin D in the course of psoriasis, rather than a central pathogenic role of vitamin D in psoriasis as a systemic disease [79].

Communication between neutrophils and macrophages is crucial in any inflammatory response and especially that underlying atherosclerosis [80], and NETosis, or the ability of neutrophils to expel cytosolic and nuclear material forming extracellular traps that ensnare extracellular microbes, has been proposed to have a role in atherosclerosis as well as psoriasis, but these findings seem too general [80][81].

Further studies are certainly needed to further investigate the role in the systemic involvement of psoriasis of other cells and molecules than IL-17, IL-23, and TNF-α, which currently seem “more central”.

5. Other Links and Further Complexity in “Systemic PsO”

Scientific research has revealed other and increasingly complex associations of cutaneous psoriasis with other extracutaneous conditions. Psoriatic patients have a higher incidence and prevalence of uveitis, and the involvement of IL-17, IL-23, TNF-α, and IL-6 molecules unite both conditions [82][83]. Asthma and psoriasis can coexist and what they have in common is IL-17A [84]. Psoriasis is also linked to polycystic ovary syndrome and it has been shown that skin clinical features can vary depending on the PCOS phenotype [85]. A recent meta-analysis found that patients with psoriasis appear to have a slightly increased risk of cancer, particularly keratinocyte cancer and lymphomas, although data for National and International Registries on treatment with biologic agents did not show an increased risk of cancer, and data on cancer in patients with psoriatic arthritis remain inconclusive [86]. The prevalence of having depression or anxiety is higher in psoriasis patients than in controls, and TNF-α could be a pathophysiologic link between the two conditions [87] [88].

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