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Paradoxical psoriasis: The flip side of idiopathic psoriasis or an autocephalous reversible drug reaction?

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ABSTRACT

Psoriasis is a common, chronic skin disease that results mainly from the complex interplay between T cells, dendritic cells, and inflammatory cytokines including TNF-α, IL-17, IL-12, and IL-23. Successful therapy with anti-cytokine antibodies has proved the importance of these key cytokines, especially TNF-α. During the *anti*-TNF-α treatment of classical idiopathic psoriasis, a small portion of patients develop new psoriasiform lesions. This contradictory phenomenon was named paradoxical psoriasis which resembles idiopathic psoriasis clinically but presents overlapped histological patterns and distinct immunological processes. In this review, we discuss the differences between idiopathic psoriasis and paradoxical psoriasis with an emphasis on their innate immunity, as it is predominant in paradoxical psoriasis which exhibits type I IFN-mediated immunity without the activation of autoreactive T cells and memory T cells. We also put up an instructive algorithm for the management of paradoxical psoriasis. The decision on drug discontinuation or switching of biologics should be made based on the condition of underlying diseases and the severity of lesions.

1. Introduction

Psoriasis is a common chronic inflammatory skin disease caused by the interplay between diverse environmental risk factors in genetically predisposed individuals, with sustained inflammation playing a core pathogenic role. It affects about 2%–3% of the population worldwide with a similar prevalence in men and women, and a slight preference in adults over children [1]. Infections, mechanical stress, air pollution [2], vaccination [3], smoking [4], and alcohol are considered extrinsic risk factors while mental stress [5], obesity, diabetes mellitus, metabolic syndrome, and hypertension [6] are significant intrinsic risk factors of psoriasis.

According to morphologic characteristics, the clinical variants of idiopathic psoriasis include plaque, guttate, erythrodermic, pustular, and inverse psoriasis. Plaque psoriasis is the most prevalent subtype featuring erythematous scaly patches or plaques over the trunk, scalp, and extensor body surface. Histopathologically, it is typified by the presence of conspicuous epidermal acanthosis, hyperkeratosis, parakeratosis, and elongation of rete ridges, exhibiting chronic inflammatory infiltration mainly of T lymphocytes, neutrophils, macrophages, and mast cells in the dermis and epidermis.

In the early phase, plasmacytoid dendritic cells (pDCs) are activated by complexes of host DNA and epidermis-produced antimicrobial peptides (AMPs), such as LL-37. Then pDCs secrete interferon (IFN)-α which contributes to the activation of conventional dendritic cells (cDCs). IL-12, IL-23, TNF-α, and other pro-inflammatory cytokines produced by cDCs subsequently drive the activation of potentially autoreactive T lymphocytes, such as T helper (Th) 1, Th17, and Th22 cells (Fig. 1).

Tumor necrosis factor-alpha (TNF-α) is a pleiotropic cytokine that can amplify inflammation through several pathways. TNF-α is secreted from activated cDCs as well as other types of immune cells, including macrophages, lymphocytes, keratinocytes, and endothelial cells. TNF-α/IL-23/Th17 axis plays a predominant role in plaque psoriasis. Once activated, Th17 cells produce a variety of mediators such as IL-17 and IL-22. These cytokines add to the proliferation of keratinocytes and chronic immune response in vivo.

In the past decades, an accumulated understanding of the role of TNF-α and other cytokines in the pathogenesis of psoriasis has brought in various biologic agents in clinical application. As a consolidated treatment for moderate-to-severe psoriasis patients, *anti*-TNF-α treatment proves a remarkable efficacy. However, about 2%–5% of the patients experience a new onset of psoriasis or exacerbation of pre-existing

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psoriatic lesions during the treatment of biologics, especially TNF-α inhibitors. This immune-mediated, non-infectious inflammatory side effect of biological agents is named paradoxical psoriasis (PP). In addition to TNF-α inhibitors, multiple biologics (IL-12/23 inhibitor: Ustekinumab; IL-17A inhibitor: Secukinumab, Ixekizumab, Brodalumab; IL-4/13 inhibitor: Dupilumab; IL-6 inhibitor: Tocilizumab, Siltuximab; IL-23 inhibitor: Risankizumab, Guselkumab) were reported to have induced PP. Though PP shares similar clinical manifestations with classical idiopathic psoriasis, their immunological processes are quite divergent.

2. Idiopathic psoriasis

2.1. Innate and adaptive immunity

Emerging evidence shows that innate immunity plays a vital role in active severe psoriasis while adaptive immunity is dominant in chronic stable patients. Endogenous AMPs expression and activation of pDCs are the initiations of innate immunity in psoriatic lesions. AMPs are innate immune effectors of skin and are often produced by keratinocytes or infiltrating neutrophils in pathological conditions like infections or injuries [7,8]. A group of AMPs is found highly expressed in psoriatic lesions, such as cathelicidin, β-defensins, S100 proteins, lysozyme, RNase 7, elafin, and neutrophil gelatinase-associated lipocalin [9]. As effector molecules against microorganisms, the persistent expression of AMPs in psoriatic lesions leads to activations of keratinocytes and innate immune cells, including neutrophils, macrophages, and DCs, mainly in a pattern recognition receptor (PRR)-dependent manner. AMPs bind to fragments of nucleic acid and form a complex resistant to degradation [10,11]. The complex transfers to endosomes and activates the toll-like receptor (TLR), leading to the recruitment of neutrophils and macrophages, neutrophil extracellular trap (NET) formation, and the production of IFN-α. pDCs-derived IFN-α promotes the maturation of cDCs which accumulate autologous reactive T cells, especially $CD8^+$ T cells, into the dermis [12,13].

The pathophysiology of chronic psoriasis is mainly mediated by activated T cells and the sustained overactivation of the adaptive immune system after DCs activation. The activated cDCs secrete two key psoriatic cytokines: IL-12 and IL-23.

The mutation of TYK2, one of the intracellular tyrosine kinases of the JAK-STAT superfamily, was found to be related to the onset of psoriasis [14]. The combination of TYK2 and JAK2 initiated the downstream signal transduction of receptors for IL-12, IL-23, and type I IFN family [15,16], the inhibition of which resulted in all but complete disfunction of IL-12, IL-23, and type I IFN signaling [17].

Naive T cells differentiate into Th1 cells and promote the secretion of IL-12 which is markedly increased in psoriatic lesions. Th1 cells are recruited to psoriatic plaques by chemokines derived from myeloid cells and keratinocytes, such as CXCL9, CXCL10, and CXCL11. The Th1-biased profile then leads to the overproduction of IFN-γ and TNF-α. IL-12 shares the subunit p40 with IL-23 and differs in the second subunit p35. Since previous studies revealed the link between the p40 subunit and the increased level of IL-12, more attention was paid to the IL-23/Th 17 immune axis and its main downstream effector, IL-17A.

Myeloid cell-derived IL-23 is recognized by the IL-23 receptor expressed on naive T cells, which is considered important for the differentiation and preservation of Th17 cells [18]. The complex of IL-23R and IL-12Rβ1 activates the signal transducer and activator of transcription 3 (STAT3) and then leads to an increased level of IL-17 and retinoid-related orphan receptor (ROR)-γt [19]. Cells of innate immunity such as DCs and macrophages produce inflammatory cytokines (e.g. TGFβ1, IL-1β, IL-23, and IL-6) facilitating the ROR-γt-dependent differentiation of naive T cells to Th17 cells [20]. It is also discovered that in pustular and plaque psoriasis, mast cells and neutrophils markedly elicit the accumulation of IL-17 and transcription factor ROR-γt through the NET formation [21,22]. IL-23 mainly contributes to the maintenance and expansion of the Th17 phenotype. In IL-23p19 knock-out mice, IL-17A and IL-17F induction were completely defeated [23]. Clinical trials have shown that psoriatic lesions express a higher level of

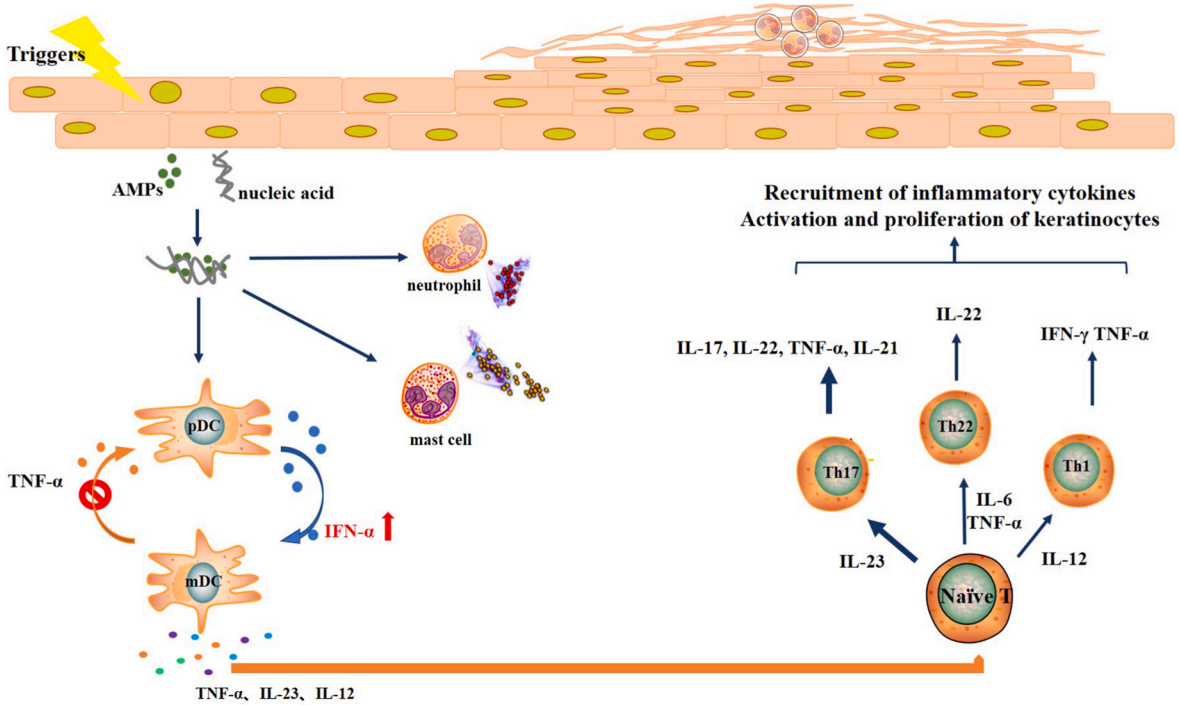

Fig. 1. Pathogenesis of idiopathic and paradoxical psoriasis. Keratinocyte-generated AMPs such as S100 proteins, β-defensins, and cathelicidin, combine to nucleic acids. Complexes of LL37 and nucleic acids stimulate pDCs which afterwards secrete type I IFN. mDCs are activated by IFN-α and produce TNF-α, IL-12 and IL-23. TNF-α induces the maturation of DCs and deprives their ability of producing IFN-α. Different cytokines drive the differentiation of naïve T cells into Th1, Th17 and Th22 cells, which leads to the activation and proliferation of keratinocytes. In PP, the inhibition of TNF-α results in the dysmaturity of DCs and sustained production of IFN-α. The autoreactive T cells are absent, but PP remains as the type I IFN-mediated inflammation with uncertain downstream mechanism.

IL-23p19 messenger RNA compared with normal skin. Also, psoriasis patients overexpress the IL-23 receptor on dermal DC and Langerhans cells.

As the most functional isoform of the IL-17 family, IL-17A is produced by Th17 cells, $CD8^+$ T cells, and neutrophils of innate immunity [24]. Also, γδT cells and natural killer cells can produce IL-17A independent of IL-23 [24,25]. IL-17 is the main downstream effector cytokine of IL-23. It elicits the proliferation of keratinocytes and adds to the following inflammatory process by inducing the production of pro-inflammatory cytokines, AMPs such as LL-37, and chemokines, which circularly intensifies the aggregation of neutrophils, Th17 cells, and DCs [26]. This process collectively makes up a positive feedback loop [27]. CXCL-1, CXCL-2, and CXCL-8(IL-8) are of service to the recruitment of neutrophils [28]. IL-17 is increased in psoriasis patients and contributes to vascular changes in psoriatic lesions. IL-17A participates in angiogenesis through the expression of VEGF, IL-8, migration of endothelial cells, and functioning with IL-17F as a heterodimeric cytokine [29]. Though IL-17A is thought to be the pivotal effector cytokine of Th17 cells, five other IL-17 isoforms (IL-17 B to F) are all involved in the pathogenesis of psoriasis to varying degrees [30–32]. Among them, IL-17A, E, and F are the primary isoforms overexpressed in psoriasis [32,33]. In addition, Th17-mediated inflammation can be induced by exogenous factors such as ultraviolet radiation, 12-O-tetradecanoyl phorbol-13-acetate (TPA), and other cytokines like IL-9 [34–36]. Dazzling than ever, the pathogenicity of the IL-23/IL-17 pathway is well recognized with a better understanding of the innate and adaptive immunity of psoriasis. In the end, cytokines produced by Th1 and Th17 cells collectively lead to the activation and proliferation of keratinocytes, and the manifestation of psoriasiform eruptions.

2.2. Histological features

The classic histological features of idiopathic psoriasis are in accord with its clinical appearance. Due to the lack of normal differentiation, an incrassated epidermis is characterized by the thickened stratum corneum, the appearance of nuclei in the upper layers and stratum corneum, and the disappearance of the normal granular layer. Neutrophils assemble in the epidermis and stratum corneum and are separately named Kogoj pustules and Munro's micro-abscesses. Mononuclear cells are abundant in the dermis. Dilated blood vessels are responsible for the erythema of psoriasis.

3. Paradoxical psoriasis

3.1. Pathogenesis of paradoxical psoriasis

Gene polymorphisms are significantly linked to the response to the *anti*-TNF-α treatment. Various single-nucleotide polymorphisms (SNPs) have been found associated with paradoxical psoriasiform in the genes TNF-α, TNFR1B, TNFAIP3 [37], IL23R [38], FBXL19, CTLA4, SLC12A8, and TAP1 [39]. The TNF-α rs1799964 rare C allele may be a predisposing genetic factor to PP in inflammatory bowel disease patients, especially those treated with adalimumab. The HLA-C *w* 06 rs 10484554 is a predisposing genetic factor for classical psoriasis, but not for PP [40]. A recent case-control study containing 97 patients found that psoriasis family history, psychological stressors, and tobacco use were risk factors for developing PP [41,42].

PP presents a similar immunological process with the early phase of idiopathic psoriasis characterized by cellular players of innate immunity including pDCs, neutrophils, mast cells, macrophages, and monocytes [43,44]. PP is primarily mediated by the overexpression of pDCs-derived IFN-α. It goes through an immunologic process independent of T cells, which is contrary to conventional psoriasis [45]. A boosted number of pDCs were found in lesions of PP than in normal healthy skin and classical plaque psoriasis lesions [46]. This increase was remarkable when compared with the level of pDCs in classical plaque psoriasis [45]. pDCs are not visible in peripheral tissues normally but may be recruited to the skin in case of abnormal autoimmunity, infections, and wounds. pDCs produce large amounts of type I IFN in response to nucleic acid sensors, TLR7 and TLR9. Type I IFN activates intracellular antimicrobial procedures and influences the process of immune responses. Previous studies have found an increased level of IFN-α after *anti*-TNF-α treatment in autoimmune diseases such as juvenile arthritis and systemic lupus erythematosus [47–50]. IFN-α elicits the release of TNF-α from DCs, which later drives the maturation of DCs and gradually deprives DCs of their ability to produce IFN-α. Therefore, early transient overexpression of IFN-α is later replaced by TNF-α-dominant inflammation in conventional psoriasis. The use of TNF-α inhibitors brings about the defects of DCs maturation and allows for persistent production of type I IFN. As a result, PP fails to establish an adaptive immune response while classical psoriasis develops into a T-cell-mediated autoimmune process. This is compatible with their clinical courses that no recurrences take place in PP after the regression and classical psoriasis tends to be chronic and recurrent.

In addition to the predominant role of IFN-α in PP development, various studies have revealed the polarization skewing of immune cell subtypes in PP. *Anti*-TNF-α inhibitors-associated PP was mostly characterized by Th17- and Th1-type cytokines infiltrates [51,52]. The expression of morbific cytokines, such as IL-17A and IL-22, was observed upregulated in the lesions of PP [53]. β-Defensins and IL-36, marker of the psoriasis-like/IL-17 pathway phenotype, were also remarkably elevated in *anti*-TNF-α-associated psoriasiform dermatitis [54]. A recent study showed the correlation between the number of IL-17A-expressing T cells and the severity of psoriasiform skin lesions, and *anti*-IL-12/IL-23 treatment proved effective in these cases [51]. Also, the *anti*-TNF-α treatment promotes the interaction between monocytes and Tregs by enhancing the combination of monocyte membrane TNF and TNF-RII expressed on Treg cells. Consequently, the blockage of TNF-α expanded functional Foxp3 (+) Treg cells and suppressed Th17 cells through an IL-2/STAT5-dependent mechanism [55,56]. An inverse correlation was found between the percentage of Tregs and the percentage of Th1 and Th17 cells in RA patients following infliximab treatment [57]. However, the result of TNF-α blockage is not consistent in different kinds of underlying autoimmune diseases, biological agents, or groups with different responses to treatments. For example, Th17 cells and IL-17 production were found upregulated after *anti*-TNF-α therapy in rheumatoid arthritis (RA) [58]. In another research, Th1 prevalence was higher than baseline only in the etanercept- or infliximab-treated group in RA, but stable in the adalimumab-treated group, and Th17 prevalence was at the baseline in the three groups [56]. Infliximab application resulted in a decrease in the number of Th1 cells while a completely adverse phenomenon was observed in the etanercept-treated group in ankylosing spondylitis patients [59].

Obvious chaos is in the inflammatory cytokines and chemokines of PP. IL-6, IL-8, IL-1β, CCL13, and MCP-1 were observed downregulated with the application of TNF-α inhibitors. It was recently reported that with the inhibition of TNF-α, the increment in TIMP-3 (that is regulated by levels of miR-21) would support the involvement of other inflammatory cytokines apart from TNF-α in the pathogenesis of the PP [60]. The increase of peripheral Th17 cells in RA patients was reported accompanied by a decrease in the expression of CCR6, a characteristic surface marker of Th17 cells' recruitment [58]. A significant reduction of CX3CL1 and its receptor CX3CR1 were discovered in the responsive group of RA patients with infliximab treatment [61]. Similar phenomena were observed in CCL18, CXCL10, CXCL13, and CCL20. *Anti*-TNF-α treatment leads to the accumulation of IFN-α which can elicit the expression of CXCR3, a chemokine receptor highly expressed on Th1-type CD4 (+) T cells and effector CD8 (+) T cells [62]. The recruitment of activated Th1 and T cytotoxic cells and memory CD4 (+) T cells to the inflammatory sites of the skin was CXCR3-dependent [63,64]. These transitional cytokines and chemokines can affect the subtype of immune cells reversely. For example, a shift from central memory T

cells to effector memory T cells proceeded in RA patients using golimumab. At the same time, TNF-α, IL-2, and IL-17 were all found upregulated, which may result from the compensatory release of TNF-α from memory T cells [65]. The exact functions of these alterant cytokines and chemokines are still uncertain due to the limited samples and research to date.

3.2. Clinical and histopathologic features

Since its first report in 2003, multiple cases have been documented [66]. According to the published articles, women account for 72.2%–73.5% of PP [67]. The age of onset ranges from 7 to 83 years old and only 11.8% of these patients had a family history of psoriasis [68]. The incidence rate of PP was reported higher in children with chronic nonbacterial osteomyelitis than in juvenile idiopathic arthritis or inflammatory bowel disease [69].

PP usually occurs within one month [70] to three years [71] after the use of biologics, with an average time of 11 months [67]. It often regresses upon the discontinuation of therapy. The most common inciting agents are infliximab and adalimumab, two of the *anti*-TNF-α inhibitors. Others include IL-12/23 p40 inhibitors, IL-17 inhibitors, IL-4Ra inhibitors, and IL-23 p19 inhibitors [72]. Presentations of PP can be blended and variable. The most frequent clinical types are plaque, pustular, guttate, erythrodermic, and inverse psoriasis [67]. Palmoplantar or scalp involvement is usual as well and scalp involvement can develop into alopecia in severe cases. Nail involvement is less often and may present with onycholysis, discoloration, and pitting [62].

PP shares similar histological features with classical psoriasis, but histological patterns of PP are usually overlapping [45]. There are mainly three patterns: (1)eczematiform spongiotic pattern; (2) psoriasis-like dermatitis (with infiltration of intraepidermal or subcorneal neutrophils); and (3) lichenoid reaction with focal interface dermatitis. Recently a retrospective study found that confluent parakeratosis, neutrophils in the stratum, and papillary plate thinning were more likely to be seen in idiopathic psoriasis; while complete lack of parakeratosis, neutrophils in the epidermis and $\geq$3 eosinophils in the dermis were more common in PP. Specimens of infliximab-induced psoriasis showed a tendency to have acanthosis than those of etanercept- or adalimumab-induced PP, which may be due to sampling bias though. No difference was observed between responders and non-responders to topical medications [73].

We can distinguish PP from the aggravation of original psoriasis with the following points. Firstly, there is a duration of obvious or complete improvement of the patient's psoriasis before the appearance of PP, but original psoriasis usually has a protracted clinical course and the aggravation often occurs under certain circumstances, such as the use of beta-blockers, antimalarial, lithium or nonstandard use of glucocorticoid. Secondly, PP may show some atypical signs infrequently seen in the histopathology of original psoriasis, including spongiosis and eosinophils, as mentioned above. Thirdly, PP usually subsides with the discontinuation of biologics, while original psoriasis probably won't improve or even get worse in the same condition without additional medications.

Laboratory tests might provide some clues to confirm PP according to the results in some case reports, but the practical significance is uncertain due to the lack of large sample data. For example, PP could present evaluated expression of IFN-α both in the blood and lesion [46]. The number of IL-17A-expressing T cells was reported to correlate with the severity of PP [51].

4. Management of PP

The outline treatment for PP includes the management of underlying disease and alleviation of skin symptoms. Half of the patients spontaneously regress after the discontinuation of the culprit drug, but others suffer from persistent lesions. Unconditional withdrawal of drugs could end up with the aggravation of underlying diseases [74].

It is now believed that patients with controlled underlying disease should proceed with current therapy when the eruption is mild to moderate. Topical steroids, vitamin D3 analogues, and calcineurin inhibitors are recommended. For moderate-to-severe skin eruptions, additional UV therapy and systemic therapy (e.g. steroids, methotrexate, cyclosporine, mycophenolate mofetil, and acitretin) should be applied when topical treatment is insufficient. Among them, cyclosporine is only advised for short-term bridge therapy when necessary. Notably, in this stage, the discontinuation of biological therapy is not a prerequisite [75].

When it comes to patients with uncontrolled underlying diseases, the suspension or replacement of *anti*-TNF-α therapy is predominant together with topical and/or systemic therapy mentioned above [72]. It has been reported that extra application of cyclosporine showed a better effect on PP than methotrexate or steroids [67,76]. Methotrexate used with a high dosage (more than 15 mg/week) is superior to a dosage of less than 10 mg/week. Less than 50% of the cases benefited from switching to another TNF-α inhibitor though adalimumab presented a slight superiority over other TNF-α inhibitors [67]. In addition, topical corticosteroids proved effective in a case of pustular psoriasis associated with infliximab [75]. A few cohort studies reached a consensus that the replacement of TNF-α inhibitor with another biologic, especially ustekinumab, is beneficial to PP [77,78]. Moderate-to-high anti-nuclear antibody titers and extensive pustular presentations may be negative prognostic indicators in PP patients [79]. DNA copy number variations may be a candidate marker to predict response to adalimumab and the development of PP [80,81].

The treatment of PP is still challenging. A few algorithms were put forward for the management of PP recently, but there is divergence among them [67,82–84]. The essence of the management is keeping the balance between the underlying disease and the cutaneous side effects. The decision to continue, suspend or replace the TNF-α inhibitor should be weighed carefully. Overall, in patients with well-controlled underlying disease, replacement of TNF-α inhibitor is appropriate for moderate or severe eruptions. In case of uncontrolled underlying disease, and/or intractable lesions such as scalp psoriasis with alopecia, severe genital lesions, or palmoplantar involvement with a disability, replacement with other biologics is recommended. The choice of substitutive biological agent depends on different diseases. For example, tocilizumab and rituximab are appropriate for RA; ixekizumab, ustekinumab and brodalumab [85] are suitable for psoriasis; ustekinumab and vedolizumab are optional for inflammatory bowel disease [77,83]; and secukinumab in pyoderma gangrenosum [86].

5. Conclusion

Currently, the mechanism underlying PP is still uncertain, especially the downstream immune response of IFN-α. Firstly, polymorphisms in a variety of genes have indicated the role of host factors. Secondly, pDCs are crucial to the occurrence of PP. pDCs can recognize nucleic acids dependent on TLR7 and TLR9 in injured skin and transiently produce type I IFN. Cathelicidin peptides, as an assistant of nucleic acid recognition, are sufficient for the production of pDCs, type I IFN, IL-17A, and IL-22 [87]. Also, pDCs can promote the differentiation of Th17 cells and amplify Th17 cells' effector function in response to TLR7 stimulation [88]. It is reasonable that sustaining activation of pDCs and boosted IFN-α mediate the activation and differentiation of Th17 cells similarly. Though the lack of samples and research makes the current results controversial, we have noticed an innate immunity-biased pathway of initiating the psoriasiform lesions in addition to the traditional Th17/Th1 cells-dominant immune response. As mentioned above, Th17 cells are considered prominent in connecting adaptive and innate immunity. It seems that recruited Th17 and Th1 cells mediate the pathogenesis of psoriasis distinct from the conventional pathway. According to previous studies, TNF-α functions in a time-dose-dependent way, but

it is uncertain about the pattern of TNF-α inhibition. If similar, this may be the underlying mechanism of spontaneous regression without cessation of TNF-α inhibitors.

Though our understanding of PP is still limited, we have accumulated quite a bit of experience in handling it with more and more research conducted. Additional novel targets could be around the corner for therapeutic intervention of PP, idiopathic psoriasis, and other inflammatory diseases only if we have a better identification of involved cytokines and their cellular sources.

Credit author statement

Lu Jiawei: Investigation, Software, Writing – original draft.Lu Yan: Conceptualization, Supervision, Writing- Reviewing and Editing.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Abbreviations

AMPs: antimicrobial peptides
pDC: plasmacytoid dendritic cell
mDC: myeloid dendritic cell
IFN: interferon
IL: interleukin
TNF: tumor necrosis factor
Th: T helper
PP: paradoxical psoriasis