# Molecular consideration relevant to the mechanism of the comorbidity between psoriasis and systemic lupus erythematosus (Review)

YUYING QU[1], DONGMEI LI[2], WEIDA LIU[3] and DONGMEI SHI[4]

[1]Department of Dermatology, College of Clinical Medicine, Jining Medical University, Jining, Shandong 272067, P.R. China; [2]Department of Microbiology and Immunology, Georgetown University Medical Center, Washington, DC 20057, USA; [3]Department of Medical Mycology, Chinese Academy of Medical Sciences Institute of Dermatology, Nanjing, Jiangsu 272002; [4]Department of Dermatology, Jining No. 1 People's Hospital, Jining, Shandong 272011, P.R. China

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**Abstract.** Systemic lupus erythematosus (SLE), a common autoimmune disease with a global incidence and newly diagnosed population estimated at 5.14 (range, 1.4-15.13) per 100,000 person-years and 0.40 million people annually, respectively, affects multiple tissues and organs; for example, skin, blood system, heart and kidneys. Accumulating data has also demonstrated that psoriasis (PS) can be a systemic inflammatory disease, which can affect organs other than the skin and occur alongside other autoimmune diseases, such as inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis and SLE. The current explanations for the possible comorbidity of PS and SLE include: i) The two diseases share susceptible gene loci; ii) they share a common IL-23/T helper 17 (Th17) axis inflammatory pathway; and iii) the immunopathogenesis of the two conditions is a consequence of the interactions between IL-17 cytokines with effector Th17 cells, T regulatory cells, as well as B cells. In addition, the therapeutic efficacy of IL-17 or TNF-α inhibitors has been demonstrated in PS, and has also become evident in SLE. However, the mechanisms have not been investigated. To the best of our knowledge, there remains a lack of substantial studies on the correlation between PS and SLE. In the present review, the literature, with regards to the epidemiology, genetic predisposition, inflammatory mechanisms and treatment of the patients with both PS and SLE, has been reviewed. Further investigations into the molecular pathogenic mechanism may provide drug targets that could benefit the patients with concomitant PS and SLE.

*Correspondence to:* Professor Dongmei Shi, Department of Dermatology, Jining No. 1 People's Hospital, 6 Jiankang Road, Jining, Shandong 272011, P.R. China
E-mail: shidongmei28@163.com

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## 1. Introduction

Psoriasis (PS), a chronic T cell-mediated inflammatory disease, affects ~3% of the general population worldwide, and has increased in recent years (1). Systemic lupus erythematosus (SLE) is a recurrent and remitting autoimmune disease that occurs in a number of organs and systems, for instance, skin, blood system and kidneys (2). Environmental and genetic variables have been considered as dominant causes to induce autoimmune responses, resulting in the overproduction of inflammatory cytokines, for instance IL-6, and autoantibodies from B cells, especially in SLE. Indeed, the presence of antibodies against nuclear and cytoplasmic antigens is a diagnostic indication of SLE (3). PS and SLE affect the appearance and quality of life of the patients. Both autoimmune disorders manifest as chronic inflammatory conditions, which cause skin lesions and damage to the joints and other organs, such as those in the cardiovascular system. However, these two disorders have long been considered as distinct diseases on the basis of their relatively disparate pathologic mechanisms. While the chronic inflammatory condition has been associated to T helper (Th)1 and Th17 cell activation in PS (4,5), overacted B cells and Th2 cell-associated abnormalities are associated to SLE development (6,7). It has also been hypothesized that the pathogenic mechanisms for SLE and PS are opposite (8); however, this cannot explain the numerous published cases of comorbid PS and SLE (9-14).

The key factors that cause autoimmunity in SLE include the overproduction of autoantibodies, complement activation and immune-complex deposition (15-19). A number of

recent studies have observed that patients with PS not only have affected skin but also have other accompanying autoimmune conditions, such as rheumatoid arthritis, alopecia areata, celiac disease, systemic sclerosis, Crohn's disease, Sjögren syndrome, vitiligo, ulcerative colitis, giant cell arthritis and SLE (20-22). PS is considered an autoimmune condition that may be induced by the activation of T cells and B cells in the absence of persistent infection or other discernible causes (23).

In the present review, a number of developments in humoral and cellular immunities that occur in patients with comorbid SLE and PS are presented and discussed. The present review aimed to find the possible links between PS and SLE by reviewing the epidemiological data, immunopathogenic mechanisms, genetic traits and therapeutic efficacies.

## 2. Epidemiological evidence of PS coexistence with SLE

*Prevalence of SLE in patients with preexisting PS*. Two types of comorbid diseases have been reported in patients with PS: Those diseases sharing the main pathogenic mechanisms and those not sharing pathogenesis but with clinically severe chronic inflammatory conditions (24). SLE belongs to the latter category (25). According to an epidemiological study of PS comorbidity, patients with PS were at greater risk of developing an immune-mediated inflammatory disease (IMID) compared with general population controls (26). The majority of concurrent IMIDs appeared before the diagnosis of PS, indicating that there could be a pathophysiologic mechanism underlying PS and concurrent IMIDs (27-33). A population-based case-controlled study of the coexistence of PsA and SLE in Israel revealed a 2.3-fold increase in the prevalence of SLE among patients with PsA compared with age and sex-matched controls from the general population (34). According to research reports, when analyzed by level of severity, severe PS demonstrated a 3- to 7-fold increased risk for SLE compared with mild PS, especially in Asian patients (28,35,36). The explanation was that patients with moderate to severe PS may be more likely to be receiving additional phototherapy. Both of these treatments increase the risk for the development of SLE (37,38). A 10-year retrospective study identified 42 cases of SLE in 9,420 patients with PS (39). In the same study, the prevalence rate of PS that coexists with SLE was ~1.1%, and was slightly higher in female patients due to the fact that prevalence of SLE is higher in women compared with men. Therefore, when treating female patients with PS, caution should be exercised in medication and vigilance should be exercised against the occurrence of SLE.

*Prevalence of PS in patients with preexisting SLE*. A previous study, investigating the prevalence of PS in patients with principally diagnosed SLE, analyzed a large national population database for admission probabilities of patients with SLE, and demonstrated that 150 of a total of 20,630 hospitalized patients with SLE (0.7%) had a co-existing PS condition (40). In another study, it was reported that 0.6% of 520 patients with SLE had PS (41). Patients have a sequential occurrence of PS and SLE, but the probability of both occurring together is <1.2%, and the lower incidences in both cases suggest that comorbidity between two diseases could be an accidental event. According to reports, patients with SLE experienced a psoriatic flare that was likely due to the use of antimalarial drugs such as hydroxychloroquine (10,42). Therefore, when treating patients with SLE and a family history of PS, an alternative drug to hydroxychloroquine would be more appropriate, such as mycophenolate mofetil.

## 3. Common immunopathogeneses between PS and SLE

*Inflammatory mechanism*. Prior to the discovery of comorbid PS and SLE, it was hypothesized that the pathological mechanisms of PS and SLE were different; PS is a systemic inflammatory reaction caused by Th1 cell activation while abnormalities of SLE are due to highly reactive Th2 responses (43,44). To initiate an inflammation, exposure to external infectious or non-infectious substances, such as bacteria, viruses and ultraviolet radiation, damage the host cells to form an antigen complex with released nucleotides and antimicrobial peptides in the epidermis. Antigen-presenting cells, such as plasmacytoid dendritic cells (DCs), identify this complex and stimulate antigen-specific T cell growth in the skin and lymph nodes (45). The plasmacyte DCs secrete type I interferon that increases the production of IL-23 and TNF-α in myeloid DCs (46). These cytokines promote Th17 cell differentiation, which together with IL-1 stimulation, produce IL-17 and IL-22 that further increase the expression of TNF-α, C-C motif chemokine ligand 20 (CCL20) and antimicrobial peptides such as LL37 (47), leading to an inflammatory response in the skin and to keratinocyte proliferation (48). Cytokines associated with SLE include IFN-α, IL-6 and IL-17 (49). These inflammatory cytokines, in particular B-cell activating factor of the TNF family (BAFF), also serve roles in autoimmunity and autoantibody production in SLE.

A number of B cell subsets may be strongly associated with SLE. Currently, there are three known B cell effectors involved in the pathogenesis of SLE: i) Pathogenic plasmablasts may be produced without the assistance of T cells, as demonstrated in the BAFF transgenic model (50); ii) autoreactive B cells and $CD4^+$ T cells interact at the T cell: B cell boundary after initial autoantigen recognition; and iii) co-stimulatory signals and cytokine crosstalk activate B cells and autoantibody production through a T cell-dependent extrafollicular route or inside spontaneous, autoimmune germinal centers (51,52). Therefore, the aberrant activation of human B cells is a phenotypic hallmark of SLE and is associated with the progress of the disease.

*Th17 cells and associated cytokines with B cell activation in comorbid PS and SLE*. Th17 cells are associated with the pathogenesis of various autoimmune and inflammatory diseases, such as rheumatoid arthritis, SLE, multiple sclerosis, PS, inflammatory bowel disease and allergy and asthma (53), by producing several effector molecules. They are characterized by the expression of the orphan nuclear factor receptor retinoic acid receptor-related orphan receptor-γ-t (RORγt), the cytokines IL-17 and IL-22, the chemokine CCL20, and the inflammatory chemokine receptor C-C motif chemokine receptor 6 (CCR6) (54-56). IL-17 is a potent proinflammatory cytokine produced by highly activated Th17 cells and is known to serve a role in maintaining chronic inflammation in PS. Indeed, highly expressed IL-17, IL-22 and IL-23 have been

demonstrated in skin biopsies from patients with PS (57,58). IL-22 is also known to be essential for maintaining the immune barrier within the epidermis and is able to induce the release of antimicrobial agents and β-defensins from keratinocytes and promote epidermal hyperplasia (57). In the recruitment of Th17 cells to local tissues, the CCL20/CCR6 axis has been demonstrated to serve a crucial role (59). Finally, several other factors associated to the Th17 response also engage in the vascular inflammatory pathway by recruiting leukocytes, activating B cells and producing autoantibodies, and therefore may contribute to the occurrence and development of SLE and PS (60,61). The current data indicates the factors that are common between SLE and PS are an increase in the number of Th17 lymphocytes and an increase in the serum levels of IL-17 and IL-23, in which IL-17 is a main proinflammatory cytokine that serves a crucial role in the pathogenesis of various inflammatory diseases, including PS and SLE (62-64).

Patients with SLE have higher serum levels of IL-17 and IL-23 compared with healthy controls (65). Furthermore, IL-17 levels in the plasma are correlated with the severity of SLE (66). Compared with a healthy control group, the concentration of IL-17 in the serum of patients with SLE and the expression of IL-17 mRNA in activated peripheral blood mononuclear cells were increased, which were positively correlated with the Systemic Lupus Erythematosus Disease Activity Index (67-69). The skin biopsy examination of patients with SLE and skin involvement demonstrated that the expression level of IL-17 was increased compared with that of normal individuals, confirming that IL-17 is involved in the immune pathogenesis of SLE (70). IL-17 promotes inflammation and tissue damage in the context of SLE by recruiting neutrophils and monocytes, facilitating T-cell tissue infiltration and promoting antibody production (71). By contrast, IL-17 also facilitates T-cell activation and infiltration into the tissues along with increased expression levels of intercellular adhesion molecule-1 (ICAM-1) and matrix metalloproteinase (MMPs) (72,73).

The IL-23/Th17 axis has previously been suggested to be essential in developing lupus nephritis, both in mice models and in patients with SLE (74,75). In mouse models, IL-17 is associated not only to T cell-mediated tissue injury, but also to the production of pathogenic autoantibodies and it was demonstrated that Th17 cells were increased in a MRL/lpr lupus nephritis mouse model (76). The IL-23/IL-17 axis is involved in the pathogenesis of SLE where activated DCs produce the inflammatory cytokines IL-6 and IL-23, which then stimulate Th17 cells to produce IL-17 (77). In two *in vitro* studies, T cells from patients with SLE increased their IL-17 production and concomitantly limited production of the regulatory cytokine IL-2 in the presence of IL-23, leading to exacerbated inflammation (56,57). Additionally, an attenuated inflammation with a striking decrease in the accumulation of double-negative T cells were revealed in the kidneys and secondary lymphoid organs when a IL-23 receptor deficient MRL/lpr mouse SLE model was used (78,79).

It is well known that B cells and autoantibodies directed against numerous nuclear and cell surface antigens serve roles in SLE immunopathogenesis. Given the fact that SLE-derived B cells would increase anti-DNA production in the presence of IL-17 (66), an extensive body of data obtained in mice models and humans in terms of the T cell-B cell interactions have revealed that T cells aid the activation of the autoantibody-producing B cells in SLE (80-82). However, the exact function of IL-17 that leads to SLE remains unknown. In the SLE development process, B lymphocyte stimulator (BLyS) can become upregulated and it may act as a survival factor to inhibit B cell apoptosis, to stimulate B cell proliferation and differentiation through an interaction with IL-17, and ultimately to increase the production of autoantibodies (83,84). In addition, increased levels of BLyS would promote the proliferation of Th17 cells leading to increased levels of IL-17, which in turn could act in conjunction with BAFF to promote the survival and proliferation of human B cells and their differentiation into antibody-producing cells (81). In addition to IL-17, the roles of other cytokines in the T cell-B cell interaction have been noted with regard to SLE pathogenesis. For example, IL-21, produced by Th17 cells, stimulates $CD8^+$ T cell proliferation and B cell differentiation for immunoglobulin production (66,85,86). These roles of IL-21 have been validated in a lupus-prone mouse model, in which the IL-21/IL-21 receptor pathway was blocked by the administration of a fusion protein, resulting in an alleviated disease progression (87,88). Finally, the production of autoantibodies by activated B cells leads to the activation of DCs and the secreted IL-23 can increase production of IL-17 (89) (Fig. 1).

Collectively, this data indicates that the multifarious functions of the Th17 cells and B cells as well as the inflammatory environment created by the T cell-B cell interaction all function together to lead to SLE, as demonstrated in other human IMIDs.

*Regulatory T (Treg) cells and B cells in comorbid PS and SLE*. Treg cells are a distinct lineage of T-cell subsets (90) and control the immune responses to self- and non-self-antigens (91). Under normal physiological conditions, Treg cells serve a critical role in maintaining a balance in the immune homeostasis, and abnormalities in the function Treg cells have been associated with the pathogenesis of autoimmune disorders, allergic diseases and even cancer, such as PS, asthma, prostatic carcinoma and lymphoma (92). For autoimmune diseases, low volume or inactivated Treg cells fail to suppress self-reactive T cell proliferation and cytokine production, leading to the imbalanced activities of other effector immune cells such as Th1 and Th17. The suppressive functions of the Treg cells occur mainly through direct contact and/or through its secretion of suppressive cytokines, such as IL-10 and transforming growth factor (TGF)-β (93). In addition, Treg cells reduce the differentiation of cytotoxic $CD8^+$ T cells and inactivate B cells (94). Furthermore, the suppressive function of Treg cells is impaired in patients with PS and an altered Th17/Treg ratio in the peripheral blood of patients with PS is due to a decreased number of Treg cells and an increased number of Th1 and Th17 cells (95). The imbalance in the Th17/Treg ratio promotes inflammation due to the production of inflammatory cytokines such as IFN-γ or IL-17 (96,97). Similar phenotypic effector cells and Treg cells are also considered to contribute to SLE pathogenesis (98-100). Therefore, it is possible that the inflammatory environment of PS could be conducive to the development and deterioration of SLE. Although IL-10 is the key cytokine

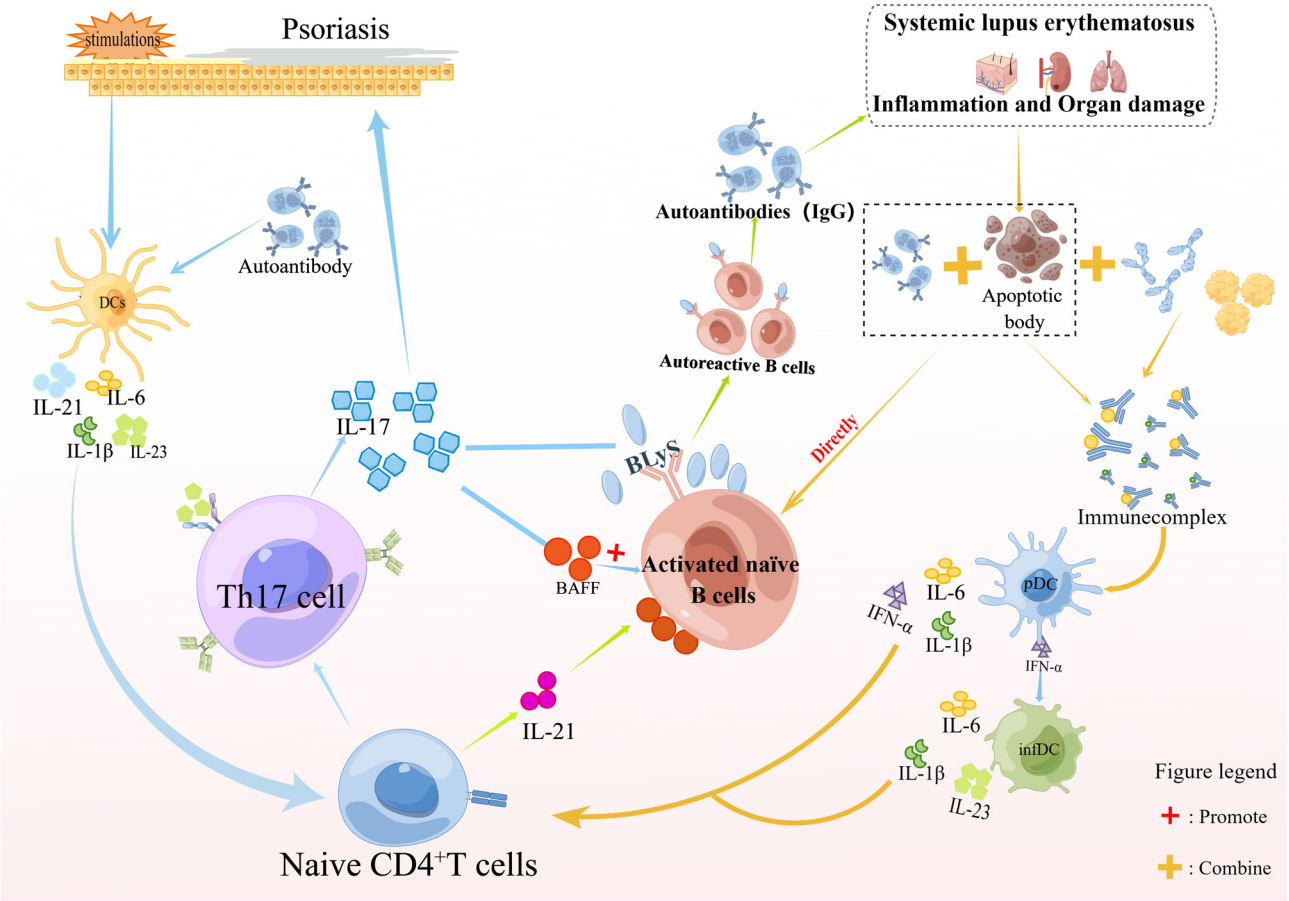


Figure 1. Involvement of the Th17 cells and B cells in comorbid PS and SLE. In patients with comorbid PS and SLE, environmental and physicochemical stimuli, for example microorganisms, drugs and trauma, would activate DCs to secrete large amounts of cytokines, including IL-6, IL-21, IL-1β and IL-23. These cytokines promote the differentiation of naive CD4+ T cells into Th17 cells for IL-17 secretion. Meanwhile, apoptosis in injured tissues and organs leads to the release of a large amount of double-stranded DNA and ribonucleoproteins, which combine with autoantibodies to form nucleic acid immune complexes and activate pDC. Activated pDC secrete large amounts of IL-1β, IL-6 and IFN-α that further promotes the response of the Th17 cells. Additionally, IFN-α can activate infDC to further amplify the aforementioned processes, resulting in a large infiltration of IL-17 in the tissues and serum. IL-17, in combination with BAFF and BLyS, promote B cells to proliferate and differentiate into plasma cells and to maintain the generation of germinal centers to continuously produce autoantibodies. Furthermore, autoantigens from apoptosis directly stimulate primitive B cells to enhance the aforementioned process. The figure was created using Figdraw (www.figdraw.com). Th, T helper; PS, psoriasis; SLE, systemic lupus erythematosus; DC, dendritic cell; infDC, inflammatory DC; pDC, plasmacytoid DC; BAFF, B-cell activating factor of the TNF family; IL-23R, IL-23 receptor; BLyS, B lymphocyte stimulator.

that is produced by Treg cells ($CD4^+CD25^+FOXP3^+$), it has also been revealed that the $D4^+CD25^+FOXP3^-$Treg cells could also secrete high levels of IL-10 (in a $FOXP3^+$ independent manner) to inhibit the *in vitro* proliferation of $CD4^+CD25^-$ T cells with a similar efficiency to that of $FOXP3^+$ Tregs (91). However, no matter the origin of IL-10 in PS and SLE, the increased levels of IL-10 are associated with the increased levels of antibodies in patients with SLE (101). The increased levels of IL-10 has been hypothesized to stimulate the proliferation of B cells (102,103) and to promote their synthesis of IgG through the upregulation of the interactions between cytokines and B cell receptors (102,104). In addition to secreting IL-10, Treg cells collected from patients with SLE were demonstrated to directly suppress the B cell-mediated antibody production in an *in vitro* experiment (105), in which Treg cells induced a contact-dependent apoptosis of the B cells through the perforin- and granzyme-pathways (106). Therefore, functional defects in Treg cells, or a lack of Treg cells and IL-10 are considered to contribute to SLE pathogenesis (98-100).

*TNF-α in comorbid PS and SLE*. TNF-α is a pleiotropic cytokine that affects the activities of variant cell types in various physiological and pathological conditions, such as in the development of T cells, B cells and DCs. This cytokine is a potent inflammatory mediator and also an apoptosis inducer. Overexpression of TNF-α has been observed in patients with PS for two decades and it was revealed to be distributed throughout the epidermis and specifically localized to the upper dermal blood vessels (107).

The significance of the involvement of TNF-α in the pathogenesis of SLE remains controversial. Previous evidence has suggested that this cytokine serves a dualistic, proinflammatory, and an immune- or disease suppressive role in SLE progress (108). TNF-α was reported to be increased in patients with SLE and was correlated with disease course, and the immunopathogenesis of SLE (109,110). Anti-TNF-α administration also demonstrated that this treatment can suppress the inflammatory responses in an experimental SLE model, which was induced by the injection of human anti-DNA autoantibodies in mice (111). However, the use of an anti-TNF-α

agent can also lead to increased levels of autoantibodies for double-stranded DNA (dsDNA) and cardiolipin (112). Higher levels of TNF-α have been reported in patients with PS than in healthy individuals (113); therefore, the pathogenic roles of TNF-α in both diseases should be further classified.

*Causes of pathophysiological changes*. Different subpopulations of T cells (Th1, Th2, Th9, Th17, Th22 and Treg cells) and their corresponding proinflammatory cytokines are all involved in the pathophysiology of PS and SLE (114). Activated T cells secrete proinflammatory cytokines, which in turn stimulate the resident tissue cells to recruit immune cells and further increase the secretion of IL-2, IL-4, IL-9, IL-17 A, IL-22, TNF-α, IFN-γ and GM-CSF in perivascular and renal systems of affected patients with PS or SLE (84,115-118). Nevertheless, chronic inflammation due to abnormal immune responses is the pathogenic bases of SLE and PS. In addition to the aforementioned cytokines and effector cells, other inflammatory mediators, such as those from fibroblast-like synoviocytes (FLSs), could also crosstalk with these factors to lead to pathophysiological conditions and to accelerate inflammation in PS and SLE. Previously, local stromal cells, such as FLSs, have been revealed as inflammatory effectors that affect the phenotype and function of different organs, such as kidney, gastrointestinal tract, and joints, in autoimmune disease (119). For example, the involvement of FLS in inflammation and cartilage destruction has been observed in PsA; however, how activated T cells modulate the release of the inflammatory mediators is not fully understood in both diseases.

## 4. Genetic predispositions of PS and SLE

Genetic studies on patients with autoimmune conditions have identified the susceptibility loci for a number of diseases, including for PS and SLE (120-123). A number of loci identified by genome-wide association studies have been associated with both PS and SLE, such as protein tyrosine phosphatase non-receptor type 22 (PTPN22), TNF receptor associated factor 3 interacting protein 2 (TRAF3IP2), signal transducer and activator of transcription 4 (STAT4) and TNF-α-induced protein 3 interacting protein 1 (TNIP1) (121,123-128). The TRAF3IP2 locus, located on chromosome 6q21, encodes NF-κB activator 1, which is both a negative regulator of the humoral immunity and a positive signaling adaptor of the IL-17-dependent NF-κB activation. As a downstream target of the IL-17 receptor, it may have a pivotal role in the IL-23/IL-17 axis in the pathogenesis of PS (129). The PTPN22 gene encodes lymphoid tyrosine phosphatase, a lymphoid-specific tyrosine phosphatase that acts as a negative regulator of T cell signaling. A gain of function for PTPN22 could allow it to participate in the release of autoantibodies and increase the formation and deposition of immune complexes, which would trigger an inflammatory response resulting in the possible development of SLE and its clinical manifestations (130,131). A number of studies have revealed an association between PS and rs1217414 located in intron 1 of PTPN22 (122,132). The level of PTPN22 transcription could negatively regulate T-cell function and thereby changes susceptibility to PS (122). The STAT4 protein is located in T and B lymphocytes, monocytes, macrophages, natural killer cells, and DCs. Its expression may be associated to immune cell differentiation into inflammatory subsets, the production of inflammatory cytokines and autoantibodies, the suppression of apoptosis, and the presentation of autoantigens, all of which may promote the development of SLE and PS (133). TNIP1 also serves a critical role in immunological homeostasis and autoimmunity prevention, since mice with TNIP1 knocked out have been demonstrated to acquire almost all autoimmune characteristics, including spontaneous germinal center development, isotype switching and autoantibody production (134,135). Additionally, the protein level of TNIP1 was negatively associated with the disease activity of SLE and was decreased in the peripheral blood mononuclear cells of patients with SLE compared with in that of healthy controls (136). In an imiquimod-induced mouse model of dermatitis, downregulation of the TNIP1 expression levels resulted in an increased proliferation of human keratinocytes and a more severe PS-like condition (137).

According to a study in China, the NF-κB-inhibitor α (NFKBIA) and IL-28 receptor α (IL-28RA) loci occur at increased frequencies in Chinese Han populations with PS compared with Chinese Han populations without PS. In this study, the susceptible loci, NFKBIA and IL28RA, for SLE in the Chinese Han population were also identified (138). NFKBIA is an inhibitor of NF-κB signaling, acting to inhibit Th17 cell activity and IL-17 expression in a healthy individuals (139). In patients with PS and/or SLE, the insufficient levels of NFKBIA will in turn increase the levels of IL-17, which has been revealed in the skin lesions of patients with PS and/or SLE (140). Although IL-28RA mRNA expression levels are increased in the peripheral blood mononuclear cells of patients with SLE, they are decreased in the lesional tissues from individuals with PS plaques. After the cause of PS has been confirmed as due to the reduced expression levels of IL-28RA, IL-28RA could be a useful pharmacological target, at least for the therapy of PS (138,141).

These genetic predispositions may provide hints for the early inflammatory mechanism of the coexistence of PS and SLE. The present review considers that identification of new common susceptible genes for both diseases may provide an understanding of the immunopathogenesis of the coexistence of SLE and PS and may inspire further treatment options for these two conditions.

## 5. Treatment

The different drugs that are used to treat SLE and PS, with regard to treatable and inducible disease are summarized in Table I.

*Treatment of the IL-17 cytokine signaling pathway in PS and SLE*. In the lupus-induced mouse model, IL-17 production was positively associated with disease progression since the manifestation could be eliminated by reducing IL-17 production and IL $17^{-/-}$ mice did not develop anti-dsDNA, anti-single stranded DNA, anti-nuclear ribonucleoprotein and anti-chromatin autoantibodies (78). In mouse models, overexpression of IL-17 using an adenovirus increased the severity of lupus nephritis, while inhibition of IL-17 using neutralizing antibodies resulted in a reduced severity of lupus nephritis (142). These results suggest that IL-17 is

Table I. Drugs that are used to treat SLE and PS.

| | Treatable diseases | | Inducible disease | |
|---|---|---|---|---|
| Therapeutic drug | SLE | PS | SLE | PS |
| Methotrexate | √ | √ | No | No |
| Cyclosporine | - | √ | No | No |
| Retinoids | - | √ | No | No |
| TNF-α inhibitors | √ | √ | Yes | Yes |
| IL-12/23 antibody | √ | √ | No | No |
| IL-17 antibody | √ | √ | No | No |
| UV-B radiation | - | √ | Yes | No |
| Anti-CD20/CD22 | √ | - | No | Yes |
| Anti-BAFF | √ | - | No | No |
| Hydroxychloroquine | √ | - | No | Yes |
| Anti-IFN-α | √ | - | No | Yes |

√, can be used to treat this disease; -, not available for treatment of this disease or unknown; PS, psoriasis; SLE, systemic lupus erythematosus; BAFF, B-cell activating factor of the TNF family.

involved in the pathogenesis of SLE (71). Currently, a number of IL-17 inhibitors, including the anti-IL-17 monoclonal antibodies secukinumab, ixekizumab and bimekizumab, and the anti-IL-17 receptor A monoclonal antibody brodalumab, have been demonstrated to be effective as PS treatments (143-145). Furthermore, a case report described the efficacy of an IL-17 inhibitor, secukinumab, in a patient with SLE (146). The use of an IL-17 monoclonal antibody to treat lupus was approved by the US Food and Drug Administration. Additionally, a double-blind phase II study has demonstrated the efficacy and safety of ustekinumab (an IL-12 and IL-23 antagonist) in patients with active SLE (147). Ustekinumab has been demonstrated to improve a number of mucocutaneous and musculoskeletal diseases, such as atopic dermatitis, Crohn's disease and ankylosing spondylitis, perhaps by decreasing the levels of anti-dsDNA titers and complement 3. It was also revealed to improve the renal function of the patients with SLE (146,148). After receiving secukinumab treatment, a patient with PsA combined with SLE had improved clinical symptoms along with decreased levels of IL-17 in the serum and renal tissue (149). The success in treating this patient with both SLE and PsA suggests that the IL-17/IL-23 axis is the common immunogenic mechanism for developing both diseases.

*CD20 inhibitors in PS and SLE*. Cytokines that activate B cells and promote the interaction between B and T cells contribute to the production of autoantibodies (150,151). Inhibition of B cell-associated molecules should downregulate the overactive immune responses in SLE. B-lymphocyte antigen (126,127) (called CD20) is highly expressed on the surface of all B-cells and also serves critical roles in cell cycle progression during human B cell proliferation and activation. Anti-CD20 antibodies have been employed in treatment of a number of diseases (152). In patients with rheumatic arthritis, anti-CD20 therapy achieved a rapid and almost complete B-cell depletion in the peripheral blood and suppressed the generation of plasma blasts, sustainable for at least 6 months (153,154). The disappearance of the anti-neutrophilscytoplasmic antibody (ANCA) in ANCA-associated vasculitis or anti-desmoglein antibodies in pemphigus confirmed the efficacy of the anti-CD20 monoclonal antibody (155,156). In addition, a study revealed that an anti-CD20 antibody, Rituximab, can reduce the expression levels of RORγt and IL-22 and decrease the numbers of Th17-positive cells (157). In a case report of palmoplantar pustulosis, a less severe and localized variant of pustular PS, after treatment failure with an TNF-α blocker, an improvement was demonstrated with rituximab treatment (158). The present review considered that rituximab might reverse the effects of TNF-α via the antigen-antibody complex. However, contradictory effects of anti-CD20 are also observed in the literaturs. For example, the use of anti-CD20 therapy (Rituximab) for autoimmune diseases such as SLE may be the cause of the development of PS (159,160). It is likely that the depletion of B-lymphocytes in these patients caused an imbalance between the T and B cells and this interaction may promote a hyperactive T cells response.

*TNF-α and IFN-α inhibitors in PS and SLE*. Unlike Th17 antagonists, the efficacy of IFN-α antagonists on PS is uncertain. Collamer *et al* (161) found that the number of patients with new onset or exacerbation of preexisting PS is increasing due to TNF therapy. This does not seem to be consistence with the fact that IFN-α is a key element in the early phase of psoriatic skin lesion induction (46). It was suspected that an IFN-α antagonist may also be involved in other mechanisms for PS induction (161), and inhibition of TNF-α has been demonstrated in turn to induce the overexpression of IFN-α (162). Increased expression levels of IFN-α in the psoriatic lesions of patients that have been administered with anti-TNF-α therapeutics were also reported (163). The increased production of IFN-α will stimulate myeloid DCs, promote the polarization of Th1 cells and lead to an excessive proliferation of keratinocytes via IL-15 (164).

Likely acting via the same mechanism, treatment with anti-TNF-α agents is controversial in SLE as well, since it may further induce antinuclear antibodies, anti-dsDNA and anti-cardiolipin antibodies. Indeed, cases of drug-induced lupus have been observed in patients with rheumatoid arthritis (165).

*Treatment concerns for the patients with SLE and PS*. Treatment of patients with both PS and SLE or prevention of the occurrence of comorbidity is challenging. The onset of PS and SLE could appear in a different order of precedence, which may not only affect the profiles of the inflammatory cytokines (such as IL-17, IL-10 and IL-23) but also may change the efficacy of the treatment in each individual patient. For example, phototherapy for PS can exacerbate SLE and hydroxychloroquine or systemic corticosteroids for SLE treatment would exacerbate PS (42).

When ultraviolet (UV) light is used to control PS through triggering keratinocyte apoptosis, it also promotes an immunopathogenesis in lupus (166). As a result, nucleoprotein autoantigens will be transported to the surface of

keratinocytes to stimulate the release of further inflammatory cytokines, including IFN-γ, TNF-α, IL-1, IL-6, IL-8, IL-10 and IL-17 (167-170). The accumulation of these apoptotic keratinocytes would increase the aforementioned changes to cause a secondary necrotic process and to amplify the release of proinflammatory cytokines and potential autoantigens (171). These factors would recruit inflammatory cells into the skin and cause tissue inflammation.

By contrast, after the patients with a genetic predisposition to PS and lupus receive UV treatment, the skin cells of the patients will be more likely to have thymine dimmers in their DNA (172). The photo-induced thymine-dimmers in the DNA are then the target antigens of the autoimmune response, thus causing lupus. However, the pathophysiology of induced lupus is still poorly understood. In addition, the mechanism of drug-induced PS is not completely understood. A study concluded that hydroxychloroquine disrupts the barrier of the epidermis by inhibiting transglutaminase activity (173,174). Following this initial break in the skin barrier, the epidermis undergoes a physiological proliferation in an attempt to restore the integrity of the barrier. In a genetically predisposed individual, this damage to the skin barrier may be sufficient to initiate a non-specific stimulus-induced epidermal proliferation (173).

At present, TNF-α inhibitors have been widely investigated for the treatment of PS (175), and anti-TNF-α drugs are frequently reported to induce systemic drug-induced lupus erythematosus (176,177). A number of hypotheses have been proposed for the mechanism of autoantibody induction by anti-TNF-α agents as follows: i) An imbalance between IFN-α and TNF-α induces an apoptosis in inflammatory cells; ii) decreased expression levels of CD44 causes nucleosome accumulation in apoptotic cells and leads to the production of DNA and other nuclear antigens; iii) infections in patients receiving anti-TNF-α can lead to lymphocyte activation and subsequently to polyclonal B lymphocytes production; and iv) suppression of the Th1 response caused by the anti-TNF-α and Th2 response, IL-10, and INF-α, promotes humoral autoimmunity and autoantibody production and suppresses cytotoxic T-lymphocytes (178-181) (Fig. 2).

In a case report, the symptoms of lupus nephritis in patients with both PS and SLE diseases worsened after secukinumab treatment (182). Certainly, caution is necessary when administering drugs to patients with PS and SLE, since it may effective for one of these diseases but it may not be effective for the other disease, particularly when TNF-α antagonists are used. As aforementioned, TNF-α inhibitors have well been documented to cause lupus-like syndromes with the onset of antinuclear antibodies and anti-dsDNA, as well as an exacerbation of PS. Therefore, when treating patients with biological agents, their immunological profiles and family history should be evaluated in detail in order to avoid a deterioration in the inflammation of both diseases.

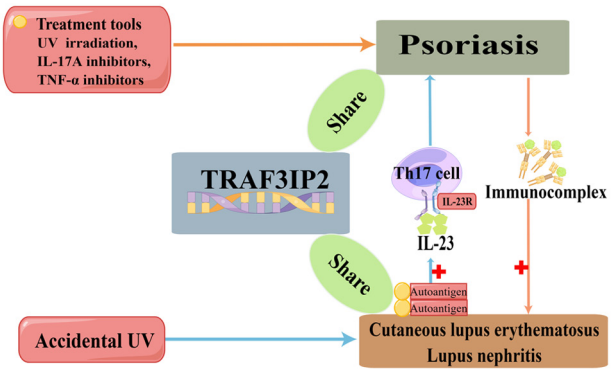


Figure 2. Genetic predisposition and therapeutic or stimulated effects promoted by UV light and drugs in comorbid PS and systemic lupus erythematosus. Lupus patients and psoriasis patients share a common susceptibility gene TRAF3IP2. Exposure to UV light in patients with lupus causes apoptosis of the keratinocytes, and the release of autoantigens and cytokines, including IL-1, IL-6, IL-10 and IL-17. The transportation of autoantigens to the surface of damaged keratinocytes further stimulates more inflammatory cytokines associated to the Th17/IL-23 axis, which would increase the possibility of developing PS in patients with lupus with genetic predisposition (TRAF3IP2). When UV light, TNF-α inhibitors and IL-17A inhibitors are used to treat PS, the apoptosis of keratinocytes may release autoantigens and change the inflammatory cytokine profiles. This would promote the formation of immune complexes and cytokines, and thus promote the immunopathology of lupus. The figure was created using Figdraw (www.figdraw.com). PS, psoriasis; IL-23R, IL-23 receptor; Th, T helper; TRAF3IP2, TNF receptor associated factor 3 interacting protein 2; UV, ultraviolet.

## 6. Conclusions and perspectives

PS is a disease that occurs worldwide and its prevalence varies from 2-11% according to the region. The global prevalence of SLE ranges from 13-7,713.5 per 100,000 individuals (183). A 40-year follow-up study that was carried out in the US, revealed that the incidence and prevalence of SLE had increased each year (overall prevalence increased from 30.6 in 1985 to 97.4 in 2015), and PS and SLE occurred in all age groups and in both men and women (184). At present, the comorbidity of PS and SLE is still a rare skin condition. In the present review, the animal and clinical evidence to support the possibility of SLE coexisting with PS has been summarized. Firstly, both diseases share the same susceptibile gene loci (138,185-188), which are associated with IL-17 signal transduction (186,189), and the interactions with Treg cells and B lymphocytes that form the foundation of pathogenesis of PS and SLE. Secondly, biological agents demonstrated efficacy in patients with PS and SLE. For example, IL-17 inhibitors that have been widely used for PS, are now being tested as treatments for SLE in clinical trials (190). Nevertheless, current evidence cannot completely exclude that this is simply a coincidence; however, caution may be needed when dealing with immunotherapy treatments for patients with single PS, SLE or both conditions.

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## Availability of data and materials

Not applicable.

## Authors' contributions

DS contributed to the conception of the present work. YQ and DS examined the literature and drafted the manuscript. YQ and DS produced the figures. DS, WL, DL and YQ made critical revisions to the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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