# Advances in research related to heat shock protein 90 and autoimmune dermatoses

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## ABSTRACT

Autoimmune dermatoses result from immune imbalances due to aberrant immune responses to self-antigens. Heat shock protein 90 (HSP90), as a member of a highly conserved family of stress proteins, plays an important role in inflammation and immune responses. It has been suggested that HSP90 is related to the occurrence and development of autoimmune dermatoses, but the exact mechanisms involved remain unclear. In this report, we review the evidence indicating a potential link between HSP90 and three common autoimmune dermatoses, bullous dermatoses, psoriasis and lupus erythematosus. In addition, the progress of research involving HSP90 inhibitors as potential therapeutic targets is assessed.

**Key words:** heat shock protein 90, bullous dermatoses, psoriasis, lupus erythematosus

## HEAT SHOCK PROTEINS

Heat shock proteins (HSPs), a highly conserved class of molecules in eukaryotes and prokaryotes, are usually induced in cells under stressful conditions. In general, HSPs serve as molecular chaperones that assists in the normal folding and degradation of client proteins, which in turn regulates cellular pathways such as apoptosis, the cell cycle, and cell signaling.[1,2] Interestingly, a significant increase in HSP synthesis can be induced in response to a variety of non-physiological stressors, including environmental exposures (heavy metals or ultraviolet [UV] radiation), infections, tumors and autoimmune diseases.[3–5] As based on their molecular weights, HSPs can be classified into HSP60, HSP70, HSP90 and HSP100 as well as a group of small molecular weight HSPs. Of these HSP family members, HSP90, with a molecular weight of approximately 90 kDa, is considered as one of the most notable

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members of the HSP family and plays an important role in normal physiological processes of cells, as well as in the development of autoimmune diseases.

## HSP90: Isoforms, Structure and Expression

In eukaryotes, four different HSP90 isoforms have been identified within different locations of eukaryotic cells, with HSP90α and HSP90β found in the cytoplasm and glucose-regulated protein 94 (GRP94) and tumor necrosis factor receptor-associated protein 1 (TRAP-1) in the endoplasmic reticulum and mitochondrial matrix. These four isoforms have different structures, physiological functions and disease mechanisms of action. HSP90 is an ATP-dependent homodimer, and each unit can be divided into three different functional regions. Under normal, non-stressed cellular conditions, HSP90 exists as a monomer and does not possess DNA-binding activity. However, in response to inflammation, unfolded/misfolded proteins or other stressors, heat shock factors (HSFs) are released and translocate to the nucleus. Within the nucleus they form trimers and phosphorylate, eventually binding to specific DNA sequences and activate transcriptions of the HSP90 gene.[4,6]

## HSP90 and the immune system

HSPs are typically considered as intracellular proteins. Given their highly conserved nature, HSPs are not only associated with host immune regulation, but may also play an important role in autoimmune diseases.[7,8] Under stress and/or pathological conditions, some HSPs can be expressed on cell membrane surfaces and, can even be released extracellularly with increases in corresponding titers of anti-HSPs antibodies being observed in peripheral blood.[9-11] These extracellular HSPs overexpress toll-like receptors (TLRs) and scavenger receptors (SRs) on antigen presenting cells (APCs) to activate innate immune responses. Simultaneously, they enhance the ability for their associated molecules to activate immune responses by effectively targeting antigen-presenting cells. Interestingly, small levels of antibodies against HSPs can also be detected in the peripheral blood of healthy individuals.[12,13] With regard to HSP90, increases in expression are observed in tissues exposed to various stressors, which represent an adaptive response to enhance cell survival and is required in disease states. Moreover, it has been suggested that HSP90 serves as an important link in the development of immune diseases.

## HSP90 AND AUTOIMMUNE DERMATOSES

## HSP90 and psoriasis

Psoriasis is a chronic, inflammatory, systemic dermatoses that is predominantly immune-mediated, with the main clinical manifestations being red skin patches covered with silvery-white scales. Its exact pathogenesis remains unclear, but it is considered to be an immune disease resulting from a combination of genetic and environmental factors. Results from a current study suggest that the development of psoriasis is associated with T-cell-dominant immune cell activation, cytokine-induced hyperproliferation of keratinocytes, epidermal proliferation and angiogenesis.[14] It is also believed that multiple immune signaling pathways play an important role in the development of psoriasis. The presence of metabolic syndrome (Mets) has been found with increasing prevalence in patients with psoriasis and, it has been suggest that elevated expressions of HSP27, HSP60, HSP90 and a reduced expression of CCND1 may be the main mechanisms for the development of Mets in these patients.[15] HSPs, as immunodominant protein molecules, can stimulate the immune system to induce T cell-based immune responses. Antibodies against these HSP proteins can be found in healthy individuals, and their overexpression can reflect the specific pathological conditions of the cytogenesis. With regard to HSP90, its levels and the rate of release from keratinocytes have been shown to be sensitive to cell-stimulating factors in serum.[16]

Stress signals can induce the expression and secretion of HSP90α by epidermal keratinocytes. This HSP90α can then activate the HSP90 receptor, CD91, on the surface of plasmacytoid dendritic cells (DCs), leading to migration, antigen presentation and secretion of pro-inflammatory cytokines by DCs.[17] HSP90α also promotes the secretion and release of DCs and tumor necrosis factor-α (TNF-α) from DCs, as well as stimulating the activation of myeloid dendritic cells (mDCs) and migration of mDCs to lymph nodes.[18] It is worth noting that activation of DCs represents a key cellular component in the initiation of this pathway and HSP90 plays an important role in this process. Once DCs are activated, their secreted interleukin (IL)-23 can induce T helper 17 (Th17) activation and produce IL-17, which in turn drives the inflammatory response of keratinocytes by binding to IL-17 receptors on keratinocytes. Meanwhile, in this response pathway cycle, cell secretory factors such as TNF-α and IL-17 can also induce increased expressions and secretions of HSPα90 by keratinocytes, further promoting the self-amplifying cycle of psoriasis inflammation. In this way, keratinocytes are thought to trigger inflammation in psoriasis and play an important role in the maintenance of the lesions resulting from this condition.[19] HSP90 and its chaperone protein, Act1, are important components of the IL-17 signaling pathway. Wang *et al.*[20] provided the first demonstration that HSP90 plays an important role in regulating Act 1function, and that upregulation of HSP90 can promote IL-17 signaling as well as responsiveness to this signal. Inhibition of HSP90 significantly reduced the phenotype response in a mouse model of IL-17-induced inflammation. With regard to the differential regulation of Act1 isoforms (Act1-D10N/Act1-D19N) by HSP90 in the IL-17 signaling pathway, Wu *et al.*[21] reported that Act1-D10N is a protein incapable of transducing IL-17 signaling for gene expression, while HSP90 with Act1-D19N fully responds to the IL-17 signaling pathway. Such findings further reveal some of molecular processes involved in psoriasis onset and progression.

Kakeda *et al.*[22] performed a comparative immunohistochemical, semi-quantitative analysis of immunoreactivity in normal appearing skin as well as in non-damaged skin, damaged skin, and psoriatic skin treated with ustekinumab (monoclonal antibody conjugated to IL-12/IL-23 P40 secreted by dendritic cells and antigen-presenting cells) as an approach to elucidate the protein expression and distribution of HSP90 and its isoforms, HSO90α and HSP90β. Their results demonstrated that HSP90α, but not HSP90β, was significantly upregulated in epidermal keratinocytes and mast cells in psoriatic skin. However, the functional relevance of high expressions of HSP90α in mast cells within psoriatic skin lesions is unclear. Damasiewicz-Bodzek *et al.*[23] used ELISA to assess the concentrations of anti-HSP90α and anti-HSP90β antibodies in the serum of psoriasis patients during the disease and compared them with the peripheral serum of a healthy group. In this study they found that the mean concentrations of anti-HSP90α antibodies were significantly increased in both the active and remission phases of the psoriasis group while the mean concentrations of anti-HSP90β antibodies were not significantly different between the psoriasis and healthy group. No statistically significant differences were obtained between the different activity stages of the psoriasis patients. These results, as obtained from both the active and remission psoriasis groups, provided further evidence indicating that the specific expression of high levels of HSP90 in damaged psoriatic skin was due to an upregulation of HSP90α. Therefore, the detection of elevated concentrations of anti-HSP90α antibodies in the peripheral blood of psoriasis patients may serve as a guide for assessing the clinical dynamics and treatment efficacy of the disease. In addition, these findings suggest that inhibition of HSP90, and more specifically the inhibition of HSP90α, may be a new therapeutic approach for the treatment of psoriasis.

Debio 0932 is a novel oral HSP90 inhibitor that is mainly used as an anti-cancer treatment. Stenderup *et al.*[24] found that Debio 0932 attenuated the clinical manifestations of psoriasis in a psoriasis xenograft model, with an approximately 29% reduction in epidermal thickness and an effect on all relevant pathological histological parameters. Such findings suggest a potential role for Debio 0932 in the treatment of psoriasis.

HSP90 appears to interact with the stress function of the hypothalamic-pituitary-adrenal (HPA) axis, as it plays a role in the regulation of glucocorticoid receptor (GR) activity associated with stress responses. Interestingly, in patients with psoriasis, cortisol levels are negatively correlated with stress levels after chronic exposure to high levels of stress and HPA axis reactivity is reduced.[25] These findings suggest that HSP90 plays a specific role in regulating cortisol levels and attenuating HPA axis reactivity after stress exposure in psoriasis patients. The exact mechanisms involved in these interactions remain unclear (Figure 1).

## HSP90 and bullous dermatoses

The increasing recognition that HSP90 plays an important role in processes such as antigen presentation, activation of lymphocytes and macrophages and activation and maturation of dendritic cells suggests that HSP90 may be involved in the pathophysiological processes of inflammatory diseases.[7] One such possibility is bullous dermatoses, which are a group of severe autoimmune dermatoses in skin and mucous membranes, with blisters and macules presenting as skin lesions.

HSPs also play a role in the physiology and pathophysiology of epidermal keratinocytes. For example, repeated local injections of recombinant HSP90 into injured areas of nude mice accelerates
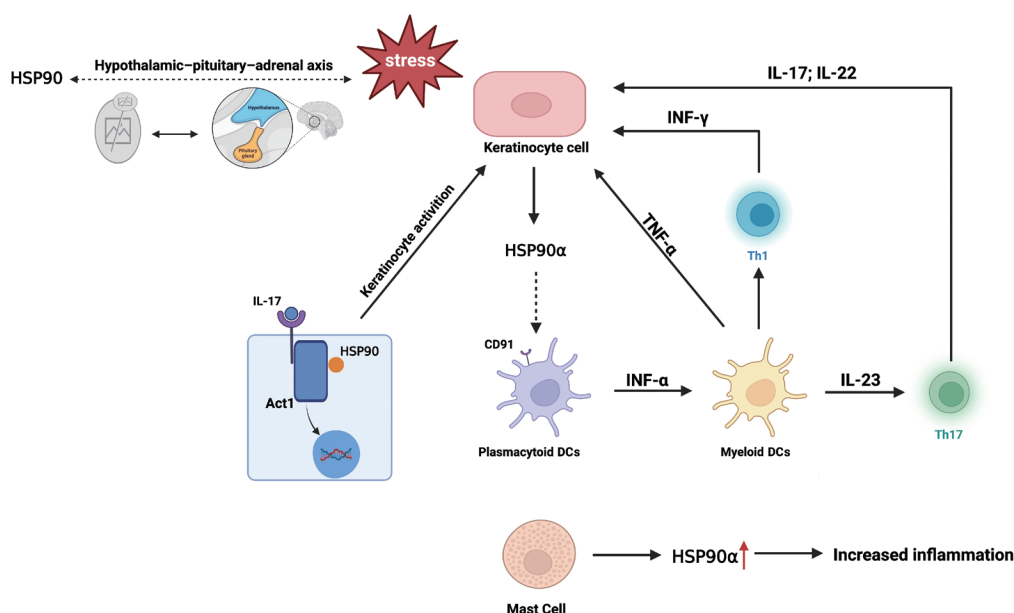


**Figure 1. Contribution of HSP90 in pathogenesis of psoriasis. The red arrow means up-regulated. HSP90: heat shock protein 90, IL: interleukin, TNF: tumor necrosis factor, INF: interferon, Th: T helper 17, DCs: dendritic cells.**

wound healing by 30%.[26] Dysfunctions of HSP90 as related to immune responses and cell differentiation may lead to the degradation of intercellular adhesion material in bullous dermatoses, followed by the loss of bridging granule function, a key factor in epidermal loosening and intra- or sub-epidermal blister formation.[27] Therefore, further investigations into HSP90 and the development of autoimmune dermatosis herpetiformis as well as its treatment are clearly warranted.

Epidermolysis bullosa (EBA) is a difficult-to-treat subdermal bullous autoimmune dermatoses in which type VII collagen is the autoantigen responsible for blister formation.[28] A variety of experimental protocols for inflammatory EBA have been developed, including *in vitro* and *in vivo* autoantibody transfer and development of autoantigen immunity. Results from follow-up studies have demonstrated the efficacy of anti-HSP90 inhibitors (*e.g.* 17-DMAG/TCBL-1457) in the treatment of mice with experimental herpetic epidermolysis bullosa. These HSP90 inhibitors, as administered to a 6–8-week-old SJL mouse model of experimental herpetic epidermolysis bullosa, resulted in improved type VII collagen immune responses, neutrophil infiltrations at the dermal-epidermal junction and reductions in basal granulocyte infiltrations as well as circulating autoantibody levels in the basement membrane zone. Simultaneously, an *in vivo* lymphocyte analysis and T cell proliferation assessment in these mouse models revealed that lymphocytes isolated from mice treated with HSP90 inhibitors responded less to *in vitro* anti-CD3/CD28 antibodies or autoantigen restimulation, demonstrating a significant suppression of T cell proliferation.[29,30]

Results, as obtained with investigations on redox signalling, have revealed a key role for HSP90 in stabilizing the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex during respiratory bursts.[31,32] Tukaj *et al*.[33] further demonstrated that *in vitro* ROS production could be inhibited by blocking HSP90, as observed not only in neutrophils activated by nonspecific microbial stimuli, but also in EBA-specific neutrophils activated by immune complexes composed of recombinant type VII collagen fragments and recombinant chimeric mono-anti-type VII collagen antibodies. Thus, these studies on the role of HSP90 in EBA indicate that neutrophils represent an additional important target site for HSP90 inhibition and therefore suggest that the targeting of neutrophils by HSP90 blockade would not only disrupt inflammatory processes already initiated by autoantibody deposition in the post-epidermal effector disease stage, but also synergistically modulate early autoantibody responses, thereby enhancing disease control.

Bullous Pemphigus (BP) is the most common subcutaneous maculopapular autoimmune dermatoses characterized by pathogenic autoantibodies against BP180 and BP230 at the dermal-epidermal junction. Autoantibodies to the BP180 immunodominant region (BP180-NC16A) are frequently associated with disease activity in these patients, with symptoms sharing some similarities with the inflammatory effects of EBA.[34] HSP90 expression in epidermal keratinocytes in the perilymphatic skin region of patients with herpetic aspergillosis and autoantibodies (BP180-NC16A immunoglobulin G [IgG]) from patients with herpetic aspergillosis are inhibited by HSP90 secretion from keratinocytes, whereas IgG from healthy donors is not affected.[35] The exact reason for the abnormal distribution of HSP90 in BP patients, and whether it is related to the pathogenesis of BP mechanisms or mainly reflects secondary reactive changes resulting from inflammation, remain unclear. This HSP90 may be related to inflammatory responses induced by anti-BP180 NC16A autoantibodies through the production of pro-inflammatory mediators (*e.g.* cytokines), which indirectly leads to enhanced intracellular HSP90 expression. It should also be noted that immunomodulatory effects of HSP90 inhibitors have been reported to be effectively blocked in bullous autoimmune dermatoses models.[36,37]

A review of current studies suggests that an insufficient frequency or activity of T regulatory cell population (Treg) expansion is associated with the development of autoimmune dermatosis herpetiformis and, that the targeting of this cell population may provide a new focus for anti-HSP autoantibody immunotherapy. Studies in experimental models involved with the testing of anti-HSP90 therapy for autoimmune maculopathy suggest that HSP90 represents a significant pathophysiological factor in the pathogenesis of autoimmune dermatoses including EBA and BP. However, associations between HSP90 and other autoimmune dermatoses and attempts to further identify HSP90 as a therapeutic target have yet to be established.

## HSP90 and cutaneous lupus erythematosus

Lupus erythematosus is a classical autoimmune disease, with skin involvement in 70% to 80% of patients. Systemic lupus erythematosus (SLE) is the most severe type of lupus erythematosus, often involving multiple internal organs and systems in addition to the skin and mucous membranes. Cutaneous lupus erythematosus (CLE) can present as an isolated dermatoses or as a manifestation of SLE. The clinical manifestations of CLE can be wide ranging, from isolated discoid plaques to extensive skin lesions. The close association between CLE and SLE is also reflected in the high percent of antinuclear antibodies (about 80%) or anti-double-stranded DNA antibodies (about 30%–40%) that can be found in CLE and SLE patients.[38,39]

As most studies on CLE are reported within the scope of SLE, no clear distinction exists between the pathogenesis of these two disorders and, the issue of whether SLE and CLE with skin characteristics are independent diseases remains controversial. Therefore, in this report the relationship between HSP90 and CLE represents a more theoretical analyses and data sources reviewed include studies involving HSP90 and SLE.

Association and haplotype analyses of SLE gene polymorphisms as performed at the Anhui Medical University revealed a

susceptibility relationship between HSP90AB1 and SLE. In addition, polymorphic expressions of the HSP90AA2 gene may be associated with a susceptibility for lupus in Chinese women.[40,41]

Deguchi *et al.*[42] first reported that, in a sample of 20 SLE patients, elevated levels of HSP90 were present in peripheral blood mononuclear cells (PBMCs). These findings were subsequently corroborated from data showing that HSP90 levels in SLE patients were elevated and observed in PBMCs within approximately 30% of their SLE patients.[43] Moreover, Erkeller-Yüksel *et al.*[44] found that elevated levels of HSP90 expression were present on the surface of lymphocytes in some SLE patients and that the intensity of HSP90 expression correlated with disease activity. These patients with elevated HSP90 expressions appear to constitute a unique subgroup of SLE patients who are significantly more likely to show HLA A1/B8/DR3 negative haplotypes as compared with that in patients with normal or reduced HSP90 levels. Notably, expressions of other major HSPs were not significantly elevated in these particular patients.

Inhibition of HSP90 gene expression results in an increased expression of transposon factors, which in turn leads to increased levels of interferon and thus can participate in the pathogenesis of SLE.[45] These findings suggest that it is the specific elevation of HSP90 which is involved in the development of SLE, rather than a non-specific induction of HSPs resulting from a combination of pathophysiological factors such as stress.[43,46] A role for IFN-α in the pathogenesis of SLE has also been demonstrated in mouse models, including positive feedback induction of plasma cell maturation and autoantibody production.[47] The HSP90 found in the serum of SLE patients can stimulate IFN-α production by DCs through interactions with TLR/9.[48,49] Simultaneously, the complex

formed by HSP90 and autoantibodies is effectively transported into the nucleus of DCs through endocytosis and targeting, which in turn stimulates increased IFN-α secretion.[50] Thus, the control of DC overactivation and abnormal production of IFN-α may provide an alternative therapeutic strategy for SLE. Although the issue as to whether HSP90 is directly involved in the pathogenesis of lupus has yet to be established, these finding suggest that HSP90 inhibitors have the potential to treat IFN-α-mediated autoimmune diseases, including SLE.

In addition, results from cell culture experiments have demonstrated that IL-6 or IL-10 can induce an enhanced transcription of HSP90. It is well known that IL-6 and IL-10 are elevated in the peripheral serum of SLE patients and these levels correlate with disease activity.[51–54] HSP90 expression is enhanced in transgenic animals overexpressing IL-6 and in those animals producing autoantibodies against.[55] In SLE patients, peripheral blood levels of HSP90 protein correlate with IL-6 levels and anti-HSP90 autoantibodies, but not with IL-10 levels. IL-6 levels in SLE patients lead to elevated HSP90 protein levels, which in turn promotes the production of anti-HSP90 autoantibodies (Figure 2).[56]

SLE-associated deposition of antigen-antibody complexes has been shown to play a role in vascular and renal tissue injury. The MRL/MpJ-Faslpr (MRL/lpr) mouse is a classic animal model of autoimmune disease, which to some extent, reflects the pathology and pathophysiology of human SLE.[57,58] Shimp *et al.*[59] observed that MRL/lpr mice treated with a HSP90 inhibitor (17-DMAG) showed reduced proteinuria and decreased serum anti-double-stranded DNA antibody levels, but no significant effects on glomerulonephritis, intra-glomerular IgG and C3 deposition were
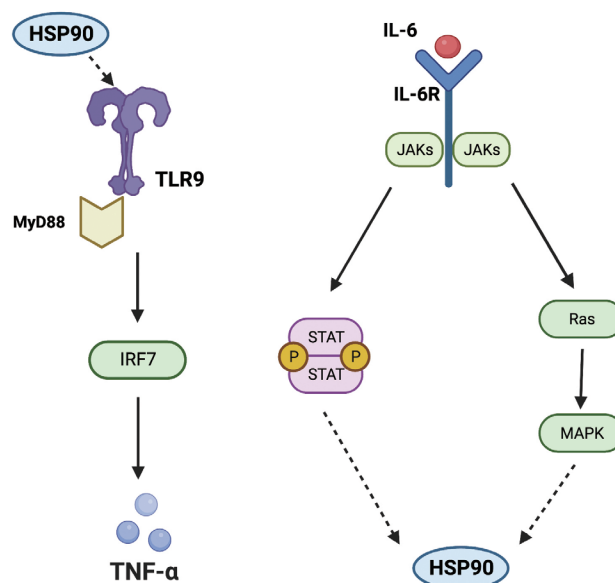


**Figure 2. Contribution of HSP90 in pathogenesis of systemic lupus erythematosus. HSP90: heat shock protein 90, IL: interleukin, TNF: tumor necrosis factor, TLR: toll-like receptor, IRF7: interferon regulatory factor 7, JAKs: Janus Kinases, STAT: signal transducers and activators of transcription.**

observed. Other effects of 17-DMAG included the induction of an increase in the number of CD8-positive T cells, along with decreases in the levels of double-negative T cells, the CD4/CD8 ratio and a small decrease in the number of B cells. Taken together, these results suggest that HSP90 may also play an important role in regulating T cell differentiation and activation.

DNA vaccines containing plasmids encoding specific antigens can effectively modulate immune responses to selected specific antigens.[60] HSPs, which are aberrantly expressed in autoimmune diseases, have been successfully encoded on a specific plasmid.[61] Liu *et al*.[62,63] reported that an HSP90-DNA vaccination alleviated the manifestations of symptoms in Lupus-prone (NZB × NZW) F1 mice and effectively prolonged their survival time. It has also been suggested that the protective effects of HSP90-DNA vaccine may be associated with the expansion of DCs and Treg cells.

Exposure to UV light is considered as the most recognized excitatory factor for the induction of CLE. UV exposure induces cell damage and inflammatory responses including cell death, release of reactive oxygen species and significant modifications of DNA.[64] In addition, UV stimulates the release of pro-inflammatory factors by mast cells, as well as producing an increase in the number of mast cells in the skin of CLE patients.[65,66] Results from a prospective analysis indicated that SLE and CLE patients showed significant type I interferon-mediated symptoms as their primary manifestations in response to UV stimulation.[67] UV exposure also upregulated the expression of IFN and MHC-related genes in the skin of CLE patients, but not in healthy individuals.[68] The inhibitory effects of 17-AAG on SCCs was associated with an inhibition of UV radiation-induced proliferative responses and 90HSPβ-PKC expression interactions in the skin of a mouse model.[69] Given these findings, it seem likely that HSP90 may be involved in some aspects of CLE development as induced by UV radiation and thus there is a possibility that HSP90 inhibitors could serve as topical treatments for CLE. More detailed investigations on the molecular mechanism of UV radiation-induced CLE and experimental observations and mechanistic analyses of 17-AAG for the prevention of UV radiation-induced cutaneous CLE will be required to substantiate these proposals.

## SUMMARY

The mechanisms underlying autoimmune dermatoses such as herpetic dermatosis, psoriasis and CLE are complex. One potentially critical component may be HSP90. Accordingly, investigations directed at examining the inflammatory role of HSP90, especially processes involved with its immune altering effects, would not only be beneficial for understanding the role and mechanisms of HSP90 in the development of autoimmune dermatoses, but also offer the possibility for development of new diagnostic protocols, as well as therapeutic directions and targets for the treatment of autoimmune dermatoses.

## Conflicts of interest
There are no conflicts of interest.

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