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Heat shock proteins and psoriasis

Psoriasis is a chronic disfiguring skin condition which may be induced or exacerbated by stress. Heat shock proteins (HSPs), as molecular chaperones, play a central role in protein folding and cellular protein homeostasis. The many different functions of HSPs in the cell depend on the specific HSP involved. HSPs play crucial roles in inflammation and immune reactions, and have emerged as promising therapeutic targets. In this review, we compile current lines of evidence concerning the roles and molecular mechanisms of HSPs that lead to the occurrence and development of psoriasis.

Key words: psoriasis, heat shock proteins, protein folding, microbe

Psoriasis is a common inflammatory skin disease that can be triggered by physical trauma, stress, cigarette smoking, obesity, infection, and medicines [1]. Heat shock proteins (HSPs) are a highly conserved family of proteins that are upregulated when cells are under conditions of stress [2]. Under physiological conditions, HSPs facilitate protein folding, degradation of misfolded proteins, and the transportation and chaperoning of proteins [2, 3]. Classification of HSPs is based on their approximate molecular weight, *e.g.* HSP27, HSP40, HSP60, HSP70, HSP90 and HSP110 [4]. In human skin, HSPs can protect cells from ultraviolet light or physical strain and regulate keratinocyte differentiation [5]. Based on previous studies, HSPs may play crucial roles in the development of psoriasis. In this review, we examine the current evidence regarding the relationship between HSPs and psoriasis. In addition, we review the potential mechanisms associated with HSPs in psoriasis. Moreover, we also discuss pre-clinical data that may be useful to evaluate HSPs as potential therapeutic targets of psoriasis.

HSP27 and psoriasis

HSP27 belongs to the small HSP family with a molecular weight of ~27 kDa and plays important roles in cell survival, cytoskeleton dynamics, cell differentiation, and embryogenesis [6]. HSP27 is localized in both the cytoplasm and nucleus, and transfers into the nucleus when exposed to heat shock and various other stress conditions [7]. HSP27 has pro-apoptotic and anti-apoptotic functions through both intrinsic and extrinsic pathways depending on the stimulus and cellular conditions [8]. Furthermore, HSP27 plays a role in resistance to heat shock or oxidative treatments [9]. Previous studies suggest that an increase in ROS production and a decrease in antioxidant activity may be involved in the pathogenesis of psoriasis [10, 11]. However, the role that HSP27 may play in oxidation/antioxidation associated with psoriasis requires further examination.

Biopsies of psoriatic lesional skin show a thickened, hyperproliferative epidermis with parakeratosis. Constanze *et al*. found that the expression of pro-filaggrin and loricrin at the protein level and the expression of filaggrin, keratin 10, and transglutaminase 1 at the mRNA level, induced by calcium, can be inhibited by p38-MAPK inhibitor; knockdown of HSP27 can disturb the differentiation process and delay the switch from basal to suprabasal keratins in an organotypic skin culture model. The study suggested that the phosphorylation of HSP27 by p38-MAPK and the expression of HSP27 were required for keratinocyte differentiation [12-14]. The expression of HSP27 in psoriatic lesions was increased compared with uninvolved skin [15]. The upregulated HSP27 expression in the skin of psoriasis patients is inconsistent with the positive association between HSP27 and keratinocyte differentiation. Besides aspects of differentiation, an exploratory study showed that HSP27 may play a protective role in psoriasis. The study found that HSP27 may inhibit the expression of IL-8 and PGE2 stimulated by TNF-α through NF-κB signalling in keratinocytes [16]. Becker *et al*. showed that after UV treatment, HSP27 mRNA in keratinocytes was induced, which indicates that HSP27 functions to protect keratinocytes against UV-induced apoptosis [17]. Clinically, the onset of psoriasis or psoriasis relapses are related to infection by Group A β-haemolytic streptococci [18, 19]. A study including 76 HLA Class I-typed patients with chronic plaque psoriasis and 22 healthy individuals showed an increased prevalence of streptococcal infection in HLA-Cw6+ patients. An antibody induced by streptococcal immunization and sera from psoriasis patients may target various human keratinocyte proteins. The study revealed that HSP27 induces the activation of T cells in psoriasis patients, particularly in HLA-Cw6+ individuals. Additionally, HSP27 may serve as an autoantigen associated with a pathogenic T cell response in streptococcal-induced psoriasis [18]. As mentioned, an increase in the expression of HSP27 genes in psoriasis patients with metabolic syndrome has been reported [20]. In summary, HSP27 may play a role in the pathogenesis of psoriasis.

HSP70 family and psoriasis

The heat shock protein-70 (HSP70) family is composed of constitutively expressed and inducible proteins with an

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approximate molecular weight of 70 kDa (66-78 kDa) [21]. HSP70 can block the production of the apoptosome by associating with Apaf-1 and suppress nitric oxide-mediated apoptosis by preventing mitochondrial translocation of Bax [22, 23]. Previous studies also revealed that HSP70 family can rescue DNA breaks from ROS-induced insults [24, 25]. The HSP70 family can reduce the stress-induced denaturation and aggregation of intracellular proteins, act as protective factors in tissue injury, play important roles in the activation and maturation of dendritic cells (DCs), and reflect systemic inflammation and oxidative stress [26, 27]. With regards to the effect of HSP70 on keratinocytes, a study suggested that decreased HSP70 production may be related to increased heat-induced death of old keratinocytes compared with young keratinocytes [28].

CD91 is a common receptor of HSP70 and is expressed predominantly by activated antigen-presenting cells (APCs). Boyman *et al.* showed that CD91-expressing cells accumulate during development of psoriatic lesions, which are mainly dendritic APCs. Furthermore, the expression of HSP70 was upregulated in keratinocytes in close vicinity to CD91+ APCs in psoriatic lesions [29]. These data suggest that HSP70 and CD91 may play an important role during early lesion development in psoriasis. When evaluated using the immunoreactivity intensity distribution index, the level of HSP70 was markedly lower in the basal, suprabasal, and superficial epidermal layers of psoriatic lesions when compared with that of normal skin [30]. However, in another study, the level of HSP70 was considerably higher in psoriatic patients when compared with the HSP70 levels in control patients [31]. In addition, Curry *et al*. revealed that psoriatic scales and psoriatic epidermis contain abundant levels of HSP27, HSP60, and HSP70 [32].

Several reports have suggested an association between Malassezia furfur and psoriasis [33, 34]. Baroni *et al*. demonstrated that Malassezia furfur-positive psoriasis-affected patients showed an increase in HSP70 expression [35]. Borska *et al*. found that an increase in HSP70 levels indicated higher genotoxic risk and cellular stress in sensitive paediatric patients immediately following GR (Goeckerman regimen; a combination of crude coal tar and UV-irradiation as dermal treatment for psoriasis) [36]. In addition, Federico *et al*. found that alfalfa-derived HSP70 can reduce skin inflammation in the mouse model of imiquimod (IMQ)-induced psoriasis. The study showed that both the 50 and 250-μg alfalfa-derived HSP70-treated groups had significantly lower PASI scores compared with the IMQ-only group. With regards to cytokines, the expression of IL-4 and IL-5 mRNA was downregulated in both the 50 and 250-μg alfalfa-derived HSP70-treated groups compared to that in the IMQ-only group. The expression of IL-17F mRNA was decreased in the 50-μg alfalfa-derived HSP70-treated group compared to that in the IMQ-only group. In contrast, expression of IL-17A mRNA was upregulated in the 50-μg alfalfa-derived HSP70-treated group relative to the IMQ-only group. The mRNA expression of IL-22 was increased in both the 50 and 250-μg alfalfa-derived HSP70-treated groups relative to IMQ-only group [37]. Future work on the effects of topical HSP70 on skin physiology are needed.

HSP72 is an inducible protein. HSP72 can inhibit apoptosis, through both activation of JNK phosphatase and binding to Apaf-1 to prevent binding of caspase-9. In addition, HSP72 can affect the expression and phosphorylation state of Akt, which positively regulates cell proliferation [38]. In general, HSP72 plays a role in the activation of the immune system and may, for example, stimulate neutrophil chemotaxis [39] or neutrophil microbicidal capacity during exercise-induced stress [40]. However, important studies have also indicated that HSP72 affects the immune system negatively [41, 42]. In an LPS-induced systemic inflammation model, HSP72 induced by thermal pre-treatment can inhibit the production of IL-6 and TNF-α. HSP72 may have an anti-inflammatory role [43, 44]. The expression of HSP72 was upregulated in the basal and suprabasal layer cells of heat-stressed normal skin and psoriatic lesions when compared with untreated normal skin or uninvolved psoriasis, which suggests that HSP72 performs a protective role in the proliferative compartment of normal and involved psoriatic skin [45]. The epidermal expression of HSP65 and HSP72 in lesions of AIDS -associated psoriasiform dermatitis was less intense than in lesions of psoriasis not associated with AIDS. This may have been related to the abnormal immune situation associated with AIDS [46].

Thus, the HSP70 family may be involved in the pathological processes of psoriasis. Further efforts are warranted to illuminate the exact role of HSP70 family in psoriasis.

HSP90 and psoriasis

The 90-kDa heat shock protein (HSP90) is a ubiquitously expressed molecular chaperone and focally expressed throughout the epidermis in normal-appearing skin [5, 47]. In humans, there are four HSP90 isoforms: HSP90α, HSP90β, glucose-regulated protein 94 (Grp94), and mitochondrial tumour necrosis factor receptor-associated protein-1 (Trap-1) [48, 49]. Expression of HSP90α is induced under stress conditions, whereas HSP90β is expressed constitutively [48].

Currently, psoriasis is generally considered a T-cell-mediated immune disease with a mixed Th1/Th17 cytokine environment. Act1 is an essential adaptor molecule in IL-17-dependent signalling. Studies have shown that IL-17A is up-regulated at sites of inflammation in psoriasis [50]. Wang *et al*. have demonstrated that HSP90 plays an essential role in regulating Act1 function, thus facilitating IL-17A-signalling [51]. A study conducted by Kakeda and colleagues showed that HSP90α, but not HSP90β, was significantly overexpressed in epidermal keratinocytes and mast cells of psoriatic skin, and down-regulated after ustekinumab therapy [5]. In another study involving 50 patients with psoriasis (25 with metabolic syndrome) and 50 control patients (25 with only metabolic syndrome), an increase in the expression of genes for HSP27, HSP60 and HSP90 in patients with metabolic syndrome was observed [20].

Debio 0932, an oral HSP90 inhibitor, has been developed for anti-cancer therapy. Stenderup *et al*. revealed that Debio 0932 alleviates the clinical manifestation of psoriasis and reduces epidermal thickness in a psoriasis xenograft transplantation model, which indicates the potential role of Debio 0932 in the treatment of psoriasis [52]. In studies on tumours, HSP90 inhibition was found to potentially alter the composition of the TNFR1 complex, which induced the caspase-8-dependent apoptotic pathway [53]. There are some studies that have shown that HSP90 inhibitors can induce cell differentiation at low doses [54]. These findings

highlight that the different effects of HSP90 inhibition on the fate of cells are dependent on the various cell types. Further efforts are needed to determine the role of HSP90 inhibition in the therapy of psoriasis.

Hsp90 plays a role in the regulation of glucocorticoid receptor (GR) activity and stress response, and is able to modulate stress-induced hypothalamic-pituitary-adrenal (HPA) activity [55, 56]. In psoriasis patients, a negative relationship is reported between cortisol and stress levels after stress exposure, as well as blunted HPA axis responsiveness in psoriasis [57]. FK506-binding protein 5 (FKBP51/FKBP52) acts as a co-chaperone that regulates GR activity. Hsp90 can slow or enhance GR translocation into the nucleus by interaction with FKBP51 or FKBP52 [58]. However, whether HSP90 plays a particular role in regulating cortisol levels after stress exposure and blunted HPA axis responsiveness in psoriasis remains to be determined. Taking these findings together, HSP90 may play a role in the pathogenesis of psoriasis. Currently, the exact role and mechanism of HSP90 and the effect of its inhibitor in psoriasis remain largely unknown.

Microbial HSPs and psoriasis

HSP65 is a highly conserved antigen of mycobacteria. A previous study demonstrated a positive correlation between antibody activity toward HSP65 and psoriasis disease activity. In addition, 47% of the psoriasis patients showed significantly elevated antibody titres to HSP65 when compared with the levels in control groups, and there was a significant positive correlation between the antibody response based on ELISA and psoriasis disease activity [59]. The results of Mario *et al*. revealed that the IgG response to 60 fractions of *Streptococcus pyogenes* (*S. pyogenes*) is important in psoriasis and suggested that there was an association between high response to *S. pyogenes* HSP60 and the chronic form of psoriasis [60]. This observation is consistent with the study by Pérez-Lorenzo *et al*., in which IgG levels to the heat shock-induced *S. pyogenes* in psoriatic patients were shown to be significantly different in control patients [61]. In pustulosis palmaris et plantaris (PPP) patients, the titres of IgG against synthetic *Mycobacterium bovis* HSP65 and recombinant HSP60 did not differ significantly when compared with those in the control group [62].

Mice transplanted with tonsillar lymphocytes (TL) and skin grafts harvested around PPP lesions showed no significant difference in anti-HSP65-IgG levels in sera compared with mice transplanted with peripheral blood lymphocytes (PBL) and PPP skin. In addition, the authors reported strong expression of HSP60 in keratinocytes of the skin grafts. After stimulation with HSP60, the mice transplanted with TL from PPP patients showed a significantly higher anti-HSP65-IgG level in serum when compared with that of the control groups [63]. These findings suggest immune cross-reactivity between human-HSP60 and bacterial-HSP65 in PPP.

Although human HSP60 has been detected at extra-mitochondrial sites, this HSP is located primarily within the mitochondrial matrix [64]. Studies show that human HSP60 is involved in pro-caspase-3 activation in cytochrome c-dependent apoptosis and can activate Bax [65, 66]. The level of HSP60 has been reported to be significantly higher in plaque and guttate psoriasis when compared with normal skin [67]. As mentioned, there is an increase in the expression level of HSP60 in the epidermis of psoriasis patients [32]. Although the exact mechanism is still obscure, these observations indicate that HSP60 may be related to the pathogenesis of psoriasis.

Taken together, heat shock-induced proteins from microbial agents and their interaction with human-derived HSPs may be associated with psoriasis, however, the mechanisms of action are believed to be complex.

Conclusion and future perspectives

HSPs are molecular chaperones that present as double-edged swords. There are conflicting results in the literature concerning the role of HSPs during the pathogenesis of psoriasis, and this discrepancy is dependent on the specific HSP examined. Studies also suggest that HSPs produced by microbes play roles in psoriasis, but further research is required to clarify the role of microbial HSPs in the process of psoriasis. Given the potential important association between HSPs and psoriasis, understanding the exact role of HSPs is a prerequisite for the development of new approaches to treat psoriasis. Nevertheless, the studies did not include an independent cohort for validation. Studies with larger cohorts of patients are needed to clarify the clinical significance of HSPs in psoriasis. Despite our current knowledge, it remains unclear how to best use these agents. This remains a major challenge that requires further studies to determine the safety and efficacy of HSP inhibitor treatment for psoriasis patients. ■

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