Chapter 21
Heat Shock Protein 60 in Skin Diseases

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Abstract In addition to serving as a stress regulatory/response protein, heat shock protein 60 (Hsp60) also plays important roles in disease mechanism and progression. This chapter summarizes all aspects of the current knowledge on Hsp60 related to various skin diseases, including acne, atopic dermatitis (AD), dermatitis herpetiformis (DH), vasculitis, Behçet's disease (BD), microscopic polyangiitis (MPA), systemic sclerosis (SSc), dermatomyositis, lichen planus (LP), and psoriasis. The data have shown that not only human Hsp60 but also its homologs in bacteria or microbes (e.g., GroEL) are involved in immune response and inflammatory cascade of these skin diseases. Furthermore, Hsp60 expression is also associated with severity of some diseases. Therefore, Hsp60 can be considered as a potential target for future development of a useful biomarker for diagnostics and prognostics in skin diseases. Moreover, it may also serve as a new therapeutic target for better treatment outcome.

Keywords Chaperone · Dermatology · Hsp60 · Immune response · Inflammation · Skin disorders

Abbreviations

AD	atopic dermatitis
AECA	anti-endothelial cell antibodies
ANCA	anti-neutrophil cytoplasmic antibodies
BD	Behçet's disease

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DH	dermatitis herpetiformis
Hsp60	heat shock protein 60
ICAM-1	intercellular adhesion molecule-1
IFN-γ	interferon-γ
IL	interleukin
LP	lichen planus
MPA	microscopic polyangiitis
MPO	myeloperoxidase
PBMC	peripheral blood mononuclear cells
SLE	systemic lupus erythematosus
SSc	systemic sclerosis
TGF-β	transforming growth factor-β
TLR	toll-like receptors
TNF-α	tumor necrosis factor-α

21.1 Introduction

Heat shock proteins are generally considered as the stress regulatory/response molecules induced by various types of stimuli and are involved in several inflammatory and autoimmune disorders. In human skin, heat shock protein 60 (Hsp60) has been demonstrated to play roles in various stress conditions. For example, ultraviolet A and B radiation, which frequently induces cellular apoptosis, causes increased level of Hsp60 in keratinocytes in a dose-dependent manner (Wang et al. 2013). In addition, hyperthermia can increase nuclear expression of Hsp60 in the normal human skin (Subjeck et al. 1982). The increased Hsp60 expression has been also observed in cellular compartment of skin fibroblasts during an early stage of senescence (Di Felice et al. 2005). Such increases in expression of Hsp60 following stress conditions have been thought to be involved in the refolding process of cellular proteins to protect human keratinocytes and other skin cells from stress-induced damage (Wilson et al. 2000).

In addition to human Hsp60, its homologs in bacteria or microbes (e.g., GroEL) also play crucial roles in cutaneous response against pathogens. A previous study has demonstrated that human keratinocytes increased secretion of tumor necrosis factor-α (TNF-α), interleukin-1α (IL-1α), IL-6 and soluble intercellular adhesion molecule-1 (ICAM-1) after 48-h exposure to GroEL from *Escherichia coli* (Marcatili et al. 1997). Hsp60 purified from *Actinobacillus actinomycetemcomitans*, the oral pathogen, could induce proliferation and migration of HaCaT human keratinocytes through activation of ERK1/2 MAP kinase pathway, whereas exogenous recombinant human Hsp60 showed no such effect (Zhang et al. 2001). This process might be involved in wound repair of the skin and oral mucosa after exposure

to bacterial pathogens. However, prolonged exposure of HaCaT cells to bacterial Hsp60 caused decrease in cell viability (Zhang et al. 2004).

Hsp60 not only serves as the stress regulatory/response protein but also plays important roles in pathogenic mechanisms of several skin disorders. This chapter summarizes all aspects of the current knowledge on Hsp60 related to various skin diseases, including acne, atopic dermatitis (AD), dermatitis herpetiformis (DH), vasculitis, Behçet's disease (BD), microscopic polyangiitis (MPA), systemic sclerosis (SSc), dermatomyositis, lichen planus (LP), and psoriasis.

21.2 Hsp60 in Acne

Acne (also known as acne vulgaris) is a common skin problem associated with sebaceous follicles and *Propionibacterium acnes* infection (Das and Reynolds 2014). Acne has a varied spectrum of manifestations, including non-inflammatory comedones, inflammatory papules, pustules, nodules and cysts. Common sites of acne include face, chest, upper back and upper arms (Eichenfield et al. 2013). The pathophysiology of acne involves follicular epithelial hyperproliferation, inflammatory processes, sebum overproduction and proliferation of *P. acnes*, which is a Gram-positive rod bacterium that resides in pilosebaceous follicles (Das and Reynolds 2014).

P. acnes can induce inflammatory processes leading to diffuse infiltration of inflammatory cells around the hair follicle and rupture of follicular wall (Beylot et al. 2014; Das and Reynolds 2014; Harper 2004). In addition, *P. acnes* may induce a cell-mediated inflammatory response to physiological stress and increase production of heat shock proteins. Wilcox et al. investigated the proliferative response of peripheral blood mononuclear cells (PBMC) to *P. acnes*, Hsp60/Hsp70 derived from *P. acnes* and Hsp65 derived from *Mycobacterium bovis* BCG isolated from acne patients, resolved acne subjects and healthy controls (Wilcox et al. 2007). The data have indicated that PBMC stimulated by mycobacterial Hsp65 from acne patients showed significantly higher proportion of positive responders (as determined by purified $CD4^+$ T-cells) than those derived from the resolved acne subjects and healthy controls (Wilcox et al. 2007). However, the proportion of such positive response was comparable between stimulation with *P. acnes* vs. Hsp60/Hsp70 derived from *P. acnes*. Although these results could not conclude that *P. acnes* Hsp60 plays a crucial role in the pathogenesis of acne, the limiting dilution analysis showed a significantly lower proportion of the resolved acne subjects responded to *P. acnes* fitting the single-hit kinetic model than acne patients and controls, suggesting an association of spontaneous resolution of acne and negative regulation of the $CD4^+$ T-cell response to *P. acnes* (Wilcox et al. 2007).

21.3 Hsp60 in Atopic Dermatitis (AD)

AD is a common chronic inflammatory skin disorder affecting approximately 20% of children and 10% of adults (Flohr and Mann 2014). AD patients usually have personal or family history of other atopic symptoms, such as asthma and allergic rhinitis, and frequently have xerosis, pruritus and eczema at flexural areas (Weidinger and Novak 2016). Distribution of AD skin lesions varies according to the patient age. In infants, the commonly affected areas are cheeks, forehead and scalp, whereas flexures, neck and hands are more common in older children (Akdis et al. 2006; Wollenberg et al. 2016). Lichenification may occur from repeated scratching and rubbing (Akdis et al. 2006; Wollenberg et al. 2016). The pathogenesis of AD is considerably complex and is associated with genetic factors, skin barrier disruption and immune dysregulation. Mutation of gene encoding filaggrin (a filament aggregating protein) has been reported in AD patients, leading to disruption of the skin barrier (Thyssen and Kezic 2014). The impaired epidermal barrier then increases transepidermal permeability, water loss and penetration of external antigens that subsequently activate innate immune response (Weidinger and Novak 2016).

Roles of Hsp65 in the pathogenesis of AD have been investigated. Ghoreishi et al. studied the expression of Hsp65 in AD skin lesion compared with contact dermatitis lesion and normal skin (Ghoreishi et al. 2000). Hsp65 expression was more intense in keratinocytes of the whole epidermis in AD lesion than in contact dermatitis lesion and normal skin (Ghoreishi et al. 2000). Infiltrating lymphocytes in the dermis of approximately half of AD patients showed Hsp65 expression, which was not observed in contact dermatitis, suggesting that Hsp65-expressed lymphocytes may play a role in the pathogenic processes of AD (Ghoreishi et al. 2000).

Subsequent studies also support roles of Hsp60 in AD (Jassies-van der Lee et al. 2008; Kapitein et al. 2013). Kapitein et al. have demonstrated increased Hsp60 expression in AD lesion as compared to the non-lesional skin and suggested that Hsp60-specific T-cell response might affect local inflammation found in AD (Kapitein et al. 2013). Another study in dogs has shown that intradermal injection of recombinant human Hsp60 at AD lesion could induce regulatory cytokines (i.e., IL-10, transforming growth factor-β (TGF-β) and IL-12p40) and Th1 phenotype in the skin (Kapitein et al. 2013).

21.4 Hsp60 in Dermatitis Herpetiformis (DH)

DH is an autoimmune blistering disease associated with gluten sensitivity and celiac disease. These patients usually present with pruritic papules or vesicles mainly on extensor surfaces of the elbows, buttocks, knees, back and scalp, but frequently spare the mucosal areas (Nicolas et al. 2003). Pathogenic mechanism of DH is not completely understood but multiple factors (e.g., genetic and environmental factors) have been demonstrated to get involved in the disease process. Following the ingestion of gluten-containing foods, tissue transglutaminase can modify gliadin (a

fraction of gluten) into an autoantigen, leading to activation of the gluten-responsive T-cells (Nicolas et al. 2003). IgA1 is the main type of autoantibody detected in DH and granular deposition of IgA1 in dermal papillae and along the basement membranes serves as one of the hallmarks for the diagnosis of DH (Bolotin and Petronic-Rosic 2011a; Nicolas et al. 2003). Neutrophilic microabscess can be found in the area of IgA deposition, suggesting that IgA may trigger inflammatory cascade (Bolotin and Petronic-Rosic 2011a; Nicolas et al. 2003).

In celiac disease, cross reaction of autoantibodies to the celiac peptide and Hsp60 may induce intestinal mucosal damage and increase intestinal permeability (Tukaj et al. 2017; Zanoni et al. 2006). Serum anti-tissue transglutaminase and anti-Hsp60 IgA antibodies were detected in active celiac patients (Tukaj et al. 2017; Zanoni et al. 2006). These antibodies were no longer detectable after elimination of gluten from the diet (Zanoni et al. 2006). Because DH is closely related with gluten-sensitive disease, Hsp60 may also play such important role in the pathogenesis of DH (Bolotin and Petronic-Rosic 2011a, b).

Kasperkiewicz et al. studied the role of heat shock proteins in autoimmune vesiculobullous diseases, including DH, bullous pemphigoid and pemphigus vulgaris (Kasperkiewicz et al. 2014). They have demonstrated that serum anti-Hsp60 IgG antibody was significantly increased only in patients with active DH, not in those with other active autoimmune vesiculobullous diseases (Kasperkiewicz et al. 2014). In addition to dapsone therapy, gluten-free diet is the mainstay treatment for DH (Bolotin and Petronic-Rosic 2011b; Nicolas et al. 2003). The strict gluten-free diet leads to resolution of the skin lesion and improvement of gastrointestinal symptoms in association with reduction of anti-Hsp60 IgG autoantibody (Kasperkiewicz et al. 2014).

21.5 Hsp60 in Vasculitis

Anti-endothelial cell antibodies (AECA) are the circulating autoantibodies targeting to endothelial cells (Guilpain and Mouthon 2008). There is evidence suggesting the role of AECA in the pathogenesis of various vasculitides (Alard et al. 2008; Guilpain and Mouthon 2008). Nevertheless, the AECA-targeting antigens are not well characterized. Hsp60 is commonly localized in the cytoplasm of human endothelial cells. When endothelial cells are exposed to heat stress, Hsp60 can be translocated to the cell membranes and thus be accessible to antibodies (Jamin et al. 2005). An interaction between AECA and Hsp60 has been reported to play pathogenic role in vasculitis-associated systemic autoimmune diseases (Alard et al. 2008, 2011; Jamin et al. 2005). Furthermore, anti-Hsp60 could trigger an inflammatory response of vasculitis by inducing apoptosis of endothelial cells (Jamin et al. 2005). However, apoptosis could be inhibited only partially by pre-incubating recombinant Hsp60 with purified IgG, indicating that there should be other antibodies associated with AECA-induced apoptosis (Jamin et al. 2005). Details of roles for Hsp60 in specific types of vasculitis are discussed below.

21.5.1 Behçet's Disease (BD)

BD is a rare chronic systemic vasculitis of unknown etiology that may affect multiple parts of the body. Common manifestations include recurrent aphthous and genital ulcers, uveitis and cutaneous lesions (Pineton et al. 2012). Etiopathogenesis of BD is highly complex and remains unclear. Genetic predisposition, immune dysregulation, infections, and environmental factors have been implicated in the pathogenic mechanisms of BD (Greco et al. 2018; Mendoza-Pinto et al. 2010; Pineton et al. 2012). Increasing evidence has supported the role for Hsp60 in the etiopathogenesis of BD (Kaneko et al. 2011; Shaker et al. 2007; Shimizu et al. 2012). In addition, Hsp60 level has been found to increase in peripheral blood lymphocytes, intestinal tissues, mucocutaneous lesions and plasma of patients with BD (Ergun et al. 2001; Imamura et al. 2005; Shaker et al. 2007). Moreover, it has been reported that excessive Th1 immune response and Hsp60-reactive T-cells also play roles in active BD (Greco et al. 2018; Imamura et al. 2005).

A precipitating factor of BD is infection (Lule et al. 2017; Mendoza-Pinto et al. 2010; Pineton et al. 2012). Cho et al. have demonstrated that GroEL from *Streptococcus sanguinis* is a target for anti-*S. sanguinis* IgA antibody reactivity, which is higher in BD patients than in healthy controls (Cho et al. 2013). Interestingly, T-cell immune response to Hsp60 peptide was markedly increased in patients with BD comparing to those with rheumatoid arthritis and healthy controls (Kaneko et al. 1997). Furthermore, Hsp60 peptide up-regulated mRNA expression of proinflammatory cytokines, i.e., IL-8, TNF-α and TNF-β (Kaneko et al. 1997). Hsp60 can also activate immune response through toll-like receptors (TLR). A previous study has shown that TLR were involved in the pathogenesis of BD and level of TLR-6 expressing granulocytes of BD patients was significantly increased after Hsp60 stimulation (Yavuz et al. 2008).

21.5.2 Microscopic Polyangiitis (MPA)

MPA is an autoimmune disease affecting small vessels and characterized by necrotizing vasculitis, but without paucity of immune deposits within blood vessel walls. MPA can affect several organs, including skin, lungs and kidneys. Although the etiology of MPA is still unclear, the autoimmune process has been thought to play a critical role in the pathogenesis of MPA. Anti-neutrophil cytoplasmic antibodies (ANCA) are positive in most of the MPA patients and targets mainly to myeloperoxidase (MPO) (Kallenberg 2014). A study in 58 patients with MPO-ANCA positive MPA has shown significantly higher frequency and titer of anti-human Hsp60 antibody in these patients than in those with rheumatoid arthritis, systemic lupus erythematosus (SLE) and healthy controls (Komiya et al. 2011).

21.6 Hsp60 in Systemic Sclerosis (SSc)

SSc or diffuse scleroderma is an uncommon autoimmune disease characterized by extensive fibrosis of skin and internal organs, as well as vasculopathy (Denton and Khanna 2017). Other common clinical manifestations of SSc include sclerodactyly of the fingers, digital tip ulcers, telangiectasia, Raynaud's phenomenon, interstitial lung disease, and renal involvement (Denton and Khanna 2017). Histopathology commonly shows excessive collagen accumulation, vascular injury, and autoimmune activation (Yazawa et al. 2007). Danieli et al. studied serum levels of antibodies against *M. tuberculosis* Hsp65 in 53 SSc patients, 36 patients with primary Raynaud's phenomenon, and 36 SLE patients (Danieli et al. 1992). The data showed that 47% and 38% of patients with SSc and primary Raynaud's phenomenon, respectively, had serum antibodies against Hsp65, whereas such antibodies were detected only in 5% of SLE patients (Danieli et al. 1992). While the role of immunity to bacterial Hsp65 has been implicated in rheumatoid arthritis, its role in SSc is controversial (Gaston et al. 1989, 1990).

21.7 Hsp60 in Dermatomyositis

Dermatomyositis is a systemic autoimmune disease affecting mainly children who present with rash and proximal muscle weakness. Both genetic and environmental conditions have been reported as the pathogenic factors affecting dermatomyositis. However, its mechanism and autoantigen(s) remain poorly defined (Quartier and Gherardi 2013; Thompson et al. 2018). Expression of Hsp60 has been reported to increase in muscle tissues of inflammatory myositis patients (Hohlfeld and Engel 1992). In addition, Elst et al. studied the expression of Hsp60 in juvenile dermatomyositis tissues and found that all of these muscle tissues had increased Hsp60 expression in both degenerating and regenerating muscle fibers and in the mural layer of small blood vessels (Elst et al. 2008). Moreover, muscle tissue-derived mononuclear cells and PBMC from juvenile dermatomyositis patients could activate T-cell proliferation (Elst et al. 2008). In vitro activation of PBMC isolated from juvenile dermatomyositis patients with human and microbial Hsp60 significantly induced secretion of IL-1β, TNF-α, and IL-10 (Elst et al. 2008). This study has suggested that Hsp60 induced both effector and regulatory T-cell response to control inflammation in juvenile dermatomyositis (Elst et al. 2008).

21.8 Hsp60 in Lichen Planus (LP)

LP is an idiopathic chronic inflammatory disorder that is mediated through T-cell immune response. The most frequently affected site is oral mucosa (found in approximately 70% of cases), followed by genital mucosa and skin (Farhi and

Dupin 2010; Kurago 2016). Cutaneous LP presents as polygonal, pruritic, flat-topped violaceous papules on the trunk or extremities overlying with whitish lacy lesions known as Wickham striae. In the oral cavity, the commonly involved areas include buccal mucosa, tongue and gingiva, characterized by multiple papules typically with Wickham striae (Alrashdan et al. 2016; Olson et al. 2016).

Multiple factors, including genetic background, infections, dental materials, medications and autoimmunity, can affect the pathogenesis of oral LP (Olson et al. 2016). A meta-analysis has demonstrated the association between hepatitis C seropositivity and oral LP in certain populations, such as Mediterranean and Japan (Shengyuan et al. 2009). Some medications are also associated with this disease, including beta blockers, angiotensin-converting enzyme inhibitors, anti-inflammatory drugs, diuretics and dapsone (Alrashdan et al. 2016; Roopashree et al. 2010). Contact hypersensitivity to dental materials, such as amalgam, dental acrylics, cobalt, composite and nickel has been also reported as the priming cause of LP. Moreover, replacement of such dental materials lead to resolution of the LP oral lesions (Ismail et al. 2007). Histopathology includes liquefaction degeneration of the basal layer, saw-tooth rete pegs, band-like infiltration of lymphocytes in subepithelial layer, necrotic keratinocytes, hyperkeratosis and acanthosis (Fernandez-Gonzalez et al. 2011). The immunoreaction of oral LP is mediated through T-cells, whereas antigen that can induce such immune process can be exogenous antigen or autoantigen (Alrashdan et al. 2016; Roopashree et al. 2010). Activation of $CD4^+$ and $CD8^+$ T-lymphocytes can then induce secretion of inflammatory cytokines, such as IL-2, interferon-γ (IFN-γ) and TNF-α, leading to apoptosis of basal layer due to a cytotoxic reaction (Olson et al. 2016; Roopashree et al. 2010).

Hsp60 has been implicated in the pathogenesis of oral LP but with unclear mechanism. It may serve as an autoantigen that can induce T-cell mediated immune response or associated with an autoimmune response to basal cell antigens (Bayramgurler et al. 2004; Bramanti et al. 1995). Hsp60 expression was found in the basal layer (Bramanti et al. 1995; Chaiyarit et al. 1999) and epithelial-connective tissue interface of oral LP tissues (Bramanti et al. 1995). A study by Chaiyarit et al. has suggested that Hsp60 expression in basal keratinocytes might be up-regulated by cytokines produced from T-lymphocytes in the subepithelial layer (i.e., IL-6, granulocyte-macrophage colony stimulating factor (GM-CSF) and TNF-α) (Chaiyarit et al. 1999).

21.9 Hsp60 in Psoriasis

Psoriasis is a common chronic inflammatory skin disease, which can be classified into five subtypes based on historic descriptions of its underlying histology and morphology (Menter et al. 2008). The most common form is psoriasis vulgaris, in which well demarcated erythematous plaques are covered by thick silvery scales. The second subtype, guttate psoriasis, classically presents as small circumscribed erythematous scaly lesions, which usually occur in young adults. The third subtype,

inverse psoriasis, is the uncommon form localized at flexural and intertriginous areas in which scales are rarely present due to the local moist environment. The forth subtype is (localized and generalized) pustular psoriasis, which is characterized by pustules without or with fever and systemic symptoms. The last form is erythrodermic psoriasis with diffuse erythema and scaling of the skin covering nearly the entire body. Nails and scalp are commonly involved in psoriasis, whereas systemic symptoms (i.e., fever and malaise) may also present (Boehncke and Schon 2015; Menter et al. 2008).

Although its etiology is unclear, the pathogenic mechanism of psoriasis has been thought to involve genetic and environmental factors, as well as infections, stress, drugs and trauma (Menter et al. 2008). Both innate and adaptive immune processes, particularly cell-mediated adaptive immune response triggered by environmental factors, are also considered to be involved in the disease mechanism (Gaspari 2006). Infiltrating $CD4^+$ and $CD8^+$ T-lymphocytes are commonly found in the affected skins (Griffiths and Barker 2007). Additionally, many cytokines have been shown to be up-regulated in psoriatic lesions, including IL-12, IL-17, IL-22, IL-23, TNF-α and IFN-γ (Gaspari 2006; Kim and Krueger 2015).

The role of Hsp60 has been implicated in the pathogenic mechanism of psoriasis. A previous study has demonstrated that Hsp60 expression was significantly greater in epidermal keratinocytes of plaque psoriasis and guttate psoriasis than those of the normal skin (Seung et al. 2007). A study in severe combined immunodeficient (SCID) mice transplanted with skin-grafts from pustulosis palmaris et plantaris patients has demonstrated the strong expression of Hsp60 in epidermal keratinocytes of the animals (Hayashi et al. 2009). The role of association between Hsp60 and TLR has been also suggested in the innate immune response of psoriasis. Zanin-Zhorov et al. have shown that soluble Hsp60 regulated response of T-cells by interacting with TLR2 (Zanin-Zhorov et al. 2003). Ohashi et al. have demonstrated that TLR4-defective macrophages isolated from C3H/HeJ mice did not response to Hsp60 (Ohashi et al. 2000).

Human immunodeficiency virus (HIV)-infected patients are frequently associated with more severe form of psoriasis and refractory skin lesions (Mallon and Bunker 2000). Puig et al. has demonstrated intense expression of Hsp65 in psoriatic skins and lesions of AIDS-associated psoriasiform dermatitis (Puig et al. 1995). This study has suggested that immunodysregulation background in HIV-infected individuals may be associated with severity of psoriasis through modified or increased expression of Hsp65 in the skin (Puig et al. 1995).

21.10 Conclusions

Increasing evidence has indicated that Hsp60 is involved in pathogenic mechanisms of a broad spectrum of skin diseases. The data have shown that not only human Hsp60 but also its bacterial or microbial homologs (e.g., GroEL) play important roles in immune response and inflammatory cascade of these skin diseases.

In addition, Hsp60 expression is associated with severity of some diseases. Therefore, Hsp60 can be considered as a potential target for future development of a useful biomarker for diagnostics and prognostics in skin diseases. Moreover, it may also serve as a new therapeutic target for better treatment outcome.

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