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Significance of heat shock proteins in the skin upon UV exposure

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TABLE OF CONTENTS

1. ABSTRACT

The expression of heat shock proteins (Hsp) expression is induced in all cells by exposure to heat and other environmental stress and Hsp can protect cells from damage through further exposure. Hsp are highly conserved and it is likely that they are essential for survival in a potentially harmful environment. Most Hsp are molecular chaperones sensing unfolded proteins and mediating their re-folding, transport, and interaction. In human epidermis Hsp are associated with differentiation, photoprotection, and skin disease. Recent research has mainly focused on the 27kD and 72kD Hsp that are constitutively expressed in keratinocytes. Cell death induced by ultraviolet radiation (UV) can be inhibited by previous heat shock and UV itself can induce Hsp experimentally. Regulation of Hsp can be pharmacologically modified and topical and systemic inducers and inhibitors of Hsp expression are under development. Whether phototherapy exerts its clinical efficacy by modulation of Hsp has not been sufficiently studied. The UV-wavelength ranges, -intensities and -doses that are required to interfere with the heat shock response in the skin still remain to be elucidated.

2. INTRODUCTION

In 1962 the Italian genticist Ferruccio Ritossa incidentally observed a previously unseen puffing pattern in drosophila chromosomes that occured after exposure to heat (1, 2). This finding initiated further research resulting in the discovery of a broad and heterogeneous group of proteins, termed heat shock proteins (Hsp). It turned out that Hsp are expressed in all cells and organisms from prokaryotes up to higher mammals (3). Today Hsp are classified according to their molecular weight and knowledge as to their regulation of expression and function has accumulated. Not only elevated temperatures but also other forms of pathophysiological stress are able to induce the expression of Hsp and the cascade of molecular events that lead to increase in cellular Hsp is called the heat shock response. The heat shock response enables cells to resist damage from further stress exposure and the high evolutionary conservation of Hsp genes implicates that they are necessary for successful survival under hostile environmental conditions. Most Hsp function as molecular chaperones (polypeptide chain binding proteins) (4). Chaperones are defined by their ability to bind to other

proteins and mediate their folding, transport, and protein-protein interactions (5). Proteins that are denatured by any form of proteotoxic stress are cooperatively recognized by Hsp and directed for refolding or degradation. Under non-stressful conditions Hsp have important functions in cell physiology such as in transmembrane protein transport and in enabling assembly and folding of newly synthesized polypeptides.

Subsequent to stress exposure transcription of Hsp coding genes is specifically induced while at the same time general protein synthesis decreases. Hsp gene transcription is controlled by specific promoters (heat shock elements, hse) and under stressful conditions is initiated by proteotoxicity and the appearance of unfolded proteins (6). Specific transcription factors (heat shock transcription factors, hsf) are activated and bind to hse inducing transcription. The heat shock response is controlled by a feedback mechanism where members of the Hsp70 family bind to and inactivate hsf. Cells with increased levels of Hsp are protected from stress that would be otherwise lethal. This inducible cellular resistance was first described after heat shock and was thus called thermotolerance (7). The broader term stress response was introduced because in addition to heat a number of other stress conditions induces similar or identical reactions (8). The phenomenon is transient and not specific for the initiating event, i.e. hyperthermia can induce resistance against other stressors and vice versa. During proteotoxic stress partially denatured proteins expose hydrophobic sites that might lead to the formation of aggregates. Through their chaperone function Hsp inhibit aggregation and mediate refolding or degradation under consumption of ATP. At physiological conditions most Hsp are constitutively expressed at low levels and have important basic functions in the life cycle of proteins (9).

3. HEAT SHOCK PROTEINS IN HUMAN SKIN

The skin is a large protective organ which is constantly affected by many environmental stimuli such as heat and cold, UV, chemicals, and allergens. Hsp are assumed to be important for fundamental processes in cutaneous biology, including protection against UV-induced damage and wound healing and repair (10-13). In normal human skin some Hsp have been described to be constitutively expressed: Hsp27, 60, 70, 90, and 110 have been detected predominantly within the epidermis (14-19). Their levels are further induced by the various environmental stressors mentioned above including possibly also UV (20, 21).

Early evidence for the expression of Hsp27 in human skin came from investigations demonstrating the differentiation-related expression of an estrogen receptor-associated protein (ER-D5) in human keratinocytes; as was later demonstrated this protein is identical to Hsp27 (22). The expression of Hsp27 in human skin was subsequently investigated in normal skin as well as in epidermal tumors. Expression of Hsp27 was found to be highly associated with keratinocyte differentiation *in situ* and *in vitro* (14, 23). Low or absent expression is observed in basal keratinocytes with increasing Hsp27 expression as the cells differentiate and build up the upper layers of the epidermis. The protein is found in the cytoplasm near the Golgi complex and - after stimulation – is predominantly translocated into the nucleus (24). Basal cell carcinomas, squamous cell carcinomas and other malignancies arising from keratinocytes do not express significant amounts of Hsp27 (14).

Constitutive expression of Hsp70 in the skin is confined mainly to keratinocytes, with negative staining in melanocytes, fibroblasts, and other epidermal and dermal cells (25). Heat treatment of freshly biopsied human skin leads to a further induction of Hsp70 expression in epidermal keratinocytes and to de novo expression in all other dermal and epidermal cells. These results have been confirmed *in vitro* using transformed cell lines as well as normal human keratinocytes. Hsp70 has been detected in these cells at the protein as well as at the mRNA level and heat stress leads to a superinduction of Hsp70 (26). Similar results have been described in rodent skin (27-29).

At the molecular level it is assumed that epidermal Hsp serve specific functions that are essential for skin physiology. Hsp27 stabilizes the actin cytoskeleton and is involved in the regulation of cell growth and differentiation (24, 30). Its expression correlates with increasing epidermal differentiation in developing skin (31) and morphological and experimental evidence support the view of Hsp27 as a major chaperone of cornification (32, 33). It has been demonstrated that in addition to stress expression and phosphorylation Hsp27 is regulated by the inflammatory cytokines tumor necrosis factor alpha (TNF-alpha) and interleukin 1 (IL-1) suggesting a possible role for Hsp27 as a protective factor in inflammatory diseases (34, 35). With regard to its role in skin cancer it has been observed that overexpression of Hsp27 in a squamous cell derived cell line leads to inhibition of growth and tumorigenesis in nude mice (36).

Hsp70 is rapidly induced at wound sites in many tissues and is speculated to provide important functions in wound healing (12). Altered Hsp70 expression e.g. in diabetes may contribute to delayed healing (37). At the site of cutaneous wounds Bimoclomol, a “co-inducer” of Hsp improves healing (38). Furthermore, hyperthermia is able to inhibit ultraviolet B (UVB) induced cell death in murine and human keratinocytes (see below) (39). Constitutive and induced expression of Hsp70 is thus considered an inherent protective mechanism in epidermal cells and its overexpression is at least in part involved in heat-induced UVB resistance. This function of Hsp expression most likely is wavelength dependent, with only few data available for UVA compared to UVB (40).

Hsp are important targets of the immune response. Within the skin, the importance of Hsp is in part due to the presence of gamma/delta T cells in the epidermis, which are known to recognize and respond to antigenic portions of Hsp60 (41). It is speculated that infected/stressed keratinocytes expressing Hsp are recognized by these cells providing a primitive early

response and resulting in cytokine release and recruitment of more specific lymphocytes. The possibility of cross-reactivity between microbial and human Hsp leading to the development of autoimmune disease has been raised since Hsp of the pathogen and those of the host frequently share homologous epitopes (42).

Hsp90 is another heat shock protein that is expressed in the skin. It is involved in the activation of certain transcription factors, able to bind steroids, and required for maintenance of glucocorticoid receptor stability (43). Concerning the widespread use and clinical efficacy of topical corticosteroids in dermatology further understanding of Hsp-glucocorticoid receptor interactions could reveal new insights into disease pathology and improve our understanding of glucocorticoid action in the skin.

In summary, accumulating evidence indicates that Hsp in the skin are not only inherent means of protection from stressful situations. As in other organ systems Hsp through their abundance and functions in cell and tissue physiology are involved in the pathology of infectious, inflammatory, neoplastic, and hereditary conditions. Consequently, Hsp are increasingly recognized as targets of therapeutic intervention (see below) (44-46).

4. HEAT SHOCK PROTEINS IN SELECTED INFLAMMATORY SKIN DISEASES

In the following sections the current state of knowledge on the expression and possible role of Hsp in some common inflammatory skin diseases will be discussed. According to the focus of this review conditions have been selected that are related to photodermatology, i.e. they usually improve with UV-phototherapy and often also with exposure to natural sunlight.

4.1. Atopic Dermatitis

Atopic dermatitis (AD) is a chronic, genetically determined disease, with the involved genes and the pattern of inheritance not yet fully established. Multiple genes seem to be involved and many factors are known to contribute to or to trigger exacerbation of skin lesions in AD. Filaggrin a major protein component of mammalian epidermis, has been recently implicated in AD. Distribution and appearance of lesions varies with age and between individuals. Common clinical features are flares with inflamed, red, sometimes blistered and inevitably pruritic patches. Between flares skin may appear normal or suffer from chronic eczema with dry, thickened, itchy areas. Generalized erythroderma might be observed in patients with severe disease (47, 48).

Skin in AD is prone to receive many stressors such as mechanical injury from rubbing and scratching, attack from infection, allergens and chemicals, which are all potential inducers of Hsp. In addition many patients with AD experience improvement with UV and expose their skin to sunlight and phototherapy. Hsp70 and Hsp60 were found to be more intensely expressed in AD than in contact dermatitis and normal healthy skin. Constantly and relatively stronger expression of Hsp27 was observed in AD, but the pattern did not significantly vary from other eczematous skin diseases (49). Enhancement of Hsp70 and Hsp60 expression was not only confined to epidermal keratinocytes. Infiltrating lymphocytes, mainly CD4+ cells, were also strongly positive for Hsp70 and Hsp60. In contrast, Hsp was absent from dermal components such as sweat glands and hair follicles. Hsp expression in AD seemed to be neither related to age nor to sun exposure, suggesting other inducers for Hsp expression in AD skin lesions: Allergens, infection and chemicals including topical medication might induce expression of Hsp in AD. Furthermore, it is well known that cytokines are produced and released by keratinocytes and infiltrating lymphocytes in AD and these and other mediators of inflammation might induce Hsp expression. The other way round it is also possible that stress-induced Hsp expression may result in cytokine release from keratinocytes to exacerbate AD skin lesions (50). It has been shown experimentally that Hsp can induce the release of cytokines such as IL-2, IL-6, and TNF-alpha in cultured human keratinocytes (51). Cell surface expression has been described recently and its occurrance in AD suggests that extracellular Hsp might be accessible to keratinocytes and infiltrating lymphocytes (52). Production and release of cytokines may be induced by these accessible Hsp. Alternatively, cytotoxic T cells might be activated by Hsp overexpression in AD as it has been shown that CD4+ and CD8+ T-cells can be activated by Hsp60 resulting in secretion of TNF-alpha, interferon-gamma (IFN-gamma), and other cytokines (53). As bacterial infection is a frequent exacerbating factor in AD enhanced amounts of Hsp60 have been found. Bacterial Hsp60, which has homology with human mitrochondrial Hsp60, is produced by many bacteria probably resulting in cross-reactivity. Epidermal cells and infiltrating cells of AD lesions strongly express Hsp60 probably reflecting chronic stimulation of skin by environmental factors. Subsequently the gamma/delta T cell subset might be activated as has been described in animal models of bacterial infection (54).

4.2. Psoriasis

Psoriasis is a another common inflammatory skin disease that is characterized by abnormal epidermal differentiation, hyperproliferation of keratinocytes and accumulation of inflammatory cells resulting in inflamed skin lesions covered with silvery white scales. Etiology and pathogenesis of psoriasis are unknown. Complex hereditary mechanisms suggest that one or more primarily determined defects are present in psoriasis that predispose for the development of the disease (55). Histologically skin lesions are characterized by an abnormal pattern of keratinocyte growth and differentiation, alteration of the skin capillary network, and inflammation of both dermis and epidermis (56). Altered expression of several cytokines was correlated with the disordered cell proliferation in psoriasis (57, 58). Among others, altered levels of transforming growth factor (TGF)-beta, TGF-alpha, IL-1 and IFN-gamma and overexpression of epidermal growth factor (EGF) have been reported in psoriatic lesions (59, 60). These alterations can result in autocrine stimulation of epidermal cell proliferation, T cell activation, chemotaxis, and consequent inflammation of the skin.

In one study strong correlation of Hsp70 immunostaining with proliferative activity was observed in 12 cases of psoriatic skin (61). The localization of Hsp70 to the proliferative compartment of involved psoriatic skin is probably a response to stress factors intrinsic to psoriatic hyperproliferation. This hypothesis is supported by results from other disease models and organ systems (62, 63). Similar than in AD, the enhanced expression of Hsp70 and Hsp60 that has been described in psoriasis might also result either as a direct response to injury or occur as an effect of cytokines and other mediators of inflammation (64). According to recent evidence immunologic crossreaction to Hsp60 may be significant in patients with psoriasis. Strong antibody activity against 65kd and 48/45 doublet antigens from Mycobacterium tuberculosis has been found in 58% of psoriatic patients and 47% of these patients showed antibody activity to purified recombinant mycobacterial Hsp60. Hsp60 again stimulates cytotoxic CD4+ and CD8+ lymphocytes as well as natural killer cell activity that lyse specific targets *in vitro* in an antigen-specific MHC II-restricted manner. Furthermore, human epidermal cytokeratin1/2 shares a carboxy-terminal epitope with mycobacterial Hsp60 providing a basis for immunologic crossreactivity against a major structural epidermal protein (65, 66). Accordingly, epidermal cytokeratins might be among the possible targets for the autoimmune response that results in psoriasiform skin lesions.

Increased numbers of CD91+ cells which paralleled the development of new psoriatic lesions in a mouse model and in established psoriatic plaques compared with symptomless or healthy skin were observed. CD91, a cell surface receptor for various Hsp, was predominantly expressed by dermal dentritic antigen presenting cells (APC). The presence of keratinocytes expressing Hsp70 close to these CD91 expressing APC provides further evidence to suggest a functional involvement of Hsp through binding to the common Hsp receptor CD91 in the development of psoriatic lesions (67).

Many stressful agents can trigger psoriasis and simultaneously induce Hsp expression and thus explain the abundant levels of various Hsp found in psoriatic scales and psoriatic epidermis (68-70). One of these Hsp-inducing agents might be the lipophilic yeast Malassezia furfur, a saprophyte of the normal human cutaneous flora (71). It is associated with several skin diseases such as Malassezia folliculitis, seborrhoic dermatitis, and probably also with atopic dermatitis, and psoriasis. M. furfur has a special need for exogenous fatty acids and this is probably the cause for its prevalence on skin with high sebum production such as the scalp (72). Accordingly, M. furfur has been not only associated with common dandruff but also with the triggering of psoriatic scalp lesions (73, 74). M. furfur has been described to induce Hsp70 expression in human keratinocytes and Hsp70 levels are higher in M. furfur positive psoriatic skin than in M. furfur negative (75).

It can be assumed, that skin Hsp in psoriasis are also influenced by therapy although this has not been systematically studied to date. A possible example are analogues of the steroid hormone 1,25 dihydroxyvitamin D3 that are widely used in topical treatment of psoriasis (76): 7-dehydrocholesterol, a precursor of vitamin D3, has been shown to induce Hsp expression in keratinocytes and increase their resistance to UV (77). Although this hypothesis has not been investigated in clinical or experimental trials it is thus well possible that the beneficial effects of vitamin D3 analogues and UV in psoriasis are related to their Hsp modifying effects.

4.3. Graft-versus-host disease

Most recipients of an allogeneic stem cell/ bone marrow transplantation experience some degree of acute graft-versus-host disease (GVHD) after transplantation. This severe reaction is defined as a rapidly progressing systemic illness characterized by immunosupression and tissue injury in various organs such as the liver, skin and intestinal mucosa. Cell destruction in this areas results in rush, mucosal denudation, subsequent diarrhea and biliary stasis (78).

Apoptosis is considered to be a characteristic feature in the pathology of acute GVHD and Hsp70 and other Hsp are well known to interfere with the apoptotic program thus prolonging cell survival (79-82). Extensive apoptosis of epidermal cells in acute phase of GVHD induces bullous skin lesions and interestingly the complete absence of Hsp70 was the most predominant finding in skin lesions of GVHD (83). In contrast, Hsp70 was moderately present in the skin lesions of Stevens-Johnson-Syndrome (that is also characterized by apoptotic keratinocytes) and other drug eruptions. The expression of another Hsp (Hsp27) was maintained in epidermis of GVHD. Immunohistological absence of Hsp70 in cutaneous lesions of GVHD may simply indicate the death of keratinocytes, but the observed presence of Hsp27 provides evidence to the contrary. Thus, one mechanism that facilitates or enhances cell death in GVHD might be downregulation of anti-apoptotic Hsp. It has been speculated that the overwhelming accumulation of damaged proteins in GVHD might exhaust chaperone capacity and eventually result in suppression of heat shock factor activation and subsequent suppression of Hsp gene transcription (84).

4.4. Lichen planus

Lichen planus (LP) is a relatively common inflammatory skin disease. Cell mediated immunity plays an important role in its pathology. In a study it was shown that similar to other inflammatory skin diseases the expression of Hsp60 in the basal, suprabasal, and superficial layers of cutaneous LP lesions was significantly higher than in healthy skin control biopsies (85, 86). In contrast, Hsp70 expression was significantly decreased in the basal layers but not in the suprabasal and superficial layers of LP lesions compared with normal human skin in the study mentioned above (85). As described above suppression of the induction of Hsp70 will result in increased apoptosis of epidermal cells. The lower Hsp70 level in LP demonstrated in this study might suggest the loss of the protective function of Hsp70 against apoptosis, which is a prominent finding in the pathology of LP.

Whether these findings are primarily involved in the pathogenesis of LP or only reflect secondary reactive changes induced by inflammation is again unknown and has to be determined in further investigations. Furthermore, the already described cross-reactivity between Hsp60 and human suprabasal cytokeratins might lead to the speculation that also in LP epidermal cytokeratins might serve as a possible immunological targets (65). It could be further speculated that the T-lymphocyte infiltration in the epidermis in LP is induced by cell-mediated immunity to microbial agents associated with LP (e.g. hepatitis C virus). Hsp may be upregulated by cytokines in the adjacent basal keratinocytes. If a patient is predisposed to react to Hsp by certain HLA antigens a cytotoxic T-lymphocyte response targeting basal keratinocytes and resulting in tissue destruction might develop (85). However, it is also possible that the upregulated expression of Hsp60 might reflect a physiological, protective response to cell injury (87).

5. HEAT SHOCK PROTEINS AND PHOTOBIOLOGY

5.1. Heat shock proteins and UV induced cell death

Heat induced inhibition of UVB induced cell death has been found in culture and *in situ* in murine as well as in human skin (10, 28, 39, 88, 89). Kinetic studies indicate that this effect parallels Hsp expression: With keratinocytes in culture maximal effects were observed when the recovery period between heat and UVB was about 6 h and the protective effect disappeared beyond 12h after heat treatment (39). It has been found that inhibition of protein and mRNA synthesis as well as specific inhibition of Hsp70 block the development of heat-induced UVB tolerance (90). Furthermore, constitutive and heat induced expression of Hsp70 in an epidermal cell line was inhibited by a Hsp-inhibiting bioflavonoid (quercetin) as well as by a specific antisense oligo-DNA. The cell damaging effect of UVB was enhanced by both treatments indicating that constitutive expression of Hsp70 is an inherent protective mechanism in epidermal cells, and overexpression of Hsp70 is at least in part involved in heat induced UVB resistance. Overexpression by gene transfer instead of inhibition of protein synthesis was used by another group to investigate the role of Hsp70 in UVB tolerance (90). A murine fibrosarcoma cell line stably transfected with a Hsp70 expression vector was significantly more resistant to UVB than mock transfected control cells. Formation of sunburn cells (SBC), resembling UV induced apoptotic epidermal keratinocytes, was used as an endpoint in a mouse study (28). The number of SBC in heat treated skin (41°C, 3h) was significantly reduced compared to a sham control. These results were later also confirmed in human skin (26). The role of Hsp27, another major epidermal Hsp, in the response to UV is less clear: overexpression of Hsp27 in the squamous carcinoma cell line A431 does not protect cells from UVA and UVB induced death (36, 91).

SBC formation is the result of a p53 dependent apoptotic pathway aiming to eliminate aberrant, irreversibly damaged keratinocytes (92). Thus the question arises whether inhibition of UV induced cell death by Hsp overexpression is beneficial for the host or might impair cancer surveillance. The inhibitory effect of hyperthermia on SBC formation could be interpreted by a protective as well as by a potentially harmful mechanism: The effect of hyperthermia might protect cells from UV-induced DNA damage and thus prevent keratinocytes from entering apoptosis. On the other hand, heat induced inhibition of a DNA surveillance pathway involving p53 might result in the survival of cells carrying mutations that may give rise to the onset of skin cancer. This hypothesis is support by the fact that Hsp are able to interfere with various steps of the molecular pathways of apoptosis, including p53 (82, 93). On the other hand, considering the general protective function of Hsp it has been speculated that Hsp might enhance repair efficiency after UV exposure due to stabilization of components of the repair complex. This hypothesis has found some experimental evidence from experimental studies that indicate improved DNA-repair after heat shock (94, 95). However, evidence to the contrary exists and the issue is not yet finally solved (96).

The results described above have been mainly obtained with UVB. Less information is available on the influence of heat shock and Hsp on UVA-induced effects. Preliminary data and unpublished observations from our group indicate that the inhibitory effect of heat shock on UVA-induced cell death is cell type specific, e.g. can be observed in the squamous cell carcinoma cell line A431 but not in fibroblasts, and might be associated with inhibition of oxidative damage (unpublished data).

5.2. UV and the induction of heat shock proteins

As UV from the sun is among the most important potentially harmful environmental factors and UV-phototherapy is widely used for the treatment of the above mentioned and other skin diseases it seems reasonable to question whether UV itself modifies Hsp expression. As with other environmental hazards it might be assumed that exposure at low doses might induce a heat shock response with a subsequent rise in resistance against further irradiation damage. However, this concept still awaits confirmation. In mouse epidermis and in human keratinocytes in culture transient increases in Hsp70 mRNA were related to UVB exposure (11, 29, 97). Furthermore, low levels of Hsp70 immunoreactivity have been detected in skin biopsies by immunofluorescence 12h after exposure to UVB and 8-methoxypsoralen plus UVA (98). In another study it was found that in cultured keratinocytes upon exposure to UVB hsf was activated followed by detectable synthesis of Hsp70 mRNA and protein (11). Furthermore, UVA has been shown to be able to induce Hsp70 mRNA and protein expression as well as of heme oxygenase (HO-1, Hsp32), an antioxidative protein that has been grouped by some authors into the Hsp-family (99). Oxidative damage seems to be the trigger signal for Hsp induction upon UVA (100). For Hsp70 the induction in fibrosarcoma cells by UVA was about 1/10 of the amount that could be found after heat shock and increased resistance to subsequent UVB exposure was not observed in these cells (101). In another study pretreatment with low-dose UVB did neither induce thermotolerance nor resistance to subsequent high-dose UVB (10). As is true for

many other areas in photobiology, the wide variety of experimental models, radiation sources, dose levels, and monitoring devices used in the various studies does not allow to reach consistent conclusions. Thus, the questions whether, to what extent, and under which circumstances UV itself induces Hsp and whether these Hsp play a role in mediating increased resistance to further damage by UV have not been conclusively answered.

6. STRATEGIES FOR THERAPEUTICAL MODIFICATION OF HEAT SHOCK PROTEIN EXPRESSION

Pharmacological manipulation of Hsp expression appears as a promising new approach for the treatment and prevention of acute and chronic conditions, including skin diseases and acute and chronic photodamage (44, 46). As most Hsp inducing agents are inherently toxic, they appear not appropriate for therapeutic purposes. However, molecules have been recently identified which with a well established favorable side effect profile in humans such as aspirin or indomethacin (102, 103) which at clinically relevant concentrations are able to induce the enhanced transcription of heat shock genes. Furthermore, some anti-inflammatory prostaglandins can induce Hsp70 synthesis in experimental systems for extend periods (12-24h) in the absence of apparent cytotoxicity (104). From the evidence described above, protection from photodamage and prevention/repair of intrinsic and extrinsic skin aging appear to be the most promising fields of application for Hsp inducing agents (38). One of the open questions associated with the therapeutical use of Hsp inducing agents relates to the feasibility of repeated application since repeated use might lead to adaptation, attenuation of the heat shock response, and abrogation of the Hsp-inducing effect. A recently published study addressed this question in a model using cultured human keratinocytes. It was found that daily exposure to hyperthermia or a Hsp-inducing prostaglandin (15-deoxy-Δ12,14-prostaglandin J2) over a period of 4 days did not result in additional cytotoxicity and was accompanied by maintenance of both, Hsp70 induction and stress tolerance (105). These data provide further initial support for the development of non-toxic Hsp-inducers that can be repeatedly applied without loss of effect. Further studies should focus on the effect of the currently used phototerapeutic regimens on Hsp levels in diseased and normal skin including the combination of Hsp-modifying agents with phototherapy.

7. PERSPECTIVE

Considering the high protein concentration within the cell, formation of pathological aggregates is a permanent threat and molecular chaperones including Hsp have evolved to avoid these “sticky situations”. It is highly likely and there is accumulating evidence that in the skin these chaperones are important to cope with one of the most abundant environmental stress factors, namely solar UV. In addition, epidermal Hsp are involved in keratinocyte physiology and various inflammatory skin diseases are characterized by induction and – more rarely – also by reduced expression of specific Hsp family members. At least under experimental conditions and rather likely also *in vivo* UV itself can induce the expression of Hsp in the skin. Among the many open questions that await further investigation are UV-wavelength and dose dependence of Hsp modifying effects, tissue specificity, and interference with other cellular responses to UV such as DNA-damage and repair, mutagenesis, apoptosis, and cancerogenesis. Thus, much more research is currently needed to fully understand the specific interaction of UV with the heat shock response and the various pathways of protein degradation and repair before the knowledge gained from basic science can be translated into clinically applicable treatment protocols.

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Abbreviations: AD: atopic dermatitis, EGF: epidermal growth factor, GVHD: graft-versus-host disease, Hsp: heat shock protein, IFN: interferon, IL: interleukin, LP: lichen planus, SBC: sunburn cell, TGF: transforming growth factor, TNF-alpha: tumor necrosis factor, UV: ultraviolet radiation

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