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Role of Serum Heat Shock Protein 70 (HSP70) in Patients with Alopecia Areata

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Abstract

Background: An immune-mediated assault on hair follicles causes non-scarring hair loss in alopecia areata (AA), a common autoimmune condition. Numerous autoimmune and inflammatory diseases have been linked to heat shock protein 70 (HSP70), a molecular chaperone involved in immune regulation and cellular stress response. Recent research has also shown a possible connection between sensorineural hearing loss (SNHL) and autoimmune illnesses, maybe as a result of similar pathogenic pathways involving inflammation and immunological dysregulation. Aim: To review the relation between HSP70 and AA. Data Sources: Medline databases (Pub Med and Medscape) were searched and analysed in order to find research that examined the function of HSP70 in AA that were published up to 2024. Study Selection: Every study was evaluated for inclusion on its own. If they met the following requirements, they were accepted: 1. English-language writing and publication. 2. Printed in journals with peer review. 3. Examine the involvement of HSP70 in AA. Data Extraction: Studies were eliminated if they failed to meet the requirements for inclusion. Whether ethical permission was obtained, eligibility requirements were stated, suitable controls were used, sufficient information was provided, and evaluation metrics were clearly established were all taken into consideration when evaluating the quality of the study. To gather information on the research results we were interested in, data from every eligible study was separately abstracted using a data collecting form. Results: HSP70 may be a prognostic biomarker for AA, showing a correlation with the length of the illness but not its severity. There may be a connection between AA and hearing impairment, which might be caused by processes involving melanocytes.

Key words: Alopecia areata, heat shock protein 70, hearing sensitivity.

1. Introduction

Alopecia areata (AA) is a chronic, immune-mediated condition that results in the loss of hair from the scalp and other body areas. It is characterized by the infiltration of immune cells, particularly T lymphocytes, around hair follicles, leading to their dysfunction and subsequent hair loss (1). While AA is primarily considered a dermatological disorder, emerging evidence suggests that it may have systemic implications, including associations with other autoimmune conditions and potential extra-cutaneous manifestations. Among these, auditory dysfunction has been increasingly reported in patients with AA, raising questions about shared pathogenic mechanisms involving immune dysregulation and inflammation (2).

Heat shock protein 70 (HSP70) is a highly conserved molecular chaperone that plays a critical role in cellular stress responses, protein folding and immune modulation. Elevated levels of HSP70 have been observed in various autoimmune and inflammatory diseases, where it may act as a double-edged sword—protecting cells from stress while also potentially exacerbating immune responses. In AA, the role of HSP70 remains underexplored, particularly in the context of systemic inflammation and its potential impact on other organ systems, such as the auditory system (3).

Sensorineural hearing loss (SNHL) has been reported in some autoimmune disorders, possibly due to immune-mediated damage to the cochlea or auditory pathways. Given the autoimmune nature of AA, it is plausible that similar mechanisms could contribute to hearing impairment in affected individuals. However, the relationship between AA, HSP70 levels, and hearing sensitivity has not been thoroughly investigated (4).

2. Materials and methods

Data Sources: By searching and reviewing Medline databases (Pub Med and Medscape) and looking for studies that reviewed HSP70 role in AA available till 2024.

Study Selection: Every study was evaluated separately before being included. If they met the following requirements, they were accepted: 1. English-language writing and publication. 2. Printed in journals with peer review. 3. Examine the involvement of HSP70 in AA.

Data Extraction: The studies were eliminated if they failed to meet the inclusion requirements. Whether ethical permission was obtained, eligibility requirements were stated, suitable controls were used, sufficient information was provided, and evaluation metrics were clearly established were all taken into consideration when evaluating the quality of the study. To gather information on the research results we were

interested in, data from every eligible study was separately abstracted using a data collecting form.

3. Review of literature

AA is a complex autoimmune disorder characterized by the sudden onset of patchy or complete hair loss. The pathogenesis of AA involves a combination of genetic, immunological, and environmental factors that disrupt the normal hair growth cycle and lead to hair follicle damage. Central to the disease is the collapse of immune privilege in the hair follicle, which normally protects it from immune attack. This breakdown allows immune cells, particularly T lymphocytes, to infiltrate the hair follicle and trigger an inflammatory response, ultimately resulting in hair loss (5).

Immunopathogenesis of alopecia areata

The immune privilege of hair follicles is maintained by the local expression of immunosuppressive molecules, such as transforming growth factor-beta (TGF-β) and indoleamine 2,3-dioxygenase (IDO), which inhibit immune cell activation. In AA, this immune privilege is lost, possibly due to genetic predisposition, environmental triggers, or stress. The loss of immune privilege exposes hair follicle antigens to the immune system, leading to the activation of autoreactive T cells. cluster of differentiation 8 (CD8)+ cytotoxic T cells are the primary effector cells in AA, infiltrating the hair follicle bulb and targeting keratinocytes in the hair matrix. This immune attack disrupts the normal hair growth cycle, pushing hair follicles into the telogen (resting) phase and preventing their re-entry into the anagen (growth) phase (6).

Role of Oxidative Stress

Another element that contributes to the pathophysiology of AA is oxidative stress. AA patients have been shown to have lower antioxidant defenses and higher levels of reactive oxygen species (ROS), which may cause cellular damage and additional immunological activation. In addition to contributing to the degeneration of hair follicle cells, oxidative stress may intensify the inflammatory response. The autoimmune assault on hair follicles is sustained by a vicious loop that is created by the interaction of oxidative stress, immunological dysregulation, and hereditary vulnerability. (7).

Role of Genetic Factors

Genetic factors play a significant role in the pathogenesis of AA, with several susceptibility genes identified, particularly those involved in immune regulation. Major histocompatibility complex (MHC) genes, such as human leukocyte antigen – DR isotype and human leukocyte antigen – DQ isotype HLA-DQ, are strongly associated with AA, highlighting the importance of immune dysregulation in the disease (8). Other genes implicated in AA include those involved in cytokine signaling, such as interleukin-2 (IL-2) and its receptor (IL-2R), as well as genes related to T cell activation and function. These genetic predispositions, combined with environmental triggers like viral infections, stress, or trauma, can initiate or exacerbate the autoimmune response in susceptible individuals (9).

Role of cytokines and chemokines

In AA, cytokines and chemokines play a crucial role in mediating the inflammatory response. Increased levels of pro-inflammatory cytokines, including interleukin-15 (IL-15), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ), are seen in the hair follicle microenvironment in AA. By encouraging immune cell recruitment and activation, these cytokines intensify the inflammatory response (10). In particular, IFN-γ is essential for the pathophysiology of AA because it increases the expression of MHC classes I and II in hair follicles, which increases their visibility to immune cells. The cycle of inflammation and hair loss is further prolonged by IFN-γ, which also causes the synthesis of chemokines like C-X-C motif chemokine ligand 10 (CXCL10), which draw T cells to the hair follicle. (11).

Role of HSP70 in alopecia areata

A highly conserved molecular chaperone, HSP70 is essential for immunological control, protein folding, and cellular stress responses. HSP70 has been identified as a possible important contributor to the pathophysiology of AA, an autoimmune illness marked by immune-mediated hair loss. It is a molecule of interest in comprehending the intricate processes underpinning AA because of its dual function in regulating immune responses and shielding cells from stress. (12).

HSP70 and immune regulation in AA

HSP70 is known to interact with the immune system in various ways, influencing both innate and adaptive immune responses. In AA, the immune system mistakenly targets hair follicles, leading to their destruction and subsequent hair loss. HSP70 may contribute to this process by acting as an autoantigen, triggering immune responses that exacerbate the autoimmune attack. Studies have shown that HSP70 can be released from stressed or damaged cells, where it may be recognized by immune cells as a danger signal. This recognition can activate dendritic cells and other antigen-presenting cells, leading to the activation of autoreactive T cells, particularly CD8+ cytotoxic T cells, which are central to the destruction of hair follicles in AA (13).

Additionally, HSP70 has been implicated in the regulation of pro-inflammatory cytokines, such as IFN-γ and TNF-α, which are elevated in AA. These cytokines play a critical role in perpetuating the

inflammatory response in the hair follicle microenvironment. By modulating cytokine production, HSP70 may influence the severity and progression of AA. Furthermore, HSP70 can interact with regulatory T cells (Tregs), which are essential for maintaining immune tolerance. Dysregulation of Treg function is thought to contribute to the loss of immune privilege in hair follicles, a hallmark of AA. HSP70's role in Treg modulation may therefore be a key factor in the disease's pathogenesis (14).

HSP70 and oxidative stress in AA

Hair follicles in AA are subjected to significant oxidative stress, which contributes to their damage and dysfunction. HSP70 is a critical component of the cellular stress response, helping to protect cells from oxidative damage by stabilizing proteins and preventing apoptosis. In AA, the upregulation of HSP70 in response to oxidative stress may initially serve a protective role, attempting to preserve hair follicle integrity. However, chronic stress and sustained HSP70 expression could lead to maladaptive responses, including the activation of inflammatory pathways and immune dysregulation (15).

HSP70 as a potential biomarker and therapeutic target

Given its involvement in immune regulation and stress responses, HSP70 has been proposed as a potential biomarker for AA. Elevated levels of HSP70 in serum or tissue samples could indicate ongoing immune activation and oxidative stress, providing insights into disease activity and severity (12). Moreover, targeting HSP70 therapeutically may offer new avenues for treating AA. For example, modulating HSP70 expression or activity could help restore immune tolerance, reduce inflammation, and protect hair follicles from oxidative damage. However, the dual nature of HSP70—acting as both a protective and pathogenic molecule—complicates its therapeutic targeting, necessitating further research to fully understand its role in AA (16).

Alopecia areata and sensory neural hearing loss

Both AA and SNHL are thought to involve autoimmune processes, where the immune system mistakenly targets self-tissues—hair follicles in AA and cochlear structures in SNHL. In AA, the collapse of immune privilege in hair follicles allows autoreactive T cells, particularly CD8+ cytotoxic T cells, to infiltrate and damage the follicles. Similarly, in autoimmune SNHL, immune cells attack the inner ear, leading to inflammation and damage to the cochlea or auditory pathways (17).

Clinical Implications

The association between AA and SNHL, mediated by HSP70, highlights the systemic nature of autoimmune diseases and their potential to affect multiple organ systems. Patients with AA should be monitored for auditory dysfunction, particularly if they exhibit other autoimmune conditions or elevated markers of inflammation. Conversely, individuals with SNHL and a history of autoimmune disorders, including AA, may benefit from dermatological evaluation (18).

4.Conclusion

The results of the current review revealed that HSP70 can be a predictive biomarker for AA, correlating with disease duration but not with severity. There is a possible link between AA and auditory dysfunction, potentially mediated by melanocyte-related mechanisms.

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