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Citation

Azzawi, Soraya. 2019. Immune Privilege Collapse and Alopecia Development: Is Stress a Factor?. Doctoral dissertation, Harvard Medical School.

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Immune Privilege Collapse and Alopecia Development: Is Stress a Factor?

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ABSTRACT

Stress as a cause of hair loss has been the subject of anecdotally shared knowledge for decades; however, the molecular link underlying this process has yet to be fully elucidated. To protect against hair loss and to enable regeneration, the hair follicle is thought to enjoy immune privilege similar to select other regions of the body. A growing body of evidence suggests that collapse of this hair follicle immune privilege (HFIP) contributes to the pathogenesis of autoimmune hair loss disorders, including alopecia areata (AA) and lichen planopilaris (LPP). One possible trigger for the process of HFIP collapse in autoimmune hair loss is stress. This review appraises the current literature to shed light on molecular mechanisms for HFIP collapse that lead to hair loss, as well as role that neurogenic stress plays in triggering this process. While research in this field is still nascent, current evidence suggests that skin has its own system analogous to an “endocrine axis” that may be vulnerable to stress, which is one possible explanation bridging the link between stress and hair loss.

INTRODUCTION

Hair follicles coalesce to form one of the defining mammalian features, and serve as a hallmark of communication in human civilization. In a 1972 case that reached the highest echelon of the American judicial system, the Supreme Court, Justice William Douglas argued that jurors could attach racial prejudice to certain styles of hair growth and thus should be asked to disclose potential prejudices. Justice William Douglas observed, “Nothing is more indicative of the importance currently being attached to hair growth by the general populace than the barrage of cases reaching the courts evidencing the attempt by one segment of society to control the plumage of another.” Given the critical significance ascribed to hair in diverse social, religious, and political contexts, it is important to understand how hair follicles are maintained and how they ensure future proliferation.

A discussion of the mechanisms underlying autoimmune hair loss requires understanding the hair follicle (HF) and its cycle. The proximal HF continually cycles through alternating phases of growth (anagen), apoptosis-mediated regression (catagen), rest (telogen), and shedding

(exogen) [1, 2]. Within the isthmus at the insertion of the arrector pili lies the bulge region as depicted in Figure 1. It is thought that HF immune privilege (HFIP) aims to protect the bulge, which houses the epithelial HF stem cells (HFSC) that are essential to follicle regeneration [3–6].

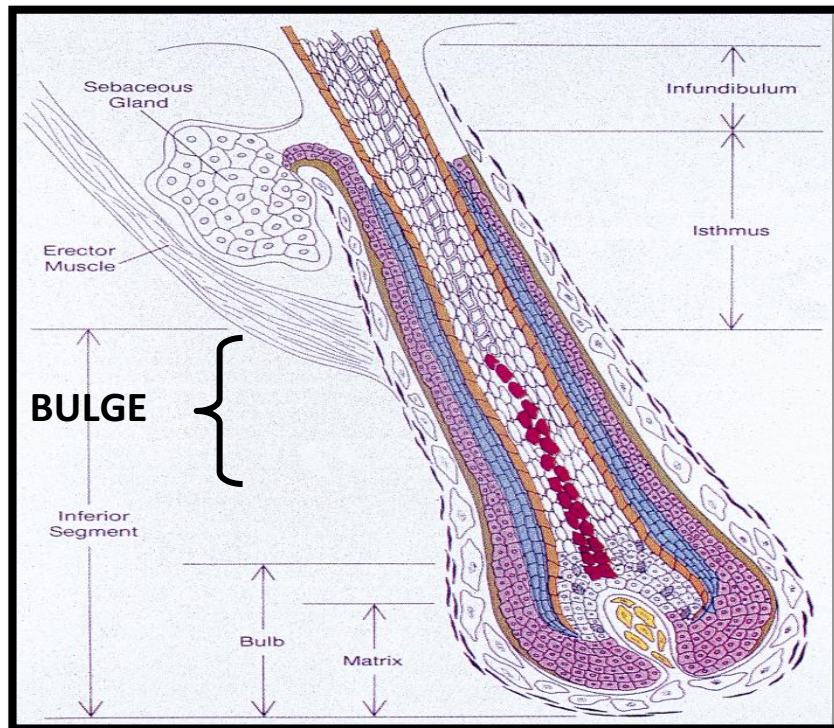


Figure 1: Hair Follicle Anatomy (Harries, Trueb et al. 2009) adapted from "Color Atlas of Differential Diagnosis of Hair Loss" by David Whiting MD., courtesy of Cranfield Publishing².

Alopecia is classified as cicatricial (scarring), which results in permanent hair loss, or noncicatricial, which preserves regenerative potential. This may be accounted for by varying locations of inflammatory processes. HFSC renewal is thought to be maintained in the upper portion of the follicle. Inflammatory processes associated with noncicatricial alopecias spare this fragile upper portion, permitting the possibility of hair regrowth.

This review will focus on two forms of hair loss: lichen planopilaris (LPP) and alopecia areata (AA). These disorders represent examples of cicatricial and noncicatricial hair loss, respectively. In LPP, activated T lymphocytes obliterate HFs, ultimately begetting irreversible hair loss. Clinical findings include follicular hyperkeratosis, perifollicular erythema and perifollicular scaling [3,6–9]. Women appear to be more frequently affected than men, and it is primarily observed in

postmenopausal females [10–12]. AA, a noncicatricial autoimmune alopecia, involves T-cell-mediated disruption of the HF cycle. Peritubular inflammation induces premature termination of the growth phase [13, 14]. Approximately 2% of the global population suffers from AA [15]. It can occur at any age, is frequently associated with other autoimmune conditions, and affects both sexes similarly [16]. Both LPP and AA have the potential to lead to extensive hair loss with significant psychosocial impact.

While the exact pathogenesis of LPP and AA remains unknown, evidence increasingly implicates HFIP collapse as a possible initial step [17]. This begs the question if an inciting event elicits collapse. One proposed factor is emotional stress. In soon to be published data, over 65% of AA patients in our clinic identify emotional stress as a trigger for initial AA episode or flare.

HAIR FOLLICLE IMMUNE PRIVILEGE

Over 140 years ago, it was observed that introducing tissue grafts to specific anatomical compartments enables prolonged survival, suggesting that certain sites are exempt from standard immune surveillance [18]. Prominent examples of immune privileged sites include the ocular anterior chamber, fetomaternal placental unit, and parts of the gonads. Immune privilege is a dynamic process maintained by several mechanisms that collude to limit recognition of foreign antigens, deviate immune responses to favor tolerance, and suppress immune-mediated inflammation [18–22].

One of the earliest observations of HFIP was reported when black murine ear epidermis was transplanted onto genetically incompatible white guinea pigs. Donor melanocytes were recognized as foreign and rejected, as evidenced by transplanted black skin rapidly losing pigment. However, black hair shafts grew through the white epidermis, indicating that some donor melanocytes could evade immune rejection [23–25].

UPHOLDERS OF IMMUNE PRIVILEGE

Several mechanisms that are believed to uphold HFIP are shown in Figure 2a, and are discussed in more detail below.

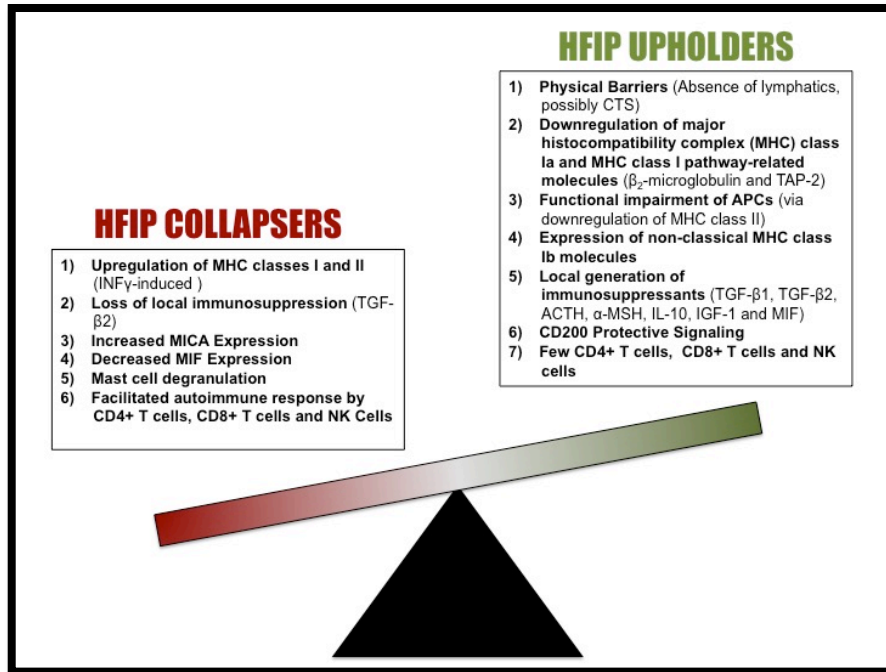


Figure 2a: Summary of proposed mechanisms maintaining and collapsing HFIP.

Impeding immune cell trafficking is one described mechanism of HFIP. The HF lacks lymphatic drainage [26]. The connective tissue sheath may serve a similar purpose, as it generates proteoglycans during anagen in rats, which are thought to guard against immune cell infiltration [27].

Expression of major histocompatibility complex classes (MHC Ia and II) is markedly reduced in the proximal follicular epithelium during anagen [28–30]. MHC-Ia is expressed on all nucleated cells, unless an IP-protected area, and functions to present antigens to cytotoxic CD8+ T cells [6]. Two related molecules, β_2 -microglobulin and TAP (transporter associated with antigen processing), are crucial for stabilization of MHC-Ia [31]. Absence of MHC-Ia and β_2 -microglobulin, and reduced expression of TAP-1 has been documented in murine HFs [32, 33]. In human proximal HFs, decreased MHC-Ia expression is observed at protein and transcriptional levels [2, 3, 28-30], and anagen bulb melanocytes lack MHC-Ia [28, 34]. Downregulation of the MHC-Ia pathway minimizes opportunities for misinterpretation of autoantigens, thus preventing possibly destructive immune responses. However, cells lacking MHC-Ia are susceptible to destruction by natural killer (NK) cells [35]. MHC class II, expressed predominantly on antigen presenting cells

(APCs), interacts with helper CD4⁺ T cells to engage phagocytes and trigger activation of antibody-producing B cells. Studies reveal total absence of MHC-II expression from the hair bulb and reduced expression in the proximal HF, which results in functional impairment of APCs [28, 36]. It is important to note that downregulation of MHC Ia and II was largely observed during anagen [2, 28]. Inflammatory assault against the bulge during anagen could thwart HF growth, and compromise regenerative capacity. In contrast, MHC-Ib expression may uphold HFIP [37].

Immunomodulation through local production of immunosuppressants also contributes to HFIP. Transforming growth factor- β (TGF β), a powerful immunosuppressive growth factor, has been demonstrated to impede APC activity and T-cell activation [38–40]. TGF β 1 expression is highest in the outer root sheath during late anagen [41]. Therefore, its major contribution to HFIP may be insulating autoantigens associated with anagen and/or melanogenesis from CD8⁺ T cell-mediated destruction [23, 42, 43]. TGF β 2 is expressed in the bulge region, where it is thought to help preserve melanocyte stem cell quiescence [44, 45]. Proopiomelanocortin-derived hormones, adrenocorticotrophic hormone and α -melanocyte stimulating hormone (α -MSH) act as powerful immunosuppressants [23, 46–48]. Interestingly, proopiomelanocortin gene transcription and translation exhibit an HF cycle-dependent pattern, rising during anagen in C57BL/6 mice and contributing to HFIP [49–51]. Adrenocorticotrophic hormone is detected in the outer root sheath of anagen follicles, while α -MSH is found in both the outer root sheath and hair matrix [46, 47, 52].

α -MSH is generated within the follicle and likely acts as an immunomodulator via its effects on APCs that express melanocortin receptor [47, 51, 53–55]. α -MSH suppresses NF κ B activation and upregulates cytokine synthesis inhibitor IL-10 [54, 55]. Insulin-like growth factor-1, a local immunomodulator, downregulates ectopic MHC-I expression, as do α -MSH and TGF β 1 [42]. Macrophage migration inhibitory factor (MIF) expression is increased in the proximal follicular epithelium compared to the distal follicle [6]. With a location near the vital eHFSC population, MIF is thought to contribute to HFIP via its immunomodulating properties and suppression of NK attack [35, 56, 57].

Another HFIP mechanism is “no danger” signaling via the type-1 transmembrane glycoprotein CD200, which is prominently expressed in the bulge region [3, 6, 58]. Interaction of CD200 and its receptor, CD200R significantly diminishes APC activity and secretion of

proinflammatory cytokines by activated T cells [59, 60]. CD200-CD200R interaction is thought to promote tolerance and prevent autoimmunity within the HF [61].

The immune cell milieu, or lack thereof, protects against HFIP collapse. In human HFs, CD4+ and CD8+ T cells are localized primarily to the distal epithelium and connective tissue sheath [2]. No intraepithelial T cells have been appreciated in the hair bulb [28]. Regulatory T cells are postulated to preserve IP regions by promoting tolerance, although this has yet to be observed in the HF [42]. As mentioned, NK cells target MHC-I-negative cells (such as melanocytes), raising a question about how the proximal follicular epithelium is spared from NK attack. Firstly, NK cells within the follicle are scarce and exclusive to the distal HF [28]. Previously noted IP mechanisms (expression of nonclassical MHC molecules, production of local immunomodulators) may also contribute to NK inhibition [6, 35, 56, 62]. Additionally, killer cell Ig-like receptors, which are essential to preventing NK cell-mediated destruction of MHC-I cells, are demonstrated at high levels in the HF [35]. By a combination of these mechanisms, the MHC-I-negative HF epithelium is exempt from NK cell destruction.

COLLAPERS OF IMMUNE PRIVILEGE

Collapse of mechanisms that maintain HFIP renders the HF susceptible to inflammatory assault. When subjected to immune attack, the hair growth cycle may adjust to enable follicle rehabilitation. Hair shaft proliferation might even persist, albeit inadequately, throughout the inflammatory response. Alternatively, collapse of immune privilege may engender HF destruction, which is one proposed mechanism for the pathogenesis of certain alopecias.

Collapse of immune privilege can be characterized by upregulation of MHC-I and -II expression. Growing evidence implicates the proinflammatory cytokine interferon- γ (IFN γ) in triggering HFIP collapse and ensuing immune-mediated eHFSC damage by enhancing expression of MHC I and II [6, 30, 63]. In AA, it has been proposed that greater expression of MHC-I may facilitate autoimmune attack by CD8+ T cells [64]. Compared to other cytokines believed to induce MHC-I (i.e., IL-1 β , TNF- α), IFN γ has been shown to act as a robust upregulator of MHC-I in vivo in anagen hair bulbs from murine back skin [30, 33]. Furthermore, Ito and colleagues treated human scalp HFs with IFN γ ; minimal doses were sufficient to trigger ectopic MHC class 1

expression, and higher doses led to premature induction of catagen in vitro [3].

Not only does IFN γ appear to compromise HFIP, it also directly threatens the eHFSC population [23, 30, 33, 35, 43, 65]. Keratin 15, β_1 -integrin and CD200, all reliable eHFSC markers, are markedly reduced following IFN γ stimulation [2, 58, 63, 66, 67]. Furthermore, LPP bulge cells have diminished expression of keratin 15, β_1 -integrin and CD200, inciting IFN γ as a possible mechanism for LPP permanent hair loss [2, 66]. LPP bulge epithelium also demonstrates reduced expression of the immunosuppressant TGF β [2]. Furthermore, deletion of CD200 in mice stimulates enormous perifollicular inflammation and scarring hair loss [60,61].

Mast cells induce cytotoxic CD8+ T cell proliferation [68]. Higher levels of degranulated mast cells and immature mast cell progenitors (cKit+ cells) are found in the LPP perifollicular infiltrate compared with controls [2]. Double staining reveals greater physical connection between mast cells and cytotoxic CD8+ T cells, suggesting that mast cell degranulation incites the immune response that ushers in HFIP collapse.

In recent years, NK cells have been studied for their potential role in HFIP collapse, particularly in AA. In healthy HFs, there is almost no expression of MHC class I chain-related A gene (MICA), a stress-induced ligand that activates NKG2D recognition receptors on NK and CD8+ T cells [30, 35, 69–76]. NKG2D has been implicated in other autoimmune diseases, including rheumatoid arthritis and type I diabetes [35, 77–79]. Lesional AA HFs demonstrate extensive MICA immunoreactivity, and are observed to be surrounded by NKG2D+ NK and CD8+T cells [35]. Abnormally increased MICA expression may facilitate HF attack via activated NKG2D+ cells, leading to compromise of the anagen phase and hair loss. HF damage in AA may also arise from impeded suppression of NK cells [2, 35]. Compared to controls, AA patients have a significantly greater percentage of NK cells that lack the inhibitory receptor KIR-2D2/2D3 [35]. Additionally, there is markedly decreased MIF immunoreactivity, which, as noted above, helps prevent NK attack [55].

COULD STRESS PLAY A ROLE?

Psychological stress has garnered increased attention as a possible contributor to autoimmune pathogenesis [80]. Stress is known to impact the immune system. Several studies

have observed that up to 80% of patients endorse a major psychological stressor preceding the onset of an autoimmune disease [81–83]. How stress relates to pathogenesis remains controversial, because while stress affects the immune system, autoimmune diseases in turn can also trigger stress [84, 85].

Psychological stress has been recognized as a trigger for AA [38, 86–91]. The association of stress and LPP is not as clear, although the oral variant of lichen planus has been linked with stress [92]. Oral lichen planus often occurs 1–2 weeks following an intense psychological stressor, and erosive disease has been shown to be associated with stress [93–95].

To better characterize the role of stress in hair loss, it is important to understand how skin responds to stress. The skin utilizes a system analogous to the hypothalamic-pituitary-adrenal (HPA) axis to confront a diversity of insults [96]. During periods of physical and psychological stress, the HPA axis is activated to secrete corticotropin-releasing hormone (CRH). CRH has been found in murine HFs, and the CRH gene is transcribed by the human hair bulb [96-100].

Mast Cell Degranulation and CRH

As mentioned, mast cell degranulation can lead to collapse of anagen HFIP. In human HFs, CRH has been shown to trigger production of mature mast cells from local precursors and promote degranulation, suggesting that the local HF neuroendocrine axis and the immune system are intertwined [101]. Acute stress can stimulate greater CRH expression in skin. During stressful situations that lead to CRH release, mast cells are vital to the regulation of neurogenic inflammation [101–108]. Researchers showed that sonic stress in mice triggers mast cell degranulation [109]. In mice lacking mast cells, sonic stress fails to induce the neurogenic inflammation and HF apoptosis that are observed in murine skin following a distressing sonic stimulus [101, 105]. In rats, acute stress has also been shown to increase the CRH skin [110, 111]. Therefore, both peripheral CRH and acute stress can trigger mast cell degranulation in the skin.

One possible mechanism for CRH influence on mast cells is stem cell factor, which is known to trigger mast cell differentiation, facilitate mast cell cytokine release, and impede mast cell apoptosis. In human HFs, CRH enhances stem cell factor transcription and translation, providing a possible link for CRH-induced mast cell degranulation [101, 102, 112].

Neurotrophins

Nerve growth factor (NGF), a broadly studied neurotrophin that has been noted in murine skin, plays a major role in stress responses [113-116]. Increased NGF release during stress is thought to facilitate catagen induction by activating the p75NTR receptor expressed on the outer root sheath [117-120]. Contrarily, NGF fails to elicit premature catagen when p75NTR is antagonized [117]. P75NTR directly triggers apoptosis of HF keratinocytes, as well as downregulates keratinocyte growth factor effects [121, 122]. Similar to CRH, NGF is known to stimulate mast cell degranulation, which may facilitate the neurogenic inflammation undermining HFIP [121, 123].

Substance P

Substance P (SP) is downstream of NGF. It is a neuropeptide that has been implicated in the stress response and is thought to be enhanced by NGF. Firstly, SP yields upregulation of MHC-I and β_2 -microglobulin, and stimulates ectopic MHC-I expression in the anagen HF [124]. Secondly, SP can activate perifollicular mast cells, leading to damaging intercutaneous neurogenic inflammation [124–126]. Thirdly, SP can stimulate growth factor cascades which favor catagen by selectively upregulating NGF and p75NTR [124]. Additionally, SP may stimulate murine mast cells to release $\text{TNF}\alpha$, which has been demonstrated to prevent hair growth and induce keratinocyte apoptosis [124, 127–130]. Interestingly, administration of systemic SP recapitulated sonic stress-induced apoptosis of murine HFs, whereas co-injecting a selective SP receptor antagonist prevented it.

Connecting Stress and Autoimmune Hair Loss

Taken together, these findings elucidate a plausible mechanism to connect stressful phenomenon with subsequent hair loss, summarized in Figure 2b. Psychological stress triggers the HF equivalent of the HPA axis, resulting in increased CRH secretion, which stimulates mast cell production and degranulation. The resulting neurogenic inflammation collapses HFIP and induces premature destruction of the follicle. To date, whether NGF and/or SP exist downstream of CRH is not well defined [131]. However, NGF can also act to trigger mast cell degranulation, either directly or possibly via SP.

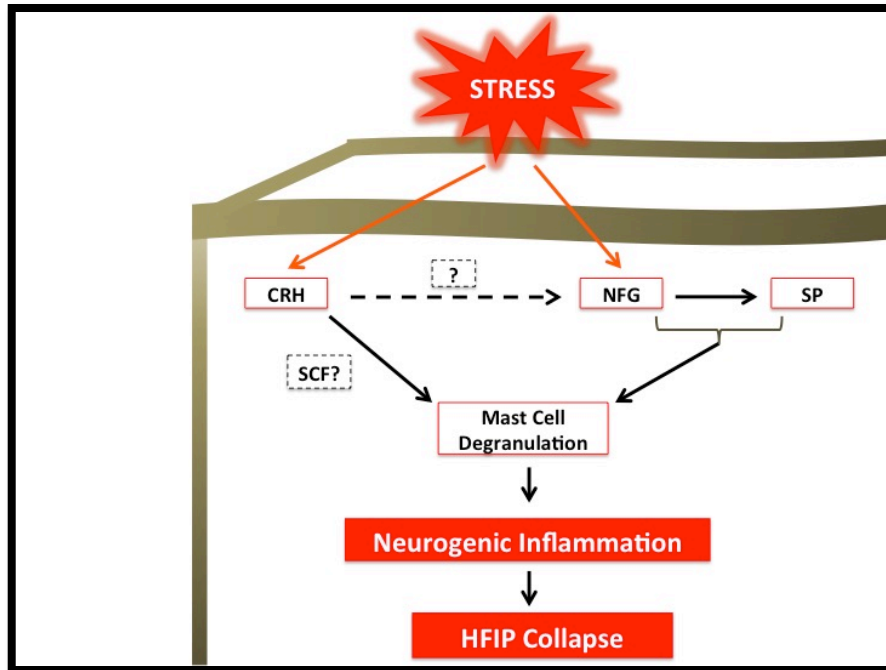


Figure 2b: *Potential connections between psychological stress and hair follicle*

CONCLUSIONS

Several mechanisms exist to protect the delicate HFSC population, collectively establishing HFIP to ensure the regenerative capacity of HFs. Collapse of HFIP is thought to contribute to the pathogenesis of autoimmune hair loss disorders. While both LPP and AA constitute examples of autoimmune hair loss, certain mechanisms may be more important for triggering HFIP collapse in one disease than the other.

Despite the complex etiology of autoimmune disease and the missing links in the relationship between psychological stress and hair loss, we conclude that psychological stress plays a key role in autoimmune hair loss. The skin features a local neuroendocrine axis enabling it to respond to stress. Increased activity of this HPA axis equivalent can promote neurogenic inflammation that facilitates HFIP loss.

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Appendix after References (Editorial Comments)

Legend(s)

Fig. 1. Hair follicle anatomy [8]. Adapted from *Color Atlas of Differential Diagnosis of Hair Loss* by David Whiting, courtesy of Cranfield Publishing.

Fig. 2. Immune privilege. **a** Summary of proposed mechanisms involved in the maintenance and collapse of hair follicle immune privilege (HFIP). **b** Proposed connections between neurogenic stress and HFIP collapse.