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Invited review article

Hair follicle is a target of stress hormone and autoimmune reactions

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ABSTRACT

Interest in the hair follicle (HF) has recently increased, yet the detailed mechanisms of HF function and immune privilege (IP) have not yet been elucidated. This review discusses the critical points of immunobiology and hormonal aspects of HFs. The HF is a unique mini-organ because it has its own immune system and hormonal milieu. In addition, the HF immune and hormonal systems may greatly affect skin immunobiology. Therefore, knowledge of HF immunobiology and hormonal aspects will lead to a better understanding of skin biology. The HF has a unique hair cycle (anagen, catagen and telogen) and contains stem cells in the bulge area. The HF is closely related to sebaceous glands and the nervous system. This article reviews the interaction between the endocrine/immune system and HFs, including the pathogenesis of alopecia areata associated with stress.

Contents

1. Introduction

The hair follicle (HF) is a very small but extremely unique mini-organ. The life cycle of the HF consists of anagen, the growth stage, followed by catagen, the regression stage, and telogen, the resting stage [1]. Each phase has its own unique immune milieu. The most intriguing feature of the HF life cycle is the HF immune privilege (HF-IP) that occurs in the anagen phase [2,3]. The endocrinology of the HF is involved in this immunosuppressive phenomenon. The HF is both a prominent target organ and a main source of hormones. Interestingly, the HF maintains its own peripheral functional equivalent of the hypothalamic–pituitary–adrenal (HPA) axis. The most proximal element of this axis in the HF is stress hormone, corticotropin-releasing hormone (CRH) [4]. CRH induces mast-cell degranulation that may be a trigger for catagen change. Furthermore, the HF is an extramedullary reservoir for mast-cell precursors [5].

Autoimmune hair loss disease, alopecia areata (AA), is induced by the collapse of HF-IP. Therefore, reestablishment of the IP milieu would be a novel treatment for AA. The present article focuses on the interaction between the endocrine/immune system and the HF mini-organ, including the pathogenesis of AA associated with stress.

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2. The unique immune system of the hair follicle

2.1. Hair follicle immune privilege

Immune-privileged sites include the anterior eye chamber, parts of the testis and ovary, the adrenal cortex, segments of the central nervous system behind the blood–brain barrier, the fetomaternal placental unit and the hamster cheek pouch [2,3].

The specialized immune milieu of IP is needed to prevent destructive immune reactions in critical sites (Table 1). For example, severe inflammation of the anterior eye chamber could lead to blindness. An immune reaction in the central nervous system could cause serious damage to brain function. Through the maintenance of IP, the functional loss of critical sites is avoided. Although hair may be important for the mental well-being of some humans, hair is not necessary for human survival. However, for other mammals, such as polar bears, seals and reindeer, a huge loss of hair volume could be deadly.

Decades ago, it was discovered that hair follicles provide a special milieu that enables transplanted allogeneic cells to escape detection and elimination by the host immune system [6,7]. This concept of IP is supported by Billingham's pioneering experiments, in which some transplanted anagen hair bulbs survived in a genetically incompatible recipient [7,8]. When black ear skin epidermis was transplanted onto skin beds of genetically incompatible white guinea pigs, the transplant quickly lost its pigmentation, indicating that the allogeneic melanocytes were rejected. However, after a while, some black hair shafts penetrated the (now white) epidermis—indicating that at least some donor melanocytes had survived in the host anagen hair bulbs.

The HF-IP is maintained by several factors (Table 2), including the lack of major histocompatibility complex (MHC) class I in proximal outer root sheath (ORS) and matrix cells. Unlike the IP of other sites, HF-IP has the unique feature of recurring in a cyclic pattern. HF-IP occurs during anagen, but not during the regression phase (catagen) or the resting phase (telogen) of the hair cycle. Thus, HF-IP is restricted to the proximal epithelium of anagen HFs. During anagen, melanogenesis in the hair bulb is activated. It appears that HF melanocyte autoantigens play a key role as potential immune targets in one of the most common human autoimmune diseases, AA. Autoantibodies against melanocyte-associated autoantigen have long been identified in cases of alopecia areata [9,10]. Therefore, it is reasonable to expect that HF-IP occurs only during anagen in order to conceal the HF autoantigen, melanin-associated protein.

Table 1
The mechanisms of immune privilege.

- Absence of lymphatics
- Downregulation or absence of classical MHC class I expression
- Functional impairment of antigen-presenting cells
- Expression of non-classical MHC class I molecules (such as the MHC class Ib molecules HLA-G in humans and Qa-1 and Qa-2 in mice)
- Expression of Fas ligand (FasL, CD95L)
- Downmodulation or absence of appropriate co-stimulatory signals
- Local production of potent immunosuppressants such as TGF-β1 or TGF-β2, IL-10, CGRP, α-MSH, and MIF
- Induction of peripheral tolerance to IP tissue-derived antigens
- Establishment of extracellular matrix barriers
- Local downregulation of the level of tryptophan

Table 2
The mechanisms of hair follicle immune privilege.

- Absent or barely detectable expression of MHC class I
- Melanocytes of the hair follicle pigmentary unit of human anagen scalp hair follicles are MHC class I-negative
- Downregulation of the MHC class I pathway-related molecules β2-microglobulin and transporter of antigen processing-2 (TAP-2)
- Downregulation of interferon regulatory factor-1 expression
- Upregulation of immunosuppressants such as TGF-β1 and TGF-β2, ACTH, and α-MSH
- Absence of MHC class II+ or NLDC-145+ Langerhans cells
- Sparse distribution of CD4+ T cells, CD8+ T cells and NK cells
- Absence of lymphatics

2.2. Anagen-dependent immunosuppression

The HF immune condition likely affects the skin immune system. In the murine skin immune system, the hair cycle is prone to synchronization, and each hair cycle stage has a different immune state that changes the skin immune system. Depilation of hair shafts on the back of mice induces highly synchronized HF cycling with all hair follicles in telogen [11]. Most notably, the delayed-type hypersensitivity reaction (contact hypersensitivity, CHS) and photosensitivity are influenced by hair cycling in C57BL/6 and BALB/c mice [12,13]. Mice were sensitized on the skin of the lower back with picryl chloride between 0 and 25 days after anagen induction by depilation. Five days after sensitization, the mice were challenged with picryl chloride on their earlobes. If mice were sensitized when the back skin is in telogen, the earlobe challenge with the hapten induced vigorous ear swelling. However, the immune response was abrogated if sensitization was performed on synchronized depilation-induced anagen back skin [14]. This anagen-dependent suppression of type IV skin immune responses appears to be associated not only with local intracutaneous immunosuppression, but also with systemic immunosuppression. The mechanisms of this immunosuppression are still unclear. However, the level of tumor necrosis factor alpha (TNF-α) mRNA is markedly decreased and the level of interleukin-1 receptor antagonist (IL-1ra) mRNA is increased in epidermal cells from early anagen to telogen in mice [10,15]. Melanogenesis actively occurs during anagen, and melanin-associated protein is strongly speculated to be the HF autoantigen, especially in AA pathogenesis [9,16]. Therefore, anagen-dependent immunosuppression is reasonable to decrease autoreactivity during the anagen phase and to conceal autoantigen against autoreactive T cells.

2.3. Immunosuppressants and hair follicle immune privilege

HF-IP is maintained by several factors [Table 2]. Immunosuppressive hormones, such as adrenocorticotropic hormone (ACTH) and α-melanocyte-stimulating hormone (MSH), are key factors. Proopiomelanocortin (POMC)-derived peptides include ACTH, MSH and β-endorphin. POMC gene transcription and translation is hair-cycle dependent in the skin of C57BL/6 mice and increases significantly in anagen [17]. In normal skin, ACTH immunoreactivity is localized in ORS of anagen HFs and is not detected in the epidermis or dermis of corporal skin [18]. α-MSH is detected in ORS and hair matrix during anagen [19]. The concentration of ACTH significantly increases during depilation-induced anagen, as measured by radioimmunoassay [20]. In addition, ACTH stimulates intrafollicular cortisol generation [4].

Transforming growth factor (TGF)-β is one of the most potent immunosuppressive growth factors [21]. Interestingly, TGF-β1 immunoreactivity (IR) is prominently expressed in the HF epithelium of mice and humans, and it is strongest during late anagen and the onset of catagen in cells of the ORS and epithelial strand [22]. Therefore, in addition to ACTH, α-MSH, and cortisol, TGF-β1 may be involved in the maintenance of HF-IP. The main role of TGF-β1 may be to sequester anagen- and/or melanogenesis-associated autoantigens from immune recognition by autoreactive CD8+ T cells [2,10,23].

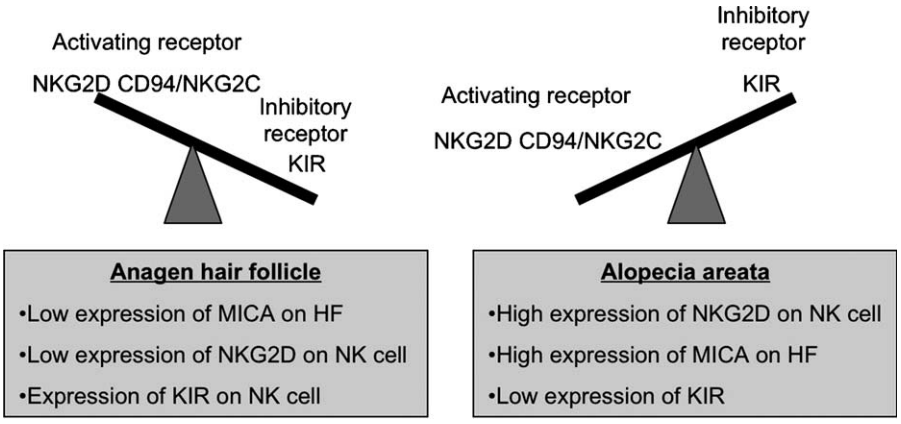

Fig. 1. Human anagen HFs largely lack MICA expression that inhibits recognition by NKG2D+ NK cells. NK cells highly express inhibitory receptor KIR in healthy control. On the other hand, both of infiltrating CD56+ NK cells and CD8+ T cells show prominent expression of the NK cell activating receptor, NKG2D in AA letion. This observation implies that the progression of AA is accelerated by an unknown stimulus that induces MICA expression on HFs, thus facilitating an attack of infiltrating NKG2D+ cells on MICA+ HFs.

2.4. Natural killer cells and hair follicle immune privilege

Natural killer (NK) cells have become an area of interest in AA research. The absence or low expression of MHC class I expression in the HF-IP system raises the question of how self/non-self discrimination and self-tolerance are maintained [24]. Normally, NK cells are primed to recognize and eliminate the cells with absence or low expression of MHC class I expression [25–31]. However, very few perifollicular NK cells are found around healthy human anagen HFs [32]. Because of this phenomenon, we speculate that HFs indeed inhibit or contain NK functions within tightly controlled limits of activity. NK cells express inhibitory receptors, such as Killer cell immunoglobulin (Ig)-like receptors (KIR) and heterodimeric CD94/NKG2A [33]. NK cell activation can be abrogated through interaction with inhibitory KIR (KIR-3DL2, KIR-3DL1, or KIR-2DL1-3) by phosphorylation of the immunoreceptor tyrosine inhibitory motif followed by binding to phosphatases, including SHP-1 and SHP-2, if target cells express MHC class I molecules [33,34]. Target cells lacking MHC class I expression (e.g., virally infected or significantly transformed cells) do not block NK cell activity and are activated by signals from activating receptors, such as NKG2D and CD94/NKG2C [35,36].

NKG2D is expressed not only in NK cells but also in CD8+ T cells. NKG2D recognizes MHC class I chain-related A gene (MICA) on target cells, and this recognition stimulates the immune cells to attack the target cells [35–40].

KIRs belong to the Ig superfamily and contain two or three Ig domains (represented as 2D or 3D) [41]. They can be further subdivided into inhibitory and stimulatory receptors. The inhibitory forms (KIR-3DL2, KIR-3DL1, KIR-2DL1-3) are longer (L) as denoted by the L in their names, and have intracellular immunoreceptor tyrosine inhibitory motifs (ITIMs) in the cytoplasmic domain [34,42–46]. The stimulatory receptors (KIR-2DS1 through KIR-2DS5 and KIR-3DS1), are shorter (as denoted by the S), lacking ITIM motifs, but contain the charged residue in the membrane comparable to the non-inhibitory forms of CD94/NKG2 [47].

Human anagen HFs *in situ* largely lack MICA expression, just like other healthy tissues [48–51]. In AA lesions, both infiltrating CD56+ NK cells and CD8+ T cells show prominent expression of the NK cell activating receptor, NKG2D. This observation implies that the progression of AA is accelerated by an unknown stimulus that induces MICA expression on HFs, thus facilitating an attack of infiltrating NKG2D+ cells on MICA+ HFs [48]. Furthermore, CD56+ NK cells and CD8+ T cells from the peripheral blood of AA patients have increased levels of NKG2D expression as compared to cells from normal controls and patients with other chronic inflammatory skin diseases, such as atopic dermatitis [48]. AA patients also have a significantly increased percentage of NK cells that do not express NK cell-inhibitory KIR-2D2/2D3, as compared to NK cells from healthy controls [48] [Fig. 1].

In summary, immune-privileged MHC class I-negative HFs are protected from NK cell attack *via* MICA-negative ORS, low expression of NKG2D on NK cells and inhibitory KIRs. The collapse of any of these mechanisms may induce AA.

However, conflicting data has been generated from an established mouse model of AA, in which lesional skin from older C3H/HeJ mice with AA is grafted onto young C3H/HeJ female mice. In this murine model, unexpectedly, the onset of hair loss in C3H/HeJ mice was accelerated with NK-cell depletion by continuous administration of rabbit anti-asialo GM1. The NK-cell depletion was accompanied by a significant increase in the number of perifollicular CD49b+ T cells in the alopecic skin of anti-asialo GM1-treated mice [52]. Careful studies of the roles of pure NK cells in the pathogenesis of AA are further needed.

2.5. Hair bulge and hair follicle immune privilege

The epithelial stem cell region, termed the bulge, also represents an area of relative IP. Like the immune-privileged anagen hair bulb, the CD200+ stem cell-rich bulge region is characterized by the downregulation of MHC class Ia, β2-microglobulin and MHC class II immunoreactivity and the upregulation of the immunosuppressants α-MSH, TGF-β2, MIF and indoleamine-2,3-dioxygenase (IDO). These CD200+ cells also coexpress human leukocyte antigen (HLA)-E. In addition, interferon-γ induces significant ectopic MHC class Ia expression in not only the proximal ORS but also the bulge cells of organ-cultured human scalp skin [53]. Bulge IP presumably protects the HF epithelial stem cell reservoir from autoaggressive immune attack, whereas a loss of bulge IP may play a central role in the pathogenesis of cicatricial alopecias. In the bulge region of AA lesional follicles from three cases of primary cicatricial alopecias, the expression levels of MHC classes I and II and β2-microglobulin are increased as compared with uninvolved follicles in each case.

The novel immunosuppressive molecule, CD200, induces immunoregulation after interaction with its receptor(s), CD200R, through the augmented induction of regulatory T-cell populations

and the increased expression of indoleamine-2,3-dioxygenase [54]. A 1.98-fold increase in CD200 was found in the bulge ORS as compared with the sub-bulge ORS, as determined by MASv5.0 analysis [55]. In addition, CD200 immunoreactivity is restricted to the outermost layer of the ORS between the arrector pili muscle insertion point and the level of the sebaceous gland, which corresponds to the bulge area [55]. Although it is still under consideration whether cicatricial alopecia is induced by an autoimmune reaction against hair follicle autoantigen, the collapse of epithelial hair-follicle stem cell IP may trigger primary cicatricial alopecia.

3. Stress hormone and the hair follicle hypothalamic–pituitary–adrenal axis

The most important role for skin is its role as the first-line guardian against stressors such as ultraviolet rays, mechanical energy, or chemical and biological insults. Emotional stress also challenges skin homeostasis, because atopic dermatitis, AA and several other skin diseases often worsen during periods of emotional stress. In order to maintain the systemic biological status, skin must respond to every type of stressor. Skin stressors are managed by an equivalent of the hypothalamic–pituitary–adrenal (HPA) axis that acts as a cutaneous defense system, which coordinates and executes the local responses to stress [56]. CRH is the key stress-induced hormone. The overstimulation of the HPA system and elevated secretion of hypothalamic CRH have been implicated in the pathology of depression [57–61]. Moreover, the hyperactivity of the CRH neuronal system normalizes following successful antidepressant treatment [62]. CRH, the most proximal element of the HPA axis, has been found in murine hair follicles, and its expression shows hair cycle-dependent changes [63]. CRH immunoreactivity was localized to keratinocytes of the basal epidermis, the ORS, and the matrix region of anagen HFs. The highest intensity stain occurred during anagen IV/VI, and the lowest levels were found in catagen and telogen HFs. In humans, immunoreactivity to CRH and CRH-R1 occurs throughout the ORS [64]. The melanin-producing HF melanocytes and selected amelanotic melanocytes of the proximal hair bulb are CRH-R1-negative [64]. In addition, the human hair bulb actually transcribes the CRH and CRH-R1 genes. The band generated with RNA derived from microdissected anagen hair bulbs is stronger than the band generated from the total scalp skin extracts, which suggests that most CRH transcripts in human scalp skin are actually located in the anagen hair bulb. Furthermore, the human HF has a fully functional peripheral equivalent to the classical HPA axis, and it may locally manage the peripheral stress response systems in the skin [4]. CRH treatment increases POMC transcription and immunoreactivity to POMC products in human HFs in vitro. Moreover, CRH stimulates cortisol secretion by organ-cultured human HFs that also possess feedback systems [4] [Fig. 2]. Of course, it is still unclear how emotional stress relates to the peripheral HF-HPA axis. However, several murine studies illustrate the association between emotional stress and skin reactions. For example, sound stress promotes premature catagen development in CBA/J mice [65]. In this model, stress exposure upregulates the protein expression of SP nerve fibers in the dermis, and NK1 receptor antagonist normalizes most stress-induced alterations. Emotional stress may affect the production of neural hormone from the peripheral nerve system, and this hormone modulates the HF-HPA axis to manage peripheral stress damage. Interestingly, sound stress also affects mast cells. Sonic stress significantly increases the number of degranulated (activated) mast cells in the dermis. Mast cells and the hair follicle immune system are closely related. In the next paragraph, the relationship between CRH and mast cells will be introduced.

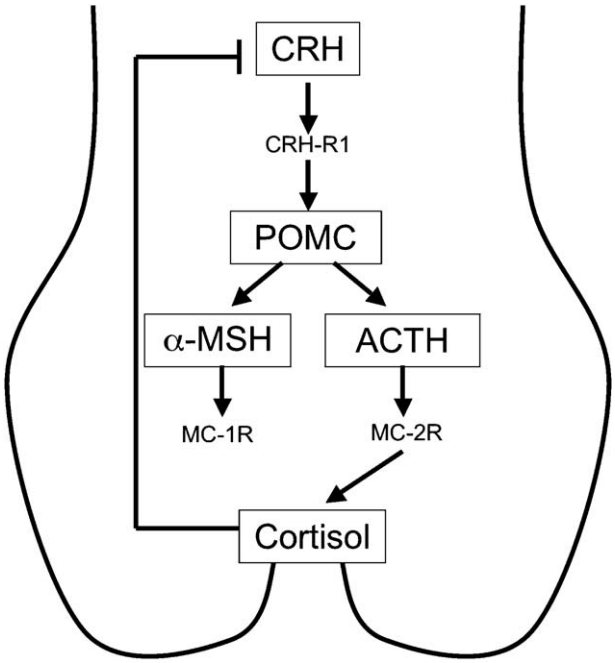

Fig. 2. Human anagen hair follicle maintain fully functional HPA axis and manage peripheral stress damage to protect hair follicles.

4. Stress hormone and hair follicle mast cells

Mast cells are distributed around HFs, and the murine hair cycle is largely associated with the degranulation of mast cells. Degranulated perifollicular mast cells significantly increase during late anagen VI just before the onset of catagen. Catagen development is retarded by the inhibition of mast cell degranulation [66]. Moreover, mast cell secretagogues, such as substance P, induce early catagen. Interestingly, we found that CRH induced mast cell degranulation in human HFs in vitro via SCF stimulation [67]. Hence, the HF immune system and hormone system may be tightly interconnected. We cultured human HFs (without the hair bulge area) with 10^{-7} M CRH. After 6 days, histochemically identifiable, strongly degranulated mast cells were found both in the HF connective tissue sheath (CTS) and the interfollicular dermal mast cells [5]. Surprisingly, the total number of toluidine blue/Giemsa-stained CTS mast cells was also significantly increased after 6 days of CRH treatment. Moreover, 3–4 times more cells with the typical morphology of mast cells could be detected by the c-kit tyramide signal amplification method as compared to toluidine blue staining, and CRH treatment further upregulated the number of c-kit-positive cells significantly. CRH treatment also significantly increased the number of tryptase+ cells in the CTS of organ-cultured human HFs. These organ culture results indicate that mature mast cells can arise from resident precursors in the connective tissue sheath of human scalp HFs, independent of continued access to hematopoietic stem cells; these results are consistent with results from murine vibrissae HFs [67]. In addition, CRH treated HFs shows significant increase of stem cell factor (SCF) expression. Antibody against SCF decreased degranulation of mast cells around HFs in vitro [66].

Based on these studies, we can understand the association between stress and hair loss induction as follows: stressors induce CRH production in HFs that increases the mast cell number and maturation via SCF. In addition, the CRH causes the degranulation of mast cells via SCF, which may induce catagen by chemical mediators from mast cells [Fig. 3].

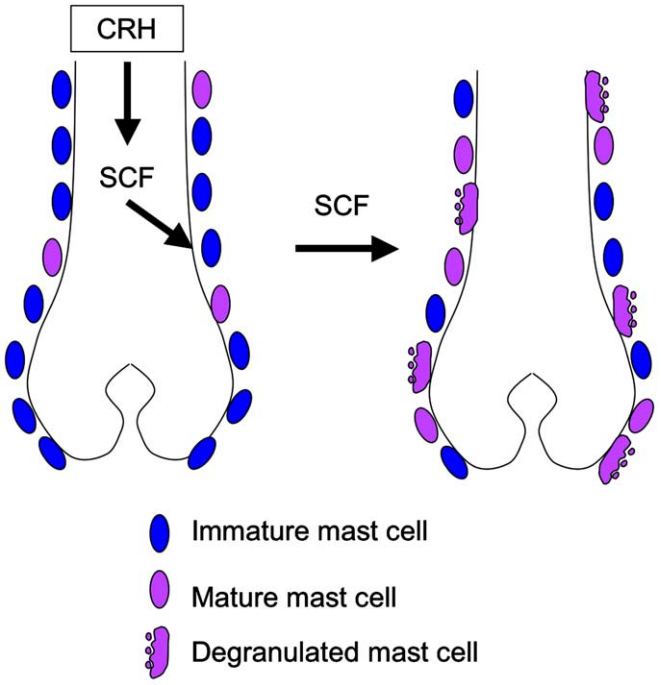

Fig. 3. Stressors induce CRH production that increases SCF expression in HFs. Then, the number of c-kit+ mast cells are increased and matured by SCF. In addition, the CRH causes the degranulation of mast cells *via* SCF, which may induce catagen by chemical mediators from mast cells.

5. Alopecia areata, stress hormone and the immune system

Emotional stress is considered to be a trigger for the onset of AA [68–73]. Stress hormone, CRH, may be associated with AA induction. As mentioned before, CRH may induce mast cell degranulation that results in histamine release. Several studies have shown the potential benefits of anti-histamine drugs for AA [74–76]. These data also support the role of CRH and mast cells in the pathogenesis of AA.

There is one case report of CRH receptor expression in three alopecia areata patients who experienced great emotional stress prior to hair loss. Skin from the affected scalp areas of the three patients showed an intense signal for CRH-2β. Samples from unaffected scalp areas of the same patients or from healthy controls showed only a weak background signal for the receptor [77]. CRH, ACTH and α-MSH expression was significantly increased in the epidermis, hair follicles and sebaceous glands of the AA patients as compared to healthy controls. This result strongly indicates the presence of an active neurogenic system and local HPA axis activity in AA lesions [78]. Activation of the immune system can modulate not only CRH expression, but also the HPA axis [69,79–83].

Recently, functional data was reported on the status of both the central and peripheral HPA axis under basal (unstressed) conditions as well as following stress in AA-affected mice in comparison to non-AA-affected (normal) mice [84]. Normal mice exhibited a marked plasma corticosterone elevation as compared with the basal condition, whereas AA-affected mice showed no significant changes in corticosterone levels. This result suggests that AA-affected mice have a blunted response to an acute physiological stressor. In the central nervous system, pituitary POMC mRNA levels were also increased in AA mice by 2.61- and 2.76-fold under basal and repeated stress conditions, respectively. Moreover, AA mice showed enhanced HPA activity in the skin. For example, POMC mRNA expression was also significantly elevated under basal (7.74-fold) and repeated stress (16.28-fold) conditions. Hence, emotional stress may largely affect patients because of the blunt corticosteroid response against hormone and immunological damage. The authors concluded that altered HPA activity may occur as a consequence of the immune response associated with AA.

6. Guardians of hair follicle immune privilege and the treatment of alopecia areata

The key to the pathogenesis of AA is the collapse of IP in the hair bulb. If HF-IP is collapsed by stress, autoantigens are revealed, resulting in an autoimmune reaction by T cells against the HF autoantigens. This reaction causes the unique pathological feature called "swarm of bees" in the acute phase of AA. The identity of the autoantigen has not been confirmed, but melanocyte-related protein has been suggested as the HF autoantigen in several studies [16]. Gilhar et al. [9] clearly showed that melanocyte-associated T-cell epitopes were capable of functioning as autoantigens to induce AA in the human scalp graft/SCID mouse model. HLA-A2-restricted

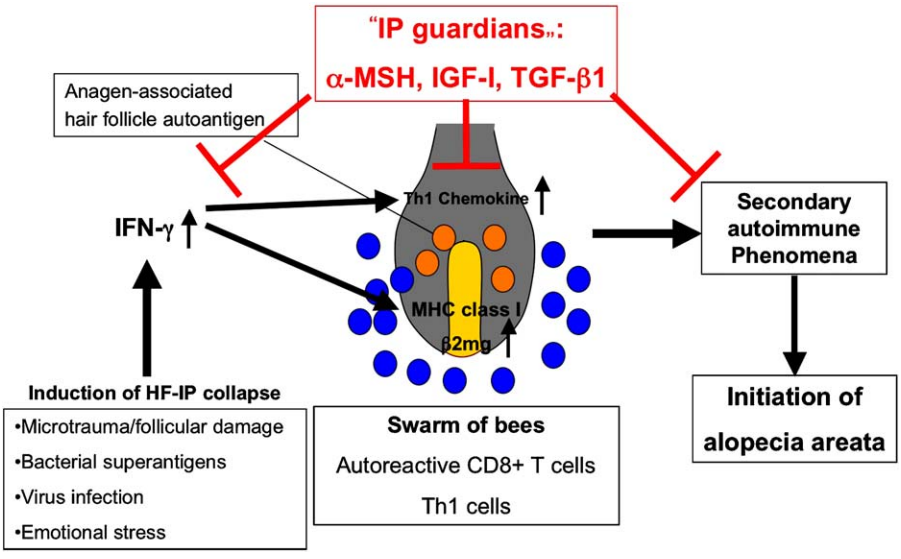

Fig. 4. The pathogenesis of AA and strategy of the treatments. IP guardians protect autoimmune reaction against hair follicle autoantigens and keep HF-IP.

peptides can activate T cells for the transfer of AA to autologous scalp skin grafts on severe combined immunodeficiency (SCID) mice, indicating that melanocyte-associated autoantigens can be one of the autoantigens. Therefore, the reestablishment of IP appears to be the most straightforward solution to the management of AA. Immunosuppressive molecules IGF-1, TGF-β1, and α-MSH are potent downregulators of ectopic MHC class I expression in human HFs. These substances may be very attractive candidates for IP restoration and could be recruited by the anagen HF as guardians of IP to maintain and restore the HF-IP [85] [Fig. 4]. Although an effective treatment for AA has not yet been developed, the restoration of HF-IP is a promising direction for exploitation of AA therapies.

7. Conclusion

The HF is a unique and dynamic mini-organ that affects skin conditions through the immune and hormone systems. The most intriguing feature of the HF immune system is the IP that is characterized by the downregulation of MHC class I. The HF immune system is closely associated with the HF hormone system. An important recent discovery is the existence of the functional HPA axis in the HF itself. Environmental stress may influence both the HF immune and hormone systems and result in the induction of autoimmune hair disease, such as AA. Effective treatments for AA are still needed. One of the future targets of treatment will be the modification of HF-IP and the HPA axis.

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