Acad Med J 2025;5(Suppl 1):S70-S80.
UDC: 616.594.1
https://www.doi.org/10.53582/AMJ255170s
Review article

DISRUPTION OF HAIR FOLLICLE IMMUNE PRIVILEGE IN ALOPECIA AREATA: ENIGMATIC MECHANISMS AND EMERGING CONCEPTS

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Abstract

Immune privilege (IP) is a specialized immunological state that protects certain tissues, including the hair follicle (HF), from immune-mediated destruction. The maintenance of hair follicle immune privilege (HFIP) is crucial for uninterrupted hair growth and is mediated by several mechanisms. These include the downregulation of major histocompatibility complex (MHC) class I molecules, the secretion of immunosuppressive cytokines such as transforming growth factor-beta (TGF-β) and alpha-melanocyte-stimulating hormone (α-MSH), and the recruitment of regulatory immune cells that suppress pro-inflammatory responses.

Additionally, the blood-hair follicle barrier limits immune cell infiltration, further preserving immune privilege. However, in alopecia areata (AA), HFIP collapses triggering an autoimmune attack against follicular structures. This breakdown is marked by increased antigen presentation, heightened expression of MHC class I and II molecules, and an influx of autoreactive cytotoxic CD8+ T cells. These T cells, particularly those expressing the NKG2D receptor, recognize stress-induced ligands on follicular keratinocytes and initiate a cytotoxic response. Interferon-gamma (IFN-γ) and interleukin-15 (IL-15) play central roles in amplifying inflammation by activating the JAK-STAT signaling pathway, further promoting immune cell infiltration and follicular destruction. Additional immune cells, including natural killer cells, dendritic cells, and macrophages, contribute to disease pathogenesis by enhancing antigen presentation and sustaining the inflammatory cascade.

Given the central role of HFIP collapse in AA, therapeutic strategies aimed at restoring immune privilege represent a promising avenue for long-term disease management. Future research should focus on identifying key molecular regulators of HFIP and developing targeted interventions to re-establish immune tolerance within the hair follicle.

Keywords: hair follicle, alopecia areata, immune privilege, immune privilege collapse, JAK-STAT signaling

Introduction

The hair follicle (HF) possesses a unique immunological environment, characterized by a state of immune privilege (IP) [1]. This IP is a crucial set of mechanisms that prevent or suppress cytotoxic attacks from immune cells, thereby protecting the follicle from inflammatory damage and ensuring uninterrupted hair growth and regeneration [1]. The anagen-stage hair follicles exhibit this "immune privilege" from the level of the bulge downwards to the bulb [2]. This is essential to protect the bulge, which houses the epithelial HF stem cells

(HFSC) that are vital for follicle regeneration [3]. Several factors contribute to this privileged status, including reduced expression of major histocompatibility complex (MHC) class I molecules on follicular keratinocytes, the secretion of immunosuppressive factors, and the presence of regulatory immune cells [1]. Melanocytes located in the hair bulb also secrete immunosuppressive factors such as α-MSH, aiding in immune privilege by suppressing inflammation [1]. Mast cells contribute by releasing mediators such as histamine and tryptase, modulating local immune responses and reducing inflammation [1]. These mechanisms collectively minimize immune surveillance and prevent inappropriate immune responses within the HF [2]. However, the HFIP is not absolute, and its collapse is a critical event in the pathogenesis of several hair disorders, most notably alopecia areata (AA) [2]. In AA, the delicate balance of the HFIP is disrupted, leading to an autoimmune attack against the hair follicle. This involves the infiltration of immune cells, increased expression of MHC molecules, and the release of pro-inflammatory cytokines [2,3].

This review aimed to explore the intricate mechanisms that establish and maintain HFIP, detail the factors contributing to its collapse in AA, and discuss the key molecular players involved in the subsequent immune-mediated destruction of the hair follicle. By focusing on HFIP and its disruption, we aimed to provide a deeper understanding of AA pathogenesis and to highlight potential therapeutic strategies that restore immune tolerance within the hair follicle.

I. The Hair Follicle: An Immune-Privileged Site

The hair follicle (HF) is a complex structure that not only serves as the site for hair production but also functions as an immune-privileged environment [4]. This section delves into the anatomy of the hair follicle, the mechanisms that confer its immune privilege, and how these mechanisms work together to protect the follicle from immune-mediated damage.

The hair follicle is composed of several distinct regions, each playing a critical role in hair growth and regeneration:

- Bulge Region: Located in the outer root sheath, this area contains a population of epithelial stem cells responsible for hair follicle regeneration during the hair cycle. The bulge region also plays a pivotal role in maintaining immune privilege.
- Hair Bulb: The bulb is situated at the base of the follicle and contains actively dividing keratinocytes that produce the hair shaft. The bulb is also home to melanocytes, which provide pigmentation to the hair.
- Dermal Papilla: This specialized structure at the base of the bulb contains mesenchymal cells that interact with keratinocytes to regulate hair growth through signaling pathways.

The cyclical phases of hair growth - anagen (growth), catagen (transition), telogen (rest), and exogen (shedding) - are intricately linked to these structural components and their interactions with surrounding tissues.

Mechanisms of Immune Privilege in the Hair Follicle

The immune privilege of the hair follicle is maintained through several key mechanisms:

1. Reduced Expression of MHC Class I Molecules

One of the primary mechanisms underlying HFIP is the downregulation of major histocompatibility complex (MHC) class I molecules on keratinocytes within the hair follicle.

MHC class I molecules are crucial for presenting endogenous antigens to CD8+ T cells. By reducing their expression, hair follicles minimize their visibility to cytotoxic T cells, thereby evading immune surveillance [4].

2. Immunosuppressive Factors

Several immunosuppressive factors are secreted by cells within or surrounding the hair follicle:

- Transforming Growth Factor-beta (TGF-β): This cytokine plays a significant role in promoting immune tolerance by inhibiting T cell activation and proliferation [5]. TGF-β also contributes to maintaining stem cell quiescence in the bulge region.
- Alpha-Melanocyte-Stimulating Hormone (α-MSH): Produced by melanocytes, α-MSH has anti-inflammatory properties and can suppress pro-inflammatory cytokine production, thereby protecting against inflammatory damage [6].
- Indoleamine 2,3-Dioxygenase (IDO): IDO catalyzes the degradation of tryptophan, leading to local immunosuppression and promoting T regulatory cell activity [7]. This further enhances immune tolerance within the HF.

3. NK Cell Inhibition

Natural killer (NK) cells play a crucial role in innate immunity by targeting infected or transformed cells. However, in the context of HFIP, several factors inhibit NK cell activity:

- Expression of Ligands: Hair follicle cells express ligands that can engage inhibitory receptors on NK cells, preventing their activation and cytotoxicity [8].
- Local Cytokine Environment: The presence of immunosuppressive cytokines within the HF microenvironment contributes to inhibiting NK cell function.

Blood-Hair Follicle Barrier

The blood-hair follicle barrier is another critical component that helps maintain immune privilege. This barrier restricts access to circulating immune cells while allowing for essential nutrient exchange. The structural integrity of this barrier is maintained by tight junctions between keratinocytes and endothelial cells, which limit permeability and prevent unwanted immune cell infiltration [9].

The unique structure and immunological mechanisms that confer immune privilege upon the hair follicle are vital for its function and longevity. Disruption of these mechanisms can lead to autoimmune conditions such as alopecia areata, where immune tolerance is lost, resulting in targeted destruction of hair follicles.

II. Alopecia Areata: Disruption of the Immune Privilege

In alopecia areata (AA), the meticulously maintained immune privilege of the hair follicle is compromised, instigating an autoimmune assault directed at the follicular structures. This section delves into the mechanisms underlying the breach of immune tolerance, the specific immune cells orchestrating the attack, and the roles of critical cytokines and chemokines in sustaining the inflammatory cascade.

Breakdown of Immune Tolerance

The disintegration of immune privilege in AA is hallmarked by the failure of self-tolerance, precipitating an aberrant immune response that targets hair follicle antigens. This intricate process entails several key steps:

- Autoantigen Presentation: Hair follicle-specific autoantigens, which are ordinarily shielded from the immune system within the confines of the HF, are presented to T cells by antigen-presenting cells (APCs), prominently dendritic cells (DCs). This presentation may occur in the lymph nodes draining the scalp or directly within the peribulbar region, where DCs can capture and present antigens locally. The identification of specific autoantigens remains a critical area of research, with candidates including melanocyte-associated proteins, structural components of the hair follicle, and enzymes involved in hair growth [2]. The presentation of these autoantigens, in the context of co-stimulatory signals, is pivotal for initiating the autoimmune response.
- T Cell Activation: Upon encountering autoantigens presented by APCs, naïve T cells undergo activation and differentiate into effector T cells, including CD8+ cytotoxic T lymphocytes (CTLs) and CD4+ helper T cells. This activation is driven by the interaction between the T cell receptor (TCR) and the MHC-antigen complex, along with co-stimulatory molecules such as CD28 and B7. Once activated, these effector T cells proliferate and acquire the capacity to migrate to the hair follicle, guided by chemokines and adhesion molecules [10]. The process of T cell activation also involves intricate signaling pathways, including the JAK-STAT pathway, which modulates the expression of cytokines and effector molecules.
- Loss of Regulatory T Cell (Treg) Function: Regulatory T cells (Tregs), characterized by the expression of the transcription factor Foxp3, are indispensable for upholding immune tolerance and suppressing autoreactive T cells. In AA, Treg function is frequently compromised, marked by reduced numbers of Tregs in affected skin and impaired suppressive capacity. This deficiency can be attributed to factors such as cytokine dysregulation, epigenetic modifications, and defects in Treg signaling pathways [11]. The diminished ability of Tregs to restrain autoreactive T cells exacerbates the autoimmune response and perpetuates hair follicle destruction.

Immune Cell Infiltration

The infiltration of immune cells into the peribulbar region of the hair follicle stands as a defining feature of AA. These infiltrating cells assume a central role in targeted destruction of the hair follicle, orchestrating a coordinated assault that disrupts normal hair growth.

CD8+ T Cells

CD8+ T cells are the foremost effectors of hair follicle destruction in AA, executing targeted cytotoxicity against follicular keratinocytes. These cells recognize hair follicle-specific antigens presented on MHC class I molecules, triggering release of cytotoxic granules encompassing perforin and granzymes. Perforin facilitates entry of granzymes into target cells, inducing apoptosis through activation of caspases [12]. The sustained presence of CD8+ T cells surrounding the hair bulb leads to miniaturization of follicles and cessation of hair growth. Furthermore, CD8+ T cells secrete cytokines such as IFN-γ that amplify inflammatory cascades and promote recruitment of additional immune cells [13].

CD4+ T Cells

CD4+ T cells play a multifaceted role in AA pathogenesis by orchestrating inflammatory responses through secretion of distinct cytokine profiles. Different subsets of CD4+ T cells - most notably Th1 and Th2 - exert disparate effects on disease progression.

- Th1 Cells: These cells produce interferon-gamma (IFN-γ), a pivotal pro-inflammatory cytokine in AA pathogenesis. IFN-γ enhances MHC class I expression on hair follicle cells, rendering them more susceptible to CD8+ T cell-mediated killing [6]. Additionally, IFN-γ activates macrophages to produce reactive oxygen species that contribute to tissue damage while promoting differentiation into Th1 cells that sustain inflammation.
- Th2 Cells: These cells secrete cytokines such as IL-4, IL-5, and IL-13 associated with allergic inflammation and humoral immunity [5]. While their precise role in AA remains unclear, Th2 responses may contribute to chronicity by promoting B cell activation and antibody production.

NK Cells

Natural killer (NK) cells emerge as active participants in AA despite their normally inhibited state within healthy hair follicles. NK cells possess capacity to directly kill stressed or damaged hair follicle cells, augmenting cytotoxic assaults orchestrated by CD8+ T cells [14]. Their activity is often amplified by pro-inflammatory cytokines like IL-15 that promote NK cell survival and proliferation.

Other Immune Cells

- Dendritic Cells (DCs): These antigen-presenting cells initiate autoimmune responses by capturing and presenting hair follicle antigens to T cells. DCs express co-stimulatory molecules that provide critical signals for T cell activation while secreting cytokines that promote Th1 differentiation [7,9].
- Macrophages: These versatile immune cells contribute to inflammation through diverse mechanisms including secretion of pro-inflammatory cytokines such as TNF-α and IL-1β that amplify inflammatory cascades. Macrophages also participate in clearing cellular debris resulting from hair follicle destruction.
- Mast Cells: Mast cell degranulation releases mediators like histamine that exacerbate inflammation while promoting immune cell infiltration. Mast cell interactions with other immune populations further modulate overall immune responses within affected areas.

Cytokine and Chemokine Involvement

The inflammatory microenvironment in AA is typified by dysregulation of various cytokines and chemokines that play crucial roles in orchestrating recruitment and activation of immune cells within hair follicles.

Pro-Inflammatory Cytokines

- Interferon-Gamma (IFN-γ): IFN-γ is a pivotal cytokine in AA pathogenesis with pleiotropic effects on both immune and hair follicle cells. It enhances MHC class I expression on follicular keratinocytes while activating macrophages to produce reactive oxygen species contributing to tissue damage [15].
- Interleukin-15 (IL-15): IL-15 plays critical roles in survival and activation of CD8+ T cells and NK cells. Upregulation during AA contributes to sustained presence of cytotoxic populations surrounding follicles while amplifying pro-inflammatory responses.
- Other Cytokines: Pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6 contribute to inflammatory milieu by promoting chemokine production that recruits additional immune populations while also affecting keratinocyte function [4,7,15].

Chemokines and Chemokine Receptors

Chemokines regulate migration dynamics among infiltrating immune populations essential for effective responses during AA progression.

- CXCL9/CXCL10: These chemokines bind CXCR3 receptors expressed on activated T/NK populations facilitating their recruitment towards inflamed follicles. IFN-γ stimulates production, enhancing this recruitment mechanism [16].
- Other Chemokines: Additional chemokines, such as CCL5, attract diverse immune subsets including macrophages while maintaining inflammatory cascades around the follicles [17,18].

III. Molecular Mechanisms and Signaling Pathways

The pathogenesis of alopecia areata involves a complex interplay of various molecular mechanisms and signaling pathways that contribute to the disruption of immune privilege and the sustained autoimmune attack on hair follicles. This section provides information on the key signaling pathways and molecular processes implicated in AA, including JAK-STAT signaling, altered chemokine signaling, regulation of cell death, and epigenetic modifications.

JAK-STAT Signaling

The Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway is a crucial conduit for cytokine-mediated immune responses and has been strongly implicated in the pathogenesis of AA [19, 21, 23]. This pathway transmits signals from various cytokines involved in AA, thereby impacting disease outcomes [19,21].

- Role in Cytokine Signaling: Many pro-inflammatory cytokines implicated in AA, such as interferon-gamma (IFN-γ), IL-15, IL-2, IL-7 and IL-6, signal through the JAK-STAT pathway [19,21]. These cytokines bind to their respective receptors, activating Janus kinases (JAKs), which phosphorylate signal transducers and activators of transcription (STATs) [19,24]. Once phosphorylated, STATs dimerize, translocate to the nucleus, and regulate the expression of target genes involved in immune cell activation, proliferation, and differentiation [24]. The JAK family consists of four members: JAK1, JAK2, JAK3, and TYK2 [24]. JAK3 expression is mainly in bone marrow and the lymphatic system, while other members express themselves in nearly all tissues [24].
- Dysregulation in AA: Studies have demonstrated increased activation of JAK-STAT signaling in lesional skin of AA patients, skewing the hair follicle microenvironment away from a homeostatic state and toward active inflammation [19]. This dysregulation contributes to the sustained production of pro-inflammatory cytokines and the activation of immune cells, perpetuating the autoimmune response against hair follicles[19]. The T-cell mediated inflammatory response is thought to be the driving factor behind AA pathogenesis. Genetic research has also identified the crucial role of these signaling pathways for the growth and cycling of hair follicles and implicated the role of genes in T-cell pathways and autoimmunity [22].
- Therapeutic Targeting: Given the central role of JAK-STAT signaling in AA pathogenesis, JAK inhibitors have emerged as promising therapeutic agents [19,21,23]. By suppressing JAK-STAT pathways, these inhibitors block the downstream signaling of different cytokines and decrease perifollicular T-cell infiltration [22]. These inhibitors block the activity of JAKs, thereby suppressing downstream signaling and reducing inflammation [19]. Several JAK inhibitors, such as baricitinib, tofacitinib, ruxolitinib, ritlecitinib and brepocitinib, have shown efficacy in treating AA, leading to hair

regrowth among AA patients [19,20,21,22,23]. Demonstrated efficacy from large-scale clinical trials of the JAK inhibitor baricitinib led to the first-in-disease FDA-approved treatment for AA in June 2022 [19,21]. In a systematic review and meta-analysis of 7 randomized clinical trials with 1710 patients, JAK inhibitors were associated with more hair regrowth compared with placebo [23]. The outcome of oral JAK inhibitors seemed better than external routes of administration [30]. While the effectiveness of JAKin treating alopecia areata may not exceed that of systemic glucocorticoids, their targeted immunosuppressive properties may offer a safer alternative to long-term systemic therapy [20].

Altered Chemokine Signaling

Chemokines and their receptors play a particular role in regulating the migration of immune cells to the hair follicle. Dysregulation of chemokine signaling can lead to the excessive recruitment of immune cells, contributing to the inflammatory microenvironment in AA.

- Impact on Immune Cell Recruitment: Chemokines such as CXCL9, CXCL10, and CCL5 are upregulated in AA lesions, attracting T cells, NK cells, and macrophages to the peribulbar region. These chemokines bind to their respective receptors (e.g., CXCR3, CCR5) on immune cells, triggering intracellular signaling pathways that promote cell migration [25,26].
- Therapeutic Potential of Targeting Chemokine Receptors: Blocking chemokine receptors or inhibiting chemokine production represents a potential therapeutic strategy for AA. By interfering with the recruitment of immune cells to the hair follicle, these approaches could reduce inflammation and promote hair regrowth [25,26].

Regulation of Cell Death

Apoptosis, or programmed cell death, plays a crucial role in the pathogenesis of AA. Dysregulation of apoptotic pathways can lead to the destruction of hair follicle cells and contribute to the characteristic hair loss observed in AA patients.

- Fas/FasL Pathway: The Fas/FasL pathway is a key regulator of apoptosis. Fas (CD95) is a death receptor expressed on various cell types, including hair follicle cells, while FasL (CD95L) is a ligand expressed on activated T cells. Interaction of FasL with Fas triggers a signaling cascade that leads to caspase activation and apoptosis [26].
- Other Apoptotic Pathways: Other pathways involved in cell death include the TNF-related apoptosis-inducing ligand (TRAIL) pathway and the intrinsic mitochondrial pathway. These pathways can also contribute to the destruction of hair follicle cells in AA [26].

Epigenetic Modifications

Epigenetic modifications, such as DNA methylation and histone modification, play a pivotal role in regulating gene expression and can influence the development and progression of autoimmune diseases, including AA.

- DNA Methylation: DNA methylation involves the addition of a methyl group to cytosine bases in DNA, typically leading to gene silencing. Alterations in DNA methylation patterns have been observed in immune cells from AA patients, affecting the expression of genes involved in immune regulation and inflammation [26].

- Histone Modification: Histone modification involves the addition of chemical tags to histone proteins, which can alter chromatin structure and affect gene transcription. Histone acetylation, for example, is generally associated with increased gene expression, while histone deacetylation is associated with gene silencing [26].
- Potential Role in Pathogenesis: Epigenetic modifications can influence the expression of genes encoding cytokines, chemokines, and other immune-related molecules, thereby contributing to the dysregulation of the immune response in AA. These modifications may also affect the function of Tregs and other regulatory immune cells, further exacerbating the autoimmune attack on hair follicles [26].

IV. Therapeutic Strategies and Future Directions

Alopecia areata presents a significant therapeutic challenge due to its complex immunopathogenesis and unpredictable clinical course. Current treatments primarily focus on suppressing the immune response and promoting hair regrowth, but many patients experience limited or transient benefits. This section presents current therapeutic strategies, discusses novel approaches under development, and highlights future research directions aimed at improving the management of AA.

Current Treatments

The current treatment landscape for AA includes a variety of approaches aimed at modulating the immune system and stimulating hair growth [29,30,31].

- Topical and Intralesional Corticosteroids: Corticosteroids are widely used due to their anti-inflammatory and immunosuppressive properties. Topical corticosteroids are often used as a first-line treatment in most patients with patchy AA. Intralesional injections of corticosteroids (e.g., triamcinolone acetonide 5-10 mg/ml) are effective for treating localized conditions involving less than 50% of the scalp, resulting in localized hair growth in about 60% of treated sites. Injections are typically administered every 4-6 weeks. However, long-term use can lead to side effects such as skin atrophy and telangiectasia.
- Topical Minoxidil: Topical minoxidil is a vasodilator that promotes hair growth by prolonging the anagen phase of the hair cycle. It is often recommended as a treatment option in AA. Initial regrowth can be seen within 3 months, but continued application is needed to achieve cosmetically acceptable regrowth. Minoxidil appears to be effective in the treatment of alopecia areata in patients with extensive disease (50-99% hair loss).
- Immunotherapy: Immunotherapy involves inducing an allergic reaction on the scalp to stimulate hair regrowth. Topical sensitizers such as diphencyprone (DCP) or squaric acid dibutyl ester (SADBE) have been used in the treatment of extensive alopecia areata for over 30 years.
- JAK Inhibitors: As discussed earlier, JAK inhibitors have emerged as a promising treatment option for AA. Several JAK inhibitors, such as tofacitinib, ruxolitinib, baricitinib, ritlecitinib and brepocitinib, are currently being investigated in clinical trials, and some have received regulatory approval for the treatment of AA [23, 32, 33].
- Other Systemic Treatments: Oral corticosteroids or other immunosuppressants may be prescribed to arrest rapidly progressing and extensive hair loss in AA and in refractory cases.

Novel Therapeutic Approaches

In addition to the current treatments, several novel therapeutic approaches are under development for AA, targeting specific aspects of the disease pathogenesis.

- Targeting Specific Cytokines or Chemokines: Given the central role of cytokines and chemokines in AA pathogenesis, targeting these molecules represents a rational therapeutic strategy [27].
- Modulating Immune Cell Activity: Approaches aimed at modulating the activity of specific immune cell populations, such as T cells or NK cells, are also under development. This includes strategies to enhance Treg function, suppress effector T cell activity, or inhibit NK cell cytotoxicity [34].
- Restoring Immune Privilege in the Hair Follicle: Restoring the immune privilege of the hair follicle represents an attractive therapeutic goal [28].
- Stem Cell Therapy and Regenerative Medicine Approaches: Stem cell therapy and regenerative medicine approaches hold promise for restoring hair growth in AA patients[35].

Future Research Directions

Future research efforts should focus on gaining a deeper understanding of the immunopathogenesis of AA, identifying novel therapeutic targets, and developing more effective and personalized treatments.

- Identifying Novel Autoantigens: Identifying the specific autoantigens that trigger the autoimmune response in AA is a critical step towards developing more targeted therapies.
- Developing Personalized Therapies Based on Genetic Profiling: Genetic studies have identified several susceptibility genes for AA. Future research should focus on using genetic profiling to identify patients who are most likely to respond to specific treatments.
- Understanding the Role of the Microbiome in AA: The skin and gut microbiome have been implicated in various autoimmune diseases. Further research is needed to investigate the role of the microbiome in AA and to determine whether modulating the microbiome can improve treatment outcomes.

Conclusion

Alopecia areata represents a complex autoimmune disorder underpinned by a breakdown in the immune privilege of the hair follicle. This breach initiates an immune-mediated attack targeting follicular structures, culminating in non-scarring hair loss. The pathogenesis of AA is characterized by a multifaceted interplay involving genetic predispositions, environmental exposures, and a range of immunological aberrations. These include dysregulation of cytokine signaling cascades, aberrant chemokine activity governing immune cell trafficking, and dysregulated apoptotic pathways contributing to follicular destruction. While current therapeutic strategies largely focus on broad immunosuppression and stimulation of hair regrowth, these interventions often yield limited or transient efficacy. The emergence of targeted therapies, such as JAK inhibitors, offers a promising avenue by selectively modulating key signaling pathways central to AA pathogenesis. However, the development of more effective and durable treatments necessitates further investigation into the intricate mechanisms driving disease progression. Future research should prioritize the identification of novel, disease-specific autoantigens, elucidating the role of epigenetic

modifications in shaping immune cell behavior, and investigating the influence of the microbiome on AA pathogenesis. A deeper understanding of the molecular intricacies that govern the AA disease process will be critical for the rational design of personalized therapeutic strategies capable of restoring immune tolerance within the hair follicle and inducing sustained, cosmetically significant hair regrowth.

Conflict of interest statement. None declared.

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