

Hair follicle immune privilege and its collapse in alopecia areata

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Abstract

Anagen stage hair follicles (HFs) exhibit “immune privilege (IP)” from the level of the bulge downwards to the bulb. Both passive and active IP mechanisms protect HFs from physiologically undesired immune responses and limit immune surveillance. IP is relative, not absolute, and is primarily based on absent, or greatly reduced, intra-follicular antigen presentation via MHC class I and II molecules, along with prominent expression of “no danger” signals like CD200 and the creation of an immunoinhibitory signalling milieu generated by the secretory activities of HFs. Perifollicular mast cells, Tregs and other immunocytes may also contribute to HF IP maintenance in healthy human skin. Collapse of anagen hair bulb IP is an essential prerequisite for the development of alopecia areata (AA). In AA, lesional HFs are rapidly infiltrated by NKG2D + T cells and natural killer (NK) cells, while perifollicular mast cells acquire a profoundly pro-inflammatory phenotype and interact with autoreactive CD8+ T cells. Using animal models, significant functional evidence has accumulated that demonstrates the dominance of the immune system in AA pathogenesis. Purified CD8+T-cell and NK cell populations alone, which secrete $\gamma\gamma$, suffice to induce the AA phenotype, while CD4+T-cells aggravate it, and Tregs and iNKT cells may provide relative protection against AA development. While IP collapse may be induced by exogenous agents, inherent IP deficiencies might confer increased susceptibility to AA for some individuals. Thus, a key goal for effective AA management is the re-establishment of a functional HF IP, which will also provide superior protection from disease relapse.

KEYWORDS

alopecia areata, IFN γ , immune privilege, immune privilege collapse, mast cell, NK cell, NKG2D

1 | INTRODUCTION

One of the most striking features of healthy anagen stage hair follicles (HFs) is the relative immune privilege (IP) that their epithelium exhibits from the bulge region, the niche for HF stem cells,

downwards to the hair bulb.¹ Several passive and active mechanisms of IP are present in HFs, the nature and potency of which vary over time and in response to changes in the local environment. The net effect of IP conferring factors, set against pro-inflammatory IP collapse inducing actions, can determine the development of HF focal

Abbreviations: AA, alopecia areata; APC, antigen-presenting cell; HF, hair follicle; IP, immune privilege; MHC, major histocompatibility complex; NK, natural killer.

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inflammation. Functionality and failure of HF IP has become recognized as a chief element in the pathobiology of several inflammatory hair loss disorders, such as primary cicatricial alopecias,^{2,3} and alopecia areata.⁴⁻⁶

The current review defines the primary concept of IP and why it may be expressed in HFs. It examines key features of the anagen HF bulb's physiological IP, including HF cell-expressed IP-modulating receptors and ligands, the role of perifollicular immune cells and cell populations elsewhere in the body that can also support HF IP. The review then explores the central role that HF bulb IP collapse plays in alopecia areata (AA). Non-specific inflammatory mechanisms that could lead to IP failure and AA development are explored, in addition to the classic autoimmune cascade currently recognized in AA disease pathogenesis. The review closes with discussion of current and future therapeutic strategies for AA that involve restoring some aspect of HF IP. We argue that restoration of HF IP is an effective approach for the treatment of AA and for preventing AA relapse, which is typically seen after discontinuation of treatment with glucocorticosteroids or JAK inhibitors.^{7,8}

2 | BASIC IMMUNE PRIVILEGE CONCEPTS

IP is the phenomenon whereby organs or tissues are protected from challenge by the host immune system. It occurs in corneal tissue,^{9,10} testes,¹¹⁻¹³ placenta,¹⁴ liver,¹⁵ gut,¹⁶ brain¹⁷ and possibly also in mucosal tissue.^{18,19} Nobel laureate immunologist Peter Medawar first developed the concept of IP in the late 1940s²⁰ on the basis of transplantation experiments.^{21,22} However, the original concepts, that IP only permits the escape of allotransplants from immune elimination and that it is an organ-specific phenomenon, have become outdated.²³ Today, IP is understood as a dynamic, functional characteristic of anatomically defined tissue compartments within selected organs. It represents a relative state, rather than an absolute state and may actually be much more widespread than previously realized. Under certain inflammatory or therapeutic circumstances, a tissue that normally does not exhibit relative IP can develop it or can be manipulated to develop it.^{1,24-27} Consequently, IP can be acquired locally in many different tissues, either constitutively or in response to inflammation (see Ref. [28] for historical review). Many different collaborating mechanisms have been identified in tissues that enjoy relative IP (Table 1).²⁹⁻³²

It has long been argued that the evidence for the presence of relative IP in HFs is phenomenological and is awaiting conclusive functional confirmation.^{1,6,33} However, former sceptics of the HF IP collapse paradigm now embrace it, albeit with caveats (eg Ref. [33-37]), and at least some immunologists now acknowledge the existence of HF IP (eg Ref. [25,38-42]). Compelling functional evidence for the existence of HF IP has not only been provided long ago by Billingham^{21,22} but also in mutant mice overexpressing non-HF antigens (e.g.³⁹) as well as by the observation that AA does not occur without HF IP collapse.^{4,6,33,43,44}

3 | THE BIOLOGICAL FUNCTION OF HAIR FOLLICLE IMMUNE PRIVILEGE

Originally, we introduced the concept that the main biological function of HF IP is to sequester highly immunogenic autoantigens from immune recognition, such as melanogenesis-related self-peptides and other autoantigens generated during anagen.⁴³ Accordingly, IP may protect the hair bulb from autoaggressive inflammation during its immunologically vulnerable phase of pigmentary activity and hair shaft production.^{1,43} Melanocyte- and melanogenesis-associated epitopes can operate as autoantigens for the T cell-mediated transfer of AA lesions to human scalp skin transplanted onto immunocompromised mice⁴⁵; successful immunotherapy against melanoma antigens in mice induces AA-like alopecic lesions⁴⁶; the melanocytes of the human HF pigmentary unit actively downregulate MHC class I expression (Paus & Sinclair, unpublished data); and AA can be associated with vitiligo.^{4,47,48} Recently, autoreactive T cells were identified in mice and humans with AA with specific responses to melanogenesis-related antigens, and also to keratinocyte derived antigen epitopes, including trichohyalin.^{49,50} Also of note, copy number variant analysis indicates duplications in melanin-concentrating hormone receptor 2 (MCHR2) that are present in some patients with AA.⁵¹

All this supports the concept that one of the key functions of IP is to shield intra-follicularly expressed (auto-)antigens generated during anagen from immune recognition, and to induce a state of peripheral tolerance against them whenever they may become exposed to the immune system.^{1,52} Beyond immediate HF protection from immune attack, HF IP might even promote peripheral self-tolerance.⁵² For example, mouse skin with all HFs in mid-late anagen exhibits a profoundly immunoinhibitory milieu,^{53,54} most likely due to the secretion of immunoinhibitory IP guardians by HFs. Further, the number, phenotype, apoptosis-modulating activities and protein expression patterns of perifollicular macrophages significantly fluctuate during the human anagen-catagen switch,⁵⁵ similar to observations in mice.⁵⁶ While it is as yet unclear what exactly this means for HF IP, it suggests that HF cycling can alter the local immune status of skin.

We can only speculate on the selection advantage that the development of IP in HFs may have provided during evolution. In mammalian skin, relative IP has so far been identified in the HF and also in the proximal nail matrix of humans⁵⁷ and mice (Meyer/Paus, unpublished observation). The immunobiology of the feather follicle is largely unknown,⁵⁸ but conspicuously, chickens can develop spontaneous autoimmune feather loss,⁵⁹ which renders it likely that feather follicles also have some form of relative IP. Claws, teeth, horns and other skin appendages are vital for the survival of species. Auto-inflammation of appendages could occur after trauma or infection, for example in predators,⁵⁷ and any significant loss would likely lead to death for the affected animal. This suggests that the principle of protecting skin appendages from inflammation and autoimmune destruction had already been established long before the appearance of HFs during vertebrate evolution.

TABLE 1 Principal immune privilege mechanisms^(1, 26–28)

Functional category	Immune privilege mechanism	Consequences
Restricted immune cell recruitment/trafficking	Absence of lymphatic vessels	Restricts APC and activated lymphocyte migration to draining lymph nodes
	Reduced pro-inflammatory chemokine expression	Reduces pathogenic inflammatory cell chemotaxis
	Erection of extracellular matrix barriers	Reduces APC and inflammatory cell entry to tissues
Reduced antigen presentation	Downregulation or absence of classical MHC class I expression	Greatly reduced or absent capacity to present (auto)antigens to cognate CD8+ T cells
	Downregulation or absence of expression of β 2-microglobulin	Failure to stabilize MHC class I molecules and to allow the latter to properly function as antigen-presenting molecules
	Downregulation or absence of classical MHC class II expression by Langerhans cells	Failure to present (auto)antigens and activate cognate CD4+ T cells.
Active immunosuppression	Local production of potent immunosuppressants such as TGF β 1, TGF β 2, IL-10 and α MSH	Functional impairment of APC functions, for example by absence of MHC class II expression, to prevent antigen presentation to CD4+ cells, or changes in co-stimulatory factor expression to promote anergy; suppression of T cell and NK activation
	Expression of non-classical immunoregulatory MHC class I molecules such as HLA-G and HLA-E in humans	Active suppression of NK cell- and cytotoxic T cell-dependent lysis
	Downregulation of endogenous agonists (eg MICA, ULBP3) of activating cell receptors (NKG2D)	Failure of response from NK, NKT, and gamma-delta T cells expressing NKG2D primed to recognize and eliminate MHC class I-negative cells
	Expression of "death receptors" and ligands (eg Fas-FasL, TNF α -TNFR1, PD1-PDL1)	Deletion of autoreactive T cells

Hair coat maintenance is a crucial survival factor for many mammalian species. Besides key roles for hair shafts in seasonal and climate adaptation, physical protection and camouflage, they are also of elementary importance in inter-sex and social hierarchy communication, as well as in procreation.⁶⁰ Consequently, it is plausible that the appearance of pigmented hair shafts necessitated the creation of a special immunological milieu to protect these crucial skin appendages from the risk of autoimmune elimination entailed by the constitutive, cyclic production of potentially immunostimulatory autoantigens.¹ Maintenance of a functional fur coat is certainly critical for the survival of most mammalian species in the wild, and those that developed effective HF IP may well have enjoyed a considerable selection advantage during evolution.

4 | DIFFERENCES IN HF IP BETWEEN RODENTS AND HUMANS

Throughout the current review, evidence in support of IP and its collapse in AA is sourced from both human and rodent studies. Unfortunately, there are limited comparative data on HF IP between the two species. The central mechanisms of immune tolerance control that affect skin and HFs are likely comparable between rodents and humans. However, peripheral regulatory mechanisms could

differ due to species variation in the homeostatic distribution of immune cells,⁶¹ and as a consequence of hair density affecting the nature and number of immune cells in the skin.⁶² This may affect the ability to respond to, and the nature of the immune response to HF-derived (auto)antigens.

One might also anticipate differences in HF IP linked to HF cycling.⁶³ Major hair cycle-dependent changes in the number and location of various immunocyte populations can be seen in murine skin during synchronized cycling.^{31,56,64–66} With age-associated changes in anagen wave distribution,⁶⁷ and consequent fluctuation in the anagen:telogen ratio, rodent HF IP status may vary significantly over time; at least in terms of intensity. The initial synchronized growth phase may produce a relatively higher level of anagen HF-associated (auto)antigen release in rodents. This may be a desirable event given that exposure to foreign antigens when the rodent (and chicken) immune system is immature typically leads to immune tolerance promotion.^{68–70} In humans, the anagen:telogen ratio also changes with age, though the fluctuations are less extreme as compared to rodents given the mosaic pattern of hair cycling.^{71,72} The first hair growth phase in humans typically occurs in utero comprised of lanugo hair,⁷³ though in principle, this may also have an impact on the developing immune system and tolerance promotion.⁷⁴

Unfortunately, very little is known with regards to differences between rodents and humans in the molecular regulation of IP at

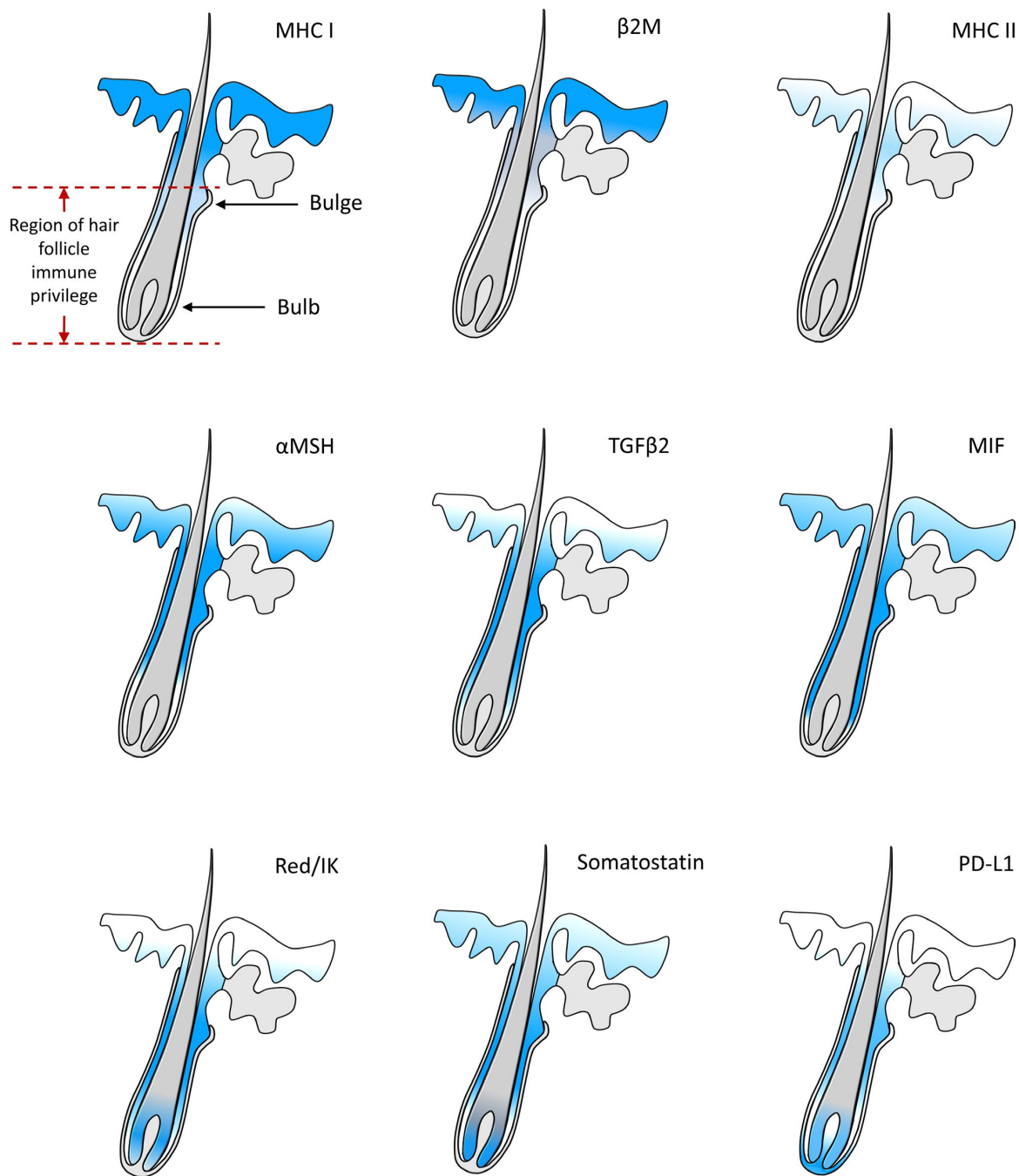


FIGURE 1 Human hair follicle immune privilege. Typical patterns are shown for the expression of select IP-related factors in normal human anagen stage hair follicles. While MHC class I molecules are characteristically found on the cell surface of all nucleated cells, in HF the follicle below the bulge region does not express MHC I. $\beta 2M$ is a component of MHC class I molecules and similarly shows a lack of expression in lower HF. MHC class II molecules are normally only found on professional antigen-presenting cells (APCs) such as dendritic cells, macrophages, and Langerhans cells in the skin of which isolated cells may be observed mostly in the upper HF. αMSH can be observed in the suprabulbar out root sheath. $TGF\beta 2$ is expressed in much of the outer root sheath with greater expression in the outer basal cell layer. MIF is present in most outer root sheath cells except those at the lowest regions of the bulb. Red/IK can be found in the in the outer root sheath and to a lesser extent in the hair matrix. Somatostatin is typically expressed by outer root sheath keratinocytes above the bulb. PD-L1 is expressed in regions of the outer root sheath, as well as in the matrix, the dermal sheath cup and some cells of the dermal papilla (Figure based on Ref. [30,34,36,37])

TABLE 2 Proximal hair follicle immune privilege markers

Category	Immune privilege-associated marker	Absent/ present expression in normal proximal hair follicle	Increased/ decreased expression in AA-affected hair follicle	References
MHC/ HLA associated immunoregulatory factors	β 2-microglobulin (B2M)	-	↑	[76]
	Major histocompatibility complex/ Human leucocyte antigen I (MHC/ HLA I)	-	↑	[31,76,311,360]
	Major histocompatibility complex/ Human leucocyte antigen II (MHC/ HLA II)	-	↑	[311,361]
	MHC class I polypeptide-related sequence A (MICA)	-	↑	[88]
	Human leucocyte antigen G (HLA-G)	+	?	[31,36]
	Transporter 2, ATP Binding Cassette Subfamily B Member (TAP2)	-	?	[76]
	Programmed death-ligand 1 (PD-L1)	+	↓	[37,362]
	UL16 binding protein 3 (ULBP3)	-	↓ ↑ (disputed)	[35,363]
	CD200	+	↓	[30,364-366]
	Indoleamine-2,3-dioxygenase (IDO)	+	?	[30,34,127]
Cell expressed immunoregulatory factors	IK cytokine (Red/IK)	+	↓	[34]
	Insulin-like growth factor 1 (IGF-1)	+	?	[367,368]
	Interleukin 10 (IL-10)	+	↓	[362]
	macrophage migration inhibitory factor (MIF)	+	?	[88]
	Transforming growth factor beta 1/2 (TGF β 1)/(TGF β 2)	+	?	[166,167,177,369]
	Thrombospondin 1 (TSP1)	+	?	[176]
	α -melanocyte-stimulating hormone (α MSH)	+	↑	[164,214,215,370-372]
	Calcitonin gene-related peptide (CGRP)	+	↓	[99,200,373]
	Cortisol	+	?	[162]
	Somatostatin (SST)	+	?	[36]
Neuropeptides and related immunoregulatory factors	Vasoactive intestinal polypeptide (VIP)	+	↓	[98]

the level of individual HFs. The two currently recognized inducers of HF IP collapse, IFN γ and Substance P, are operative in both mice^{32,75} and humans.^{76,77} However, the key-secreted IP guardians in human HF IP, α MSH, TGF β 1/2, IL-10 and IGF-1⁷⁶ failed to protect murine anagen HFs from IFN γ -induced IP collapse *in vivo*.³² This suggests that there may be important differences in the controls of human versus rodent HF IP that await systematic dissection. In the absence of comprehensive comparative data, we present mouse and human data as a *melange* in support of HF IP and its collapse in AA.

5 | MECHANISMS OF HF IP

It is very likely that multiple mechanisms, similar to those employed by other IP tissues (see Ref. [1,78-80]), are intimately involved in maintaining HF IP. Evidence from both the murine and the human system has established that HFs show at least two distinct areas of relative IP; the anagen hair bulb,^{29,31,32,81} and the bulge region (Figure 1).^{2,30,81-83} These two distinct compartments of the HF both show a prominent reduction of expression for MHC class I and β 2-microglobulin and expression of other IP markers (Table 2).³⁰ However, there are some differences in the expression of specific IP conferring mechanisms between the bulge and bulb. Only the bulge is characterized by the prominent expression of the "no danger" signal, CD200, while MHC class I and II expression is lower in the hair bulb as compared to the bulge.^{30,81} It has also been speculated that the special extracellular matrix composition of the HF mesenchyme, and specifically the expression of select glycosaminoglycans in the lower CTS, may contribute to HF bulb IP by impeding T cell trafficking in and out of the HF epithelium.^{1,84} Further investigation is needed to fully understand the mechanisms of IP in different regions of the HF structure. In the context of AA, HF bulb IP is most relevant for understanding disease pathogenesis, given the peri- and intra-follicular inflammation is primarily focused on the bulb and lower follicle.⁴

5.1 | The role of MHC molecules in hair bulb IP

MHC class I molecules are typically found on the cell surface of all nucleated cells. Physiologically, their role is to present peptide fragments from within the cell to CD8⁺ lymphocytes.⁸⁵ If the antigen epitopes presented are recognized by lymphocytes with the relevant TCR specificity, there is a rapid activation of the cells leading to production of pro-inflammatory cytokines and apoptosis promoting factors including granzymes and perforin.⁸⁶ Natural killer (NK) cells are primed to recognize and attack MHC class I-negative cells.⁸⁷ In immunologically privileged tissues and malignant cells, this mechanism tends to be circumvented in part by very low or absent expression of ligands, such as MICA, and ULBP3/6, that stimulate the NK cell-activating receptor, NKG2D.⁸⁸⁻⁹³

In contrast, MHC class II molecules are physiologically only found on professional antigen-presenting cells (APCs) such as dendritic cells, macrophages, and Langerhans cells. APCs use MHC class

II to present phagocytosed and processed antigen epitopes to CD4⁺ lymphocytes.⁹⁴ If epitopes are recognized by CD4⁺ T cells with cognate TCRs, activation ensues with rapid increase in the secretion of pro-inflammatory cytokines that classically support the activities of CD8⁺ T cells and/or B cells.^{94,95} However, MHC class II expression can also be induced on other cells,⁹⁶ including keratinocytes, by IFN γ .⁹⁷⁻⁹⁹ Keratinocytes expressing MHC class II can successfully present antigen epitopes to CD4⁺ T cells,^{100,101} although it is unclear at what level of efficacy this actually occurs in human skin *in vivo*.

Of great significance for understanding AA susceptibility, subtle changes to MHC structure, encoded by specific gene alleles, can determine increased or reduced presentation of specific antigen epitopes.¹⁰² Consequently, specific alleles for MHC class II, and to a lesser extent MHC class I, can be strongly correlated to various autoimmune diseases, and AA is no exception.^{35,91,103-106} While conflicting evidence has been published on the HLA associations of AA in different populations, large-scale genome wide association studies implicate HLA-DR as a key aetiological driver of AA,¹⁰³ consistent with an important supporting role for MHC class II mediated antigen presentation to CD4⁺ T cells. Polymorphisms in HLA-A,¹⁰⁴ HLA-B (along with MICA)¹⁰⁷ and HLA-C¹⁰⁵ are also linked to AA risk.

While it is as yet unclear what exactly these HLA associations mean for the functionality of HF IP, it is reasonable to assume that the corresponding variations in MHC structure significantly influence the strength at which (auto-)antigens are presented by HF keratinocytes via MHC class I to autoreactive CD8⁺ T cells, or by HF-associated APCs via MHC class II molecules to autoreactive CD4⁺ T cells, that have escaped (HF-dependent?) peripheral tolerance induction.⁵² Subtle, genetically coded changes in MHC structure and function could thus greatly increase the risk of an anti-HF autoimmune attack in the event of HF IP collapse (see below). Specific HLA-DR polymorphisms may also confer decreased risk of AA.¹⁰⁸ For example, it has been proposed that HLA-Dw52a may confer relative AA protection.¹⁰⁹

Given the key roles of MHC class I and II in activation of the adaptive immune system, a very effective method of conferring IP in any tissue is to avoid MHC presentation of antigen epitopes. Not surprisingly, malignant cells exploit this immune escape principle by actively downregulating the presence of MHC on their cell surface.¹¹⁰ Several IP tissues exhibit a relative lack of MHC expression.^{12,111-113} Similarly, normal human and rodent anagen VI HF bulbs are relatively deficient in both MHC class I and II as well as β 2-microglobulin (Figure 1).³⁷ This lack of MHC expression breaks down during the development of AA and both MHC I and II become strongly and ectopically expressed by the lower HF epithelium.^{46,84,114} In contrast, non-classical MHC molecules have been shown to be expressed by normal HFs in mice or human tissues in a hair cycle-dependent manner (Table 2).^{31,32,36} Some non-classical MHC molecules, such as HLA-E and HLA-G, can down-regulate immune responses.¹¹⁵ Whether these MHC immune regulators are functionally involved in HF IP is currently unknown.

Occasional intraepithelial MHC class II⁺ Langerhans cell can be spotted in close proximity to the bulge or isthmus in murine and human HF epithelium. However, the very few CD1a⁺ or ultrastructurally detectable Langerhans cells that are present in human anagen hair bulbs do

not express MHC class II.^{30,36,43,81} This suggests that they are unable to present antigens to cognate CD4⁺ T cells and thus cannot function as professional APCs in anagen HFs. Moreover, in conjunction with the immunoinhibitory mechanisms described below, this renders it likely that autoantigen epitopes which are presented via any residual low-level MHC expression in anagen hair bulbs would induce peripheral tolerance.^{1,31}

5.2 | Cell expressed molecules as “IP guardians”

Programmed death-ligand 1 (PD-L1) is expressed in several tissues and its activity is associated with IP status.^{116–118} PD-L1 delivers an inhibitory signal through PD-1 present on T cells to induce cell anergy.^{119,120} High expression of PD-L1 in placenta contributes to fetomaternal tolerance while PD-L1 deficiency reduces foetus survival.^{117,121,122} PD-L1 is present in proximal HFs on keratinocytes, connective tissue sheath (CTS) and dermal papilla (DP) cells (Figure 1)³⁷. Cultured CTS and DP cells strongly expressed PD-L1, which was involved in suppression of immune responses in co-culture assays; knockdown of PD-L1 or use of blocking antibodies partly removed the immune-suppression and allowed allogeneic peripheral blood mononuclear cells to respond to CTS and DP cells.³⁷ Therapy with PD-L1 has been demonstrated to be effective in experimental psoriasis and vitiligo.¹²³ In contrast, PD-1 or PD-L1 blocking antibody treatment in clinical trials for cancer can trigger vitiligo,¹²⁴ and AA-like hair loss.^{125,126}

The cytosolic enzyme, indoleamine 2,3-dioxygenase (IDO), is expressed by HF bulge cells,³⁰ and may also be expressed at a lower level elsewhere in the HF.^{34,127} IDO catabolizes tryptophan which is critical for T-cell activity.³⁰ IDO expression in HFs is expected to impede any local autoaggressive T-cell activities, thus mirroring the situation in eye and fetomaternal IP.^{78,80} In addition, IDO-expressing cells can increase the number of Treg cells since co-culturing immune cells with IDO-expressing fibroblasts significantly increases the number of CD25⁺ FOXP3⁺ Tregs.¹²⁸

Protein tyrosine phosphatase non-receptor type 22 (PTPN22) inhibits T-cell activation by restricting signalling downstream of T-cell receptor (TCR) activation.¹²⁹ Specific PTPN22 polymorphisms are associated with several autoimmune diseases including rheumatoid arthritis, type I diabetes and systemic lupus erythematosus (SLE).^{130,131} Variants of PTPN22 have been identified as a general risk factor in AA with a particularly strong effect observed for patients with more severe AA presentations.^{132,133} However, nothing is known in terms of the mechanistic significance of PTPN22 in HF IP and AA pathogenesis.

5.3 | The role of death receptors and ligands in hair bulb IP

HFs may also have the ability to block lymphocyte activity through the Fas-Fas ligand (FasL) system, as identified in eye graft models.^{134–136} In fact, mice with mutations in Fas or FasL are largely resistant to the development of AA: When skin from mice with non-functional Fas or FasL are grafted to AA-affected mice, the grafted skin remains resistant

to AA and hair continues to grow from the grafted skin.¹³⁶ Also of note, inhibition of Fas/FasL-mediated apoptotic signalling by the main component of *Astragalus membranaceus*, a medicinal plant with anti-inflammatory, anti-oxidant, anti-viral, and anti-apoptotic properties, improved hair growth in a mouse model of non-inflammatory hair loss.¹³⁷ This raises the as yet unanswered question whether Fas-FasL signalling plays a role in the pathogenesis of human AA. Fas-FasL interaction in AA could be important for regulation of pro-inflammatory cells and/or protection of HF cells from apoptosis.

TNF α can promote apoptosis in receptor (TNFR1)-expressing cells.¹³⁸ TNF α appears to be required for normal catagen development,¹³⁹ the apoptosis-driven HF involution stage of the hair cycle.¹⁴⁰ Classically, TNF α is produced by lymphocytes and dendritic cells and this promotes apoptosis in non-immune system cells expressing TNFR1 and also increases MHC expression.^{141,142} AA has been treated successfully with TNF α antagonist adalimumab.¹⁴³ However, while TNF α stimulation promotes keratinocyte apoptosis in the murine anagen hair bulb,¹⁴⁴ it does not induce HF IP collapse, in striking contrast to IFN γ .^{32,76} Further, there are several case reports of TNF α -antagonist drugs inducing AA.^{145–147} The question arises, therefore, whether TNF α promotes AA or might confer relative immune resistance to AA?

While TNF α can drive cell apoptosis, and induce a dysregulated type I interferon response,¹⁴⁸ it can also promote select immunoregulatory activities. For example, TNF α can induce the expression of IDO in corneal tissue and has a synergistic effect on IDO promotion when combined with IFN γ .¹⁴⁹ In the presence of TGF β , TNF α can promote a tolerogenic state in APCs,^{150,151} possibly by suppressing IL-12,^{152,153} which in turn promotes Treg cells.¹⁵⁴ TNF α can induce programmed death-ligand 1 (PD-L1) expression on mast cells.¹⁵⁵ In an experimental autoimmune encephalomyelitis (EAE) mouse model, TNF α deficiency exacerbates the disease,¹⁵⁶ and there are case reports of TNF α antagonist induced demyelination and exacerbation of multiple sclerosis.^{157,158} Whether a pro-apoptotic or anti-inflammatory role is dominant in AA is likely determined by the status of other pro- and anti-inflammatory cytokines, the expression of Fas-FasL, and/or the expression of TNFR1 versus TNFR2.^{138,141,142,159}

Other TNF family death receptors and ligands, such as TRAIL-TRAILR1/2, TWEAK-Fn14 and death receptor decoys TRAIL-R3 and TRAIL-R4,¹³⁸ have not been investigated in AA in any detail. Given these receptor-ligand interactions are all part of the same TNF superfamily, pleiotropic function might also be anticipated.^{138,141,142,159} Of particular note, TRAIL may play a significant role in maintaining tolerance to eye antigens.¹⁶⁰ Recently, increased expression of TWEAK was identified in AA patients, but whether it confers resistance or susceptibility to AA is unknown.^{161,162}

5.4 | The role of secreted factors as “HF IP guardians”

The first line of HF protection from undesired and potentially deleterious immune responses likely involves secreted factors that

create an immunoinhibitory cocoon around every healthy HF, beginning at the level of the bulge (Figure 1). Several potent immune suppressors, such as α MSH, TGF β 1, TGF β 2, cortisol and IL-10, are generated by the epithelium of healthy HFs.^{76,84,163-165} Together, under physiological conditions, these factors may allow HFs to regulate immune cells in the surrounding vicinity of the HFs and dampen their pro-inflammatory activities well in advance of any contact with HF tissues.

The functional importance of some of these secreted HF IP guardians as protectors against and as restorers of IFN γ -induced HF IP collapse, such as α MSH, TGF β and IL-10 and IGF-1, has been documented in organ-cultured human HFs and skin.^{76,166} The IP guardians TGF β 1¹⁶⁷ and TGF β 2^{30,168} are expressed in the HF outer root sheath (Figure 1). The expression of these factors may prevent the attack of NK and CD8⁺ T cells in tissue characterized by downregulated MHC class I.^{168,169} Further, TGF β 2 can help convert effector T cells into Treg cells.¹⁷⁰ An apparent deficiency in cytokine Red/IK is present in human HFs in advance of overt hair loss.³⁴ Red/IK downregulates the expression of MHC molecules and interferes with immune cell activation.^{171,172}

Macrophage migration inhibitory factor (MIF) is produced by HFs and may contribute to IP.^{88,173} It is known to inhibit innate immune cell migration, and it is a potent inhibitor of NK cell function.^{30,88,173-175} Further, thrombospondin 1 (TSP1), a secreted glycoprotein that can mediate immunoregulation,¹⁷⁶ may also be expressed by HFs.^{177,178}

There are likely other immunoinhibitory factors secreted by HFs that remain as yet unidentified, but together with those mentioned above, the immunoinhibitory functions of perifollicular mast cells (see below),¹⁷⁹ and perhaps also tolerogenic dendritic cells as seen in mouse studies,¹⁸⁰ they create an immunosuppressive, tolerance-promoting signalling milieu in and immediately around the lower HF. It is as yet very poorly understood though, which genes control this special immune environment and regulate its restoration whenever exposure to an abundance of pro-inflammatory signals/stressors threatens its collapse.

5.5 | AIRE function in HF IP

One of these as yet unknown regulatory, HF IP-protective genes could be the tolerance-promoting autoimmune regulator gene (AIRE), which may be defective in some AA patients. AIRE controls the expression of tissue specific antigens in the thymus.¹⁸¹ This helps to eliminate autoreactive T cells, induces regulatory T-cell (Treg) production and may even encourage some autoreactive T cells to

directly differentiate into Treg cells.¹⁸² AIRE expression by dendritic cells in the periphery likely promotes tolerization of autoreactive cells.^{181,183} AIRE is also expressed in HF keratinocytes and closely associates with keratin 17.¹⁸⁴ While its significance remains unclear, AIRE in keratinocytes may regulate keratin 17-dependent pro-inflammatory gene expression.¹⁸⁵

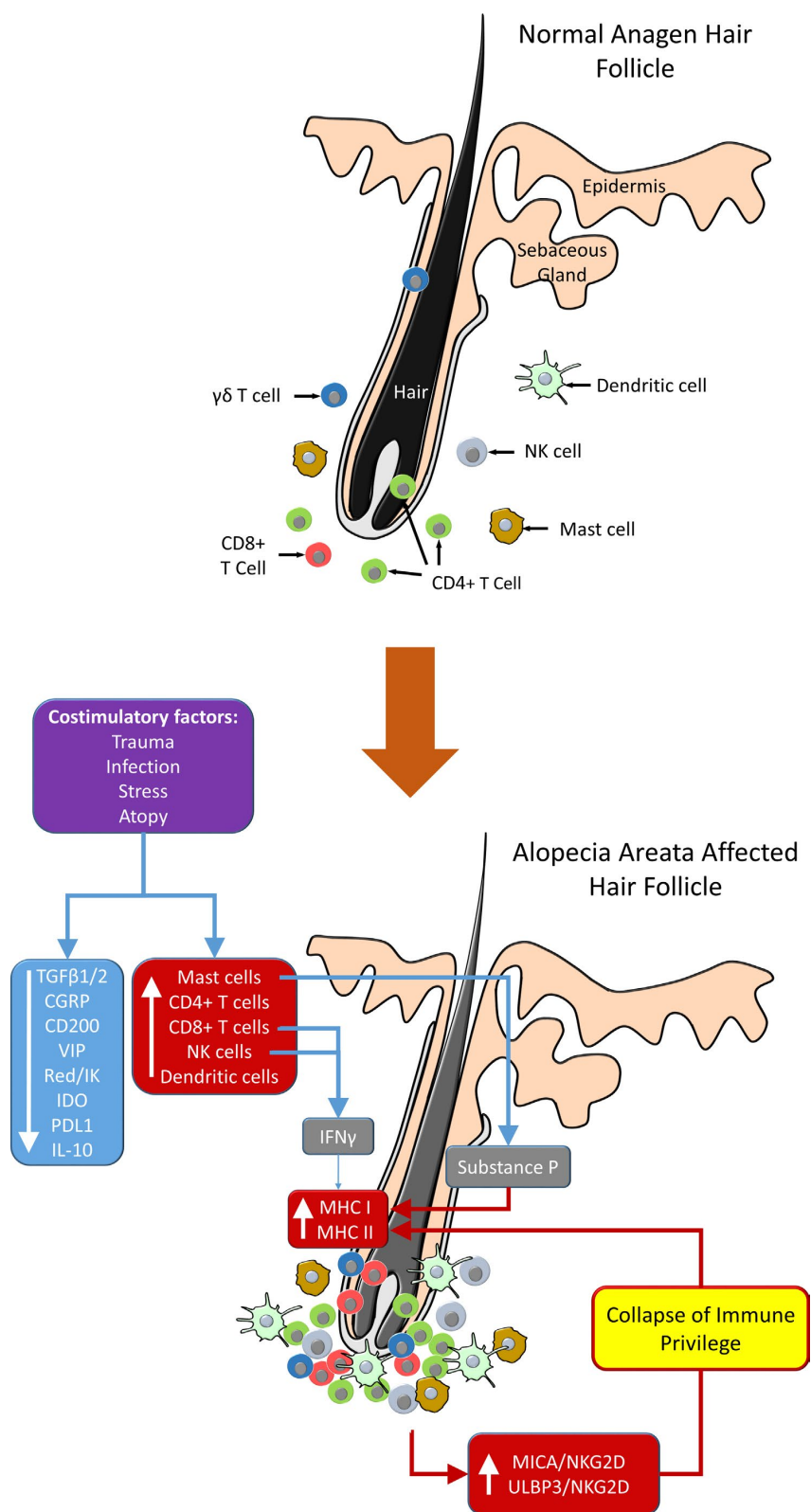
A loss-of-function mutation in AIRE interferes with autoreactive lymphocyte deletion and impairs the regulatory function of Treg cells.¹⁸⁶ AIRE mutations also skew CD8⁺ T cells towards an effector cytotoxic phenotype.¹⁸⁷ Mutations of the AIRE gene cause the monogenic autoimmune disease, polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED),¹⁸⁸ and notably, there is an unusually high frequency of AA in APECED patients.¹⁸⁹ Specific AIRE polymorphisms have been identified in association with vitiligo¹⁹⁰ and AA,^{189,191,192} though results are conflicting.¹⁹³ Identifying a significant role for AIRE has rekindled interest in the role that Tregs play in the maintenance of physiological HF IP, as opposed to defective Treg functions in AA.¹⁹⁴⁻¹⁹⁸ Owing to this progress in research, the original HF IP scenario, and how its failure predisposes and can lead to AA, has become much more complex (see Figure 2) (for discussion, see⁴ incl. supplement).

5.6 | The role of neuropeptides and neurohormones in supporting IP

Immunosuppressive neuropeptides secreted by sensory nerve fibres that insert into the densely innervated HF epithelium^{199,200} may also serve as HF IP guardians. Human HF organ culture-based evidence suggests that this includes calcitonin gene-related peptide (CGRP), a key immunoinhibitory neuropeptide that is often co-expressed with pro-inflammatory substance P in sensory nerve fibres of murine and human skin.^{200,201} CGRP significantly reduces IFN γ -induced degranulation of perifollicular mast cells.⁹⁹ That CGRP is indeed a HF IP guardian has been confirmed by independent investigators.²⁰² Also of note, CGRP suppresses nitric oxide (NO) activity in eye IP.²⁰³

More recent evidence suggests that vasoactive intestinal peptide (VIP), a central IP guardian in the anterior eye chamber,^{78,79} also contributes to human HF IP. VIP is expressed in, and released from, perifollicular sensory nerve fibres⁹⁸ that insert into the richly innervated, VIP receptor-positive HF epithelium^{200,204} in human skin, but does not appear to be expressed by the HF epithelium itself. Further, previous research demonstrated that the neurohormone somatostatin was strongly expressed in human HF epithelium and had a significant immunosuppressive effect using allogeneic co-culture cell assays.³⁶ Somatostatin suppresses T cell activity,²⁰⁵⁻²⁰⁷ inhibits

FIGURE 2 A working model of AA pathobiology. During the normal hair growth cycle (A), isolated immune cells can be found around and very occasionally within the bulb of an anagen stage HF. With the development of AA (B), the time duration of the anagen stage of the hair growth cycle is significantly shortened, and the growth of hair fibre becomes progressively disordered. A characteristic inflammatory cell infiltrate is associated with these changes to the HF. The perifollicular inflammatory cell infiltrate contains CD4⁺ T and CD8⁺ T cells, mast cells, NK cells and dendritic cells. CD8⁺ T cells are typically the first cells to penetrate to intra-follicular locations, closely followed by dendritic cells/macrophages. CD4⁺ T cells are rarely found in intra-follicular locations until late in the disease process when the integrity of the HF is severely disrupted (Figure modified from Ref. [4,196])



expression of activation markers and proliferation of T cells²⁰⁸ and decreases IFN γ release by leucocytes.^{209,210}

Together with the previous demonstration that substance P is the second-strongest HF IP collapse inducer after IFN γ reported in human HFs so far,⁷⁷ it is conceivable that sensory skin nerve-derived neuropeptides have a profound impact on HF IP, primarily in the bulge region, but also to a lesser extent in the innervated HF bulb. It has already been shown that the stress-associated neuropeptide, substance P, plays a key role in the induction of perifollicular inflammatory cell infiltrates and murine HF IP breakdown under conditions of neurogenic skin inflammation induced by perceived stress.^{211,212}

Corticotropin-releasing hormone (CRH) functions as the upstream regulator of neuroendocrine stress responses.²¹³ It controls adrenocorticotrophic hormone (ACTH) and cortisol production in human scalp HFs,^{163,164} which display a fully functional peripheral equivalent of the central hypothalamic-pituitary-adrenal (HPA) axis.¹⁶³ As discussed in-depth elsewhere,¹⁶⁴ even though many details are still obscure, the regulated neuroendocrine activity of the HPA axis equivalent in human HFs affects HF IP on several levels. Specifically, CRH, ACTH and β -endorphin activate mast cells present in the CTS, while the potent immunoinhibitors, α MSH and cortisol, can act as HF IP guardians.¹⁶⁴ During anagen, the epithelium of human scalp HFs strongly expresses ACTH and stimulates intra-follicular cortisol generation and subsequent immunosuppressive activity.¹⁶³ α MSH, derived from the cleavage of pro-opiomelanocortin polypeptide,^{30,214,215} is strongly expressed in HFs.^{76,165,216,217} Expression of α MSH can suppress the activities of IL-1 and TNF α , and blocks endotoxin activation via toll like receptor-4.^{218,219}

5.7 | Support of hair follicle immune privilege by CD4⁺ regulatory T cells

Regulatory T cells (Tregs) are a subpopulation of lymphocytes which skew immune responses towards peripheral tolerance^{10,24-26,220} and are involved in preventing autoimmunity.^{221,222} Tregs come in several forms with the most well-understood being those that are CD4⁺, CD25⁺ and Foxp3⁺ (natural Tregs).²²³ Tregs manifest their regulatory function through several mechanisms including cell-cell contact regulation via TCR, and other molecules such as cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), GITR and LAG-3.²²⁴ They also promote immunosuppression in their vicinity via secretion of immunomodulatory soluble factors such as IL-9, IL-10, TGF β and IL-35.²²⁵⁻²²⁸ Mouse studies demonstrate that Treg suppression mediated via cytokines is of particular importance at environmental interfaces, such as the gut, lungs and skin.^{225,229,230} In autoimmune diseases, a lower frequency of Tregs is often observed in the active disease state.^{231,232} Unsurprisingly, a genetic deficiency in Treg production significantly increases the risk of autoimmune disease development.²³³

Treg cells require maintenance signals from their local environment. Among these signals, TGF β appears to have a crucial role in Foxp3 maintenance of Treg cells and the ability of Treg cells to

induce non-Tregs to develop regulatory properties, a phenomenon known as infectious tolerance.^{234,235} HFs likely promote Treg cells in their immediate vicinity. Foxp3 transcription can be induced by several pathways: first by TGF β signalling through induction of SMAD3 and suppression of extracellular signal-regulated kinases (ERKs); second by IL-2, IL-7 and/or IL-15 expression (which maintains Foxp3 expression when in the presence of TGF β), signalling through the intracellular signalling molecule, signal transducers and activators of transcription TCR T cell receptor (STAT) 5, which binds the Foxp3 promoter; and third through the TCR and nuclear factor of activated T cells (NFAT).²³⁶⁻²³⁸ IL-7, IL-15 and TGF β are all expressed by HF epithelium.^{30,167,168,179,239} Overall, Tregs have a significant role to play in HF IP maintenance within the skin in close proximity to HFs and also may confer protection to HFs in other body locations where antigen presentation to T cells is active.

5.8 | Perifollicular mast cells may exert immunoinhibitory functions

The potential contribution of perifollicular mast cells to HF IP remains to be fully dissected. Mast cells have been shown to exert hair growth regulatory activities in mice.^{1,56,65} However, immunohistological evidence suggests that perifollicular mast cells are a key innate immunocyte population in the HF mesenchyme and may help to maintain HF IP under physiological circumstances. In the connective tissue sheath of healthy human scalp HFs, these perifollicular mast cells display an immunoinhibitory phenotype characterized by high expression levels of TGF β 1, IL-10 and PD-L1, which switches to a profoundly pro-inflammatory phenotype when perifollicular mast cells are associated with lesional AA HFs.¹⁷⁹

In recent years, mast cells have emerged as important contributors in the induction of tolerance or immunosuppression. They have been shown to promote tolerance through induction of Treg cells and the production of IL-9 in a mouse model of skin allografts.²⁴¹⁻²⁴⁴ In an in vitro co-culture system, murine mast cells have been shown to increase the percentage of CD4⁺, CD25⁺ and FoxP3⁺ regulatory T cells in a TGF- β 1-dependent manner.²⁴⁴ In the skin, mast cells limit inflammatory reactions by the production of IL-10.²⁴⁵ In naïve bone-marrow derived mast cells, we could show that the expression of PD-L1 was high and constitutive,²⁴⁶ further supporting that in homeostatic conditions mast cells preferentially display an immunoinhibitory phenotype. Interestingly, an inhibitory function of mast cells has also been observed in cancer. They increase with tumor progression and negatively correlate with patient survival, in part because tumor-infiltrating mast cells may suppress normal T-cell immunity through the upregulation of PD-L1.¹⁵⁵

5.9 | Other cells with a potential role in HF IP

It is expected that further dissection of HF IP will reveal that, besides Tregs, other perifollicular immunocyte subpopulations will

turn out to contribute to HF IP maintenance such as inhibitory NK cells,²⁴⁷ immunoregulatory CD8⁺ T cells²⁴⁸ and tolerogenic dendritic cells.¹⁸⁰ Throughout the ongoing exploration of HF IP in rodents and humans, prior progress in understanding fetomaternal and ocular IP has provided key pointers and theoretical concepts (reviewed in Ref. [25,78,111,249,250]). Recently, however, we have argued that these classical IP models, particularly ocular IP, may also profit greatly from investigating human HF IP, since the latter is so much more accessible and tractable than the human eye.⁷⁹ This exploratory journey continues today, and we may still have only scratched the surface of what is biologically fascinating and clinically important about HF IP.

6 | COLLAPSE OF HF IMMUNE PRIVILEGE

Billingham's visionary HF IP concept²² did not gain much traction among immunologists or hair researchers, even after Westgate and colleagues re-emphasized this concept.⁸⁴ This motivated us and others to systematically characterize the immunology of mouse and human HFs, which—until then—had largely been *terra incognita* on the map of cutaneous immunobiology and immunodermatology (reviewed in Ref. [1]). Yet, Westgate's hypothesis that IP collapse is somehow important for catagen development⁸⁴ remains unsupported and may be misleading. Currently, there is no evidence that catagen development requires HF IP collapse, and the postulated switch of the previously MHC class I-negative HF epithelium to an MHC I-positive state during catagen does not really occur: instead, a pseudo-switch in MHC Ia expression patterns is mimicked by the rapid disappearance of MHC I-negative HF keratinocytes during catagen³¹ due to massive keratinocyte apoptosis.¹⁴⁰ However, Westgate's timely resuscitation of Billingham's HF IP concept encouraged us to formulate the hypothesis that the collapse of HF IP lies at the heart of AA pathogenesis (Table 2).⁴³

Antigenic challenge or activated lymphocyte cell transfer can induce autoimmune disease against most IP sites including the testes,^{251,252} cornea²⁵³ and pregnant uterus.²⁵⁴ HF IP may also be broken by activating the immune system against HF autoantigens through active immunization, as suggested by some induction models of AA,^{45,255–257} or transgenic promotion of HF antigen-specific TCRs.³⁹ More significantly, passive transfer of lymphocytes or plasmacytoid dendritic cells from a mouse with AA to a naïve recipient lead to onset of localized AA, later leading to a more extensive hair loss.^{258,259} These observations indicate that passive sequestration of antigens behind basement membrane barriers and absence of MHC class I and II is not enough to fully explain the manifestations of HF IP. Secreted immunoregulatory factors that actively suppress the skin immune system are likely also significant in conferring IP. If so, then deficiencies in one or more of these secretory factors may leave an individual more susceptible to the onset of HF autoimmunity (Table 2). This concept has now become widely accepted as an important, if not critical element in the pathobiology of AA.^{4,33–37,42,75,260,261}

7 | ALOPECIA AREATA

Through its long history, a link between AA and inflammation has been well recognized.²⁶² It presents with a wide array of clinical and aetiological variations,^{263,264} but in all instances it is a non-scarring alopecia.^{265,266} Histopathological examination reveals anagen stage HFs affected by a peri- and intra-follicular inflammatory cell infiltrates primarily comprised of CD8⁺ T cells and CD4⁺ T cells,²⁶⁷ as well as antigen-presenting cells (APCs),^{259,268} mast cells,¹⁷⁹ NK cells⁸⁸ and sometimes eosinophils.²⁶⁹ While CD8⁺ T cells readily penetrate follicular regions, CD4⁺ T cells primarily reside in perifollicular locations in AA.^{267,270,271}

Paus and colleagues have recently postulated that AA does not necessarily represent a single disease entity, but rather it encompasses a *stereotypic HF response pattern*.^{6,272} When confronted with a defined, IFN γ -dependent pro-inflammatory signalling milieu, even perfectly healthy anagen HFs in genetically non-predisposed individuals are at risk to undergo HF IP collapse and subsequent HF dystrophy as well as premature catagen development, which can progress to the AA phenotype. According to this new paradigm, "autoimmune AA [AAA]" only occurs in a subset of AA patients on the basis of a genuine, HF autoantigen-dependent autoimmune response pattern involving autoreactive CD8⁺ T cells (see Table 3, 1a-c).⁶ No matter how this stereotypic HF response pattern is initiated, it cannot progress to the pathognomonic clinical features we diagnose as AA (ie focal or widespread hair loss in clinically healthy-appearing skin, cadaver and exclamation mark hairs, with regrowth of white hair shafts),⁴ without several events co-occurring (Table 3).

This multiple pathway concept of AA pathogenesis provides the first satisfactory explanation for the clinical heterogeneity of AA patients, including the very different clinical courses observed (eg spontaneous remission without AA ever relapsing, versus rapidly progressive course advancing towards alopecia universalis), major differences in the presence/absence of associated diseases (atopy, other autoimmune diseases) and clinical signs (nail dystrophy, uveitis), and the striking differences of AA patients in their response to therapy (even to JAK inhibitors, which fail to work in 20%-30% of patients).⁸

8 | HAIR FOLLICLE IMMUNE PRIVILEGE COLLAPSE AS A PREREQUISITE FOR ALOPECIA AREATA TO OCCUR

Initially, the concept that a collapse in human anagen hair bulb IP is a crucial component of AA pathogenesis^{1,43} met with much resistance in the field. More than a quarter of century later, not the least due to sound experimental evidence that has been presented in its support (eg Ref. [34,45,256,273]), this concept has become widely accepted as the most important element in the pathobiology of AA.^{4,33,75,260,261} In essence, the IP collapse concept of AA pathobiology postulates that HF IP breakdown is an essential prerequisite for the clinical AA phenotype to occur. However, on its own, HF IP failure is insufficient for the development of AA, and at least 3-4

TABLE 3 AA pathobiology: Current working model

	AA typically only develops when 4-5 phenomena coincide:	Clinical disease state
1a 1b 1c	Tolerance against MHC class-I presented, anagen/melanogenesis-associated HF autoantigens is lost—eliciting HF infiltration by autoreactive CD8 ⁺ T cells (an “autoimmune AA” pattern) And/or Excessive HF IP collapse inducers (such as IFN γ , substance P released from perifollicular sensory nerve fibres) are secreted by NK/NKT cells and/or other NKG2D ⁺ immunocytes in a <i>non-autoantigen-specific</i> manner, in response to HF distress signals (eg excessive MICA expression or chemokine secretion as a result of HF oxidative damage, defective autophagic flux, or dysbiosis) (a “non-specific inflammatory alopecia” pattern) And/or A constitutively weak HF IP (eg due to relatively high levels of MHC class I and MICA expression, low intra-follicular production of IP guardians, low HF expression level of IP guardian receptors and/or insufficient immunoinhibitory properties of Treg cells or perifollicular mast cells [especially in atopic individuals])	AA pathogenesis events occurring in advance of overt hair loss from the affected hair follicle(s)
2	HF immune privilege collapses , that is loses its immunoinhibitory, tolerance-promoting functionality, induced by 1a and/or 1b and/or 1c, which can no longer be counter-balanced by the combined activity of IP guardians. Step 2 is an absolute requirement for AA to develop	
3	HFs are already in, or enter into, anagen III-VI, that is the hair cycle window during which mature, anagen HF-associated, autoantigens are generated (eg melanogenesis-associated peptides)	
4	Normally sequestered HF autoantigens are now presented via ectopic MHC I/ β 2-microglobulin expression to infiltrating autoreactive CD8 ⁺ T cells Step 4 is an absolute requirement for autoimmune AA (AAA) to develop	
5	Appropriate co-stimulatory and supporting signals are received from various sources including; CD4 ⁺ T cells, mast cells, and/or dendritic cells, which promote cytotoxic CD8 ⁺ T cells' damage of HFs and counteract the attempt of HF cells to re-establish IP 1. Clinical disease develops when HF inflammation intensity, primarily driven by autoreactive T cells, reaches a threshold level of negative impact on HFs in the vicinity, whose IP also collapses, resulting in HF dystrophy and/or premature catagen development 2. HF IP collapse during AA represents a hair cycle-related dual abnormality:a) only anagen III-VI HFs are attacked by autoreactive T cells and become dystrophic, and b) HF IP collapse results in autoreactive T-cell inflammation leading to rapid, premature anagen termination (catagen induction) 3. Hair regrowth occurs when HF IP is re-established, spontaneously or as a result of therapy (currently no AA therapy reliably achieves this)	Onset of overt clinical features of AA including hair shedding

additional pathogenic conditions need to coincide for the clinical AA phenotype to develop (Figure 3; Table 3). This specific constellation likely occurs relatively rarely, thus explaining why only a small minority of individuals ever manifest the stereotypic AA response pattern of HFs to IFN γ -dominated follicular damage.

8.1 | The role of T cells in immune privilege collapse

It is now the most reasonable working model to consider the autoimmune variant of AA (AAA) as an organ-specific, CD8⁺ T cell-driven autoimmune disease.^{4,6,33,274} The key role of cytotoxic CD8⁺ cells in human AA was first demonstrated by Gilhar et al (1998) and has more recently been confirmed in a mouse model of AA, in

which the JAK pathway in CD8⁺ cells was identified as an important target for pharmacological intervention.⁴² AA can be transferred by CD8⁺ T cells alone, which recognize and respond to anagen HF-associated autoantigens that are presented by ectopically expressed MHC class I molecules, so long as they receive appropriate co-stimulatory signals (Figure 3; Table 3). Clonally expanded specific CD8⁺ T-cell populations can be identified in or immediately adjacent to AA-affected HFs.²⁷⁵ In addition, CD8⁺ T cells autoreactive against melanocyte and keratinocyte epitopes have been identified in AA.⁴⁹ While CD4⁺ T cells may not directly instigate hair loss, rodent studies suggest their classic “helper” role is significant in AA pathogenesis. Depletion of CD4⁺ T cells enables hair regrowth,²⁷⁶ while transfer of CD4⁺CD25⁻ T cells from AA mice can produce AA in recipients.²⁵⁸

8.2 | The role of NK/NKT cells in immune privilege collapse

NK and NKT cells, their receptors and their activating ligands, have prominently entered the AA pathogenesis debate.^{35,88,277,278} The number of NKG2D⁺ cells (such as NK, NKT and subpopulations of cytotoxic CD8⁺ T cells) is greatly increased in and around lesional human AA HFs, while HFs also overexpress activating NKG2D ligands such as MICA and ULBP3.^{35,42,88,278} This has integrated AA into the growing group of autoimmune disorders where pathological NK cells and/or NKT cells are appreciated to play an important role in disease pathogenesis.²⁷⁹ Using a humanized mouse model of AA, Gilhar and colleagues have provided further functional evidence for this concept: The injection of large numbers of autologous IL-2-stimulated (activated) CD56⁺ and NKG2D⁺ cells (T cells, NK and NKT cells) from healthy donors into healthy human scalp skin transplanted onto SCID/beige mice suffices to induce a clinical phenotype of AA in the skin transplants.²⁷⁸ Hence, AA should be viewed as a HF response pattern, for whose initiation a genuine autoimmune response pattern is only one of several distinct options (Figure 3; Table 3, 1a-c).^{4,6,33,44}

8.3 | The role of mast cells in IP collapse

Since mast cells can drive antigen-specific cytotoxic CD8⁺ T-cell responses²⁸⁰ and are present in the CTS of murine and human HFs,^{56,65,81,281} they may play an important role as promoters of autoimmune responses.^{282,283} Perifollicular mast cell-CD8⁺ T-cell interactions are quantitatively increased and qualitatively altered in AA.¹⁷⁹ Mast cells strikingly switch from an immunoinhibitory phenotype and infrequent interactions with CD8⁺ T cells to a profoundly pro-inflammatory phenotype and greatly enhanced interactions with CD8⁺ lymphocytes, and—highly unusual for mast cells—even proliferate around lesional HFs *in situ*.¹⁷⁹ This supports the concept that pathological mast cell-T cell interactions may contribute to the pathogenesis of human AA, perhaps particularly so in atopic individuals.^{6,44,179} Recent experiments have demonstrated that the AA phenotype can also be triggered by non-antigen-specific innate lymphocytes such as type 1 innate lymphoid cells.^{44,284} Therefore, besides mast cells, several innate and adaptive immune cell lineages may be functionally important in AA pathogenesis.

8.4 | Pro-inflammatory mediators of IP collapse

IFN γ is arguably the most important inducer of HF IP collapse.^{4,33,273,285} Mice genetically deficient in IFN γ are resistant to induction of AA.²⁸⁶ Interestingly, AA and vitiligo share many similarities as they are driven by IFN γ signalling and appear to be primarily dependent on IFN γ .⁴⁷ This cytokine is also the most potent catagen inducer in human anagen HFs known so far.²⁸⁵ Autophagy

can be induced by IFN γ ,²⁸⁷ and recent studies suggest genes related to autophagy may aberrantly expressed in AA.²⁸⁸ Autophagy is a mechanism for processing cytosolic proteins and organelles for degradation, such as with melanosomes for example,^{289,290} and is required for anagen maintenance in human scalp HFs *ex vivo*.²⁹¹ Since deficiencies in autophagy are found in several autoimmune diseases, where they lead to increased pro-inflammatory cytokine expression including IFN γ ,²⁸⁸ it is conceivable that defective autophagic flux may contribute to the cascade of pro-inflammatory events that culminates in HF IP collapse (Table II).

Besides IFN γ , the major stress- and neurogenic inflammation-associated neuropeptide, substance P,^{212,292,293} has also surfaced as a powerful inducer of HF IP collapse in mice⁷⁵ and humans.⁷⁷ Genetic and immunological studies in mouse models of AA and in AA patients have revealed additional players; these likely contribute to HF IP maintenance, while their defective function may predispose individuals to develop AA lesions. These players prominently include the following: CTLA-4, an important T-cell immunoinhibitory surface molecule, CTLA4 ligands CD80 and CD86,²⁹⁷⁻²⁹⁹ and IL-15,^{42,106,300} a key immunostimulatory cytokine that drives NK/NKT cell development and survival. IL-15 is also a key mast cell regulator and effector.³⁰¹⁻³⁰⁴

Interestingly, it has been suggested that upregulation of IL-15 by HFs in AA, and epidermal keratinocytes in vitiligo, activates effector CD8⁺ cells via JAK1 and JAK3 leading to the development or exacerbation of the disease.^{42,239,305} Yet, it remains unknown how IL-15 affects HF IP. Moreover, the fact that that IL-15 operates as a potent suppressor of apoptosis in multiple cell types and tissues,³⁰⁶ including in the HF epithelium,³⁰⁷ renders it unlikely that IL-15 is key driver of the characteristic AA-associated HF dystrophy and premature catagen development. Also, *in vivo*, an IL-15-IgG2b fusion protein that prolongs IL-15 half-life actually promoted a Th2 response in mice, rather than the Th1 response that dominates acute AA.³⁰⁸ Thus, the role of IL-15 in AA pathobiology remains to be clarified.

8.5 | Immune regulatory cells and IP collapse

In humans with AA, Treg cells may be functionally impaired.^{194,309} While these early studies did not identify a deficiency in Treg numbers, later reports suggest there is a decrease in the quantity of Tregs in humans with AA,³¹⁰⁻³¹² and in AA-affected mice.²⁵⁸ Transfer of unexpanded Treg cells from AA mice to healthy recipients was less likely to induce an AA phenotype: rather, Treg transfer could prohibit systemic AA development promoted by CD4⁺CD25⁺ cells as well as prevent injection site-specific hair loss induced by CD8⁺ T cells.²⁵⁸ Mice resistant to the onset of AA exhibit high levels of regulatory cytokines such as IL-10.³¹³ On the one hand, these observations indicate that the normal regulatory properties of Treg cell populations may be deficient in AA development.

On the other hand, Tregs are characterized by their plasticity and functional instability under inflammatory conditions.³¹⁴ It has been

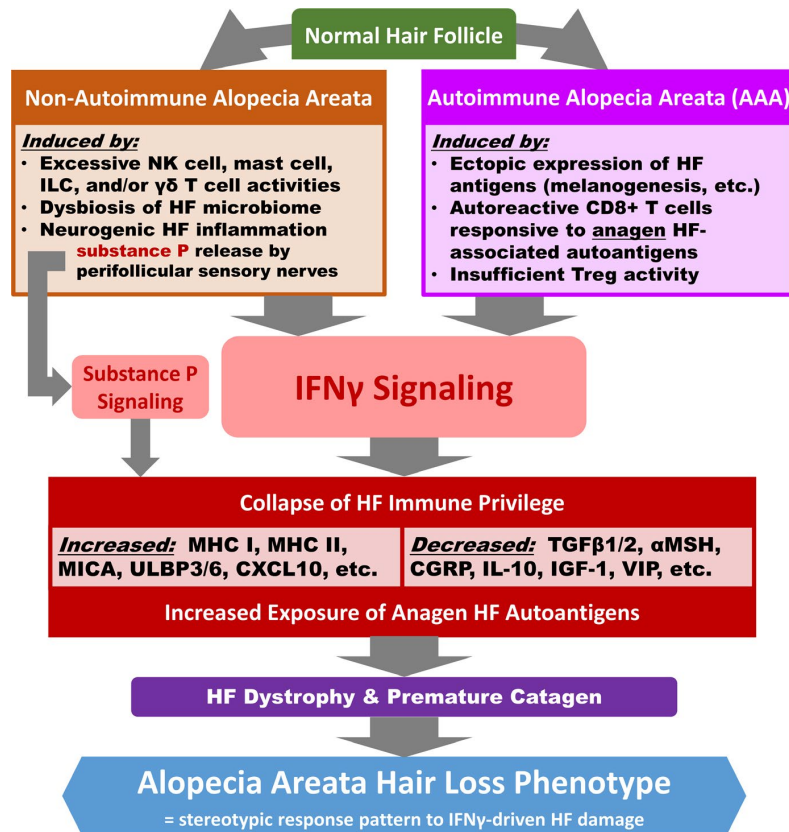


FIGURE 3 AA pathogenesis. A flowchart summarizing the cascade of events leading to the onset of AA. In non-autoimmune AA, pro-inflammatory activity from NK cells, mast cells, ILC and/or $\gamma\delta$ T cells, or alternatively dysbiosis of the HF microbiome, or neurogenic HF inflammation, elicit production of IFN γ and/or substance P release by perifollicular sensory nerves. In autoimmune AA (AAA), ectopic expression of HF antigens (during melanogenesis, inner root sheath and hair shaft production, etc) elicit a response from autoreactive CD8⁺ T cells specific for anagen HF-associated autoantigens. Onset of AAA may also involve insufficient Treg activity. AAA causes an increase in IFN γ -mediated signalling. Substance P and/or IFN γ produced as a result of non-autoimmune AA, or IFN γ produced as a result of AAA, causes IP collapse with increase in pro-inflammatory factors and significant decrease in the expression of IP guardians. The net result is a significant increase in exposure of anagen HF autoantigens to immune cell surveillance. The influx of pro-inflammatory cells responding to the exposed HF autoantigens induces HF dystrophy and premature catagen. Ultimately, the cascade of events, whether activated by non-autoimmune AA or activated by AAA, leads to the same AA hair loss phenotype climax; a stereotypic response pattern to IFN γ -driven HF damage

observed that in response to inflammatory conditions, Tregs can be converted to pro-inflammatory-helper cells and thus may serve as essential contributors to long-lasting inflammatory diseases.³¹⁵ Decreased stability of Foxp3 expression and increased proportions of Th1-like IFN γ -expressing cells have been shown to promote inflammation in autoimmune diseases, such as type 1 diabetes, juvenile arthritis and multiple sclerosis.^{316,317} In addition, studies demonstrate that the pathological conversion of Tregs contributes to the loss of corneal IP.³¹⁸ A possible role for unstable Tregs in AA pathogenesis has not been studied. However, the apparent plasticity of Tregs does not undermine their importance in the maintenance of IP, which is widely reported by the literature.¹⁰

It should be emphasized that Treg cells are not the only cells to regulate immune responses.³¹⁹ Previously, our group described

regulatory NK and NKT functions in AA mouse models.^{247,277} A role for these cells has also been described in various autoimmune diseases,³²⁰⁻³²² including rheumatoid arthritis and psoriasis.³²³ The literature reveals that there are different NK and NKT subsets including regulatory ones.^{324,325} Collectively, these studies indicate that multiple cell types may have roles in AA aetiology by breaking the delicate balance between scalp skin-resident memory T cells versus immune cells with regulatory effects.⁴⁴

9 | THERAPEUTIC PERSPECTIVES

Since failure of IP mechanisms enables AA development, it is logical to anticipate that restoring and/or supplementing IP signalling

is a highly effective way to treat AA and prevent future relapse. Exogenous factors could modify the nature and intensity of IP and its breakdown in AA including the HF and gut microbiomes,³²⁶ the bioavailability of energy for immune cell activity³²⁷ and atopic responses to environmental allergens,^{264,328} for example. As such, targeting these external factors with treatment may facilitate IP regeneration in AA-affected HFs. There is also some evidence that current therapies indirectly facilitate HF IP restoration. For example, the potent IP guardian, α MSH, increases when AA is treated with UVA-1 phototherapy.³²⁹ Diphenylprone (DCP) treatment normalizes MHC expression in HFs and promotes IL-10 and TGF β 1 expression.³³⁰⁻³³² However, more direct approaches would likely achieve greater improvements in IP to prevent and reverse AA.

Several neuropharmacological drugs³³³ and other treatments are in development or currently available that hold potential for regenerating HF IP (Table 4), though these drugs are largely untested for use in treating AA. For example, the immunosuppressive drug FK506 (tacrolimus)^{334,335} downregulates MHC class I expression and has been shown to protect HFs from IFN γ -induced IP collapse in ex vivo studies.⁷⁶ Despite some success in rodent models,^{336,337} clinical trials with topical FK506 have been unsuccessful, probably due to poor skin penetration.³³⁸⁻³⁴⁰ However, in a case report systemic FK506 produced a hair growth response.³⁴¹ Special formulations may be needed to improve transcutaneous drug penetration, or perhaps intradermal injection can be used, as for corticosteroids,^{342,343} or microneedling.³⁴⁴

Beyond repurposing and reformulating drugs developed for other diseases, the process of HF IP collapse presents multiple key events that could be targeted with more specific therapeutic interventions (Table 5). Much more systematic research and development is needed to provide clinicians with better, practically useful therapeutic options in AA management beyond corticosteroids, DCP and JAK inhibitors.

Where there are defects in normal HF IP signalling, supplementing or replacing deficiencies, or suppressing factors that break IP, are logical treatment strategies. This might be achieved by gene therapy or direct injection of specific IP-modulating products (Table 5). Research points towards a relationship between AA and genes coding for MHC II and to a lesser extent MHC I, NKG2D/ULBP3,^{35,103} MIF,³⁴⁵ AIRE,^{191,192} FOXP3¹⁹⁷ and CTLA-4.²⁹⁴⁻²⁹⁶ Gene therapies could be topically targeted to HFs to modulate expression,³⁴⁶ and preliminary studies with nanoparticle delivery to AA-affected follicles are promising.³⁴⁷ As such, gene therapy or gene product promotion/interference treatments are obvious contenders for development to reverse HF IP-signalling defects.^{348,349}

Cell therapy for AA also shows promise. Mesenchymal stem cells (MSCs) with IP³⁵⁰ can suppress IFN γ -induced HF inflammation.³⁵¹ Treatment of AA with "stem cell educator therapy," where a patient's blood cells interact with human cord blood-derived multipotent stem cells, seems to confer increased TGF β 1 and PD-1 on cells around HFs.³⁵² Injection of adipose-derived stromal cells may also have some positive effect in AA patients.³⁵³ Cultured fibroblasts, transfected to express IDO, have been used successfully to prevent hair loss in an AA mouse model.³⁵⁴ Similar approaches could be developed using cells with IP injected into the skin to help protect HFs.

Tregs have been used to induce tolerance in multiple autoimmune and inflammatory diseases.³⁵⁵⁻³⁵⁸ Consequently, adoptive transfer of Tregs has become an active area of research and clinical trial development for autoimmune diseases.³⁵⁹ CD4⁺CD25⁺ T cells can prevent the development of AA in C3H/HeJ mice, indicating some potential for Treg therapy.²⁵⁸ Once practical issues are addressed,³⁶⁰ and the antigen epitopes targeted in AA are fully defined,^{49,272,361} Treg cell therapy may be achievable for AA.³⁵⁹ Similarly, NK cells with immunoregulatory properties,²⁷⁷ and other immunoregulatory cell types, could be additional candidates for development into immunocell therapies.

TABLE 4 Drugs that may enable HF IP regeneration

Drug	Potential IP regenerative mode of action
Calcineurin inhibitors (Tacrolimus/ (FK506, Pimecrolimus, Cyclosporine)	Downregulate MHC class I expression; tacrolimus has been shown to protect HFs from IFN γ -induced IP collapse in ex vivo studies. ⁷⁶
PDE4 inhibitors (Apremilast, Crisaborole, Diazepam, Ibudilast, Roflumilast)	Block the degradative action of phosphodiesterase 4 (PDE4) on cyclic adenosine monophosphate (cAMP) in immune cells and prevent production of IP collapse inducer IFN γ . ³⁷⁶
α MSH analogs (Afamelanotide, Melanotan)	Downregulate MHC class I/ β 2M expression in HFs, stimulate production of other IP guardians, and also directly exert immunoinhibitory actions. ^{76,288,377}
CGRP receptor agonists (Calcitonin-Salmon, Pramlintide)	Promote CGRP receptor immunoregulatory function. ⁹⁹
Substance P receptor antagonists (Aprepitant, Netupitant, Rolapitant)	Interfere in the action of substance P induced HF IP collapse and expression of MHC molecules. ³⁷⁸
VIP analogs (Avipitadil)	VIP analog supplementation of VIP immunoregulatory action. ⁹⁸

TABLE 5 Potential therapeutic interventions to protect and restore HF IP

	AA pathobiology event	Primary treatment intervention objectives	Selected examples of intervention
1a	Tolerance against HF autoantigens is lost—eliciting HF infiltration by autoreactive CD8 ⁺ T cells	Re-establish tolerance to HF autoantigens Prevent cell migration and/or immunostimulatory antigen presentation by skin-resident APCs Prevent autoreactive CD8 ⁺ T-cell infiltration of skin/HFs	Use tolerogenic Tregs, dendritic cells, and other regulatory cells to “educate” potentially HF autoreactive cells. ³⁷⁹⁻³⁸¹ Use non-specific methods to promote tolerogenic Tregs or dendritic cells in situ. For example with low dose IL-2, aspirin, etc. ^{198,382} Use mesenchymal cells with inherent IP to re-establish HF antigen tolerance in autoreactive T cells. ^{351,352,383} Impede the ability of APC migration from the skin, as observed with contact sensitization in AA mice. ³⁸⁴ Interfere with T-cell chemo-attractant signalling such as preventing HF expression of, or T-cell receipt of signal for, CXC and CC chemokines, etc. ^{385,386}
1b	Excessive HF IP collapse inducers are secreted by cells in a non-autoantigen-specific manner, in response to HF distress signals	Blockade receipt of stimulatory signal to cell producers of IP collapse secreted factors Suppress, neutralize or antagonize IP collapse inducers produced by stimulated cells	Modify or block signal-ligand interactions in HFs involving NKG2D, MICA, ULBP3, etc. ^{387,388} Neutralize IP collapse inducers such as IFN γ , using monoclonal antibodies etc. ³⁸⁹ Application of substance P receptor antagonists, ³⁷⁸ Kv1.3 channel inhibitors, ³⁹⁰ PDE4 inhibitors, ³⁷⁶ etc
1c	A constitutively weak HF IP lowering the threshold for IP collapse	Increase expression of constitutively weak HF IP conferring factors Suppress expression of constitutively strong HF IP breaking factors Supplement weak HF IP with new, non-HF native IP mechanisms	Hypothetically, gene therapy could be used to increase expression of constitutively weak HF IP conferring factors. Cell therapy to provide new IP conferring factors such as IDO, etc. ³⁵⁴ Hypothetically, constitutively weak expression of HF IP conferring factors could be increased by direct injection/ addition of factors such as α MSH and analogs, ^{76,288,377} CGRP receptor agonists, ⁹⁹ VIP analogs, ⁹⁸ etc
2	HF immune privilege collapses, that is loses its immunoinhibitory, tolerance-promoting functionality	Suppress MHC class I and class II expression Block MHC plus antigen epitope–TCR binding on autoreactive T cells Block immune activation response by HF infiltrating T cells and antigen-presenting cells	Therapy to suppress or sequester MHC class I including use of MHC class I downregulating drugs such as FK506. ⁷⁶ Therapy to suppress or sequester MHC class II expression, as with the hypothetical use of IL-10, ³⁹¹ Red/IK, etc. ³⁹² Neutralize co-stimulatory factor expression or receptor binding as with CTLA4 and ligands CD80 and CD86, etc. ^{298,393}
3	HFs enter anagen III–VI, the hair cycle window during which mature, anagen HF-associated, autoantigens are generated	Modify HF-associated autoantigens to be less immunogenic Modify HF-associated autoantigen processing and presentation by MHC	Hypothetically, modify glycosylation of autoantigens to reduce immunogenic properties. ³⁹⁴ Hypothetically, modify glycosylation to control autoantigen uptake, proteolytic processing, and presentation by MHC. ³⁹⁵
4	Normally sequestered HF autoantigens are presented to infiltrating autoreactive CD8 ⁺ T cells	Re-sequester HF autoantigens Prevent HF autoantigen presentation to CD8 ⁺ T cells	Improve the physical and biochemical properties of basement membrane components to prevent HF infiltration by autoreactive CD8 ⁺ T cells. ^{84,396} Where autoantigens are known, interfere with TCR recognition of autoantigen presentation in association with MHC class I as with use of antibody-TCR mimics, etc. ³⁹⁷
5	Appropriate co-stimulatory and supporting signals are received from various sources including: CD4 ⁺ cells, mast cells, and/or dendritic cells	Suppress supporting cell types Blockade activation of supporting cell types Suppress signalling from supporting cell types	Block migration of supporting cells to the skin such as using monoclonal antibodies to block skin homing receptors CD44, etc. ^{178,398,399} Block pro-inflammatory cytokine signalling from/to supporting cells such as IL-12, etc. ^{400,401} Hypothetically, block mast cell support using anti-histamines, desensitization therapy, etc. ³²⁸

10 | CONCLUSIONS

In recognition of the developments in AA research described above, and despite the undisputed contribution of genetic factors to disease

susceptibility, clinical phenotype, course and response to therapy,⁴ AA may actually not be a unique, genetically determined disease entity. Rather, AA may represent a stereotypic HF response pattern to a number of different immunopathological events that any normal

HF, irrespective of its “genetic make-up,” can develop. According to this new hypothesis, distinct immunopathological starting events coalesce in the collapse of HF IP and result in the clinical AA phenotype (Figure 3), if certain conditions are met (Table 3).

The basic tenets of the original HF IP collapse theory and its role in AA pathogenesis⁴³ remain largely unchanged, and this pathogenesis scenario has proven to be more plausible and better-supported by published evidence than any other (for debate, see Ref. [33]). The role of MHC molecules, immunoregulatory cytokines, co-stimulatory molecules and Tregs in HF IP maintenance, collapse and restoration receives ever-increasing attention.^{33,35,42,194,197,198,294,295,297} Furthermore, perifollicular cells, particularly mast cells, are finally recognized as potentially important players in HF IP in health and inflammatory HF diseases.^{38,179}

Looking back at the history of HF IP research, the latter has become inseparable from AA research, and AA has turned out to be a uniquely instructive model disease in which the clinical consequences of a defective IP of the anagen HF bulb can be interrogated. New principles of how HF IP is generated and maintained and how it interacts with the surrounding skin immune system have been, and continue to be, characterized. New discoveries in IP derived from other tissues continue to instruct AA research and understanding, but equally, research on IP collapse in AA can inform other inflammatory diseases. According to the IP collapse concept of AA pathobiology, whenever hair shafts regrow spontaneously HF IP must have been successfully restituted. Consequently, the prevention of HF IP collapse, and the re-establishment of a functional state of HF IP, should be the key goals of effective AA therapy.^{1,4,33,43}

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CONFLICT OF INTEREST

MB is Principal Scientist, and RP is Founder & Chief Executive Officer, while KJM and SBP are Senior Consultants for Monasterium Laboratory, Skin & Hair Research Solutions GmbH. KJM is also Chief Scientific Officer for Replifelife Sciences Inc (Canada). None of these commercial interests has impacted on the authors' views communicated here.

AUTHOR CONTRIBUTIONS

MB, AG and RP conceptualized the article. M.B, KM, S.B-P. and RP compiled and wrote the text. All authors contributed to the editing of the article and have read and approved the final version of the manuscript.

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