ImmunoTargets and Therapy

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REVIEW

Alopecia Areata: An Autoimmune Disease of Multiple Players

Poonkiat Suchonwanit
Chaninan Kositkuljorn
Cherrin Pomsoong

Division of Dermatology, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Abstract: Alopecia areata (AA) is an autoimmune disease of the hair follicles. It is characterized by a well-defined non-scarring alopecic patch or patches that may extend to the entire scalp or lead to total body hair loss. Due to its unpredictable clinical course, AA causes substantial psychological harm. Despite the high prevalence of this disease and extensive research, its exact pathomechanism is unclear, and current treatments have a high relapse rate that has deemed AA incurable. Over the past few decades, researchers have investigated multiple potential factors that may help alleviate its pathogenesis and provide effective treatment. Given its complex immunopathogenesis, AA is considered an autoimmune disease with multiple factors. This review gathers current evidence that emphasizes molecular mechanisms, possible causative etiologies, and targeted immunotherapies for AA. Understanding its underlying mechanisms may shed light on new strategies to effectively manage AA in the future.

Keywords: alopecia totalis, alopecia universalis, autoimmunity, hair loss, inflammation

Introduction

Alopecia areata (AA) is an immune-mediated hair loss disorder that affects 1.7% of the general population. Its prevalence ranges from 0.1–0.2% worldwide.[1] AA's manifestations vary, from a well-defined alopecic patch, multiple patches, total scalp alopecia (alopecia totalis, AT), to complete body hair loss (alopecia universalis, AU).[2] The disease impacts quality of life and has major psychological effects for men and women, especially in social acceptance and psychological well-being.[3]

AA is diagnosed upon physical examination and trichoscopy; however, a scalp biopsy may also be performed in undecided cases.[4,5] Histopathological features of acute AA include hair follicle (HF) peribulbar lymphocytic infiltration, with perifollicular $CD4^+$ T cells and intrafollicular $CD8^+$ T cells.[6] In chronic AA there is an increase in miniaturized hairs situated in the papillary dermis with peribulbar lymphocytic infiltration.[7,8] Immunosuppressive agents such as systemic corticosteroids, cyclosporine, and contact immunotherapy highlight the autoimmune nature of AA, as patients exhibit marked improvement after administration of these agents.[9]

Although much research into AA has been conducted, its exact pathomechanisms are unknown. Emerging evidence suggests that a collapse in HF immune privilege (IP) is the leading cause of AA. When this process develops, HFs present surface autoantigens, resulting in inflammatory cells attacking HFs and eventually resulting in an alopecic patch. Other factors such as genetics, stress, and environment are also responsible for development of AA.[10] AA is considered an

Correspondence: Poonkiat Suchonwanit
Division of Dermatology, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, 270 Rama VI Road, Ratchathewi, Bangkok, 10400, Thailand
Tel +66-2-2011141
Fax +66-2-201-1211 ext 4
Email poonkiat@hotmail.com

Received: 1 June 2021
Accepted: 17 July 2021
Published: 29 July 2021

autoimmune disease with multiple players and a complex immunopathogenesis. This review explores the molecular mechanisms involved in the pathogenesis of AA, its associated factors, and current immunotarget therapies. We integrate all existing evidence to gain insights into AA immunopathogenesis and its immunotherapeutic options.

Hair Follicle Immune Privilege Collapse

The hair growth cycle is divided into three phases: anagen (growth stage), catagen (transition stage), and telogen (resting stage). When telogen hairs are shed, new anagen hairs grow to replace them, beginning a new cycle.[11–13] Current evidence suggests that the collapse of IP in HF is the principal event in AA pathogenesis. Currently, the concept of IP is believed to be a major factor in immune tolerance, particularly in the brain, eyes, gonads, fetomaternal placenta, and HFs. IP acts by suppressing immune-mediated inflammation and favoring immune tolerance from harmful effects of inappropriate immune recognition.[14] In the hair bulge, proximal HF epithelia exhibit an IP area during anagen.[15] IP protects epithelial stem cells, which are essential for remodeling capacity and HF regeneration. A previous study supported these hypotheses using a murine model for skin graft transplantation. It was observed that despite the rejection of epidermal pigment changes, donor HF melanocytes survived and evaded immune rejection.[16]

IP protects HF components from immune attacks by various mechanisms. Physical barriers, including the extracellular matrix, have reduced lymphatic permeability and guard hair bulbs against infiltrating immune cells.[15,17] It also downregulates major histocompatibility complex (MHC) class I expression and MHC class I pathway molecules (β2-microglobulin and transporter associated with antigen processing [TAP-2]). Downregulation of MHC class I is caused by the local production of immunosuppressive factors, such as α-melanocyte-stimulating hormone (α-MSH), transforming growth factor-β (TGF-β), indoleamine-2,3-dioxygenase (IDO), protein red encoded by IK gene (red/IK), interleukin (IL)-10, calcitonin gene-related peptide, insulin-like growth factor-1, and somatostatin.[18,19] Reduction of MHC class II expression on HF Langerhans cells impairs antigen-presenting cell (APC) function.[20] In addition, IP expresses "no danger" signals using type-1 transmembrane glycoprotein CD200, which lowers APC activity and pro-inflammatory cytokines secretion.[21]

The IP environment normally suppresses natural killer (NK) cell activation by downregulating MHC class I chain-related gene A (MICA) and UL16-binding protein (ULBP) in resident immune cells. These would otherwise bind to NKG2D-activating receptors on $CD8^+$ T cells and NK cells inducing inflammation and damaging local tissues. Supporting evidence shows that there are few perifollicular NK cells in healthy HFs.[22] Next, killer cell Ig-like receptors (KIRs), which are MHC class I inhibitory receptors, were significantly higher in controls than in AA patients.[23] KIRs help NK cells distinguish between normal cells and target cells, which prevents damage to healthy cells. Lastly, macrophage migration inhibitory factor, a pleiotropic cytokine presented in several IP sites, prevents the release of cytolytic perforin granules from NK cells.[24]

The HF IP environment is highly regulated and usually prevents autoimmune hair loss. Emerging evidence suggests that the collapse of HF IP contributes to AA pathogenesis. MHC class I and class II expression on the hair matrix and follicular epithelium are found in AA-affected patients.[20] The local production of immunosuppressive factors including α-MSH, TGF-β, IDO, and red/IK are downregulated in peri-lesional and lesional AA.[25,26] Histological features from AA patient scalp biopsies showed infiltrating peri-follicular $CD4^+$ T cells, intrafollicular $CD8^+$T cells,[6] mast cells,[27] NK cells,[23] and APCs.[28] MICA immunoreactivity occurred throughout AA-affected HFs, which activated $NKG2D^+$ NK cells and $CD8^+$ T cells around AA lesions, but not in normal HFs.[23]

Overview of Immune System Activation in Alopecia Areata

Cytotoxic CD8+NKG2D+ T cells and interferon-γ (IFN-γ) have been demonstrated to play an important role in the development of AA. CD8+NKG2D+ T cells infiltrate the hair follicle of AA, initiating an IFN-γ response and upregulation of γ-chain (γ_c) cytokines, especially IL-2 and IL-15.[29] These immune responses interfere with the maintenance of the HF IP by inducing ectopic expression of MHC molecules and the NKG2D ligands in the HF and promote the activation and survival of CD8 +NKG2D+ T cells. Concurrently, several immune pathways are also responsible for the autoreactivity in AA, Figure 1 outlines activation of the immune system in AA. The following section provides a summary of all relevant factors involved in AA pathogenesis including

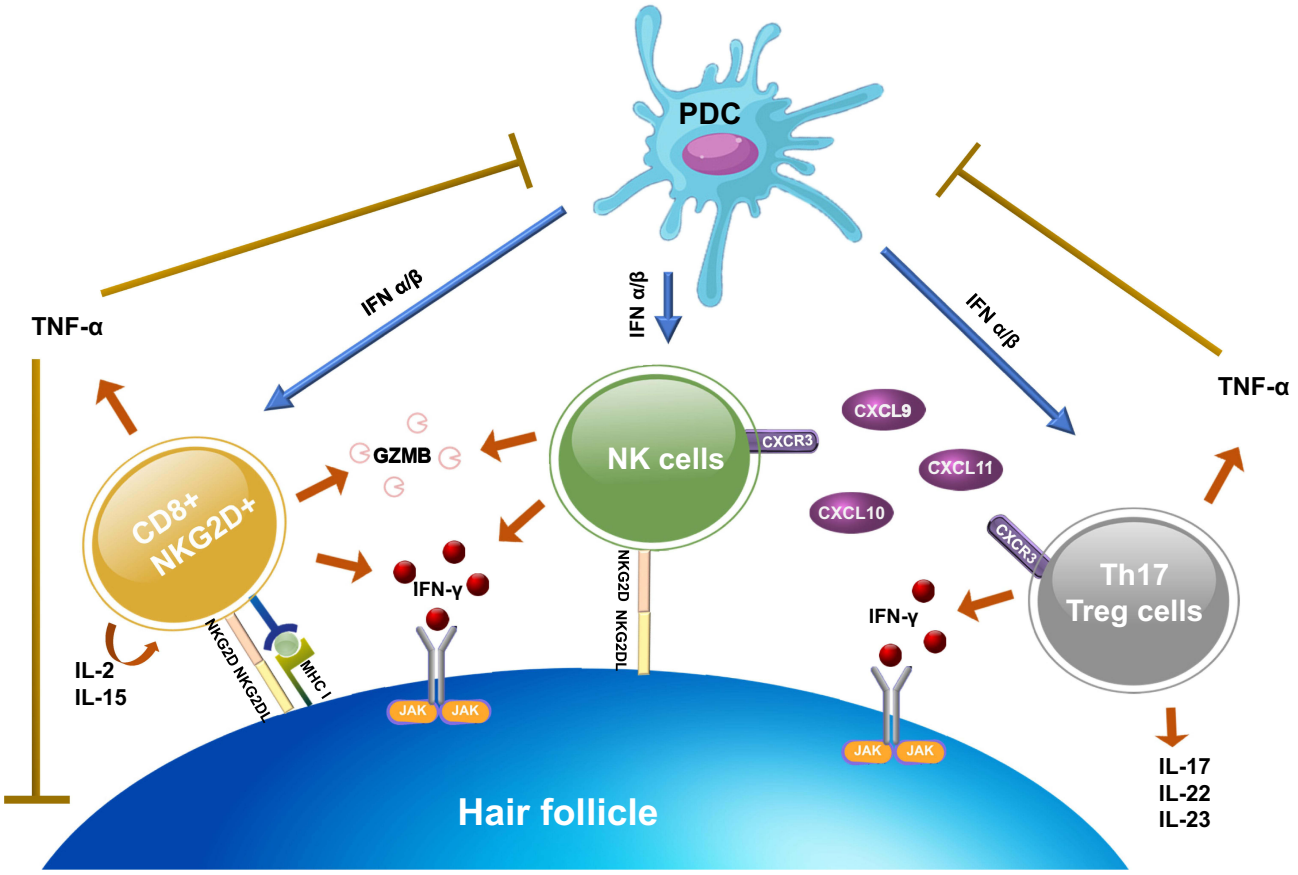

Figure 1 Immune system activation in AA. After the NKG2D receptor is recognized by the NKG2D associated ligands (MICA, ULBP3, and ULBP6), it promotes aggregation of $CD8^+NKG2D^+$ T cells. Activated $CD8^+NKG2D^+$ T cells mainly produce IFN-γ to upregulate MHC class I and II expression via the JAK-STAT pathway and generate GZMB to induce apoptotic cell death. Concurrently, $CD8^+NKG2D^+$ T cells increase an upregulation of γ-chain cytokines (IL-2 and IL-15), which create a positive feedback loop by promoting the activation of IFN-γ–producing $CD8^+NKG2D^+$ T cells. NK cells and $CD4^+$ T cell subtypes (Th17 and T reg cells) also produce IFN-γ. NK cells attack hair follicles upon the binding of NKG2D ligand to NKG2D receptor and through CXCR3 ligands expression (CXCL9, CXCL10, and CXCL11). While $CD4^+$ T cell subtypes, initiated by upregulation of MHC class II, trigger several pro-inflammatory cytokines and chemokines. PDCs play a role in the pathogenesis by producing a large amount of type I IFN to enhance the activation of $CD8^+$, $CD4^+$, and NK cells. However, TNF-α, created by $CD4^+$ and $CD8^+$ T cells, also have negative effects by suppressing PDCs activity and interfering with the keratinocytes differentiation.

Abbreviations: AA, alopecia areata; CXCL, chemokine (C-X-C motif) ligand; CXCR3, C-X-C Motif Chemokine Receptor 3; GZMB, granzyme B; IFN, interferon, IL, interleukin; JAK, Janus kinase; MHC, major histocompatibility complex; MICA, major histocompatibility complex class I chain-related gene A; NK, natural killer; PDCs, plasmacytoid dendritic cells; Treg cells, regulatory T cells; STAT, signal transducer and activator of transcription; Th cells, T-helper cells; TNF, tumor necrosis factor; ULBP, UL16-binding protein.

autoantigens, immune cells, cytokines, T helper 2 (Th2) response, genetics, stress, and environment.

Autoantigens

Two studies affirmed the hypothesis that a dysregulation in immune system homeostasis contributes to the development of AA. C3H/HeJ mouse models were used to demonstrate hair loss after full-thickness skin grafts from normal mice to AA-affected mice.[30] In addition, grafting AA-affected scalps onto severe combined immunodeficient (SCID) mice resulted in hair growth.[31] Although these models implicated T cells within the skin grafts in triggering immune activation, the involvement of autoantigens in cytotoxic T cell responses and disease development are still inconclusive.

AA specifically occurs during the anagen phase of hair growth, where HF melanocytes, keratinocytes, and dermal fibroblasts are the assumed targets of autoreactive cytotoxic T cells. The evidence for melanocyte-related peptides being autoantigens can be seen in numerous studies. Melanocyte-derived epitopes, including the melanoma antigen and glycoprotein 100, were recognized by T cells and contributed to hair loss in human AA scalp grafted onto SCID mice.[32] Protein identification by mass spectrometry revealed that keratinocyte-derived trichohyalin and tyrosinase-related protein-2 promoted significantly greater cytotoxic T cell response compared with healthy controls.[33,34] Moreover, the fact that AA preferentially targets pigmented hair over non-pigmented hair, in addition to the preferential regrowth

of white hair after treatment, provides the best evidence to support the essential role of melanocyte-related peptides as autoantigens in AA.[35–37]

Immune Cells

CD8+NKG2D+ T Cells

$CD8^+NKG2D^+$ T cells are key regulators of AA pathogenesis.[29,38–40] As NKG2D is an activating receptor expressed in both NK cells and $CD8^+$ T cells, $CD8^+NKG2D^+$ T cells recognize the NKG2D ligands (MICA, ULBP3, and ULBP6), which upregulate MHC expression and contribute to HF IP collapse. Research has been conducted to determine if $CD8^+NKG2D^+$ T cells initiate AA.[29,38–40] A study using C3H/HeJ mice showed the AA-affected scalp lesions were infiltrated by $CD8^+NKG2D^+$ T cells. Flow cytometry data on the leukocyte populations also reported a significant increase in $CD8^+NKG2D^+$ T cells and total cellularity in AA-affected mice compared to controls.[27,41]

Specifically, measurements of AA lesional skin gene expression signatures indicate HF cytotoxic T cell infiltration, increased production of IFN-γ, and the upregulation of several γ_c cytokines that promote the activation and survival of IFN-γ–producing $CD8^+NKG2D^+$ T cells.[29] IL-2 and IL-15 are cytokines known to stimulate autoreactive T cells. When injected into human scalp grafted onto SCID mice, IL-2 stimulated $CD8^+NKG2D^+$ T cells and demonstrated clinical and histological features of AA.[42] Serum IL-15 levels in AA patients were significantly higher than in control group, and there was a positive correlation between serum levels and severity.[43] Biopsies of AA scalp lesions demonstrated increases in IL-2 and IL-15 expression compared to non-lesional scalps.[44] Notably, blocking the production of these pro-inflammatory cytokines suppressed AA progression and reduced the accumulation of $CD8^+NKG2D^+$ T cells in C3H/HeJ grafted mice.[29] Lastly, granzyme B (GZMB) levels, an apoptogenic effector produced by cytotoxic cells, were elevated in both AA-affected C3H/HeJ mouse models and human HFs.[45,46] These experiments demonstrated that $CD8^+NKG2D^+$ T cells could induce AA.

T Helper 17 and Regulatory T Cells

Several autoimmune diseases, including AA, are associated with the $CD4^+$ subtypes called Th17 and regulatory T (Treg) cells.[47,48] After the upregulation of MHC class II, $CD4^+$ T cells were found abundant in the dermis and around HFs.[48] Th17 cells secrete the pro-inflammatory cytokines IL-17, IL-22, and IL-23, which induce inflammation and contribute to autoimmunity,[49] whereas Treg cells suppress excessive lymphocyte activity to prevent autoimmune reactions.[50] Using quantitative real-time polymerase chain reaction, increased IL-17 and IL-22 levels in affected scalp were found to have a positive correlation with disease severity.[51] In addition, human Th17 cells also readily produced IFN-γ, resulting in promoting autoimmunity.[52] It is suggested that increased Th17 levels and decreased Treg levels are pro-inflammatory and can induce local autoimmune reactivity.[53] Studies also showed that Th17 levels were higher during active disease than when it is dormant,[46] while Treg levels were higher in severe AA patients than in mild AA patients.[54]

Plasmacytoid Dendritic Cells

The role of plasmacytoid dendritic cells (PDCs) in AA pathogenesis is the subject of intensive study. They express the cell surface markers CD4, CD123, human leukocyte antigen (HLA)-DR, blood-derived dendritic cell antigen-2 (BDCA-2), Toll-like receptor (TLR) 7, and TLR9 within endosomal compartments. After the activation of TLR7 and TLR9, PDCs generate large amounts of type I IFN (IFN-α/IFN-β) approximately 1000 times higher than other cell types.[55,56]

PDCs regulate myeloid dendritic cells, CD4, CD8, NK, and T cell functions, thus, linking innate and adaptive immune responses.[57] This is demonstrable in AA, where intradermal injections of PDCs into C3H/HeJ mice were found to contribute to AA development.[28] Immunohistochemical analysis revealed the presence of a specific PDC marker, anti-BDCA-2, in the peribulbar regions in all cases. Moreover, intense and diffuse expression of MxA, an indirect marker of PDC activity, was observed in the hair bulbs and peribulbar regions of AA-affected patients.[55]

Cytokines

IFN-γ

As mentioned above, IFN-γ has been implicated in the development of AA, being a critical Th1 effector cytokine in AA pathogenesis. It is mainly produced by NK and natural killer T (NKT) cells. In the anagen phase hair bulb, IFN-γ specifically drives immune response by upregulating the expression of MHC I, NKG2D receptors, and

chemokine (C-X-C motif) ligands (CXCLs) in HFs.[38,39,58] A positive feedback autoreactivity of IFN-γ-producing cells resulted in maintaining lymphocytic infiltration and inducing Th1 activities, followed by increasing the disease duration and progression.[29] Sundberg et al administered IFN-γ to C3H/HeJ mice and observed AA-like characteristics over the next 36 days.[59] Similarly, an experimental study failed to transfer AA-affected skin grafts from C3H/HeJ mice to IFN-γ-deficient mice.[60]

Semiquantitative reverse-transcriptase PCR (RT-PCR) revealed that IFN-γ mRNA was significantly increased in AA skin than in normal skin.[61] Inhibiting cytokine signaling 3, a potent regulator of cytokine signaling, suppressed AA by inhibiting $CD8^+$ T cells from producing IFN-γ.[35] Administering IFN-γ antibodies inhibited AA development in graft recipients.[29] Serum IFN-γ levels also positively correlated with the degree of inflammation and severity of AA.[62] All evidence indicates that even IFN-γ alone may cause HF IP collapse.

IFN-γ has also been proposed to inhibit the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathways. This inhibits angiogenesis and stem cell proliferation and activation in the HF, which results in balding.[63] An in vitro study using cultured dermal sheath cells from C3H/HeJ mice showed that exogenous IFN-γ enhanced STAT1 activation.[29] It also suggested that IFN-γ can influence JAK/STAT signaling to prematurely terminate the anagen phase in HFs.[39,58]

TNF-α

Another pro-inflammatory cytokine implicated in AA pathogenesis is tumor necrosis factor (TNF)-α. It is secreted primarily by $CD4^+$ and $CD8^+$ T cells and has potent anti-proliferative effects on epithelial cells and keratinocytes.[64,65] In HFs, TNF-α interferes with the hair growth cycle, contributing to catagen morphology.[66–69] It suppresses PDC development and dysregulates IFN-α production.[55,70] TNF-α induces both IFN-α and IFN-γ production, while interfering with keratinocyte differentiation and the hair growth cycle.

CXCR3

The C-X-C Motif Chemokine Receptor 3 (CXCR3) and its ligands CXCL9, CXCL10, and CXCL11 are chemokine products of IFN-induced inflammation.[46,71] CXCR3 is mainly expressed on Th1, $CD4^+$ T cells, $CD8^+$ T cells, NK, and NKT cells, while resident cells, including dendritic cells, secrete CXCR3 ligands. These chemokines induce Th1-mediated immune responses by promoting infiltration of cytotoxic T lymphocytes, NK cells, NKT cells, and macrophages into HFs.[71,72] Some of these cells also produce IFN-γ, creating a positive feedback loop by stimulating the production of CXCL9, CXCL10, and CXCL11.[71] Significant increases in CXCR3 and its ligands were detected using RT-PCR in 10-week skin grafts where AA was induced.[46] CXCR3 was also found to be upregulated in effector T cells derived from AA skin lesion, while the epithelial cells showed an increase in CXCR3 ligand expression compared to that in healthy tissues. Moreover, inhibition of CXCR3 function with blocking antibodies alleviated AA development in skin grafted mice.[73]

Role of the Th2 Response

In addition to Th1, Th2 immune responses are also regulated by the cytokine pathways involved in AA pathogenesis.[44,74] Both Th1 and Th2 cytokine expression have been demonstrated in animal models of AA.[75] Moreover, the significant association between AA and atopic diseases, a group of conditions providing predominant Th2-type inflammation, also supports Th2 involvement in AA.[76] Though Th2 immune responses are not the primary pathomechanisms of AA, Th2 detection distinguishes between AA variants, predicts the prognosis, and evaluates treatment efficacy. Th2-dependent expression, comprising IL-4, IL-5, IL-6, immunoglobulin (Ig) E, C-C motif chemokine ligand (CCL) 17, IL-13, IL-31, CCL13, CCL17, CCL18, CCL22, and CCL26, was detected in AA patients.[74,77–80] A prior study found that chronic AA or AU patients had higher serum IgE and IL-4 levels than those in healthy controls.[77] The Th2 cytokines IL-13, CCL18, and CCL26 were significantly upregulated in AA lesions.[74] Song et al observed IL-13, CCL13, CCL17, CCL22, and CCL26 expression (all Th2-related cytokines) were increased in AA, and that AA severity was positively correlated with IL-13 and CCL13 expression.[78] Serum CCL17 is also significant, as it is low in patients that respond to AA treatments, moderate in mild AA, and high in severe AA.[79]

Role of Genetics

AA development appears to have a genetic predisposition. The heritable incidence of AA ranges from 10%–42%.[81–84] The estimated lifetime risk is ~5%–8% among first-degree relatives and 42%–55% in identical twins.[85–88] A person's genetic susceptibility to AA is mainly conferred by HLA alleles, especially the DQB and DR alleles in chronic AT/

AU.[89] In murine models, genetic AA susceptibility was found in chromosomes 17 (Alaa1), 9 (Alaa2), 8 (Alaa3), and 15 (Alaa4). Only the Alaa1 site on C3H/HeJ mice, a strain that spontaneously develops an adult-onset form of AA, matched with the HLA locus in humans.[90] Additionally, non-HLA candidate genes, such as the MICA, influence AA susceptibility.[91]

Genome-wide association studies reported an association between genetic variants and AA. The data identified variations in several genes controlling Treg cell activation and proliferation, including cytotoxic T lymphocyte-associated antigen 4, IL-2/IL-21, IL-2 receptor A (IL-2RA; CD25), and Eos (Ikaros family zinc finger 4; IKZF4). Regions containing genes expressed in the HF itself (PRDX5 and STX17), were associated with AA development. This study also demonstrated that ULBP3 gene upregulation on chromosome 6q25.1 are NKG2D-activating ligands.[92] Furthermore, a follow-up study identified IL13 and KIAA0350 as susceptible loci for AA.[93] Lastly, the gene encoding the lymphoid protein tyrosine phosphatase (PTPN22), which normally suppresses T-cell proliferation, and IL-1 cluster genes (IL-1 receptor antagonist) were associated with severe forms of AA.[94]

Role of Stress

Psychological stress activates the brain-HF (BHA) and hypothalamic-pituitary-adrenal (HPA) axes. In BHA, the neuropeptide substance P (SP), released from sensory nerve fibers, is one of the most effective mediators in perifollicular mast cell activation. It inhibits hair growth during anagen and facilitates HF regression during catagen.[95,96] Nerve growth factor (NGF), a potent SP releaser, triggers HF keratinocyte apoptosis and downregulates keratinocyte growth factor expression.[97] Both mediators cause neuroinflammation and result in perifollicular mast cell degranulation and APC accumulation.

Psychological stress also activates the HPA axis, resulting in the secretion of corticotropin-releasing hormone (CRH), a neuropeptide hormone involved in systemic stress responses. In human HFs, CRH promotes the degranulation of mast cells, which releases histamine, TNF-α, IL-6, and IL-1 into the microenvironment, promoting neuroinflammation.[98–101] Thus, stress-induced neuroendocrine factors, including SP, NGF, and CRH, contribute to perifollicular neurogenic inflammation followed by the collapse of IP in the HFs.[14]

Role of Environment

Although immunogenetics are the principal factors affecting patient susceptibility to AA, environmental factors including viral infections, trace elements or micronutrients, immunization, and allergies are also thought to influence the disease. After viral infection, Th1 immune responses result in supraphysiologic IFN production. Using RT-PCR, Skinner et al detected cytomegalovirus (CMV) DNA in scalp biopsy specimens from AA patients, but not in other hair and scalp diseases.[102] Nevertheless, further study using in situ hybridization failed to produce a correlation between CMV and AA.[86,103] In self-reports of prior Epstein-Barr virus (EBV) infection, 12 of 6256 individuals developed AA within 6 months of experiencing EBV infection.[104] Swine flu virus was also reported to induce AA by the overproduction of IFN-γ, contributing to Th1 immune hyperactivity.[105]

A deficiency of trace elements and micronutrients in the diet may also trigger the onset of AA by disrupting immune functions. Zinc, selenium, folate, and vitamin D deficiencies have been suggested to influence AA onset. In one meta-analysis, serum levels of zinc and selenium were significantly lower in AA patients than in controls.[106] Moreover, zinc levels were inversely correlated with disease duration, the severity of AA, and its resistance to therapies.[107] In a recent review, serum folate and vitamin D levels were lower in AA patients when compared to healthy participants. However, inconsistent results were found, and additional research may be required.

Research into vaccination-induced AA is inconclusive. One study reported an association between immunization, especially the hepatitis vaccine, and AA.[108,109] A case series indicated that the recombinant hepatitis B vaccine was associated with AA.[108] The results of a study using a C3H/HeJ mouse model also supported this finding that clinical AA developed in older female mice shortly after hepatitis B vaccination.[109]

Atopic diseases such as allergic rhinitis, asthma, and atopic dermatitis are also recognized as pathogenic events in AA. Several studies demonstrated a significant association between AA and atopic diseases.[76,110,111] A retrospective study found that 38.2% of AA patients had allergic diseases.[110] The data from a matched case-control study revealed AA patients had a significantly higher prevalence of atopic diseases than control subjects.[111] Li et al detected higher percentages of total

IgE and dust mite-specific IgE antibodies in patients with early-onset and severe AA.[112]

Immunotherapies

Current therapeutic modalities for AA include corticosteroids, topical minoxidil, anthralin, cyclosporine, photochemotherapy, and contact immunotherapies.[113,114] Since there are no Food and Drug Administration-approved medications for AA, several targeted immune therapies have been developed in recent years as new treatment options. Pathogenetic factors and immunotherapies of AA are summarized in Table 1. Understanding the molecular mechanisms of AA permits new insight for developing novel treatments. Some of which have achieved remarkable clinical results. Herein, we summarized all immune-modulating treatments for AA.

Contact Immunotherapies

Diphenylcyclopropenone (DPCP) and squaric acid dibutyl ester are currently considered effective modalities for inducing hair growth. After the allergic reaction induced by these substances, suppressor T cells are recruited and express $CD8^+$ and $CD1a^+$, which inhibit APC migration in affected HFs. Moreover, an alteration of cytokine expression levels is observed after treatment. Serum IL-2, IL-4, IL-8, IL-10, and TNF-α levels are increased after administering topical immunotherapies, whereas serum IFN-γ, IL-12, and Th17 cytokine expression are decreased.[115–118] Happle et al reported the efficacy of DPCP in 1983,[119] and it has since gained popularity and is recommended as the first-line topical sensitizer for treating AA.[120] In the literature, the efficacy of DPCP for hair regrowth ranges from 6%–77%.[121] The use of DPCP combination therapy with anthralin, minoxidil, and imiquimod to enhance the therapeutic response was investigated, but a wide range of efficacies was reported.[122–127] Additionally, since DPCP treatment protocols may take some time to achieve an acceptable treatment response for AA, modified protocols have since been established and have obtained satisfactory results.[128–132]

Janus Kinase Inhibitors

Recently, the efficacy of leveraging Janus Kinase inhibitors (JAKis) in various autoimmune and hematologic diseases has seen increased interest. JAKis are selective, competitive inhibitors of adenosine triphosphate-binding sites on JAK/STAT.[133] It predominantly blocks the downstream IFN-γ and γ_c cytokine receptors and reduces the recruitment of $CD8^+NKG2D^+$ T cells.[29,134] It also interferes with Th1 cell and Th17 cell differentiation. Notably, activation and proliferation of HF stem cells are promoted by JAKis, which accelerates HF reentry into the anagen phase.[135] Treatment of AA with JAK1/2 (IFN-γ pathway) and JAK3 (γ_c cytokines) inhibitors showed promising results. The therapeutic efficacy of oral tofacitinib and oral ruxolitinib in treating severe and recalcitrant AA has an overall response rate of 30%–75%, with transient and minimal side effects.[63,136]

Lipid-Lowering Agents

Besides their efficacy in reducing atherosclerotic cardiovascular risk, statins are also anti-inflammatory and immunomodulatory agents. In vitro and in vivo studies showed that statins downregulate Th1 cytokines and upregulate Th2 cytokines via modulation of the JAK/STAT pathway. Furthermore, it can directly modulate APCs to increase Treg cell activation.[137] Evidence also suggests that statins downregulate leukocyte activation, proliferation, differentiation, adhesion, and extravasation into target tissues.[138] The combination of statins and ezetimibe (non-statin lipid-lowering medication) showed promising results with 30%–80% hair regrowth in 28% of recalcitrant AA patients.[139] However, another study reported unsatisfactory results as none of the patients achieved hair regrowth.[140] The relapse rate was significantly lower in statin-treated patients than in the control group.[141] Thus, lipid-lowering agents, when combined with other therapies, show promise for preventing disease relapses; however, further studies to elucidate this are required.

Phosphodiesterase-4 Inhibitors

Apremilast, a selective phosphodiesterase-4 (PDE4) inhibitor, has been shown to inhibit the production of IFN-γ and downregulate target organ MHC class II expression.[142] In humanized mouse models, the injection of apremilast into skin grafts decreased IFN-γ and TNF-α production.[143] Nonetheless, treatments on moderate to severe AA and recalcitrant AA showed unsatisfactory results as most patients failed to achieve hair regrowth.[144,145] Despite the selective inhibition of PDE4, there is no evidence supporting the efficacy of apremilast in AA treatment.

Interleukin 2

IL-2 modulates Treg activity in vivo through a STAT-dependent mechanism.[146] Castela et al investigated the efficacy of low-dose recombinant IL-2 injections in five severe AA patients. All patients showed partial hair regrowth without serious adverse events, and

Table 1 Pathogenetic Factors and Targeted Immunotherapies of Alopecia Areata

Pathogenetic Factors	Roles	Immunotherapies	Mechanism of Treatment
Autoantigens	• Stimulating autoreactive cytotoxic T lymphocytes	• Not available	-
Immune cells			
- $CD8^+NKG2D^+$ T cells	• Increasing the production of IFN-γ and γ-chain cytokines via JAK/STAT pathway • Inducing apoptotic cell death by producing GZMB	• Anti-CD2	• Binding with CD2, causing deactivation of T cells • Inducing apoptosis in both $CD4^+$ and $CD8^+$ memory T cells
		• Anti-CD11a	• Inhibiting T cell activation and migration
- Th17 cells	• Secreting proinflammatory cytokines (IL-17, IL-22, and IL-23)	• Contact immunotherapy	• Decreasing the level of IFN-γ, IL-12, and Th17 cytokines • Reducing the inflammatory cells • Disturbing APCs migration
		• Anti-IL-12/IL-23	• Inhibiting Th1 differentiation, proinflammatory cytokines, and Th17 cell proliferation
- Treg cells	• Suppressing excessive lymphocyte activity	• Statins	• Downregulating Th1 cytokines and upregulating Th2 cytokines via modulation of the JAK/STAT pathway • Increasing activated Treg cells • Inhibiting of leukocyte adhesion and extravasation into HF
		• Low-dose IL-2	• Recruiting Treg cells (CD4+CD25+FoxP3+)
- PDCs	• Producing type I IFN (IFN-α and β) through TLR7 and TLR9 stimulation	• Not available	-
Cytokines			
- IFN-γ	• Inducing MHC expression that stimulates NKG2D receptors • Signaling through JAK/STAT pathway which helps promoting adaptive immune response	• JAKis	• Terminating T cell-mediated immune response • Blocking IFN-γ signaling and γ-chain cytokines • Restoring anagen phase of the hair follicle
		• PDE4 inhibitors	• Reducing IFN-γ by upregulation of cAMP • Downregulating MHC class II expression
		• Anti-IFN-γ	• Blocking IFN-γ which leads to the downregulation of MHC expression and immune-cell recruitment
- TNF-α	• Providing anti-proliferative effect on epithelial cells and keratinocytes • Abrogating hair growth and inducing catagen phase of HF • Suppressing the development of PDCs	• Anti-TNF-α	• Activating Treg cells • Inhibiting proinflammatory cytokines such as IFN-γ, IL-6, and IL-1
- CXCR3	• Promoting Th1-mediated immune responses by the accumulation of immune cells	• Not available	-
Th2 immune response	• Under investigation	• Not available	-

Abbreviations: APCs, antigen presenting cells; cAMP, cyclic adenosine monophosphate; CXCR3, C-X-C Motif Chemokine Receptor 3; GZMB, granzyme B; HF, hair follicle; IFN, interferon; IL, interleukin; JAK, Janus kinase; JAKi, Janus kinase inhibitors; MHC, major histocompatibility complex; NK, natural killer; PDCs, plasmacytoid dendritic cells; PDE, phosphodiesterase; Treg cells, regulatory T cells; STAT, signal transducer and activator of transcription; Th cells, T-helper cells; TNF, tumor necrosis factor; TLR, Toll-like receptor.

immunochemical analysis revealed a significantly increased number of Treg cells in the majority of patients (80%).[147] One explanation for the partial hair growth response is that IL-2 not only suppresses autoimmune responses by Treg activation but also worsens AA by increasing NK cell activity.[148]

Anti-IFN-γ Antibodies

Blocking major inflammatory cytokines may reduce MHC expression and immune cell recruitment. Anti-IFN-γ therapy is proposed to treat several autoimmune diseases, including AA. AA patients observed hair regrowth after administration with anti-IFN-γ antibodies, while AT and AU patients were non-responders.[149]

Anti-TNF-α

The anti-TNF-α biologic, etanercept, blocks TNF-α-mediated processes. It functions to activate Treg cells and inhibit pro-inflammatory cytokines. Despite the theoretical benefit, various clinical trials showed it has undesirable effects.[150] Moreover, some cases showed progressive balding due to activation of self-reactive T cells, which means that patients treated with anti-TNF-α may develop further immune-mediated skin lesions such as psoriasis, granuloma annulare, vasculitis, and AA.[151,152]

Anti-IL-12/IL-23

Ustekinumab is a human Ig monoclonal antibody that binds with the p40-subunit of IL-12 and IL-23. Blocking these cytokines downregulated Th1 differentiation, pro-inflammatory cytokines, and Th17 cell proliferation.[153] However, minimal improvements in extensive AA and pediatric AA were noted, while other patients even reported developing AA after initiating ustekinumab.[154–156]

Anti-CD2

Alefacept is a recombinant fusion protein of lymphocyte function-associated antigen-3 (LFA-3) and an IgG dimer that acts to inactivate T cells by binding to CD2. It also induces apoptosis in both $CD4^+$ and $CD8^+$ memory effector T lymphocytes.[157] There was a partial response after using alefacept in one patient.[158] However, a randomized controlled trial (RCT) demonstrated unsuccessful treatment with an insignificant lowering of $CD4^+$ count in severe AA patients.[159]

Anti-CD11a

Efalizumab inhibits the interaction of CD11a, which blocks T-cell activation and migration. In theory, it was proposed to attenuate AA. There are case reports of recalcitrant AT and long-standing AU patients that responded to efalizumab with no side effects.[160,161] Nevertheless, in an RCT, the results revealed no differences from placebo.[162]

Conclusion

Multiple immunomodulators are involved in the pathogenesis of AA, including autoantigens, inflammatory cells, cytokines, and chemokines. IP maintains the HF microenvironment to protect the regenerative capability of HFs. The collapse of HF IP is the key factor contributing to disease. While AA constitutes an example of autoimmune hair loss, the underlying causes of HF IP collapse may be more important. Despite the complex disease etiology and our incomplete understanding of the relationship between these factors and hair loss, we presume that genetic predisposition, stress, and environmental factors affect immune activation and influence AA occurrence.[163–169] Further, novel targeted therapies that treat AA have been reviewed. However, a complete response without relapse remains challenging. Understanding the underlying mechanisms may shed light on our future understanding of AA pathogenesis as well as new and effective strategies for the management of this disease.

Disclosure

The authors report no conflicts of interest in this work.

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