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Pathophysiology of Alopecia Areata in the Pediatric Patient

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ABSTRACT

Alopecia areata (AA) is an autoimmune non-scarring hair loss that arises in genetically susceptible individuals, potentially in combination with environmental triggers or inciting events, of which the exact mechanism is not yet fully understood. Genome wide association studies have demonstrated an association between AA and variants in HLA haplotypes on chromosome 6 which correlate with other autoimmune conditions as well as other gene variants. Familial and twin studies also confer additional evidence to a genetic component. AA pathogenesis relies on immune privilege collapse at the hair follicle (HF) bulb in the anagen hair cycle phase. Immune privilege collapse is associated with upregulation of IFN-γ, ultimately activating JAK-STAT pathway resulting in upregulation of MHC class I and II in the HF and subjecting it to attack by $NKG2D^+$ CD8 T cells. The complex interplay between pro-inflammatory cytokines such as IFN-γ, IL-2, IL-15 and their use of JAK-STAT signaling are important in perpetuation of AA.

1 | Introduction

Alopecia areata (AA) is an autoimmune condition caused by inflammation at the hair follicle (HF) bulb leading to nonscarring hair loss. AA manifests as well-circumscribed patches of hair loss on any hair-bearing area of the body, most commonly affecting the scalp. Typically, the disorder is diagnosed clinically, although a biopsy can be used for definitive diagnosis. AA may arise in genetically susceptible individuals who face as-of-yet ambiguous environmental triggers [1]. Although it is thought to develop in the setting of loss of immune privilege at the HF, setting off a complex interplay between proinflammatory cytokines such as interferon-gamma (IFN-γ), interleukin 2 (IL-2), and interleukin 15 (IL-15), these signals are mediated via Janus kinase (JAK) and signal transducers and activators of transcription (STAT), leading to potent T cell activation and execution of effector functions directed at the hair follicle [2].

The hair lifecycle consists of 3 phases: anagen, catagen, and telogen. AA is thought to disrupt hair follicles in anagen phase, the period of active growth. Anagen can be further broken down into six stages; in AA, the HF attack by immune cells arrests the hair in anagen stage III or IV, causing the HF matrix keratinocytes to undergo vacuolar degeneration [3]. Thus, the keratinocytes are unable to completely keratinize the hair shaft, leading to characteristic exclamation point hairs of AA [3]. With this weakening of the hair bulb and the premature catagen and subsequent telogen phase, abrupt hair loss ensues. Since peribulbar inflammation spares the stem cells in the HF bulge, HFs can reenter anagen and restart the hair cycle after the inflammation subsides [3]. While other disorders, such as telogen effluvium,

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can lead to nonscarring hair loss, the increased percentage of hairs in telogen phase seen in AA is due to autoimmune arrest of the hair cycle rather than due to medical conditions, stressful events, or drugs.

Knowledge of AA pathophysiology can inform our search for new therapeutic targets. Herein, we present the current knowledge of the pathophysiology of AA and identify pediatric-specific etiopathogenesis as an area for further investigation.

2 | Genetic Predisposition

Prevalence of AA in pediatric patients with a family history is 8.4%–51.6%, supporting a genetic component to disease etiopathogenesis [4–6]. Monozygotic twin studies have demonstrated concordance rates up to 55% [7], further implicating genetic predisposition combined with environmental conditions in the development of AA.

A large number of single nucleotide polymorphisms (SNPs) have been studied in AA pathogenesis. Early genetic studies involved the human leukocyte antigen class II (HLA-D) region located on chromosome 6 in AA susceptibility [8, 9]. AA-associated SNPs have been linked to different human leukocyte antigen (HLA) haplotypes implicated with other autoimmune diseases including type 1 diabetes mellitus, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematous, psoriasis, celiac disease, vitiligo, autoimmune thyroid disease, and allergic rhinitis [9, 10]. Several genome-wide association studies (GWAS) have identified several different genes associated with AA development. Many variants in the HLA region on chromosome 6 have been found to be in association with AA development including HLA-DRA, HLA-DQA1, HLA-DQA2, and HLA-DQB2 [9]. Of these, a recent meta-analysis has found the HLA-DR region as the most significant risk factor for AA [11].

GWASs have been additionally helpful in identifying several chromosomal loci, which may also be involved, alluding to the complexity of AA heritability [12]. Several T cell-associated genes have been identified in the development of AA. Natural killer cell receptor D (NKG2D) ligands including *ULBP3* and retinoic acid early transcript 1 L protein (*RAET1L*; also called *ULBP6*) have been identified as key players in AA, but not in other autoimmune diseases, making them potentially unique markers of AA [1, 9, 12]. *ULBP3* is overexpressed in the dermal sheath and papilla during active AA, and this molecule is hypothesized to provide costimulatory signals to cytotoxic T cells in AA lesions [9]. Other susceptibility loci that may be linked to AA implicate the involvement of T-cell immune signaling pathways such as interleukin 2 receptor A (*IL2RA*), cytotoxic T lymphocyte-associated antigen 4 (*CTLA4*), and protein tyrosinase phosphatase non-receptor type 22 (*PTPN22*) [9, 13, 14]. *CTLA4* encodes a T-cell receptor responsible for anergy and preventing autoimmune reactions [13, 14]. Variants in *CTLA4* may lead to reduced capacity to prevent or limit T-cell responses. *PTPN22* downregulates T-cell receptors and participates in T-cell maturation and proliferation, which is important for immune homeostasis; variants here may lead to decreased thresholds for T-cell activation that leads to aberrant T-Airecell responses [13, 15]. IL-2/IL-2RA will be discussed in greater detail in later sections.

Autoimmune regulator (*AIRE*) gene mutations can lead to autoimmune polyendocrine candidiasis ectodermal dysplasia (APECED), which confers an increased risk in developing severe or early-onset AA [16]. Patients with *AIRE* mutations who did not develop APECED have also been shown to develop AA [17], and *Aire*-deficient mice serve as an animal model of AA [18]. The known function of *AIRE* in T-cell maturation and immune recognition of self-peripheral autoantigens supports the autoimmune etiology of AA [19].

With numerous potential mutations and genes found on several chromosomes, GWAS suggest that AA is a complex polygenic disease with multiple pathways implicated that invite further investigation.

3 | Hair Follicle Immune Privilege

HF immune privilege is a highly dynamic process, thought to occur in the proximal HF in anagen phase and subsiding during catagen and telogen [20]. During anagen phase, the HF environment actively suppresses the immune responses, and it has been hypothesized that immune privilege maintenance prevents highly immunogenic self-peptides from inducing T-cell attack of the growing hair shaft [21, 22].

The HF immune privilege environment decreases immune cell trafficking and recruitment and decreases antigen presentation by downregulating MHC class I on HF and MHC class II on HF and professional antigen-presenting cells [21–24]. This is thought to be achieved by localized expression of immunomodulatory factors (TGF-β, α-MSH, IL-10, macrophage migration inhibitory factor, and somatostatin), low MHC class I chain-related gene A expression (MICA), and downregulation of NKG2D on local natural killer (NK) cells [20, 25–28]. Physical barriers to lymphocyte infiltration, including those that result from the establishment of extracellular matrix barriers and a lack of lymphatics, also help confer immune privilege [20, 29]. These immune guardians work to suppress IFN-γ production, which, if present, induces upregulation of MHC class I and II, thereby changing T-cell receptor (TCR) avidity (the total strength of multiple TCR-MHC complexes) [28]. During the pathogenesis of AA, these immune guardrails break down, leading to an autoimmune attack of the lower HF (Figure 1). Keratinocyte and melanocyte autoantigens are exposed to CD8 T cells which in turn activate a variety of cellular and molecular pathways of immune-mediated destruction [30].

Plasmacytoid dendritic cells (PDC) are specialized dendritic cells that are normally relatively absent in the skin but are seen infiltrating during active injury or disease [31]. PDCs link the innate and adaptive immune systems by expressing receptors such as CD4, HLA-DR, and toll-like receptors, thereby influencing the action of immune cells such as T cells, B cells, and NK cells [31–33]. PDCs have been proposed to participate in AA pathogenesis. In AA, inciting events may lead to PDC activation and type I IFN (α and β) production, activating cytotoxic

T cells that upregulate IFN-γ [32, 33]. This could activate the JAK–STAT pathway ultimately leading to upregulation of MHC class I and II molecules in the HFs [24]. Increased MHC class I expression and T-cell recruitment leads to autoimmune activation of NKG2D$^+$ CD8 T cells and NK cells, leading to further collapse of HF immune privilege [34]. Activated NKG2D$^+$ CD8 T cells produce granzyme B and perforin, which may act to damage HF cells [30].

4 | Inciting Events

Hypothesized inciting events that dysregulate immune guardrails include viral infection [35], reactive oxygen species associated with chronic infection or drugs [1, 36], hypersensitivity reaction secondary to vaccinations [1, 37–39], emotional or physical stress [40, 41], and immunotherapies [42]. Though the mechanism is not well-understood, in some cases these events could trigger PDCs to release large amounts of IFN α and β, which could activate CD4 T cells, CD8 T cells, and NK cells, leading to autoimmune destruction as described above [1, 31–33].

The contribution of stress to AA pathogenesis is controversial. Emotional stress and anxiety are thought to be potential triggers for AA development by increasing corticotropin-releasing hormone (CRH) receptors around HFs [41]. In a case–control study of 27 children with AA and 30 controls, nearly 52% of children with AA had at least one comorbid anxiety spectrum disorder, although diagnosis before versus after onset of AA was not specified [43]. A survey of 69 participants found that 33% of pediatric patients have stayed home from school at least once due to their alopecia [44]. Patients in this study self-reported bullying, most significantly those age 15–19 years old and males [44]. In addition, children with AA are more likely than their adolescent counterparts (14.8% vs. 3.3%, respectively) to suffer from depressive-disorder symptoms [45]. Given the substantial number of pediatric patients that have been shown to meet anxiety criteria, it is possible that emotional stress could contribute to pediatric-specific AA pathogenesis and perpetuation. Although these studies show an association between psychosocial and emotional stressors and AA, the specific biochemical role that emotional stressors may play in pathogenesis as well as disease perpetuation requires further investigation.

5 | JAK–STAT Signaling Pathway

IFN-γ is known to be a main driver in the pathogenesis of AA, contributing to the initial loss of HF immune privilege as well as perpetuating the inflammatory response against HFs [28, 46]. It carries out these effects in AA via signaling through JAK proteins, a family of tyrosine kinases that allows cytokine receptors lacking intrinsic kinase activity to participate in signal transduction. Various receptors for cytokines participate in JAK-mediated signal transduction through combinations of the four JAKs including: JAK1, JAK2, JAK3, and TYK2. The receptor for IFN-γ signals via JAK1 and JAK2, while receptor complexes for IL-15 and IL-2, two other important cytokines in AA pathogenesis, signal via JAK1 and JAK3 [47, 48].

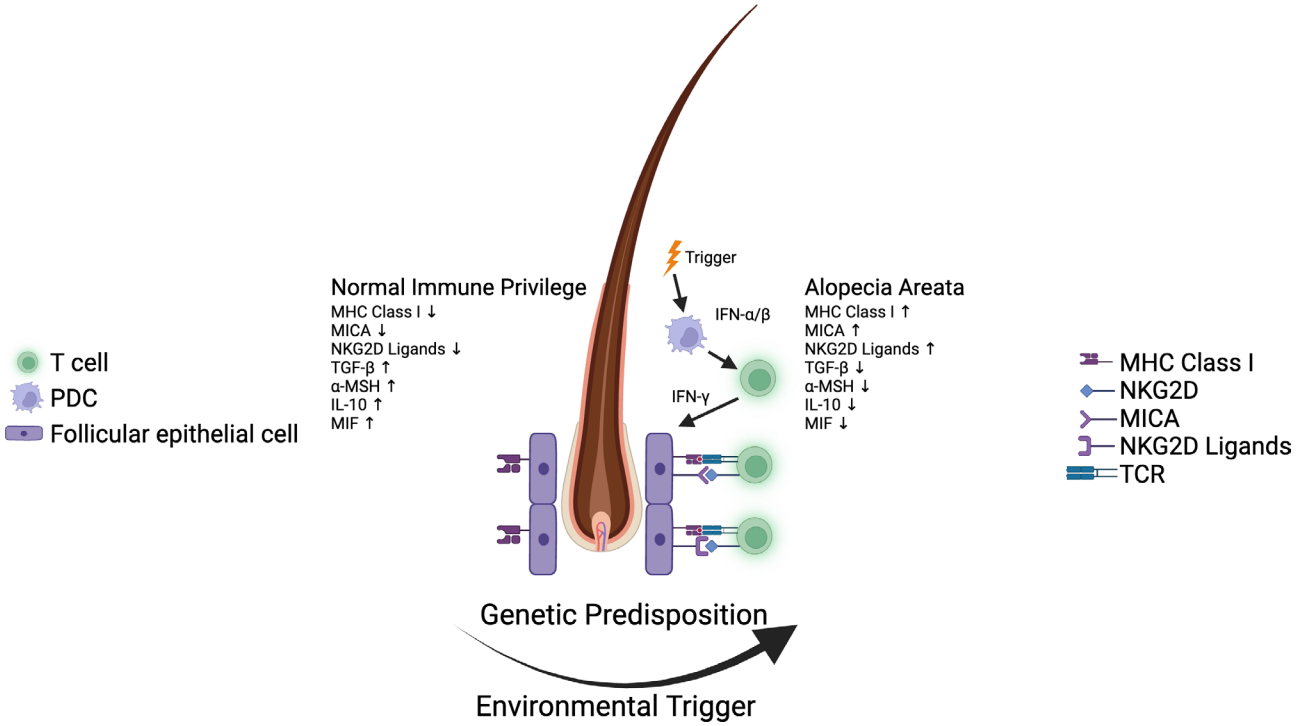

FIGURE 1 | Loss of immune privilege in alopecia areata. Plasmacytoid dendritic cells (PDC) are activated by an environmental trigger and release interferon (IFN) α and β. This mounts a lymphocytic response, primarily NKG2D$^+$ CD8 T cells, CD4 T cells, and natural killer (NK) cells. The T lymphocytes release IFN-γ which binds its receptor on the hair follicle epithelium and activates the JAK–STAT pathway. This leads to loss of immune privilege, indicated by increased expression of MHC class I and NKG2D ligands (including MICA and ULBP3/6) on follicular epithelial cells and making them more readily recognized by NKG2D$^+$ CD8 T cells. Created in BioRender.com.

JAKs are activated by ligand binding of specific receptors, leading to conformational changes which allow dimerization and subsequent auto−/trans-phosphorylation of tyrosine residues on the kinase domain of JAKs. The activated JAKs create a binding site for STATs, which contain a DNA-binding domain, and a different gene transcription activation domain depending on the STAT. Once STATs bind to JAKs, they are phosphorylated, causing release from the JAK receptor docking site, and formation of a STAT dimer which translocate to the nucleus to target pro-inflammatory gene transcription [47]. STAT-regulated pathways implicated in AA pathogenesis include those for IL-15, NKG2D ligands (MICA, ULBP3, and ULBP6), MHC class I, and CXCL10 (Figure 2).

6 | Cytokine/Chemokine Contributors

Several cytokines and chemokines play a role in AA pathogenesis and have been shown to circulate in higher serum levels of patients with moderate to severe AA compared to health controls including IFN-γ, IL-2, IL2RA, IL-15, CXCL9, CXCL10, and CXCL11 [49–51].

6.1 | IFN-γ

IFN-γ is a major driver of AA autoreactivity in the HF [28, 46, 52]. IFN-γ may be upregulated due to inciting events leading to activation of CD4 T-helper type 1 cells (Th1) [33]. IFN-γ is also secreted by CD8 T cells and NK cells. Increased levels of IFN-γ lead to upregulation of MHC class I and II proteins on the HF cells, subjecting them to immune privilege collapse and subsequent autoimmune attack by T cells as discussed above [34, 46].

IFN-γ upregulates CXCL9, CXCL10, and CXCL11, chemokines which have been implicated in other autoimmune diseases [53]. They share the common receptor CXCR3, which is expressed on Th1 CD4 T cells, CD8 T cells, and NK cells [53]. These recruited cells may further increase local IFN-γ levels, resulting in a positive feedback loop [53, 54]. CXCL10 is a chemokine released from activated HF cells, which is thought to attract $CXCR3^+$ CD4 and CD8 T cells in the acute phase of AA [33, 55, 56]. This, in part, constitutes the histopathologic "swarm of bees" appearance of dense lymphocytic infiltrate comprised mainly of CD8 T cells in follicular epithelium, perifollicular infiltrate of CD4 T cells, and innate immune cells [28, 56].

IFN-γ upregulates IL-2 and IL-15, which are other major cytokines implicated in AA pathogenesis. Both are part of the common gamma-chain (γ_c) cytokine family, sharing a common receptor subunit [57]. IL-2 induces IFN-γ production, while IL-15 is upregulated by IFN-γ [58]. This increase in IL-15 plays a role in another positive feedback loop by stimulating CD8 T cells to secrete more IFN-γ, which may perpetuate the disease [28, 48].

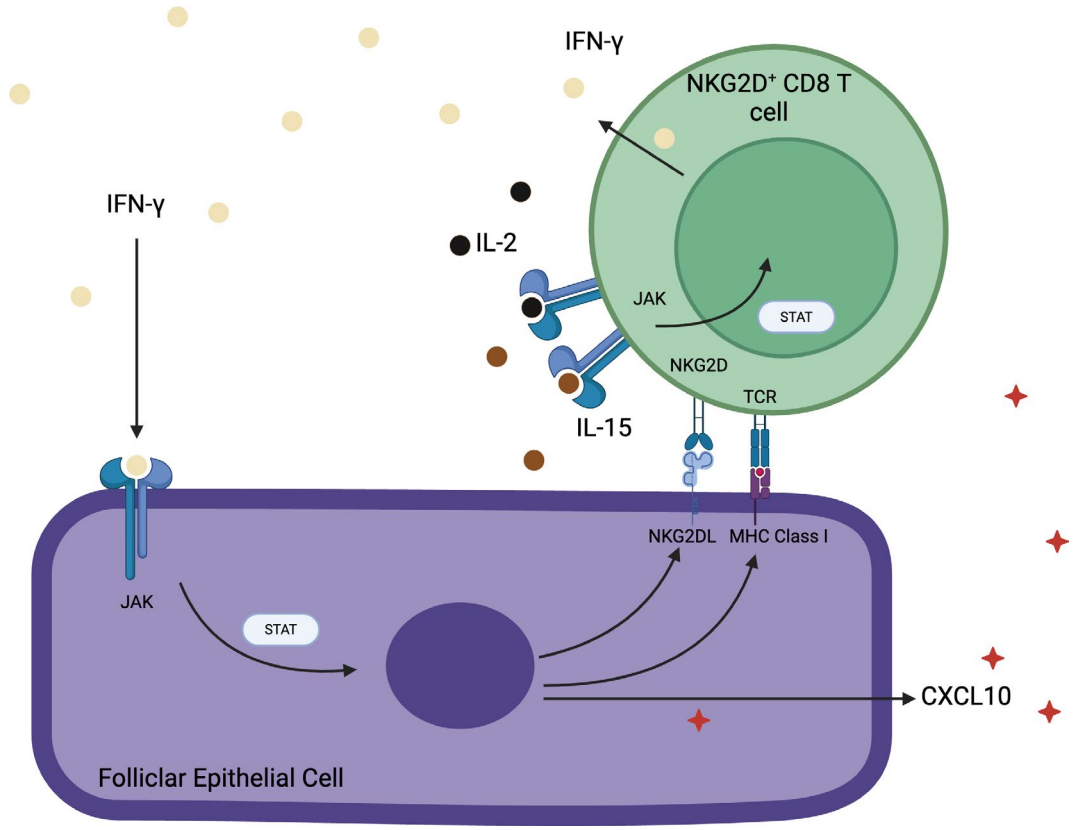

FIGURE 2 | JAK–STAT pathway in alopecia areata. Interferon gamma (IFN-γ) binds its receptor on hair follicle (HF) epithelial cells, leading to JAK1/JAK2 signaling, STAT activation and nuclear translocation, and downstream gene transcription. This causes the HF to produce CXCL10 which attracts T cells to the HF. The HF also upregulates NKG2D ligands such as MICA, ULBP3, and ULBP6, which participate in interactions with the T cells. IL-15 binds its receptor on $NKG2D^+$ CD8 T cells, which triggers JAK3/JAK1 signaling and ultimately leads to increased IFN-γ production. The surge of IFN-γ leads to a positive feedback loop. Created in BioRender.com.

6.2 | IL-2

IL-2 is produced mostly by CD4 T cells and produces effects via two receptor types. There is a high-affinity trimeric receptor, located on both immunosuppressive FoxP3$^+$ regulatory CD4 T cells (Tregs), and a fraction of proinflammatory CD4 and CD8 T cells. There is also an intermediate-affinity dimeric IL-2 receptor composed of IL-2RB and γ_c chains, located on memory CD8 T cells and NK cells. Notably, IL-15 can bind the dimeric receptor, creating competition between these cytokines [47]. IL-2RA, which has been noted in GWAS discussed in an earlier section, is a component of the trimeric receptor.

By binding to its target cell, IL-2 promotes CD8 T-cell activity, maintains regulatory T cells, and drives CD4 T-cell differentiation [59]. The specific JAK–STAT pathway that IL-2 signals through is important for inducing CXCR3 expression, as well as IFN-γ production [58]. SNPs in IL-2RA have been associated with increased AA susceptibility [9].

6.3 | IL-15

IL-15 is an important cytokine for homeostatic and basal functioning of many immune cells. Some of these roles include maintenance and proliferation of T cells, promotion of NK cell development, inhibition of Tregs, and production of TNF-α, and IFN-γ [60, 61]. While IL-15 is upregulated by IFN-γ [48], it is also participatory in a positive feedback loop which enhances IFN-γ production, thereby further enhancing IL-15 production in addition to NKG2D ligand production [48]. This ultimately results in recruitment and activation of CD8 T cells driving disease state. IL-15 levels have been found to be positively correlated with SALT scores and disease duration [62, 63].

6.4 | IL-17

An imbalance between Th17 CD4 T cells and Tregs may be involved in AA autoimmunity, although the exact mechanism is not fully understood. It has been suggested that when there is a disruption between Tregs and Th17 T cells, this leads to a proinflammatory state around the HF seen in AA [64–66]. This disruption has been demonstrated in several other autoimmune and inflammatory conditions such as psoriasis, rheumatoid arthritis, and systemic lupus erythematosus [67]. IL-17 and IL-22 cytokine levels have been shown to be elevated in AA lesions and serum, and some studies suggest correlation with disease severity [64, 65, 68]. Further research into the Th17/Treg imbalance may provide a deeper understanding of pathogenesis and possible treatments for AA.

7 | Conclusion

AA is an autoimmune condition that can have a relapsing clinical course and significant psychosocial impact, with children often having a worse prognosis than adult patients. Many genes have been identified as possible AA risk factors. The HLA region, particularly HLA-DR, has the strongest association with AA development. Several possible environmental triggers are speculated to lead to AA. IFN-γ has largely been understood to be a pivotal driver of AA pathogenesis and is involved in multiple positive feedback loops which could contribute to disease perpetuation. The γ_c family of cytokines also plays a crucial role in AA pathogenesis.

Pediatric patients may have different contributors leading to worse outcomes. Onset prior to puberty is associated with poor prognosis, in addition to nail involvement, associated atopy, ophiasis pattern of hair loss, recurrent episodes, longstanding lesions, and family history [12, 69–71]. Pediatric-specific differences in the pathophysiology of AA have not yet been identified to the knowledge of these authors and could serve as a useful area of further investigation.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

References

1. T. Simakou, J. P. Butcher, S. Reid, and F. L. Henriquez, "Alopecia Areata: A Multifactorial Autoimmune Condition," *Journal of Autoimmunity* 98 (2019): 74–85, https://doi.org/10.1016/j.jaut.2018.12.001.

2. S. J. Connell and A. Jabbari, "The Current State of Knowledge of the Immune Ecosystem in Alopecia Areata," *Autoimmunity Reviews* 21, no. 5 (2022): 103061, https://doi.org/10.1016/j.autrev.2022.103061.

3. A. G. Messenger, D. N. Slater, and S. S. Bleehen, "Alopecia Areata: Alterations in the Hair Growth Cycle and Correlation With the Follicular Pathology," *British Journal of Dermatology* 114, no. 3 (1986): 337–347, https://doi.org/10.1111/j.1365-2133.1986.tb02825.x.

4. A. Nanda, A. S. Al-Fouzan, and F. Al-Hasawi, "Alopecia Areata in Children: A Clinical Profile," *Pediatric Dermatology* 19, no. 6 (2002): 482–485, https://doi.org/10.1046/j.1525-1470.2002.00215.x.

5. F. Xiao, S. Yang, J. Liu, et al., "The Epidemiology of Childhood Alopecia Areata in China: A Study of 226 Patients," *Pediatric Dermatology* 23, no. 1 (2006): 13–18, https://doi.org/10.1111/j.1525-1470.2006.00161.x.

6. E. Tan, Y. Tay, and Y. Giam, "A Clinical Study of Childhood Alopecia Areata in Singapore," *Pediatric Dermatology* 19, no. 4 (2002): 298–301, https://doi.org/10.1046/j.1525-1470.2002.00088.x.

7. S. Verma, R. Sinclair, and A. Das, "Identical Alopecia Areata in Identical Twin Sisters," *International Journal of Trichology* 12, no. 5 (2020): 247–248, https://doi.org/10.4103/ijt.ijt_120_20.

8. N. Barahmani, M. de Andrade, J. P. Slusser, et al., "Human Leukocyte Antigen Class II Alleles Are Associated With Risk of Alopecia Areata," *Journal of Investigative Dermatology* 128, no. 1 (2008): 240–243, https://doi.org/10.1038/sj.jid.5700973.

9. L. Petukhova, M. Duvic, M. Hordinsky, et al., "Genome-Wide Association Study in Alopecia Areata Implicates Both Innate and Adaptive Immunity," *Nature* 466, no. 7302 (2010): 113–117, https://doi.org/10.1038/nature09114.

10. S.-Y. Chu, Y.-J. Chen, W.-C. Tseng, et al., "Comorbidity Profiles Among Patients With Alopecia Areata: The Importance of Onset Age, a Nationwide Population-Based Study," *Journal of the American Academy of Dermatology* 65, no. 5 (2011): 949–956, https://doi.org/10.1016/j.jaad.2010.08.032.

11. R. C. Betz, L. Petukhova, S. Ripke, et al., "Genome-Wide Meta-Analysis in Alopecia Areata Resolves HLA Associations and Reveals Two New Susceptibility Loci," *Nature Communications* 6, no. 1 (2015): 5966, https://doi.org/10.1038/ncomms6966.

12. C. H. Pratt, L. E. King, Jr., A. G. Messenger, A. M. Christiano, and J. P. Sundberg, "Alopecia Areata," *Nature Reviews Disease Primers* 3 (2017): 17011, https://doi.org/10.1038/nrdp.2017.11.

13. S. R. Gil-Quiñones, I. T. Sepúlveda-Pachón, G. Sánchez Vanegas, and L. D. Gutierrez-Castañeda, "Effect of PTPN22, FAS/FASL, IL2RA and CTLA4 Genetic Polymorphisms on the Risk of Developing Alopecia Areata: A Systematic Review of the Literature and Meta-Analysis," *PLoS One* 16, no. 11 (2021): e0258499, https://doi.org/10.1371/journal.pone.0258499.

14. K. K.-G. John, F. F. Brockschmidt, S. Redler, et al., "Genetic Variants in CTLA4 Are Strongly Associated With Alopecia Areata," *Journal of Investigative Dermatology* 131, no. 5 (2011): 1169–1172, https://doi.org/10.1038/jid.2010.427.

15. T. Mustelin, A. Alonso, N. Bottini, et al., "Protein Tyrosine Phosphatases in T Cell Physiology," *Molecular Immunology* 41, no. 6–7 (2004): 687–700, https://doi.org/10.1016/j.molimm.2004.04.015.

16. R. Tazi-Ahnini, M. J. Cork, D. J. Gawkrodger, et al., "Role of the Autoimmune Regulator (AIRE) Gene in Alopecia Areata: Strong Association of a Potentially Functional AIRE Polymorphism With Alopecia Universalis," *Tissue Antigens* 60, no. 6 (2002): 489–495, https://doi.org/10.1034/j.1399-0039.2002.600604.x.

17. D. A. Wengraf, A. J. McDonagh, T. R. Lovewell, et al., "Genetic Analysis of Autoimmune Regulator Haplotypes in Alopecia Areata," *Tissue Antigens* 71, no. 3 (2008): 206–212, https://doi.org/10.1111/j.1399-0039.2007.00992.x.

18. N. Maglakelidze, T. Gao, R. P. Feehan, and R. P. Hobbs, "AIRE Deficiency Leads to the Development of Alopecia Areata–Like Lesions in Mice," *Journal of Investigative Dermatology* 143, no. 4 (2023): 578–587.e3, https://doi.org/10.1016/j.jid.2022.09.656.

19. B. Zhao, L. Chang, H. Fu, G. Sun, and W. Yang, "The Role of Autoimmune Regulator (Aire) in Peripheral Tolerance," *Journal of Immunology Research* 2018 (2018): 1–6, https://doi.org/10.1155/2018/3930750.

20. R. Paus, B. I. Nickoloff, and T. Ito, "A "Hairy" Privilege," *Trends in Immunology* 26, no. 1 (2005): 32–40, https://doi.org/10.1016/j.it.2004.09.014.

21. R. Paus, A. Slominski, and B. M. Czarnetzki, "Is Alopecia Areata an Autoimmune-Response Against Melanogenesis-Related Proteins, Exposed by Abnormal MHC Class I Expression in the Anagen Hair Bulb?," *Yale Journal of Biology and Medicine* 66, no. 6 (1993): 541–554.

22. M. Bertolini, K. McElwee, A. Gilhar, S. Bulfone-Paus, and R. Paus, "Hair Follicle Immune Privilege and Its Collapse in Alopecia Areata," *Experimental Dermatology* 29, no. 8 (2020): 703–725, https://doi.org/10.1111/exd.14155.

23. K. C. Meyer, J. E. Klatte, H. V. Dinh, et al., "Evidence That the Bulge Region Is a Site of Relative Immune Privilege in Human Hair Follicles," *British Journal of Dermatology* 159, no. 5 (2008): 1077–1086, https://doi.org/10.1111/j.1365-2133.2008.08818.x.

24. G. E. Westgate, R. I. Craggs, and W. T. Gibson, "Immune Privilege in Hair Growth," *Journal of Investigative Dermatology* 97, no. 3 (1991): 417–420, https://doi.org/10.1111/1523-1747.ep12481002.

25. M. Ohyama, "What Is Behind the 'Swarm of Bees' in Alopecia Areata," *British Journal of Dermatology* 179, no. 5 (2018): 1023–1024, https://doi.org/10.1111/bjd.17142.

26. K. Natarajan, N. Dimasi, J. Wang, R. A. Mariuzza, and D. H. Margulies, "Structure and Function of Natural Killer Cell Receptors: Multiple Molecular Solutions to Self, Nonself Discrimination," *Annual Review of Immunology* 20, no. 1 (2002): 853–885, https://doi.org/10.1146/annurev.immunol.20.100301.064812.

27. J. W. Streilein, "Immune Privilege as the Result of Local Tissue Barriers and Immunosuppressive Microenvironments," *Current Opinion in Immunology* 5, no. 3 (1993): 428–432, https://doi.org/10.1016/0952-7915(93)90064-y.

28. T. Passerson, B. King, J. Seneschal, et al., "Inhibition of T-Cell Activity in Alopecia Areata: Recent Developments and New Directions," *Frontiers in Immunology* 14 (2023): 1243556, https://doi.org/10.3389/fimmu.2023.1243556.

29. G. E. Westgate, A. G. Messenger, L. P. Watson, and W. T. Gibson, "Distribution of Proteoglycans During the Hair Growth Cycle in Human Skin," *Journal of Investigative Dermatology* 96, no. 2 (1991): 191–195, https://doi.org/10.1111/1523-1747.ep12461019.

30. E. H. C. Wang, M. Yu, T. Breitkopf, et al., "Identification of Autoantigen Epitopes in Alopecia Areata," *Journal of Investigative Dermatology* 136, no. 8 (2016): 1617–1626, https://doi.org/10.1016/j.jid.2016.04.004.

31. J. Abou Rahal, M. Kurban, A.-G. Kibbi, and O. Abbas, "Plasmacytoid Dendritic Cells in Alopecia Areata: Missing Link?," *Journal of the European Academy of Dermatology and Venereology* 30, no. 1 (2014): 119–123, https://doi.org/10.1111/jdv.12932.

32. J. Charles, L. Chaperot, D. Salameire, et al., "Plasmacytoid Dendritic Cells and Dermatological Disorders: Focus on Their Role in Autoimmunity and Cancer," *European Journal of Dermatology* 20, no. 1 (2010): 16–23, https://doi.org/10.1684/ejd.2010.0816.

33. M. Ghoreishi, M. Martinka, and J. P. Dutz, "Type 1 Interferon Signature in the Scalp Lesions of Alopecia Areata," *British Journal of Dermatology* 163, no. 1 (2010): 57–62, https://doi.org/10.1111/j.1365-2133.2010.09775.x.

34. T. Ito, N. Ito, M. Saatoff, et al., "Maintenance of Hair Follicle Immune Privilege Is Linked to Prevention of NK Cell Attack," *Journal of Investigative Dermatology* 128, no. 5 (2008): 1196–1206, https://doi.org/10.1038/sj.jid.5701183.

35. R. P. Wise, K. P. Kiminyo, and M. E. Salive, "Hair Loss After Routine Immunizations," *Journal of the American Medical Association* 278, no. 14 (1997): 1176–1178.

36. A. Akar, E. Arca, H. Erbil, C. Akay, A. Sayal, and A. R. Gür, "Antioxidant Enzymes and Lipid Peroxidation in the Scalp of Patients With Alopecia Areata," *Journal of Dermatological Science* 29, no. 2 (2002): 85–90, https://doi.org/10.1016/s0923-1811(02)00015-4.

37. J. P. Sundberg, K. A. Silva, W. Zhang, et al., "Recombinant Human Hepatitis B Vaccine Initiating Alopecia Areata: Testing the Hypothesis Using the C3H/HeJ Mouse Model," *Veterinary Dermatology* 20, no. 2 (2009): 99–104, https://doi.org/10.1111/j.1365-3164.2008.00692.x.

38. Y. C. Lai and Y. W. Yew, "Severe Autoimmune Adverse Events Post Herpes Zoster Vaccine: A Case-Control Study of Adverse Events in a National Database," *Journal of Drugs in Dermatology* 14, no. 7 (2015): 681–684.

39. D. A. Geier and M. R. Geier, "A Case-Control Study of Quadrivalent Human Papillomavirus Vaccine-Associated Autoimmune Adverse Events," *Clinical Rheumatology* 34, no. 7 (2015): 1225–1231, https://doi.org/10.1007/s10067-014-2846-1.

40. E. M. Peters, S. Liotiri, E. Bodó, et al., "Probing the Effects of Stress Mediators on the Human Hair Follicle: Substance P Holds Central Position," *American Journal of Pathology* 171, no. 6 (2007): 1872–1886, https://doi.org/10.2353/ajpath.2007.061206.

41. A. Katsarou-Katsari, L. K. Singh, and T. C. Theoharides, "Alopecia Areata and Affected Skin CRH Receptor Upregulation Induced by Acute Emotional Stress," *Dermatology* 203, no. 2 (2001): 157–161, https://doi.org/10.1159/000051732.

42. A. Zarbo, V. R. Belum, V. Sibaud, et al., "Immune-Related Alopecia (Areata and Universalis) in Cancer Patients Receiving Immune Checkpoint Inhibitors," *British Journal of Dermatology* 176, no. 6 (2017): 1649–1652, https://doi.org/10.1111/bjd.15237.

43. N. Altunisik, I. Ucuz, and D. Turkmen, "Psychiatric Basics of Alopecia Areata in Pediatric Patients: Evaluation of Emotion Dysregulation, Somatization, Depression, and Anxiety Levels," *Journal of Cosmetic Dermatology* 21, no. 2 (2022): 770–775, https://doi.org/10.1111/jocd.14122.

44. T. Christensen, J. S. Yang, and L. Castelo-Soccio, "Bullying and Quality of Life in Pediatric Alopecia Areata," *Skin Appendage Disorders* 3, no. 3 (2017): 115–118, https://doi.org/10.1159/000466704.

45. Ö. Bilgiç, A. Bilgiç, K. Bahalı, A. G. Bahali, A. Gürkan, and S. Yılmaz, "Psychiatric Symptomatology and Health-Related Quality of Life in Children and Adolescents With Alopecia Areata," *Journal of the European Academy of Dermatology and Venereology* 28, no. 11 (2014): 1463–1468, https://doi.org/10.1111/jdv.12315.

46. T. Ito, N. Ito, A. Bettermann, Y. Tokura, M. Takigawa, and R. Paus, "Collapse and Restoration of MHC Class-I-Dependent Immune Privilege: Exploiting the Human Hair Follicle as a Model," *American Journal of Pathology* 164, no. 2 (2004): 623–634, https://doi.org/10.1016/S0002-9440(10)63151-3.

47. M. Lensing and A. Jabbari, "An Overview of JAK/STAT Pathways and JAK Inhibition in Alopecia Areata," *Frontiers in Immunology* 13 (2022): 955035, https://doi.org/10.3389/fimmu.2022.955035.

48. L. Xing, Z. Dai, A. Jabbari, et al., "Alopecia Areata Is Driven by Cytotoxic T Lymphocytes and Is Reversed by JAK Inhibition," *Nature Medicine* 20, no. 9 (2014): 1043–1049, https://doi.org/10.1038/nm.3645.

49. R. K. Gautam, Y. Singh, A. Gupta, P. Arora, A. Khurana, and A. Chitkara, "The Profile of Cytokines (IL-2, IFN-γ, IL-4, IL-10, IL-17A, and IL-23) in Active Alopecia Areata," *Journal of Cosmetic Dermatology* 19, no. 1 (2020): 234–240, https://doi.org/10.1111/jocd.12970.

50. J. W. Glickman, C. Dubin, Y. Renert-Yuval, et al., "Cross-Sectional Study of Blood Biomarkers of Patients With Moderate to Severe Alopecia Areata Reveals Systemic Immune and Cardiovascular Biomarker Dysregulation," *Journal of the American Academy of Dermatology* 84, no. 2 (2021): 370–380, https://doi.org/10.1016/j.jaad.2020.04.138.

51. E. Kasumagić-Halilovic, S. Cavaljuga, N. Ovcina-Kurtovic, and L. Zecevic, "Serum Levels of Interleukin-2 in Patients With Alopecia Areata: Relationship With Clinical Type and Duration of the Disease," *Skin Appendage Disorders* 4, no. 4 (2018): 286–290, https://doi.org/10.1159/000486462.

52. N. Borcherding, S. B. Crotts, L. S. Ortolan, N. Henderson, N. L. Bormann, and A. Jabbari, "A Transcriptomic Map of Murine and Human Alopecia Areata," *JCI Insight* 5, no. 13 (2020): e137424, https://doi.org/10.1172/jci.insight.137424.

53. J. R. Groom and A. D. Luster, "CXCR3 Ligands: Redundant, Collaborative and Antagonistic Functions," *Immunology and Cell Biology* 89, no. 2 (2011): 207–215, https://doi.org/10.1038/icb.2010.158.

54. M. Rotondi, L. Chiovato, S. Romagnani, M. Serio, and P. Romagnani, "Role of Chemokines in Endocrine Autoimmune Diseases," *Endocrine Reviews* 28, no. 5 (2007): 492–520, https://doi.org/10.1210/er.2006-0044.

55. C. G. McPhee, F. J. Duncan, K. A. Silva, et al., "Increased Expression of Cxcr3 and Its Ligands, Cxcl9 and Cxcl10, During the Development of Alopecia Areata in the Mouse," *Journal of Investigative Dermatology* 132, no. 6 (2012): 1736–1738, https://doi.org/10.1038/jid.2012.17.

56. T. Ito, H. Hashizume, T. Shimauchi, et al., "CXCL10 Produced From Hair Follicles Induces th1 and TC1 Cell Infiltration in the Acute Phase of Alopecia Areata Followed by Sustained TC1 Accumulation in the Chronic Phase," *Journal of Dermatological Science* 69, no. 2 (2013): 140–147, https://doi.org/10.1016/j.jdermsci.2012.12.003.

57. Y. Rochman, R. Spolski, and W. J. Leonard, "New Insights Into the Regulation of T Cells by Gamma(c) Family Cytokines," *Nature Reviews. Immunology* 9, no. 7 (2009): 480–490, https://doi.org/10.1038/nri2580.

58. W. Liao, J. X. Lin, L. Wang, P. Li, and W. J. Leonard, "Modulation of Cytokine Receptors by IL-2 Broadly Regulates Differentiation Into Helper T Cell Lineages," *Nature Immunology* 12, no. 6 (2011): 551–559, https://doi.org/10.1038/ni.2030.

59. O. Boyman and J. Sprent, "The Role of Interleukin-2 During Homeostasis and Activation of the Immune System," *Nature Reviews. Immunology* 12, no. 3 (2012): 180–190, https://doi.org/10.1038/nri3156.

60. A. Mishra, L. Sullivan, and M. A. Caligiuri, "Molecular Pathways: Interleukin-15 Signaling in Health and in Cancer," *Clinical Cancer Research* 20, no. 8 (2014): 2044–2050, https://doi.org/10.1158/1078-0432.CCR-12-3603.

61. P. Y. Perera, J. H. Lichy, T. A. Waldmann, and L. P. Perera, "The Role of Interleukin-15 in Inflammation and Immune Responses to Infection: Implications for Its Therapeutic Use," *Microbes and Infection* 14, no. 3 (2012): 247–261, https://doi.org/10.1016/j.micinf.2011.10.006.

62. M. A. El Aziz Ragab, E. M. Hassan, D. A. E. M. El Niely, and M. M. Mohamed, "Serum Level of Interleukin-15 in Active Alopecia Areata Patients and Its Relation to Age, Sex, and Disease Severity," *Postepy Dermatologii I Alergologii* 37, no. 6 (2020): 904–908, https://doi.org/10.5114/ada.2020.102103.

63. K. Tabara, M. Kozłowska, A. Jędrowiak, W. Bienias, and A. Kaszuba, "Serum Concentrations of Selected Proinflammatory Cytokines in Children With Alopecia Areata," *Postepy Dermatologii I Alergologii* 36, no. 1 (2019): 63–69, https://doi.org/10.5114/ada.2019.82826.

64. S. H. Loh, H. N. Moon, B. L. Lew, and W. Y. Sim, "Role of T Helper 17 Cells and T Regulatory Cells in Alopecia Areata: Comparison of Lesion and Serum Cytokine Between Controls and Patients," *Journal of the European Academy of Dermatology and Venereology* 32, no. 6 (2018): 1028–1033, https://doi.org/10.1111/jdv.14775.

65. Y. M. Han, Y. Y. Sheng, F. Xu, et al., "Imbalance of T-Helper 17 and Regulatory T Cells in Patients With Alopecia Areata," *Journal of Dermatology* 42, no. 10 (2015): 981–988, https://doi.org/10.1111/1346-8138.fa12978.

66. M. Noack and P. Miossec, "Th17 and Regulatory T Cell Balance in Autoimmune and Inflammatory Diseases," *Autoimmunity Reviews* 13, no. 6 (2014): 668–677, https://doi.org/10.1016/j.autrev.2013.12.004.

67. M. S. Maddur, P. Miossec, S. V. Kaveri, and J. Bayry, "Th17 Cells: Biology, Pathogenesis of Autoimmune and Inflammatory Diseases, and Therapeutic Strategies," *American Journal of Pathology* 181, no. 1 (2012): 8–18, https://doi.org/10.1016/j.ajpath.2012.03.044.

68. M. A. Atwa, N. Youssef, and N. M. Bayoumy, "T-Helper 17 Cytokines (Interleukins 17, 21, 22, and 6, and Tumor Necrosis Factor-α) in Patients With Alopecia Areata: Association With Clinical Type and Severity," *International Journal of Dermatology* 55, no. 6 (2016): 666–672, https://doi.org/10.1111/ijd.12808.

69. N. Barahmani, M. B. Schabath, M. Duvic, and National Alopecia Areata Registry, "History of Atopy or Autoimmunity Increases Risk of Alopecia Areata," *Journal of the American Academy of Dermatology* 61, no. 4 (2009): 581–591, https://doi.org/10.1016/j.jaad.2009.04.031.

70. A. Tosti, S. Bellavista, and M. Iorizzo, "Alopecia Areata: A Long Term Follow-Up Study of 191 Patients," *Journal of the American Academy of Dermatology* 55, no. 3 (2006): 438–441, https://doi.org/10.1016/j.jaad.2006.05.008.

71. A. Sterkens, J. Lambert, and A. Bervoets, "Alopecia Areata: A Review on Diagnosis, Immunological Etiopathogenesis and Treatment Options," *Clinical and Experimental Medicine* 21, no. 2 (2021): 215–230, https://doi.org/10.1007/s10238-020-00673-w.