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# Understanding the Biological Mechanism of Alopecia Areata

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**Abstract** Alopecia Areata or AA is a condition of patchy hair loss that results from a non-scarring, autoimmune, inflammatory skin disease. Though it has known to affect both genders, studies have shown that most male suffer AA. It is a complex and poorly understood entity. Presently, the hypotheses for AA development generally focus on the collapse of immune privilege properties of the hair follicles and the nature of self-antigen presentation that result in the induction and subsequent attack of activated lymphocytes. The treatment options for AA are limited and the effectiveness of these treatments differs. Some of the recent hypothesis and studies on AA are offered for a broader understanding of the biological mechanisms of AA.

**Keywords** Alopecia areata, Pathogenesis, Hair loss

## 1. Introduction

Alopecia Areata (AA) is an intermittent non-scarring form of hair loss that can affect any area bearing hair. [1] The hair shaft breaks off as the anagen follicles enter dystrophic catagen. [2] The disease can present as a single, well-demarcated patch of hair loss or multiple patches in which the lesions are usually round or oval patched. These may regrow to be followed by new patches of hair loss. [1] Extensive hair losses in a form of complete loss of scalp hair known as alopecia totalis or loss of entire scalp and body hair known as alopecia universalis. [3] The affected skin appears normal without any obvious epidermal modification such as scaling or follicular abnormalities. The presence of broken exclamation mark hairs at the edge of a bald area is diagnostic. Regrowth may initially be with lack of pigment resulting in blonde or white hairs and this often occurs slowly over months. [3] AA may affect both children and adults and hair of all colors. It is uncommon in children under 3 years of age but most patients are relatively young. Up to 66% are younger than 30 years of age, and only 20% are older than 40 years of age. There is generally no sex predilection, but more men were affected in a study that involved a group of subjects who were 21 to 30 years of age. [4] Treatment has no effect on the long-term progression and is more effective in patchy AA than in alopecia totalis or alopecia universalis. [5] AA is a complex and poorly understood entity. There is much that is not understood about the pathogenesis of the various clinical presentations. There are some frequent questions asked in the process of understanding the mechanisms of AA. It is not understood if an inflammatory infiltrate or a hair follicle defect happens first. In addition to that, the location of target of attack in AA-affected hair follicles is not known for sure and can AA be considered to be just one disease. [3] Additional understanding of the pathobiology, genetic component and basic immunopathology of AA can offer some perceptions into the pathogenesis of AA. [4]

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## 2. Content

### 2.1. Normal Hair Growth

Hair follicles develop in recurring cycles and one cycle can be fragmented into three phases known as anagen, catagen, and telogen. The period of rapid growth, pigmentation and hair shaft production is known as the anagen phase. Anagen is then followed by the catagen phase that is the transitional phase. This is where the hair follicle experiences a prompt, apoptosis-driven organ involution phase. The hair follicle then enters a period of relative inactivity before reenters the anagen phase and the cycle begins again. [4] Though hair follicle regeneration and cycling are stem cell dependent, the differentiated progeny of these stem cells accomplishes hair shaft production and pigmentation. Anagen hair matrix is the major target of the inflammatory attack in AA. The pigment-producing melanocytes and the rapidly proliferating keratinocytes reside in the anagen hair matrix. [4]

### 2.2. Immunobiology of the Hair Follicle

The important immunologic feature of the hair follicle is its creation of a milieu of relative immune privilege that prevents an autoimmune attack on intra-follicularly expressed autoantigens. This is achieved by generating the overall immunoinhibitory local signaling milieu and by suppressing the surface molecules required for presenting autoantigens to CD8+ T lymphocytes. Example of the surface molecules that are suppressed is the major histocompatibility complex [MHC] class 1a antigens (HLA types) in association with MHC class I–stabilizing β2-microglobulin. [6]

The physiological functions of the immune privilege in regard to hair follicles are not proven, but it is known that several autoantigens that are related with pigment production are extremely immunogenic. It is a likely theory that melanogenesis-associated autoantigens generated during active hair shaft pigmentation and possibly other anagen associated hair follicle autoantigens pose a constitutive risk of attracting autoreactive CD8+ T cells already present. [7]

A low level of expression of MHC class 1 molecules may reduce the risk that follicle associated autoantigens will be presented to CD8+ T cells. However, this action then involves the risk of the hair follicle being attacked by natural killer (NK) cells. This is because NK cells are set to recognize and eliminate MHC class 1-negative cells. Healthy hair follicles appear to reduce the expression of ligands that stimulate the activation of NK-cell receptors NKG2D and secrete molecules that inhibit NK cell and T cell functions, in order to reduce this risk. [4]

### 2.3. Clinical Presentation & Diagnosis

AA mostly presents as a sudden loss of hair in well-demarcated, localized areas. The most common presentation is the appearance of one or many round or oval bald patches. The scalp is the most common site that is affected. The onset is usually rapid and this disease can evolve to a point where all the hair is lost on the scalp or even the whole body. Variants of this disorder include an ophiasis pattern that occurs when the hair loss is localized to the sides and lower back of the scalp, diffuse forms of alopecia and sudden graying. In addition to these presentations, clinical signs such as exclamation-mark hairs, cadaver hairs, nail pitting and the growth of white hair in formerly alopecic lesions, often solidify the diagnosis. [1]

Skin biopsy is usually diagnostic, if diagnosis is not clear after a clinical evaluation. Bee-swarm pattern of dense perifollicular lymphocytic infiltrates around anagen hair follicles are found in patients with acute AA. [4]

### 2.4. Management

There are treatments that can induce hair regrowth in AA but do not alter the course of the disease. The treatment is said to be more effective in treating patchy AA than in alopecia universalis and alopecia totalis. The therapy of AA has to be altered according to the patient's age and also the severity of the condition. [6] Given the often-unsatisfactory results from current therapy, some clinicians rely on the high rate of spontaneous remission. [4] Clinicians have two principal management options that are use of immunosuppressive regimen and immune-deviation strategy that manipulates the intracutaneous inflammatory milieu. Immunosuppressive regimens are preferable for patients with acute and rapidly progressing AA whereas immune-deviation strategy is mostly favored for patients with the chronic relapsing form. [4] At the moment, only two approaches reach the level of evidence-based medicine, which are intralesional injections of glucocorticoids and induction of contact allergy. [5]

### 2.5. Understanding the Mechanism of Alopecia Areata

#### 2.5.1. What Comes First, an Inflammatory Infiltrate or a Hair Follicle Defect?

The initiating mechanism of AA is not clear. Defects in the immune system could cause an AA onset while hair follicle defects could initiate the disease with inflammation as a response event. Understanding the initiating mechanism of AA will be important as it could determine the main focus of the treatment development, if it should be regulating the immune system or the hair follicle unit. [3]

#### 2.5.2. Target of Attack in AA Affected Hair Follicle

The primary location of the inflammatory infiltrate in AA focuses on the transient region of anagen stage hair follicles. Say that the antigen target of attack is close to the location of the immune cell infiltrate, there are multiple candidates of sources for the inciting agent. Keratinocytes constitute the root sheaths and hair matrix, dermal papilla and dermal sheath cells are mesenchyme derived, and melanocytes in the hair bulb are all possible targets. [3] Several studies have implied that melanocytes could be the source of antigen epitopes. Melanoma-associated antigens have been used to stimulate T cells in culture and these lymphocytes were able to induce AA again when injected into previously AA-affected skin biopsies grafted to severe combined immunodeficient (SCID) mice. [7] However, the intrafollicular inflammatory cells in AA do not seem to focus on melanocytes. Instead, they locate themselves among root sheath and matrix keratinocytes. It is possible that lymphocytes from patients with alopecia may also target these keratinocyte antigens or similar. [3]

#### 2.5.3. Is Alopecia Areata as One Disease?

AA is found in several different phenotypic presentations from the classic distinct patches, through diffuse AA, to exclusive ophiasis AA, and nevoid AA. These differences may suggest different underlying disease development mechanisms. It is also possible that individuals presenting with similar AA phenotypes will be shown to have different causal disease pathogenesis mechanisms. It would be unlikely that the exact same mechanism is involved in every

case identified within the AA disease collective. [3]

2.5.4. Pathobiology of Alopecia Areata

Enhanced pathobiologic concepts may help in enhancing ways to better management and outcomes in AA. Note that this is a disorder of hair follicle cycling in a dual sense in which inflammatory cells attack only anagen hair follicles, which are then prematurely forced into the catagen phase. The hair shaft then can no more be firmly secured in the hair canal and is shed. This is due to inflammation-induced dystrophy of follicle. Despite that, the hair follicle retains its ability to regenerate and resume cycling. Hence, the loss of hair in this disorder is, in principle, reversible. [4] Like most other autoimmune diseases, AA is a chronically relapsing inflammatory disorder. In the absence of a perifollicular infiltrate, there is no hair loss. The main therapeutic challenge, therefore, is to avoid both recurrence and spread to the previously unaffected hair follicles and to reduce the already established inflammatory infiltrates. Unfortunately, currently available therapies meet up to this challenge. [4] A better understanding is needed of how the perifollicular infiltrate in AA develops and why it predominantly forms around follicles in the anagen phase during which pigment is produced. Since it solely affects hair follicles, nails, and (in some patients) the retinal pigment epithelium, AA can be said to be an organ specific autoimmune disease. Therefore, antigens or autoantigens that is presented in these selected tissues could be important in the pathobiology of this disease. [4] In addition, systemic interferon alfa therapy and tumor necrosis factor α antagonists, which are used to treat other autoimmune diseases, can prompt or exacerbate AA, suggesting that selected cytokines may also be important pathogenetic factors. [8]

2.5.5. Basic Immunopathology

Examining the skin lesions may best attain the understandings of the immunopathological mechanisms in AA. CD8+ T cells appear to be the first lymphocytes to enter the proximal follicular epithelium even though CD4+ T cells predominate numerically in the perifollicular infiltrates. The increased numbers of NK cells and mast cells in perifollicular infiltrates raises the question of whether these cells are also involved in the pathogenesis of AA. Although no pathogenic evidence, autoantibodies against follicular autoantigens are often found in the serum and skin of patients with AA. [4]

As a matter of fact, in murine models of AA, CD8+ T cells alone can transfer the disease. This is especially after the T cells have been prepared by contact with melanogenesis-related autoantigens. The most effective way instigating the disease in widely used murine model, is to transfer the CD8+ T cells together with CD4+ T cells, whilst the transfer of serum or autoantibodies from patients with AA fails to elicit hair loss. Contrariwise, the depleting CD8+ T cells restore hair growth in a rat model of AA. It is therefore reasonable to consider AA a CD8+ T-cell–dependent, organ-specific autoimmune disease. [4]

2.5.6. Genetic Component in Alopecia Areata

Strong genetic component can be associated to the development of AA. For instance, many patients with known family history of AA also have a history of atopy, Down's syndrome, autoimmune polyendocrinopathy- candidiasis-ectodermal dystrophy syndrome, other immune diseases or a combination of these disorders. A poorer prognosis, rapid progression, frequent relapses and greater resistance to therapy often characterize familial cases of AA. Also, relatives of affected family members are at risk of AA. The role of genetic factors in the pathogenesis of AA is further emphasized by ethnic variations in the incidence and relative risk. [4]

Martinez-Mir and friends have identified that AA can coexist with psoriasis in a genomwide association study of 20 families with AA. In psoriasis, it has been linked with Cytotoxic T-lymphocyte–associated antigen 4 (CTLA4), which is a co-stimulatory molecule that is involved in the negative regulation of T-cell activation. It may also be an exposure gene for AA especially in patients with a severe form of the disorder. The CTLA 4 association is strengthened by another study in which Petukhova and friends have stated the significance of both innate and acquired immunity in the pathogenesis of AA and emphasized the point that this disorder shares routes with other autoimmune diseases. [4] Both Martinez-Mir et al. and Petukhova et al. studies identified susceptibility loci common to AA on chromosomes 6p (HLA), 6q (UL 16 binding protein [ULBP]), 10p (IL2RA), and 18p (PTPN22). Also, Petukhova et al. identified some genes that may be related with AA and other autoimmune diseases, such as the genes for *ULBP,* which encrypt a class of ligands for activating NKG2D. [4]

# 3. Conclusions

It has been hypothesized that AA develops in a formerly healthy hair follicle because its constitutive immune privilege fails. In regard to this hypothesis, AA can occur in a genetically predisposed person only when proinflammatory signals known to up-regulate ectopic MHC class 1a expression in human hair-follicle epithelium expose previously "sequestered" follicle-associated autoantigens to preexisting auto-reactive CD8+ T cells. The lymphocytic infiltrates could attack the hair follicle, provided the assistance from other cells, such as CD4+ T cells and mast cells and stimulatory signals. The autoantigens in subject may be generated and presented during anagen phase since only anagen hair follicles are attacked. This is supported by evidence resulting from mouse models of AA. [4, 6, 9]

Proinflammatory factors and NK-cell-stimulating ligands may also be active at some stage during the development of AA, suggests genomwide association studies. NK cells and NKG2D and their endogenous ligands have been linked in

the pathogenesis of AA. Though very few NK cells are observed around healthy anagen hair follicles, lesional follicles show apparent groups of CD56+ and NKG2D+ NK cells. Furthermore, hair follicles in AA overexpress MHC class I polypeptide related sequence A (MICA) protein, a key NKG2D agonist, whereas in healthy hair follicles MICA expression is much more limited. The conclusion that excessive NKG2D-mediated signaling may contribute to the pathogenesis of AA is underscored by the genetic association between the disease and NKG2D-activating ligands from the MICA family namely, ULBP3. ULBP3 protein expression is actually up regulated around lesional hair follicles in AA. [4, 6]

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