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Alopecia Areata: A tissue specific autoimmune disease of the hair follicle

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Abstract

The goal of this review is to introduce the immunologic community to alopecia areata as a model system for the study of tissue directed autoimmune disease. Alopecia areata is marked by autoimmune assault on the hair follicle resulting in hair loss. It is linked to HLA-DQ3 and evidence suggests it is mediated by T-lymphocytes with a TH1 cytokine profile. Hair follicles are an immune protected site with deficient MHC expression. Evidence is presented suggesting that alopecia areata results from loss of immune privilege with presentation of autoantigens. Alopecia areata is one of the most common human autoimmune conditions, with a lifetime risk of approximately 1.7%. Study of alopecia areata in humans is facilitated by the accessibility of scalp for biopsy. It is possible to transfer the condition with lesional human lymphocytes in a human scalp graft/SCID mouse model. There are also spontaneous animal models which share the features of the human condition. For these reasons, alopecia areata is a powerful model for study of the induction and pathogenesis of tissue directed autoimmune disease.

Keywords: Alopecia areata; C3H/HeJ; SCID mice; Melanocyte autoantigens; CGRP

Contents

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1. Clinical features of alopecia areata

AA is characterized by the sudden appearance of round or oval patches of non-scarring hair loss with spontaneous remissions and exacerbations. The patches are well circumscribed, may have a mild peachy hue, occasionally with "exclamation point" hairs around their margin. "Exclamation point" hairs are broken short hairs with a broader distal segment as compared to the proximal end. The involved skin is usually smooth and almost always totally devoid of hair.

The most common clinical presentation AA is patchy hair loss. Five to ten percent of patients, especially children, end up losing all their scalp hair (alopecia totalis). Loss of all body hair is termed alopecia universalis. Patients with reticular variant of patchy AA exhibit hair loss in one site and spontaneous hair regrowth in another area of a bald lesion. AA tends to preferentially affect pigmented hairs, with relative sparing of white hairs.

Nail changes may be associated with AA. The frequency of nail changes ranges from 10% to 66%. Changes may be observed in one, several, or all of the nails. Nail pitting is the most common nail dystrophy observed in AA. Other changes include longitudinal ridging and thickening. The dystrophy of nails may persist for years after the resolution of the AA.

2. Genetic factors

The family history of AA in patients ranges from 10% up to 42% of cases and there are reports of identical twins developing AA simultaneously. AA has HLA association with DQB1*03 [2], HLA B-18, and possibly HLA-A2 [3]. These associations with HLA-DR and HLA-DQ suggest a role for CD4+ T-cells in AA. However, association with HLA-A, B and C were not examined in the most recent studies. An association with DQB1*0301 was found in patients with persistent and chronic alopecia totalis but not in patients with persistent and chronic patchy AA [4]. However, both patient groups had a positive association with HLA-DQ3 (DQB1*03). The genetic difference between risk of patchy AA and alopecia totalis may indicate differences in molecular pathogenesis [5].

AA may occur in diseases linked to chromosome 21 including Down's syndrome and autoimmune polyendocrinopathy. The risk of alopecia areata is increased to 30% in patients with autoimmune polyendocrinopathy candidiasis ectodermal dysplasia syndrome (APECED). This condition is associated with a mutation of the autoimmune regulator (AIRE) gene on chromosome 21q22.3 [6]. Association between AA and atopic features has been found in more than 40% of AA patients. It is likely that AA (similar to other autoimmune diseases) is polygenic, i.e. there are multiple susceptibility genes that interact with environmental factors [7].

3. Evidence for an autoimmune pathogenesis

There is increasing evidence that AA is a tissue-specific autoimmune disease. The most characteristic histological feature of AA is lymphatic infiltration around and within the hair follicles. Loss of hair during active disease is coincidental with an infiltrate of activated CD4+ cells around the hair follicles, along with a CD8+ intrafollicular infiltrate [8]. Immunosuppressive agents such as systemic corticosteroids and cyclosporine as well as immunotherapy with contact sensitizers exhibit a beneficial effect in AA [9]. AA has also been associated with various autoimmune disorders such as autoimmune thyroiditis and vitiligo [10]. Lesional (bald) scalp grafted to nude mice regrows hair coincident with loss of infiltrating scalp lymphocytes [11]. This demonstrates the potential of hair follicles to recover when removed from the immune system of the host and further supports an immune etiology.

Conflicting results regarding the presence of autoantibodies in AA cast doubt on the causative role of humoral immunity. Patients with AA have an increased frequency of autoantibodies to follicular structures. However there is little consistency in which follicular structures are labeled by the antibodies. Autoantibodies to hair follicle associated antigens also occur in C3H/HeJ mice [12], and DEBR rats [13], with alopecia areata. Injection of patient serum into human skin grafts on nude mice does not induce hair loss [14]. Alopecia areata has also been reported in a child with common variable immunodeficiency [15]. Thus, the role of autoantibodies in the pathogenesis of AA is not clear and they may simply be markers CD4+ T-cell activation.

4. Hair follicle is an immune privileged site

Hair follicles in both mice, and humans have properties of an immune privileged site. The proximal (lower) hair follicular epithelium of normal hair follicles does not express major histocompatibility complex (MHC) class I or class II molecules [16]. There is also a decrease of Langerhans dendritic cells density [17]. Other mechanisms of immune privilege in the anagen hair follicle include production of immunosuppressive cytokines alpha-MSH, TGF-beta, and IGF-1 [18,16].

Both humans and C3H/HeJ mice with alopecia areata express MHC class I and II on follicular epithelium, which is interpreted as loss of immune privilege [19]. Interferon-gamma (INF-gamma) is able to induce both MHC I and II on hair follicle epithelium [17]. Paus et al. [20] have hypothesized that induction of class I MHC in alopecia areata allows an autoaggressive response by melanocyte reactive CD8+ T-cells. It was suggested that the CD8+ cells induce HLA-DR on the affected hair follicles by production of INF-gamma, resulting in a second wave of CD4+ cells. Microvascular endothelial cells are also induced to express the adhesion molecules ICAM-1, and ELAM-1 [21]. These adhesion molecules are significant, because they are critical in the homing of lymphocytes to sites of inflammation.

5. Transfer of alopecia areata in human scalp graft/SCID mouse models

We demonstrated that AA can be transferred from patients to human scalp transplants grafted on SCID mice by injection of autologous lesional T-cells [22]. Lesional scalp skin grafts on SCID mice spontaneously regrew hair. Hair loss was observed only in the group of mice injected with T-cells which had been cultured with follicular homogenate. Injection of scalp T-cells which had been cultured with non-follicular scalp homogenate failed to induce hair loss [23]. The necessity of the follicular homogenate to induce AA suggests that T-cells recognize a follicular autoantigen. Optimal transfer of hair loss requires both CD4+ and CD8+ T-cells [24]. Complete hair growth in the Dundee DEBR rat model of AA was observed following depletion of either CD8+ or CD4+ T-cells [25]. Inflammatory T-cells of AA are cytotoxic and possess both the Fas/Fas ligand and granzyme B cytotoxic mechanisms [26]. Inflammatory T-cells of alopecia areata have a TH1 cytokine bias [27]. It is proposed that the CD4+ T-cells provide help for the effector function of the CD8+ T-cells.

6. Melanocyte autoantigens and alopecia areata

AA patients show an increased incidence of autoimmune diseases including pigmentary defects. Remarkably, white or greying hair follicles are relatively spared in AA, while regrowing hair shafts are usually white before they become repigmented. The sudden appearance of fulminant AA affects mostly pigmented hair follicles. Thus, only pre-existing grey or white hair is observed. This phenomenon is known as "overnight greying". Collectively, such evidence points to follicular melanocytes as a possible important target in the autoimmune process of AA. Indeed, follicular melanocytes in AA show both histological and ultrastructural abnormalities [28].

Using the human scalp explant/SCID mouse transfer model, we demonstrated that melanocytes-associated T-cell epitopes are capable of functioning as autoantigens to induce AA in the human scalp grafts/SCID mouse model [29]. Melanocyte HLA-A2 restricted peptides can activate T-cells for transfer of AA to autologous scalp skin grafts on SCID mice indicating that melanocytes-associated autoantigens can be pathogenic.

The onset of AA is most probably the result of several events predisposing to disease development, such as: release of proinflammatory cytokines due to non-specific stimuli, which may lead to the abnormal expression of MHC by the lower part of the follicular epithelium and the hair bulb; the abnormal MHC could expose immunogenic peptides derived from melanocytes or melanogenesis process, and the presence of autoreactive cells. The non-specific stimuli could be localized microtrauma, neurogenic inflammation, infection agents or microbial superantigen.

7. Emotional stress and neuropeptides

Many medical conditions can be exacerbated by stress. It is also likely that in a subset of patients, stressful life events lead to both the onset and the progression of AA [30]. A definitive relationship has yet to be statistically proven. However, alopecia areata is also associated with an increased incidence of depression and anxiety disorders, which may be secondary to hair loss [31].

Neuropeptides produced by cutaneous nerves have been found to modulate inflammation in the skin, providing a potential link between the brain and skin disease [32]. Immunomodulatory neuropeptides include substance P, calcitonin gene-related peptide (CGRP), and vasoactive intestinal peptide (VIP). CGRP released from cutaneous nerves can induce mast cell degranulation, with release of immunosuppressive TNF-alpha, and IL-10 [33]. CGRP containing neurons come in close proximity to Langerhans cells, and Langerhans cell antigen presenting function is inhibited by CGRP treatment [34]. This immunosuppression is mediated in part by inhibiting expression of the co-stimulatory molecule B7-2 (CD86), as well as production of IL-10. The neuropeptide alpha-MSH also has immunosuppressive effects. In addition, CGRP interacts with keratinocyte factors to promote melanization [35]. There is evidence suggesting that a deficiency of CGRP may have a role in alopecia areata. Involved scalp has reduced cutaneous levels of substance P and CGRP. Furthermore, serum levels of CGRP are depressed to about half of control values in patients with active alopecia areata. CGRP is also a potent inducer of vasodilatation of skin vasculature [36], which may be of significance to the hair cycle. Deficiency of CGRP may result in increased immune responsiveness, and vasoconstriction, both of which may have a role in the pathogenesis of alopecia areata.

8. Animal models

The aging C3H/HeJ mice is a model for human AA [37]. Female mice, 6 months of age and older spontaneously develop AA at a frequency of approximately 20%. Lesions first appear on the ventral surface of the mice and are characterized histologically by a perifollicular inflammatory infiltrate of lymphocytes, as well as abnormal expression of HLA-DR, HLA-A,B,C and ICAM-1 by follicular epithelium. Response to intralesional steroid injection and to topical immunotherapy is similar to the human disease [38]. AA can be induced in normal C3H/HeJ mice following engraftment of skin grafts obtained from affected C3H/HeJ mice [37]. It is thought that this transfer is mediated by passenger lymphocytes inducing autoreactivity by the host immune system, since the transfer is not effective in immunodeficient mice. Both CD4+ and CD8+ T-cells have a role in the alopecia [39], in a direct parallel to the human condition [24]. The DEBR rat is a second similar model of spontaneous AA [25]. Both these models may serve as an important tool to study the pathogenesis of the disease as well as potential efficacy of therapies.

9. Loss of immune privilege induces alopecia areata in C3H/HeJ mice

It was possible to accelerate the development of autoimmune hair loss (alopecia areata) in C3H/HeJ mice by injection of intravenous injection INF-γ at doses shown to induce follicular expression of MHC class I and II [40]. The histologic, and immunochemical features of the hair loss were typical for alopecia areata of C3H/HeJ mice, and not consistent with telogen effluvium, which is hair loss induced non-specifically by illness or medication. Furthermore, the hair loss could only be induced in genetically susceptible C3H/HeJ mice, and not in C57Bl/6J mice which are not known to develop alopecia areata. Induction of alopecia areata was associated with expression of MHC class I and II on proximal follicular epithelium, as well as an infiltrate of CD4+ and CD8+ T-cells and supports the hypothesis that reversal of immune privilege can induce organ specific autoimmune disease.

10. Final comments

Alopecia is a clinically and scientifically important model of tissue specific autoimmune disease. There is evidence for loss of immune privilege coupled with T-cell mediated attack of hair follicle autoantigens. The accessibility of hair follicles as well as the availability of animal models makes this condition a useful system to study induction of autoimmunity.

Take-home messages

- Alopecia areata is a tissue restricted autoimmune disease of the hair follicle resulting in hair loss. It is among the most common human autoimmune diseases.
- Hair follicules are an immune protected site with lack of expression of MHC class I and II as well as deficient numbers of dendritic antigen presenting cells.
- Disease activity is associated with a lymphocytic infiltrate and expression of MHC class I and II by the hair follicle epithelium. Alopecia areata (AA) is a common disease characterized by various forms of hair loss, especially in children, which may have a psychological impact on both patient and parents, and may lead to a high lifetime prevalence rate of major depression or generalized anxiety disorders. Although the disease itself is non-life threatening, its precipitous onset and recurrent episodes disrupts many lives of all ages. The annual incidence of AA in the United States is 20.2 per 100,000 persons, with a lifetime risk of approximately 1.7% [1]. AA affects males and females equally and strikes all ages. However, 60% of patients present with their first patch before 20 years of age.

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Antiganglion neuron antibodies correlate with neuropathy in Sjogren's syndrome

The possible implication of antibodies against dorsal root ganglion neuron in the pathogenesis of sensory neuropathy with Sjogren's syndrome was investigated. In this regard, Murata Y. et. al. (Neuroreport 2005;16:677-81) examined the pathogenic role of antiganglion neuron antibodies by immunoblotting, immunohistochemistry and immunoreactive assay. Sojogren's syndrome patients without neuropathy, patients with vasculitic neuropathy and normal volunteers were evaluated as controls. Antiganglion neuron antibodies recognizing certain proteins of several different molecular weights were detected only in patients of sensory neuropathy with Sjogren's syndrome. Those antibodies labeled specific-sized neurons in the fixed ganglion and isolated ganglion neurons under the culture condition, each of which corresponded well to clinical manifestations. These results suggest that antiganglion neuron antibodies may contribute to the pathogenesis of sensory neuropathy with Sjogren's syndrome.