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Authors
Juhász, Margit LW
Mesinkovska, Natasha Atanaskova

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Does Complement Have a Role in the Pathogenesis of Alopecia Areata?

Margit L.W. Juhász Natasha Atanaskova Mesinkovska

Department of Dermatology, University of California, Irvine, Irvine, CA, USA

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Abstract
Alopecia areata (AA) is an autoimmune disorder in which immune attack of the anagen follicle causes hair loss in approximately 2% of the population. Although the pathogenesis of AA has not been fully determined, most likely it is mediated by a variety of factors including cellular/humoral immunity and genetic predisposition. Researchers have been interested in the possible role of the complement pathway in AA since the 1970s. Given recent evidence suggesting that complement plays a role in many immunologic and inflammatory dermatologic diseases including systemic lupus erythematosus, bullous diseases, angioedema, lipodystrophy, and skin infections, it is likely that complement also contributes to AA pathogenesis. Although early serum studies and immunohistochemical staining have been unimpressive, recent genetics studies may provide evidence that complement does indeed contribute to AA. By determining if complement plays a role in AA, options for novel targeted treatments will become available for those patients with refractory disease.

Introduction

The role of a properly functioning complement system is to participate in adaptive immunity, protect against bacterial infection by opsonization, play a role in the coagulation cascade, and help clear the debris of apoptotic cells. However, more recently, scientists have come to understand that abnormal complement activation may play a role in inflammatory, degenerative, and autoimmune disorders [1].

Although alopecia areata (AA) is a relatively common autoimmune hair-loss condition, the pathogenesis of AA is poorly understood. The earliest immunopathologic studies trying to elucidate the cause of AA were conducted in the 1980s using anti-endothelial cell antibodies collected from AA patients; researchers discovered that these antibodies were specifically directed at the hair bulb capillary cells suggesting immunologic vessel involvement, as well as an overall significant decrease in circulating T cells [2]. Later studies demonstrated that serum autoantibody titers decrease after isoprinosine [3].

Current hypotheses for AA development include genetic predisposition with inflammatory receptors and cytokines (cytotoxic T-lymphocyte-associated protein 4, tumor necrosis factor [TNF], interleukin 13, TNF superfamily member 4, chemokine ligands 9 and 10, and toll-like receptor 1) causing dysregulation of T-cell differen-

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Margit Juhász
Department of Dermatology, University of California, Irvine
843 Health Sciences Road
Irvine, CA 92697 (USA)
E-Mail margit.lw.juhasz@gmail.com

tiation, increasing T-helper 17 cells, and decreasing T-regulatory cells [4]. Other causes include disturbances in immune privilege with hair follicle destruction, autoantibodies against tyrosine hydroxylase and retinol-binding protein 4, and vitamin irregularities including high retinoic acid and low vitamin D [4]. Further evidence for immune dysregulation in AA comes from recently developed mouse models, in which transferring a single CD8+ T-cell clone or lymph-node-derived cell from an alopecia-affected to an unaffected mouse induces hair loss in the healthy subject [4].

Given that complement has been implicated in a variety of autoimmune dermatologic pathologies, including systemic lupus erythematosus, angioedema, and blistering diseases (including pemphigoid and dermatitis herpetiformis), lipodystrophy, and prolonged skin infections [5], there is a possibility that aberrations in the complement system may also contribute to the development of AA.

Complement and Skin

Complement modulation has provided novel therapeutic options for rare diseases such as paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, neuromyelitis optica, and hereditary angioedema. Current research focuses on the use of complement-targeted therapies in animal models for a variety of diseases including macular degeneration, rheumatoid arthritis, Alzheimer disease, type I diabetes mellitus, cancer, and transplantation reperfusion injury [1]. It is possible that the complement pathways hold future targeted treatment options for inflammatory skin diseases as well.

Keratinocytes and fibroblasts regulate complement in the skin. Keratinocytes produce inhibiting factors including complement factor 3b (C3b) inactivator enzyme factor 1, factor H, and factor H-like protein 1; fibroblasts synthesize TNF-α-induced factor B and C3, activating the alternative complement pathway. Examples of complement dysregulation in dermatologic pathology include angioedema (decreased C1-inhibitor), systemic lupus erythematosus and vasculitides (deficiencies in the classical complement pathway), bullous skin diseases (deposition of both classical and alternative complement proteins in the dermis or basement membrane), lipodystrophy (abnormally active C3 nephritic factor and low C3), and skin infections (decreased C2 and factor 1 [an inactivator of C3b and C4b]) [5]. Deposition of C3 at the hair follicle has been linked to scarring alopecias such as lupus erythematous [6], pemphigus vulgaris [7], central and centrifugal cicatricial alopecia [8], and lichen planopilaris [9].

AA and Complement

Defining the role that complement plays in the development of AA is controversial. Initial research conducted in the 1970s demonstrated no significant difference in serum complement levels (C1q, C2, C3, C3PA, C4, and C5) in AA patients compared to healthy subjects [10]. Immunologic studies in 16 patients with AA showed that the levels of immunoglobulin (Ig)A, IgE, IgG, and IgM, as well as C3, C4, and α1-anti-trypsin were within normal limits. Three patients had low anti-nuclear antibody levels, and 2 patients had anti-thyroglobulin antibodies [11]. However, contrary to previous findings, another study did report low Ig levels in AA patients [12].

Contrary to reports in human subjects, nude mouse models with human scalp engraftment, from both normal and AA patients, injected with AA-patient serum caused deposition of Igs and complement at hair follicles of both normal and AA-affected grafts (more so in AA); however, no decrease in hair growth was noted in normal grafts [13]. Further in vitro studies have demonstrated that dermal fibroblasts and epidermal melanocytes incubated with AA serum proliferate [14]. Although researchers hypothesize that these results are congruent with a complement-mediated and antibody-dependent mechanism for AA, studies have not yet elucidated a common systemic immune defect that contributes to the pathogenesis of AA.

Microscopy results of AA-affected scalp are also contradictory. C3 deposits in the hyaline membrane of the hair bulb, as well as the connective tissue sheath of anagen hair follicles in both normal and AA-affected scalp, led to the hypothesis that C3 regulates the hair cycle [15, 16]; however, the same group was later unable to show differences in C3, C5, and C9 deposition in AA versus normal scalp with immunofluorescence [17]. Multiple groups described varying deposits of C3, IgA, IgG and IgM, perifollicularly and at base of hair follicle, proportional to AA disease severity, associated with normal to elevated serum complement proteins. A recent study using immunofluorescence to detect Ig and C3 deposition showed no difference between normal and AA-affected scalp [18–20]. After treatment with squaric acid dibutyl ester, histology of AA scalp biopsies demonstrated hair regrowth, decreased peribulbar and perivascular inflammatory infiltrates, as

well as increased Ig, fibrin, and complement deposition at the basement membrane compared to patients treated with a control [21].

It is possible that complement deposition in AA scalp is associated with the hair morphological state. Further research into self-antigens and "induced-self" has elucidated that hair follicles present self-antigens to CD8+ T cells at multiple stages of the hair cycle creating multiple CD8+ clones primed against hair follicle-specific neoantigens/epitopes. If the immune privilege of the hair follicle is disturbed, AA may occur [22].

With evidence that inflammatory disease, such as rheumatoid arthritis, is associated with genetic variants of the TNF receptor-associated factor 1 (TRAF1)/C5 locus on chromosome 9q, researchers have searched for a genetic component of AA. A single-nucleotide polymorphism (rs2416808) at locus 9q is significantly associated with severe AA [23].

Conclusions

Complement is implicated in multiple autoimmune disorders and may also contribute to the pathogenesis of AA. Histological evidence has been controversial regarding the presence and significance of complement deposition at the hair follicle. However, recent genetic research completed in 2016 suggests complement loci, such as the TRAF1/C5 locus, may play a role in severe cases of AA. By determining the role of complement in AA, novel targeted therapeutics, for example eculizumab (a long-acting humanized monoclonal antibody against C5), may be used for treatment.

Disclosure Statement

There are no conflicts of interest for the authors to disclose.

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