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Alopecia areata: pathogenesis and potential for therapy

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Although the complete picture for alopecia areata (AA) pathogenesis has yet to be determined, recent research has made much progress in our understanding of the disease mechanism. Numerous circumstantial evidence supports the notion that AA is fundamentally a disease mediated by inflammatory cells and may be autoimmune in nature. Recent research has shown the hair-loss phenotype is precipitated predominantly by $CD8^+$ lymphocytes, but the disease mechanism is driven by $CD4^+$ lymphocytes. Although genetic susceptibility is a key contributor to disease development, disease onset and phenotypic presentation are probably modified by complex environmental interplay. On the basis of our current understanding of AA disease pathogenesis, several experimental and theoretical therapeutic approaches might be possible. However, the pathogenetic disease mechanism is particularly robust and the development of a cure for AA will be a significant challenge.

In humans, the formation of hair follicles takes place in embryogenesis and no new hair follicles are formed after birth. During this complex developmental process, the outer embryonic ectoderm and its underlying mesoderm give rise to the epidermal and dermal components, which essentially build up the hair follicle unit. The hair shaft, being the end-product of hair follicle proliferation and differentiation, together with its surrounding inner and outer root sheaths, is derived from epithelial cells. By contrast, the dermal papilla, a permanent population of specialised fibroblasts located at the lower end of the bulb region, comprises a cluster of mesenchymal cells. Previous research has shown that interactions between these tissues play an essential role in the embryonic development of follicles, as well as in follicle maintenance and the subsequent cyclic growth of hair (Refs 1, 2, 3).

The mature hair follicle cycle can be divided into four relatively distinct periods: growth (anagen), regression (catagen), resting (telogen) and shedding (exogen) (Ref. 4) (Fig. 1). In the anagen phase, the follicle regenerates from the

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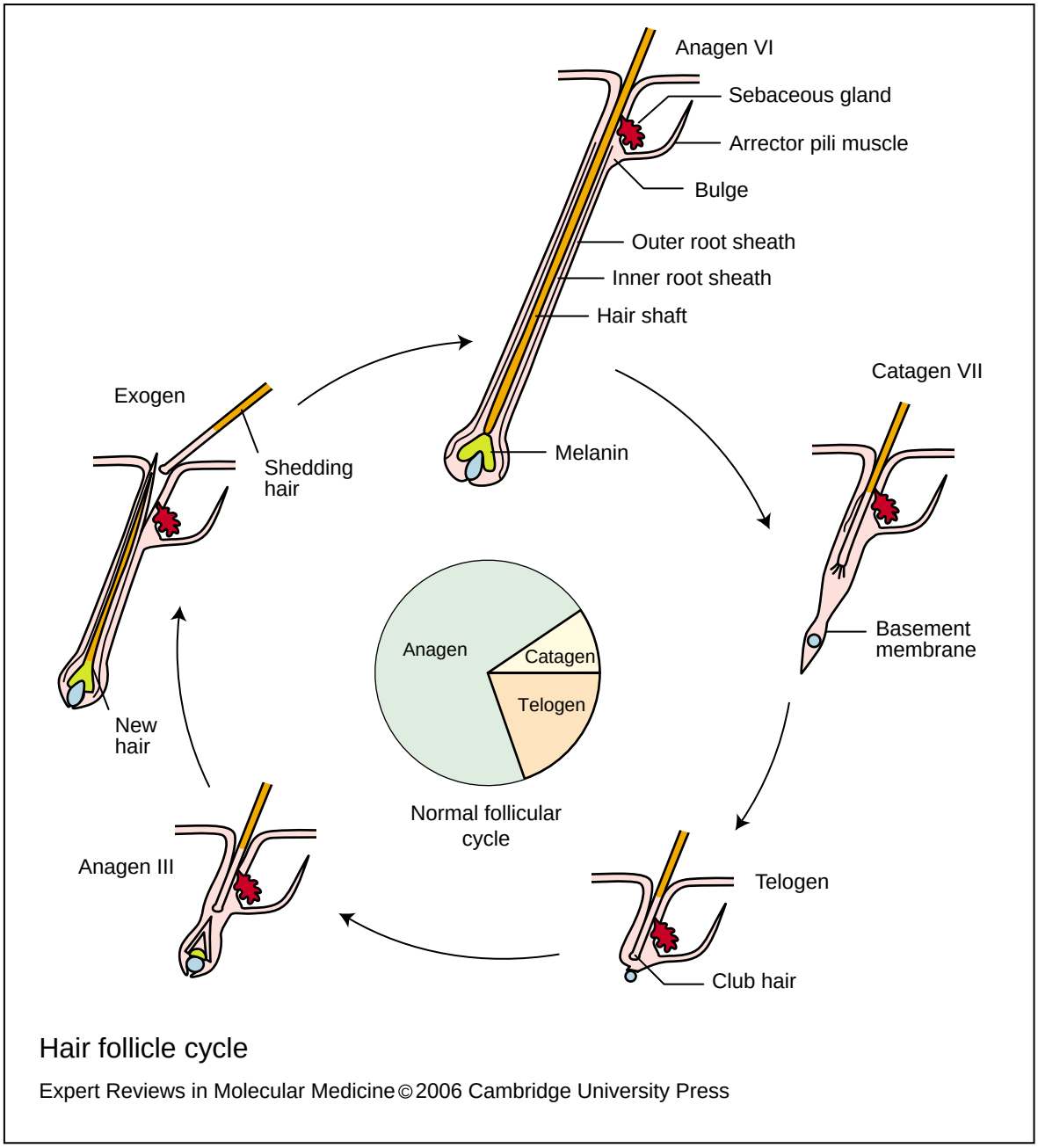


Figure 1. Hair follicle cycle. The normal hair cycle can be divided into four relatively distinct, successive periods: active growth phase (anagen), a short transition phase with regression (catagen), a resting phase (telogen) and a shedding stage (exogen). In the anagen phase, the follicle regenerates from the active epithelial stem cells, which reside in, or close to, the permanent 'bulge' region of the follicle. Although the size and length of the hair shaft are related to the size of the hair follicle and the duration of anagen, these attributes are remarkably diverse with body site and can change as a result of disease. Modified figure after Stenn and Paus (Ref. 4).

epithelial stem cells, which reside in, or close to, the permanent 'bulge' region of the follicle. The dermal papilla is implicated in triggering pro-anagen, maintaining anagen and determining the size of the epithelial matrix, which mainly consists of a transitory hair-producing structure that generates the hair shaft and root sheaths. Although the size and length of the hair shaft are

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related to the size of the hair follicle and the duration of anagen, these attributes diverge remarkably with body site, and can change as a result of disease.

Up to 40% of women and 70% of men will experience some form of hair loss in their lives (Refs 5, 6, 7). Although not a life-threatening condition, and primarily a 'cosmetic' issue, hair loss affects quality of life and can significantly influence an individual's health treatment decisions – even to the degree of risking death. Cancer patients claim that hair loss is the second most disturbing issue after the effect of cancer on their family (Refs 8, 9). Some patients consider not receiving cancer treatment owing to the risk of hair loss (Refs 10, 11). In an image-oriented society, hair loss has a significant impact on an individual's emotional state. The effect of hair loss on the quality of life is similar to that of severe psoriasis and, for women, it can have a greater impact than experiencing mastectomy (Refs 12, 13). When hair loss is sudden and extensive, as it can be with alopecia areata (AA), the emotional impact can be particularly severe. Depression associated with hair loss and curtailment of social interaction is common, particularly in women (Refs 14, 15). As such, hair loss is a significant issue for many people. This is notable in dermatology clinics, where around 10% of all patient consultations are about some form of hair loss, and AA accounts for 2% of new dermatology outpatients in the UK and the USA (Refs 16, 17; personal observation). Without effective hair-loss treatments, repeated patient consultations place a significant drain on time and resources in the patient health care system.

The most common form of hair loss encountered is androgenetic alopecia, which is characterised by a defined pattern of hair loss from the scalp and the involvement of androgens in this process (Ref. 18). By contrast, AA is an inflammatory disease of the hair follicle that is characterised by circumscribed patches of hair loss that present with sudden onset and may multiply, expand and coalesce into extensive AA. Alopecia totalis describes the complete denudation of hair from the scalp, whereas alopecia universalis is the term given for those with complete scalp and body hair loss. Nearly 1 in 50 individuals (men, women and children) are affected by AA at some point during their lifetime (Ref. 19). By extrapolation, worldwide, 100 million people will experience AA. The extent of hair loss and the course of disease vary for each individual, though more-extensive and persistent alopecia is typically associated with prepubertal onset (Ref. 20). Treatment options are limited and none is curative. Because AA is not an economically viable disease for industrial research and treatment development, AA research and treatment has so far remained in the academic domain. Recently, the National Institutes of Health (NIH) (http://rarediseases.info.nih.gov/) awarded AA orphan disease status; orphan diseases are defined as those that either affect fewer than 200,000 Americans or more than 200,000 but for which there is no reasonable expectation that the cost of developing and making a drug available in the USA for such a disease will be recovered from sales. Recognition of AA as an orphan disease enables treatments developed for AA under the Orphan Drug Act in the USA to be given tax concessions, government subsidies, and a seven-year monopoly on drug sales to induce companies to undertake the development and manufacturing of such drugs.

AA pathogenesis

A full understanding of the pathogenesis of AA has yet to be achieved. However, recent research has made much progress in our understanding of the disease mechanism and it is believed that AA is fundamentally an inflammation-driven disease and might be autoimmune in nature (Refs 21, 22). Although evidence in support of this idea is compelling, the primary requirement to prove the autoimmune nature of AA – to identify a self antigen as the primary target that can initiate the disease mechanism and lead to development of the phenotype – has yet to be proven. Without this evidence, AA can only be described as a putative autoimmune disease. The precipitation of AA onset probably requires input from multiple factors that determine the physical and biochemical status of both the immune system and hair follicles. Essentially, these can be classified as: (1) genetic susceptibility, resistance and severity-modifying factors; and (2) environmental contributors to disease susceptibility, resistance and severity. As AA is an unpredictable disease, environmental factors probably determine the timing of disease onset. However, the nature and intensity of the environmental stimuli required to precipitate AA might in turn be determined by the individual's genetic makeup (Ref. 23).

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AA: a putative autoimmune disease?

Numerous circumstantial evidence exists that support the notion that AA is an autoimmune disease.

First, the association of AA with other autoimmune diseases has been reported (Refs 24, 25). Between 7% and 27% of AA-affected patients also appear to express a thyroid disease phenotype, including goiter, myxoedema or Hashimoto's thyroiditis (Refs 26, 27, 28, 29). Co-expression of vitiligo and AA has also been reported in 4–9% of patients (Refs 20, 30). Numerous case reports detail the concordant presence of AA with other autoimmune diseases, such as diabetes and myasthenia gravis, although the statistical significance is unknown (Ref. 31). Notably, however, AA has been associated with potential resistance to the development of diabetes (Ref. 24).

Second, lymphocytic infiltrates are present in and around hair bulbs in active disease (Refs 32, 33, 34, 35). In addition, an increased presence has been demonstrated of antigen-presenting cells (APCs) such as macrophages and particularly Langerhans cells around, and sometimes within, dystrophic hair follicles (Refs 34, 36).

Third, pro-inflammatory changes occur both in the skin and in immune system organs. Inflammatory markers include the upregulation of expression of intercellular cell adhesion molecule (ICAM) and endothelial leukocyte adhesion molecule (ELAM) on the endothelium of blood vessels closely associated with affected hair follicles (Refs 34, 37, 38). Changes in cytokine levels, particularly activating cytokines such as interleukin 2 (IL-2) and interferon γ (IFN-γ), have been noted during AA inflammation, with corresponding alteration of cytokine concentrations after successful topical counter-irritant therapy (Ref. 39).

Fourth, an increased expression has been observed of class I and II major histocompatibility complex (MHC) antigens and the frequency of Langerhans cells in hair bulbs in active disease (Refs 37, 40).

Fifth, hair-follicle-specific autoantibodies are produced. Hair-follicle-specific IgG autoantibodies have been found in increased concentrations in the peripheral blood of AA-affected individuals compared with normal, non-affected humans (Refs 41, 42, 43). Deposits of immunoglobulin and complement around hair follicles, particularly at the edge of active lesions, are also apparent (Ref. 44).

Last, AA might respond to a range of immunomodulatory treatments that can be essentially classed as immunosuppressive or selectively immunostimulatory. Corticosteroids, along with 8-methoxypsoralen plus ultraviolet A light (PUVA) phototherapy, can reduce proinflammatory activity, whereas non-specific irritants such as anthralin and inducers of contact dermatitis such as dinitrochlorobenzene (DNCB), diphenylcyclopropenone (DPCP) and squaric acid dibutyl ester (SADBE) are each used in the treatment of AA (Refs 45, 46, 47).

These findings, and other circumstantial and indirect evidence, suggest that AA development could involve autoimmune disease mechanisms and targeting of as-yet-unidentified antigens within anagen-stage hair follicles (Refs 48, 49). However, detailed characterisation and functional studies are required to demonstrate the significance of these circumstantial observations and to elucidate disease mechanisms.

Genetic association studies in AA

Numerous studies indicate that AA has a genetic basis (Refs 50, 51). AA with similar times of onset or similar patterns of hair loss has been reported in monozygotic twins (Refs 52, 53, 54, 55). Several studies suggest AA is more frequently expressed in genetically related people, and 10–20% of patients with AA indicate at least one other affected family member (Refs 20, 51, 56, 57, 58, 59). A strong association between AA and trisomy 21 (Down's syndrome) has been observed: in a study of 1000 patients and 1000 control subjects, 60 cases of trisomy 21 individuals with AA versus 1 control were identified (Ref. 60). Carter and Jegasothy identified 19 cases of AA in 214 individuals with trisomy 21 (Ref. 61). The genetic mutation for autoimmune polyendocrinopathy syndrome type 1 (AIRE; a monogenic autoimmune syndrome caused by a defect in the *AIRE* gene on chromosome 21) is also associated with a 29–37% prevalence of AA (Ref. 62). These observations suggest a role for genes on chromosome 21 in AA susceptibility.

Genetic research into other autoimmune diseases has shown HLA-encoding alleles to segregate with specific disease phenotypes. Multiple HLA class I (A,B,C) alleles have been identified in several ethnic groups, although there is little consensus between studies (Refs 58, 59, 63, 64, 65, 66). MHC class I polypeptide-related sequence A (*MICA*) polymorphisms have also

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been identified in association with AA (Ref. 67). Genetic analysis studies in AA have primarily focused on the genes encoding HLA-D as the most likely region for genes that regulate susceptibility, severity or resistance to disease (Ref. 68). Consistent associations have been observed between HLA class II haplotypes and AA for DR4, DR5, DR6, DR7 and DQ3 (Refs 65, 68, 69, 70, 71, 72, 73). Allele *HLA-DRB1*1104* (DR11) is present with significant increased expression in patients with AA (Refs 72, 73, 74, 75). Allele *HLA-DRB1*0401* (DR4) was strongly associated with AA totalis or universalis sub-groups (Ref. 73). *HLA-DQB1*0301* (DQ7 by serology) was also significantly expressed only in association with AA totalis and universalis (Refs 73, 74). Other studies in families implicate other DQB1 alleles in AA, including *HLA-DQB1*0302*, *-DQB1*0601* and *-DQB1*0603* (Ref. 71). Conversely, *HLA-DRw52a* and *HLA-DRB1*0301* have been shown in association with resistance to AA onset (Refs 68, 76, 77).

The current consensus is that AA in humans has a genetic basis, but it is not always in a familial aggregation (Refs 50, 51). It has been suggested that the MHC antigens could be important for the presentation of an unknown AA antigen as for other autoimmune diseases (Ref. 78). Aberrant expression of MHC proteins in AA-affected hair follicles is common, but the question of its functional significance remains to be explored (Refs 39, 79).

More-limited research has been conducted in other areas of the genome. Investigations using a UK patient cohort suggested an association between AA and allele 2 of the gene encoding the IL-1 receptor antagonist (Refs 80, 81). Allele 2 is known to influence IL-1β production. The *IL-1β-1,2* genotype has also been identified with significantly increased frequency for individuals with extensive AA (Ref. 82). However, a second study in a US population could not confirm the allele 2 association and found instead an association between allele 1 and patchy AA (Ref. 83). Genes for immunoglobulin G heavy chains (GM) and kappa light chain (KM) genotypes have also been implicated in AA susceptibility (Refs 84, 85), with the suggestion that *IL-1β-1,2* and *KM-1,3* genotypes might interact to increase AA susceptibility (Ref. 82). Tumour necrosis factor α (TNF-α) gene polymorphism, or adjacent genes in the HLA region, might also influence AA susceptibility (Refs 86, 87). More-recent gene association studies have identified specific polymorphisms in the genes encoding MX1, AIRE and NOTCH4 (Refs 88, 89, 90).

Involvement of these gene loci, either as susceptibility or severity-modifying genes, is consistent with an autoimmune pathogenesis of AA. However, none of the above studies has involved genome-wide examination for susceptibility genes. Rather, all the studies analysed gene loci that were pre-selected based on their potential involvement in the AA disease mechanism. Thus, it is possible that the key genetic components of AA susceptibility have not so far been predicted or studied. Only recently have genome-wide screens in AA been considered (Ref. 91). With the development of the NIH-funded AA registry in the USA (http://www.mdanderson.org/departments/alopecia/), and a smaller European project underway (http://www.ehrs.org/geneticstudy01.htm), which aim to create a DNA bank from AA-affected individuals, genome-wide screening studies might soon be initiated (Ref. 92).

Environmental factors in AA

Although the fundamental mechanism of AA is essentially self-contained and defined by genetics, it is likely that there are non-genetic factors that influence the disease course. Environmental factors might be both susceptibility and severity modifiers of AA and act in two ways. They might modify an individual's general susceptibility to a disease activation event. Once onset of overt hair loss has been initiated, they might be involved in determining the future prognoses for hair loss in terms of extent and pattern of hair loss, duration or chronicity of disease, and/or resistance to treatment.

Stress has been suggested as a potential instigator of autoimmune diseases, possibly through glucocorticoid modulation of inflammatory cytokine expression (Ref. 93). Stress has also been postulated as a potential influence on AA development, although the evidence is only circumstantial (Refs 94, 95, 96, 97). The frequency and severity of AA appears to be associated with a greater frequency of allergies compared with the general population (Refs 20, 98, 99, 100, 101). It remains to be defined whether there is a direct relationship whereby an allergic response is capable of increasing immune system sensitivity and instability such that AA susceptibility increases, or whether the increased

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frequency of allergies in AA patients is merely a reflection of genetically determined immune system sensitivity. Other promoters of the immune system in autoimmune diseases might include drugs, infectious agents and toxins (Refs 102, 103, 104, 105). Experimentally, even dietary intake can play a role (Ref. 106). In principle, one or more of these factors could modulate the immune system in AA, but in practice little is known about the effects of environmental stimuli on AA in rodent models or humans.

The degree of susceptibility to AA fluctuates both with time and with changes in environmental factors that might influence AA. Thus, although an individual might have a genetic susceptibility to AA that could be regarded as an immovable baseline, additional epigenetic and environmental factors might increase or depress overall AA susceptibility. It is possible that an episode of AA will only develop if an individual receives multiple signals that cumulatively increase the susceptibility to disease above a threshold level for expression. This might also help explain why the presentation of the AA phenotype is so varied. Thus, individuals with chronic extensive AA, versus those with an isolated AA patch, could have a dominant genetic susceptibility to disease and relatively minor epigenetic modification of this genetic susceptibility. In individuals whose AA waxes and wanes, or who present with multiple episodes of AA, expression and remission could be more greatly affected by environmental factors and their changing influence with time (Ref. 23).

Rodent models are a valid approach for AA research

Multiple species and strains of laboratory animals spontaneously present with AA (Refs 31, 107, 108). However, inbred rodent models are the most immediately accessible for research. The C3H/HeJ mouse and the DEBR rat are the two extensively characterised and most frequently used models for AA. Both rodent strains initially grow a normal pelage coat. In C3H/HeJ mice, the first onset of AA develops from four months of age in females compared with six or more months in males, and affects up to 20% of a colony population with frequency equally distributed between males and females (Ref. 35). In DEBR rats, the initiation of overt onset of hair loss is most commonly observed in females aged 5–8 months and in males aged 7–10 months. Spontaneous expression of AA is apparent in 42% of individuals by 18 months of age in a colony, however, females are more likely to be affected than males by a ratio of approximately 3:1 (Ref. 109).

In both models, the lesion is often first expressed as a large, uniform thinning of hair or as multi-focal sites with symmetrical distribution on the ventrum, later progressing to the dorsum. Histologically, AA-affected rodent skin initially exhibits a focal peri- and intra-bulbar mononuclear cell infiltrate associated with only anagen-stage hair follicles; telogen hair follicles are unaffected. The infiltrates consist primarily of $CD4^+$ and $CD8^+$ T cells, macrophages and dendritic cells (DCs) (Refs 34, 35, 110, 111, 112, 113). Research has also revealed hair-follicle-specific autoantibodies to be present in significantly elevated concentrations in AA-affected rodents (Refs 114, 115).

Rodent models have provided key evidence in support of AA as an autoimmune disease

Although the spontaneous AA expression rate is only 20% in C3H/HeJ mice, all colony mice are susceptible to disease development. AA can be transferred from affected to unaffected mice by skin grafting (Ref. 116). This technique produces an almost 100% success rate in transferring the disease and enables large numbers of mice, with a predictable onset and progression of disease, to be produced for use in studies. Simple functional evidence that AA is a lymphocyte-driven disease mechanism was shown when grafting AA-affected skin to histocompatible C3Smn.CB17-*Prkdc*^{scid}/J mice. The grafting of immunodeficient mice induced neutrophil inflammation of anagen-stage hair follicles in graft and host skin but, in the absence of $CD4^+$ and $CD8^+$ T cells, hair regrowth was observed in grafted skin and no hair loss developed in host skin. Multiple studies from different laboratories and using different models have consistently shown that $CD4^+$ and $CD8^+$ T cells closely interact to promote hair loss. Both cell subsets are fundamentally involved in disease induction and persistence. Depletion of $CD4^+$ or $CD8^+$ cell subsets using monoclonal antibodies (mAbs) in AA-affected C3H/HeJ mice resulted in hair regrowth, whereas isotype-matched irrelevant mAbs had no significant effect on AA (Refs 112, 117, 118). Using a severe combined immune deficient (SCID) human-tissue-grafted mouse model, Gilhar and Kalish showed hair loss could be re-induced in previously AA-affected hair follicles by injection of activated $CD4^+$ and $CD8^+$ cells from patients (Refs 119, 120).

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Recently, the potential for leukocyte transfer and blockade of AA development was examined using the C3H/HeJ mouse model by subcutaneously injecting normal-haired mice with magnetic-bead-conjugated antibody-separated cell subsets from AA-affected mice (Ref. 113). Mice injected with $CD8^+$ cells exhibited hair loss limited to the injection site. By contrast, some mice injected with $CD4^+$ and $CD4^+/CD25^-$ cells developed extensive, multiple patches of AA and a combined injection of $CD8^+$ and $CD4^+/CD25^-$ cells increased the frequency of AA expression. Injection of a $CD4^+/CD25^+$ putative T regulatory (Treg) population of cells blocked AA induction by $CD4^+/CD25^-$ cells. The lymph nodes and skin-infiltrating leukocytes were examined by flow cytometry post cell injection. There was a strong upregulation of IL-6, TNF-α, IL-12 and IFN-γ expression in mice developing localised single patches, or extensive multiple patches, of AA. Increases in costimulatory ligands CD40 and CD80, plus increased leukocyte apoptosis resistance and reduced CD95, CD95 ligand and CD120b expression, were associated with successful AA induction. Mice receiving $CD4^+/CD25^+$ cells that did not develop AA displayed a very high expression of IL-10, suggesting that the prevention of AA development after the co-transfer of $CD4^+/CD25^+$ cells might rely on their capacity to infectiously induce regulatory IL-10 cytokine expression in $CD4^+$ cells. The results indicated $CD8^+$ cells might be the primary effectors of the hair loss phenotype, but that the extent of disease expression is determined by $CD4^+/CD25^-$ cells. In combination, $CD4^+/CD25^-$ and $CD8^+$ cells acted synergistically, suggesting that $CD4^+/CD25^-$ cells induce hair loss primarily through stimulation of autoreactive $CD8^+$ cells (Ref. 113).

An hypothesis for AA development

If AA is truly an autoimmune disease, there must be a failure in the thymic deletion of autoreactive T-cell clones, a failure of peripheral immunoregulation, and possibly a lowering of the threshold for autoimmune inflammatory cell activation (and, conversely, an increase in immune system sensitivity). Currently, the most popular hypothesis to explain the development of AA revolves around a loss of immune privilege in hair follicles (Fig. 2). Anagen-stage hair follicles are regarded as immune-privileged sites (Refs 121, 122), but follicle immunoprotection is probably only transient owing to the nature of the hair follicle cycle. Research suggests that the onset of catagen in all hair follicles is associated with an infiltration of immune cells, including candidate APCs (Refs 121, 123, 124, 125). Regression of the hair follicle in catagen involves high levels of apoptosis and significant remodelling of the lower transient portion of the hair follicle (Refs 126, 127). It is possible then that the immune system is constantly exposed to low levels of hair-follicle-derived antigens, presented by DCs, as hair follicles cycle through catagen. If, however, catagen regression became disordered and/or the immune cell infiltrate associated with catagen inappropriately presented antigenic peptides in association with expression of costimulatory molecules in response to an environmental pro-inflammatory stimulus, antigen presentation to the immune system might breach the threshold for stimulation of autoreactive cells. In a genetically susceptible individual, presentation of hair follicle antigens leading to stimulation of autoreactive cells may promote the onset of AA (Ref. 128).

Therapeutic strategies for treating AA

Immunomodulatory drugs

There are several potential avenues of therapeutic development for AA. The most realistic treatment approaches to AA in the short term are either the development of new immunomodulatory drugs or improvment in the effectiveness of those currently available. Research in other fields of autoimmune disease has led to the development of numerous immunosuppressive drug options, although few ever reach the market. In the past few years, tacrolimus has been sporadically examined for its potential in treating AA. Although tacrolimus is effective in both mouse and rat models for AA (Refs 129, 130), treatment of humans with tacrolimus has met with limited results (Ref. 131). In part, the issue may simply be one of limited drug penetration through the skin and/or a short active half-life as a result of its high rate of metabolism. Similarly, oral cyclosporin is effective in rodent models (Ref. 132) and, with the use of liposomal formulations, a pilot study suggested topical cyclosporin might also be effective for treating AA (Ref. 133). However, studies with patients have been variable and even contradictory (Refs 16, 134, 135). Recent concern over the possible mutagenic action of tacrolimus, cyclosporin and other immunosuppressive drugs (Ref. 136) has probably destroyed any further

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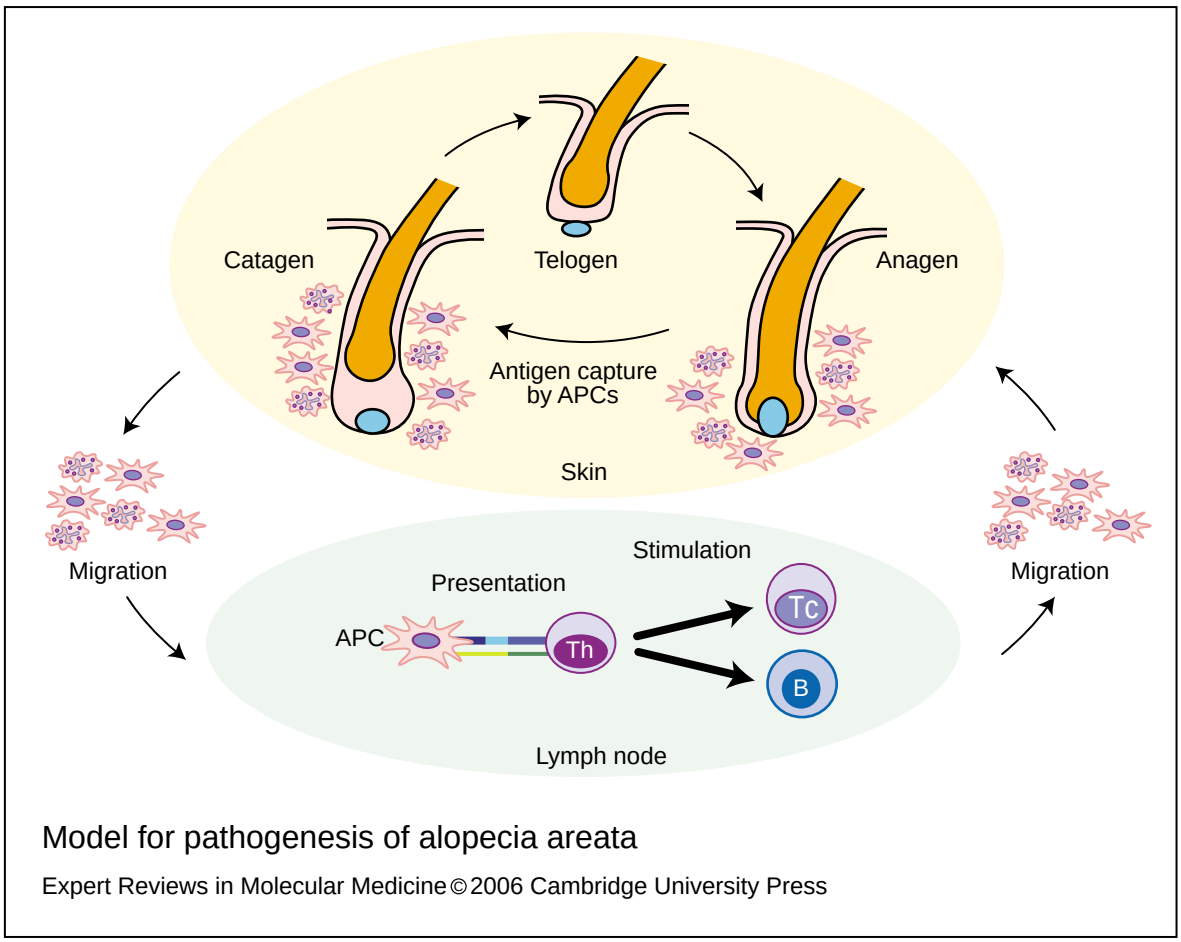


Figure 2. Model for pathogenesis of alopecia areata. The apparent immune-privileged status of anagen-stage hair follicles is thought to break down during AA, thereby exposing normally sequestered hair-follicle-specific antigens. Activated antigen-presenting cells (APCs) capture and process hair follicle antigens and present them in the context of major histocompatibility complex (MHC) class I and II. Antigen presentation, in association with costimulation and pro-inflammatory cyctokines, promotes the activation and proliferation of pathogenic, autoreactive T cells. T cells migrate to the skin and infiltrate around anagen-stage hair follicles, where a chemotactic stimulus is present. Peri-follicular inflammation disrupts hair follicle keratinocyte cells through cytokines whereas intrafollicular penetration enables cell–cell contact disruption of hair growth. The initial inflammation event increases hair follicle dystrophy and promotes continued pathogenic cell recruitment to perpetuate the autoimmune disease cycle. Hair follicles in a dystrophic state respond by truncating anagen and entering a telogen state. Any attempt to re-enter a new anagen growth phase is met with a renewed inflammatory response. Abbreviations: B, B cell; Tc, T cytotoxic cell; Th, T helper cell.

investigation of the potential use of these drugs for AA. However, other immunoregulatory drugs with potential remain to be investigated.

Thalidomide has been suggested as a potential treatment for AA (Refs 137, 138). However, its controversial history makes it difficult to conduct experimental trials with this drug. Ammonium trichloro tellurate (AS101) is a recently discovered compound with known immunomodulatory effects. Experimentally, it protects against chemotherapy-induced hair loss and induces hair growth in mouse models and humans. A preliminary investigation suggested it might have a beneficial effect on the activated cells from patients with AA (Ref. 139). Glatiramer acetate is a drug that is growing in popularity for the treatment of multiple sclerosis. The drug induces a shift of the disease cytokine profile away from a pro-inflammatory T helper 1 (Th1) state towards those characteristic of T helper 2 (Th2) cells. In

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principle, such a shift would help to treat AA. The drug notably affects the properties of APCs including monocytes and DCs (Ref. 140). There are of course many, many more immunomodulatory drug compounds that might be effective in the treatment of AA. Although rodent models are not perfect mirrors of the human disease state, their availability in large numbers should allow the rapid screening of drugs to find those with most potential. The primary problem is inevitably one of funding drug screening trials.

Is stage-specific therapeutic intervention possible in AA?

If the development of AA results from a continuous cycle of recognition and processing of hair follicle antigens, antigen presentation, stimulation of immune system response and cell-mediated disruption of hair follicle growth (Refs 49, 141), then stage-specific therapeutic intervention might be a possibility. If this model is correct, there are several points at which targeted therapeutic interventions could break the cycle of events.

Antigen exposure in hair follicles

Hair follicles are putatively sites of immune privilege. In the anagen phase of hair follicle growth, no Langerhans cells can be detected in the lower two-thirds portion of hair follicles. Follicles are also devoid of class Ia MHC antigens in the proximal hair follicle epithelium. Moreover, natural killer (NK) cells, $CD4^+$ T cells and $CD8^+$ T cells are not found in the lower portion of the hair follicle and hair bulb. Immunosuppressive cytokines such as transforming growth factor β1 (TGF-β1) and α melanocyte stimulating hormone (α-MSH) are generated locally, which can further hinder MHC class I expression in anagen hair bulbs (Refs 142, 143). If hair follicles are truly immune privileged, this must fail at some point in the AA development process, exposing antigens to the skin immunosurveillance system. Some have suggested that this might be the primary initiating event for AA (Ref. 21). A possible therapeutic strategy might therefore be to replace or reinforce immune privilege through the promoting of immune-protective cytokines and cell ligands, which might reduce hair follicle antigen exposure. In turn, limiting exposure might prevent the disease-initiating event. How these might be accomplished is not yet known.

Antigen recognition, uptake and processing

On the assumption that AA is a cell-mediated autoimmune disease and the disease development mechanism is fundamentally similar to other cell-mediated autoimmune disease mechanisms, the inciting antigens must be recognised, engulfed and processed by professional or non-professional APCs (Fig. 2). Professional APCs could be targeted and antigen uptake prohibited. With inflammatory skin diseases, the location of disease development affords the opportunity to target APCs in a localised manner. Contact sensitisation agents might be a form of treatment that crudely modifies APCs, rendering them unable to recognise autoantigens. Depleting APCs from skin might also be a non-specific way to interfere with antigen recognition by DCs. With further characterisation of the professional skin APC populations, more-refined targeting approaches might yet be identified.

Antigen presentation

Although the primary phenotype of AA is expressed in the skin, and a complex interaction of infiltrating leukocytes probably occurs in and around hair follicles, research on mice and humans has indicated pro-inflammatory activity away from the skin (Refs 144, 145). For inflammatory cells to be recruited into the pathogenic disease mechanism, they must be presented with activating antigens and appropriate costimulation. The most likely location for this event, particularly in the initial stage of AA onset precipitation, is the skin draining lymph nodes (Fig. 2). This location can only be targeted with systemic treatments. Experimentally, inhibition of AA onset has been demonstrated in a mouse model using mAbs against CTLA-4 and B7 costimulatory antigens commonly expressed on APCs (Ref. 117). Interfering with antigen presentation successfully stopped the development of AA. However, the same mAb approach in mice that had already developed AA yielded no significant effect. Thus, once the pathogenic process is in full swing, multiple redundant pro-inflammatory mechanisms appear to maintain the diseased state in the face of selective interference with costimulation of leukocytes.

If the target antigen(s) in AA were identified, it might be possible to block or modify antigen presentation to promote tolerance or deletion of pathogenic cells. Using synthetic analogues of the

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target antigens, the immune system could be exposed to large volumes of antigen peptides in constructs devoid of costimulation. The peptides might then 'smother' the T-cell receptors (TCRs) of pathogenic, potentially responsive, lymphocytes. TCR crosslinking in the absence of costimulation, or concurrently in the presence of inhibitory ligands, should lead to anergy or deletion of the antigen-responsive cells as opposed to their activation (Ref. 146).

Lymphocyte activation

Mice with AA are deficient in Treg cells (Ref. 147). Although the situation might be more complex in humans, in vitro studies indicate Treg cells from patients with AA are incapable of restraining activated lymphocytes (Ref. 145). Boosting native Treg cell activity in situ or supplementing with laboratory-generated Treg cells has been suggested as a theoretical approach to treating inflammatory-cell-mediated disease (Refs 148, 149). Experimentally, repeated exposure to low doses of antigen given orally and presented in the mucosal immune system can lead to the activation of Treg cells, which suppress immune responses by cognate interactions, and soluble or cell-surface-associated suppressive cytokines such as IL-10 and TGF-β.

Currently, numerous research groups are searching for pro-inflammatory cytokines and ligands suitable for targeting with a new class of drugs popularly termed 'biologicals'. As the generally accepted model of psoriasis may be fundamentally the same as that proposed for AA (Refs 141, 150), biological drugs developed for psoriasis might also be effective for AA (Ref. 151). Biological drugs considered for psoriasis can be divided into two basic groups: T-cell modulators and TNF inhibitors. The receptor–antibody fusion protein alefacept and the humanised mAb efalizumab block T-cell activation. Alefacept binds to CD2, which is located on the surface of T cells and is the receptor for leukocyte function-associated molecule 3 (LFA-3) (Ref. 152). CD2 also binds the Fc receptor on the surface of NK cells and macrophages. The binding of alefacept inhibits T-cell activation and proliferation, and also promotes the induction of T-cell apoptosis. Binding of efalizumab to CD11a blocks the interaction between LFA-1 and ICAM-1, its ligand on the surface of APCs (Ref. 153). T cells are thereby prevented from being activated by APCs and from binding to the blood vessel wall and migrating into the skin. The mAbs infliximab and adalimumab target the cytokine TNF (Ref. 154), whereas the receptor–antibody fusion protein etanercept targets the TNF receptor (Ref. 154). TNF plays a key role in leukocyte recruitment, activation and migration. These biological drugs inhibit TNF, stopping the activation of leukocytes and the secretion of more cytokines that perpetuate the inflammatory response (Ref. 155). Although AA might have similarities to psoriasis, the pathogenetic mechanism involved is not entirely the same. A biological tailored more specifically to the AA pathogenic mechanism might be necessary to gain the greatest therapeutic benefit. Research in animal models suggests that, of the biologicals under development, anti-IFN-γ (fontolizumab) might have the most potential as an effective treatment (Refs 156, 157).

However, on the basis of AA animal model research, the redundancy in what seems to be quite a robust disease pathogenesis mechanism suggests that the highly targeted biological drugs might not produce significant results on their own. While one signalling component of the AA pathogenic mechanism may be blockaded, other signalling components may compensate to maintain the disease cycle. Given the heterogeneity of AA and the potency of the disease mechanism(s), treatments that act at many levels of the disease simultaneously might achieve the best clinical results. A cocktail of biological drugs given simultaneously and acting synergistically at multiple points in the disease mechanism might therefore be the most effective, although such an approach is likely to be unpractical owing to cost.

Leukocyte migration and infiltration of skin and hair follicles

One step forward from blockading leukocyte-promoting activity would be to interfere with skin infiltration through targeting cell-surface markers on activated skin-homing leukocytes. Biological drugs can also act here, notably efalizumab, a humanised mAb against CD11a, which can block leukocyte trafficking (Ref. 154). In the mouse model for AA, mAbs were used to inhibit the infiltration of CD44v10-expressing lymphocytes into the skin and precipitating the onset of AA (Ref. 158). Skin-infiltrating leukocytes in AA also express cutaneous lymphocyte-associated antigen (CLA), which could be an alternative marker of activated cells for targeting and blocking skin infiltration (Ref. 159). Other activated cell-surface

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markers and variants expressed during migration might be additional targets.

Leukocyte action on hair follicles

Treatments could act at the effector stage of the autoimmune disease cycle, targeting the pathogenic lymphocytes in the skin and inhibiting their adverse action on hair follicles. Topical and intralesional corticosteroids work in this way to reduce immune cell activity in and around the affected hair follicles. Systemic corticosteroids are more potent as they can act on cells earlier in the autoimmune disease cycle, during the antigen presentation and activation stages, but they have a greater risk of side effects. The mechanisms by which the inflammatory cells adversely affect hair follicle activity could be targeted, including disruption of the interaction between Fas and Fas ligand (Refs 160, 161), prevention of granzyme and perforin action, oxygen radical neutralisation, and alteration of the cytokine milieu and cytokine receptors in hair follicles.

Towards a cure for AA

Many of the theoretical treatments described above focus on interfering with the disease process and regulating the immune system such that hair follicles are permitted to grow. This can potentially be a very successful approach and produce excellent clinical results. However, few of these treatment approaches attempt to modify permanently the fundamental disease mechanism to elicit a 'cure' for AA. As such, treatments generally need to be continued to have an ongoing benefit. If treatment is stopped, the underlying disease mechanism may reassert itself and the clinical symptoms will redevelop. A cure for AA suggests a therapeutic modality that would permanently correct the defective disease mechanism such that disease would not re-emerge after stopping the therapeutic course. Developing a cure for AA, as for any chronic disease, will be a significant challenge. Currently, only theoretical suggestions can be made as to how to cure AA. Three possible strategies are briefly described below; each of these potential cures for AA would require considerable research and development before they could become practical options.

Stem cell therapy is an experimental treatment option that in principle offers a 'cure' for autoimmune diseases (Ref. 162). If AA proves to be predominantly a defect of the immune system, haematopoietic stem cell transplantation to AA-affected individuals might condition the recipient into a non-responsive state against hair follicles; as suggested for the treatment of other autoimmune diseases (Ref. 163). In principle, haematopoietic stem cells could be harvested form allogeneic adult donors with known genetic resistance to AA and, with appropriate non-myeloablative conditioning protocols, a purified haematopietic stem cell population could be transplanted to the AA-affected individual to establish lifelong haematolymphoid chimaerism. Unlike other autoimmune diseases, where immune targeting of the host results in irreversible tissue damage, hair follicles have a regenerative capacity such that full hair regrowth is possible with successful treatment.

With knowledge of the antigenic targets in AA, mechanisms of tolerance might be considered (Ref. 164). Recently, we have shown that Treg cells can block the development of AA (Ref. 113). In other spheres of immunology it has been suggested that promotion of Treg cells could produce a long-lasting tolerance to autoantigens.

Finally, genetic modification of hair follicles through gene therapy and modification of hair follicle stem cells has been suggested as a theoretical option to make AA-affected hair follicles less immunogenic or to assert their putative immune privilege (Ref. 165).

Conclusions: research in progress and outstanding questions

The key issue for basic AA research is: what antigen epitopes are being targeted by lymphocytes in AA? Research in this area is challenging given the wide range of potential antigen targets present in hair follicles. Currently, only pre-selected antigens predicted to be involved are being evaluated for their potential role in AA. Although large-scale screening of antigen epitopes is possible, limited finances preclude such an approach. A related and equally important question is: what genes confer AA susceptibility and modify severity? Associative studies have identified several candidate susceptibility genes, and current research in several laboratories using animal models and humans is using genome-wide screening for genes involved in AA. The results of genome-wide screening might provide significant clues as to the key genes involved in AA and how AA develops.

Current clinical research is focused on the development of new treatments and improved

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therapeutic protocols. Most recently, clinical studies have evaluated biological and target-specific drugs, particularly those developed from research on psoriasis, although results have so far been mixed when the treatments were applied to AA. In principle, the development of treatments designed specifically for AA should have a greater chance of being effective. However, the lack of supporting funds for AA research means the current approach of adapting therapies developed in other research fields is more likely. A second key clinical question, although it might be answered with basic research, is whether AA is a single disease with a spectrum of phenotypic presentations or a collective of distinct diseases with related phenotypes. The variability in phenotype could indicate that different antigenic targets in hair follicles, different genetic and environmental input, and different inflammatory disease mechanisms are involved in different patterns of hair loss. Indeed, whereas AA is generally accepted as an autoimmune disease, histological observations suggest not all cases diagnosed as 'AA' have inflamed hair follicles (Ref. 146).

In recent years, significant advances have been made in our understanding of AA and the disease mechanism behind it. Inevitably, however, every new discovery elicits many new questions. We have only scratched the surface of understanding the molecular basis of AA and much more remains unknown in terms of disease susceptibility, activation events, disease development and disease cycle maintenance. With increasing knowledge, points of intervention may be identified for which superior treatments can be developed. Although the possibility of 'curing' AA is remote today, the use of information and procedures being developed in other fields of autoimmunity might eventually lead to the abolition of the disease.

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References

1 Chase, H.B. (1954) Growth of the hair. Physiol Rev 34, 113-126, PubMed: 13120379
2 Oliver, R.F. (1967) The experimental induction of whisker growth in the hooded rat by implantation of dermal papillae. J Embryol Exp Morphol 18, 43-51, PubMed: 6048979
3 McElwee, K.J. et al. (2003) Cultured peribulbar dermal sheath cells can induce hair follicle development and contribute to the dermal sheath and dermal papilla. J Invest Dermatol 121, 1267-1275, PubMed: 14675169
4 Stenn, K.S. and Paus, R. (2001) Controls of hair follicle cycling. Physiol Rev 81, 449-494
5 Hamilton, J.B. (1951) Patterned loss of hair in man; types and incidence. Ann N Y Acad Sci 53, 708-728, PubMed: 14819896
6 Birch, M.P., Lalla, S.C. and Messenger, A.G. (2002) Female pattern hair loss. Clin Exp Dermatol 27, 383-388, PubMed: 12190638
7 Gan, D.C. and Sinclair, R.D. (2005) Prevalence of male and female pattern hair loss in Maryborough. J Investig Dermatol Symp Proc 10, 184-189, PubMed: 16382660
8 de Boer-Dennert, M. et al. (1997) Patient perceptions of the side-effects of chemotherapy: the influence of 5HT3 antagonists. Br J Cancer 76, 1055-1061, PubMed: 9376266
9 Carelle, N. et al. (2002) Changing patient perceptions of the side effects of cancer chemotherapy. Cancer 95, 155-163, PubMed: 12115329
10 Batchelor, D. (2001) Hair and cancer chemotherapy: consequences and nursing care - a literature study. Eur J Cancer Care (Engl) 10, 147-163, PubMed: 11829374
11 Hesketh, P.J. et al. (2004) Chemotherapy-induced alopecia: psychosocial impact and therapeutic approaches. Support Care Cancer 12, 543-549, PubMed: 15221580
12 Tierney, A.J. (1987) Preventing chemotherapy-induced alopecia in cancer patients: is scalp cooling worthwhile? J Adv Nurs 12, 303-310, PubMed: 3648073
13 Williamson, D., Gonzalez, M. and Finlay, A.Y. (2001) The effect of hair loss on quality of life. J Eur Acad Dermatol Venereol 15, 137-139, PubMed: 11495520
14 Cash, T.F. (1999) The psychosocial consequences of androgenetic alopecia: a review of the research literature. Br J Dermatol 141, 398-405, PubMed: 10583042
15 Schmidt, S. et al. (2001) Strategies of coping and quality of life in women with alopecia. Br J Dermatol 144, 1038-1043, PubMed: 11359394
16 Shapiro, J. et al. (1997) Systemic cyclosporine and low-dose prednisone in the treatment of chronic

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©2006 Cambridge University Press

https://doi.org/10.1017/S146239940601101X Published online by Cambridge University Press

severe alopecia areata: a clinical and immunopathologic evaluation. J Am Acad Dermatol 36, 114-117, PubMed: 8996277
17 Dawber, D. et al. (1998) Disorders of hair: alopecia areata. In Rook/Wilkinson/Ebling Textbook of Dermatology (Champion, R.H. et al., eds), pp. 2919-2927, Blackwell Science
18 Ellis, J.A., Sinclair, R. and Harrap, S.B. (2002) Androgenetic alopecia: pathogenesis and potential for therapy. Expert Rev. Mol. Med 19 November, http://www.expertreviews.org/02005112h.htm
19 Safavi, K.H. et al. (1995) Incidence of alopecia areata in Olmsted County, Minnesota, 1975 through 1989. Mayo Clin Proc 70, 628-633, PubMed: 7791384
20 Muller, S.A. and Winkelmann, R.K. (1963) Alopecia Areata. An Evaluation of 736 Patients. Arch Dermatol 88, 290-297, PubMed: 14043621
21 Paus, R., Slominski, A. and Czarnetzki, B.M. (1993) Is alopecia areata an autoimmune-response against melanogenesis-related proteins, exposed by abnormal MHC class I expression in the anagen hair bulb? Yale J Biol Med 66, 541-554, PubMed: 7716973
22 McDonagh, A.J. and Messenger, A.G. (1996) The pathogenesis of alopecia areata. Dermatol Clin 14, 661-670, PubMed: 9238324
23 McElwee, K. et al. (2001) Genetic susceptibility and severity of alopecia areata in human and animal models. Eur J Dermatol 11, 11-16, PubMed: 11174130
24 Wang, S.J. et al. (1994) Increased risk for type I (insulin-dependent) diabetes in relatives of patients with alopecia areata (AA). Am J Med Genet 51, 234-239, PubMed: 8074151
25 Kurtev, A. and Iliev, E. (2005) Thyroid autoimmunity in children and adolescents with alopecia areata. Int J Dermatol 44, 457-461, PubMed: 15941431
26 Cunliffe, W.J. et al. (1969) Alopecia areata, thyroid disease and autoimmunity. Br J Dermatol 81, 877-881, PubMed: 5359449
27 Milgraum, S.S. et al. (1987) Alopecia areata, endocrine function, and autoantibodies in patients 16 years of age or younger. J Am Acad Dermatol 17, 57-61, PubMed: 3301924
28 Shellow, W.V., Edwards, J.E. and Koo, J.Y. (1992) Profile of alopecia areata: a questionnaire analysis of patient and family. Int J Dermatol 31, 186-189, PubMed: 1568816
29 Puavilai, S. et al. (1994) Prevalence of thyroid diseases in patients with alopecia areata. Int J Dermatol 33, 632-633, PubMed: 8002158
30 Main, R.A. et al. (1975) Smooth muscle antibodies and alopecia areata. Br J Dermatol 92, 389-393, PubMed: 1156552
31 McElwee, K.J. et al. (1998) Comparison of alopecia areata in human and nonhuman mammalian species. Pathobiology 66, 90-107, PubMed: 9645633
32 Perret, C., Wiesner-Menzel, L. and Happle, R. (1984) Immunohistochemical analysis of T-cell subsets in the peribulbar and intrabulbar infiltrates of alopecia areata. Acta Derm Venereol 64, 26-30, PubMed: 6203277
33 Ranki, A. et al. (1984) Immunohistochemical and electron microscopic characterization of the cellular infiltrate in alopecia (areata, totalis, and universalis). J Invest Dermatol 83, 7-11, PubMed: 6376642
34 Zhang, J.G. and Oliver, R.F. (1994) Immunohistological study of the development of the cellular infiltrate in the pelage follicles of the DEBR model for alopecia areata. Br J Dermatol 130, 405-414, PubMed: 7910477
35 Sundberg, J.P., Cordy, W.R. and King, L.E., Jr. (1994) Alopecia areata in aging C3H/HeJ mice. J Invest Dermatol 102, 847-856, PubMed: 8006447
36 Wiesner-Menzel, L. and Happle, R. (1984) Intrabulbar and peribulbar accumulation of dendritic OKT 6-positive cells in alopecia areata. Arch Dermatol Res 276, 333-334, PubMed: 6548356
37 McDonagh, A.J. et al. (1993) HLA and ICAM-1 expression in alopecia areata in vivo and in vitro: the role of cytokines. Br J Dermatol 129, 250-256, PubMed: 7506926
38 Nickoloff, B.J. and Griffiths, C.E. (1991) Aberrant intercellular adhesion molecule-1 (ICAM-1) expression by hair-follicle epithelial cells and endothelial leukocyte adhesion molecule-1 (ELAM-1) by vascular cells are important adhesion-molecule alterations in alopecia areata. J Invest Dermatol 96, 91S-92S, PubMed: 1708803
39 Brocker, E.B. et al. (1987) Abnormal expression of class I and class II major histocompatibility antigens in alopecia areata: modulation by topical immunotherapy. J Invest Dermatol 88, 564-568, PubMed: 3471816
40 Hoffmann, R. et al. (1994) Cytokine mRNA levels in Alopecia areata before and after treatment with the contact allergen diphenylcyclopropenone. J Invest Dermatol 103, 530-533, PubMed: 7930677
41 Tobin, D.J. et al. (1994) Antibodies to hair follicles

Accession information: DOI: 10.1017/S146239940601101X; Vol. 8; Issue 14; 20 June 2006
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https://doi.org/10.1017/S146239940601101X Published online by Cambridge University Press

in alopecia areata. J Invest Dermatol 102, 721-724, PubMed: 8176253
42 Tobin, D.J., Orentreich, N. and Bystryn, J.C. (1994) Autoantibodies to hair follicles in normal individuals. Arch Dermatol 130, 395-396, PubMed: 8129427
43 Tobin, D.J. (2003) Characterization of hair follicle antigens targeted by the anti-hair follicle immune response. J Investig Dermatol Symp Proc 8, 176-181, PubMed: 14582669
44 Bystryn, J.C., Orentreich, N. and Stengel, F. (1979) Direct immunofluorescence studies in alopecia areata and male pattern alopecia. J Invest Dermatol 73, 317-320, PubMed: 387883
45 Hoffmann, R. and Happle, R. (1999) [Alopecia areata. Part 2: Therapy]. Hautarzt 50, W310-315, PubMed: 10354929
46 Madani, S. and Shapiro, J. (2000) Alopecia areata update. J Am Acad Dermatol 42, 549-566; quiz 567-570, PubMed: 10727299
47 Freyschmidt-Paul, P. et al. (2001) Current and potential agents for the treatment of alopecia areata. Curr Pharm Des 7, 213-230, PubMed: 11311114
48 McElwee, K.J. et al. (1999) Alopecia areata: an autoimmune disease? Exp Dermatol 8, 371-379, PubMed: 10536963
49 McElwee, K.J. and Hoffmann, R. (2002) Alopecia areata - animal models. Clin Exp Dermatol 27, 410-417, PubMed: 12190642
50 Colombe, B.W. et al. (1995) HLA class II antigen associations help to define two types of alopecia areata. J Am Acad Dermatol 33, 757-764, PubMed: 7593774
51 van der Steen, P. et al. (1992) The genetic risk for alopecia areata in first degree relatives of severely affected patients. An estimate. Acta Derm Venereol 72, 373-375, PubMed: 1361288
52 Alsaleh, Q.A. et al. (1995) Concurrent appearance of alopecia areata in siblings. Pediatr Dermatol 12, 285-286, PubMed: 7501568
53 Scerri, L. and Pace, J.L. (1992) Identical twins with identical alopecia areata. J Am Acad Dermatol 27, 766-767, PubMed: 1430401
54 Cole, G.W. and Herzlinger, D. (1984) Alopecia universalis in identical twins. Int J Dermatol 23, 283, PubMed: 6539757
55 Jackow, C. et al. (1998) Alopecia areata and cytomegalovirus infection in twins: genes versus environment? J Am Acad Dermatol 38, 418-425, PubMed: 9520023
56 Sharma, V.K., Dawn, G. and Kumar, B. (1996) Profile of alopecia areata in Northern India. Int J Dermatol 35, 22-27, PubMed: 8838924
57 Gol'dshtein, L.M. and Chipizhenko, V.A. (1978) [Familial alopecia areata]. Vestn Dermatol Venerol 36-38, PubMed: 706730
58 Hordinsky, M.K. et al. (1984) Familial alopecia areata. HLA antigens and autoantibody formation in an American family. Arch Dermatol 120, 464-468, PubMed: 6231002
59 Valsecchi, R. et al. (1985) Familial alopecia areata—genetic susceptibility or coincidence? Acta Derm Venereol 65, 175-177, PubMed: 2408426
60 Du Vivier, A. and Munro, D.D. (1975) Alopecia areata, autoimmunity, and Down's syndrome. Br Med J 1, 191-192, PubMed: 122906
61 Carter, D.M. and Jegasothy, B.V. (1976) Alopecia areata and Down syndrome. Arch Dermatol 112, 1397-1399, PubMed: 134671
62 Betterle, C., Greggio, N.A. and Volpato, M. (1998) Clinical review 93: Autoimmune polyglandular syndrome type 1. J Clin Endocrinol Metab 83, 1049-1055, PubMed: 9543115
63 Kianto, U. et al. (1977) HLA-B12 in alopecia areata. Arch Dermatol 113, 1716, PubMed: 596904
64 Hacham-Zadeh, S. et al. (1981) HLA and alopecia areata in Jerusalem. Tissue Antigens 18, 71-74, PubMed: 7330849
65 Averbakh, E.V. and Pospelov, L.E. (1986) [HLA antigens of patients with alopecia areata]. Vestn Dermatol Venerol 24-26, PubMed: 3457498
66 Xiao, F.L. et al. (2005) Association of HLA-DQA1 and DQB1 alleles with alolpecia areata in Chinese Hans. Arch Dermatol Res 297, 201-209, PubMed: 16231148
67 Barahmani, N. et al. (2006) Major histocompatibility complex class I chain-related gene A polymorphisms and extended haplotypes are associated with familial alopecia areata. J Invest Dermatol 126, 74-78, PubMed: 16417220
68 Duvic, M. et al. (1991) HLA-D locus associations in alopecia areata. DRw52a may confer disease resistance. Arch Dermatol 127, 64-68, PubMed: 1670917
69 Friedman, P.S. (1985) Clinical and immunologic association of alopecia areata. Semin Dermatol 4, 9-15
70 Orecchia, G. et al. (1987) Human leukocyte antigen region involvement in the genetic predisposition to alopecia areata. Dermatologica 175, 10-14, PubMed: 3497062
71 de Andrade, M. et al. (1999) Alopecia areata in families: association with the HLA locus. J Investig Dermatol Symp Proc 4, 220-223,

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PubMed: 10674370
72 Welsh, E.A. et al. (1994) Human leukocyte antigen-DQB1*03 alleles are associated with alopecia areata. J Invest Dermatol 103, 758-763, PubMed: 7798612
73 Colombe, B.W., Lou, C.D. and Price, V.H. (1999) The genetic basis of alopecia areata: HLA associations with patchy alopecia areata versus alopecia totalis and alopecia universalis. J Investig Dermatol Symp Proc 4, 216-219, PubMed: 10674369
74 Duvic, M. et al. (1995) Analysis of HLA-D locus alleles in alopecia areata patients and families. J Invest Dermatol 104, 5S-6S, PubMed: 7738397
75 Morling, N. et al. (1991) DNA polymorphism of HLA class II genes in alopecia areata. Dis Markers 9, 35-42, PubMed: 1683825
76 Akar, A. et al. (2002) HLA class II alleles in patients with alopecia areata. Eur J Dermatol 12, 236-239, PubMed: 11978563
77 Broniarczyk-Dyla, G. et al. (2002) The protective role of the HLA-DR locus in patients with various clinical types of alopecia areata. Arch Immunol Ther Exp (Warsz) 50, 333-336, PubMed: 12455867
78 Wucherpfennig, K.W. (2001) Insights into autoimmunity gained from structural analysis of MHC-peptide complexes. Curr Opin Immunol 13, 650-656, PubMed: 11677085
79 Messenger, A.G. and Bleehen, S.S. (1985) Expression of HLA-DR by anagen hair follicles in alopecia areata. J Invest Dermatol 85, 569-572, PubMed: 2415641
80 Tarlow, J.K. et al. (1994) Severity of alopecia areata is associated with a polymorphism in the interleukin-1 receptor antagonist gene. J Invest Dermatol 103, 387-390, PubMed: 8077705
81 Tazi-Ahnini, R. et al. (2002) Genetic analysis of the interleukin-1 receptor antagonist and its homologue IL-1L1 in alopecia areata: strong severity association and possible gene interaction. Eur J Immunogenet 29, 25-30, PubMed: 11841485
82 Galbraith, G.M. et al. (1999) Contribution of interleukin 1beta and KM loci to alopecia areata. Hum Hered 49, 85-89, PubMed: 10077728
83 Barahmani, N. et al. (2002) Interleukin-1 receptor antagonist allele 2 and familial alopecia areata. J Invest Dermatol 118, 335-337, PubMed: 11841553
84 Galbraith, G.M., Thiers, B.H. and Pandey, J.P. (1984) Gm allotype associated resistance and susceptibility to alopecia areata. Clin Exp Immunol 56, 149-152, PubMed: 6424985
85 Galbraith, G.M. and Pandey, J.P. (1989) Km1 allotype association with one subgroup of alopecia areata. Am J Hum Genet 44, 426-428, PubMed: 2916584
86 Galbraith, G.M. and Pandey, J.P. (1995) Tumor necrosis factor alpha (TNF-alpha) gene polymorphism in alopecia areata. Hum Genet 96, 433-436, PubMed: 7557966
87 Cork, M.J., Crane, A.M. and Duff, G.W. (1996) Genetic control of cytokines. Cytokine gene polymorphisms in alopecia areata. Dermatol Clin 14, 671-678, PubMed: 9238325
88 Tazi-Ahnini, R. et al. (2002) Role of the autoimmune regulator (AIRE) gene in alopecia areata: strong association of a potentially functional AIRE polymorphism with alopecia universalis. Tissue Antigens 60, 489-495, PubMed: 12542742
89 Tazi-Ahnini, R. et al. (2003) Notch4, a non-HLA gene in the MHC is strongly associated with the most severe form of alopecia areata. Hum Genet 112, 400-403, PubMed: 12589427
90 Tazi-Ahnini, R. et al. (2000) Structure and polymorphism of the human gene for the interferon-induced p78 protein (MX1): evidence of association with alopecia areata in the Down syndrome region. Hum Genet 106, 639-645, PubMed: 10942113
91 Martinez-Mir, A. et al. (2003) Genetic linkage studies in alopecia areata. J Investig Dermatol Symp Proc 8, 199-203, PubMed: 14582673
92 Duvic, M. et al. (2003) Alopecia areata registry: an overview. J Investig Dermatol Symp Proc 8, 219-221, PubMed: 14582678
93 Elenkov, I.J. and Chrousos, G.P. (2002) Stress hormones, proinflammatory and antiinflammatory cytokines, and autoimmunity. Ann N Y Acad Sci 966, 290-303, PubMed: 12114286
94 Mehlman, R.D. and Griesemer, R.D. (1968) Alopecia areata in the very young. Am J Psychiatry 125, 605-614, PubMed: 5683446
95 Colon, E.A. et al. (1991) Lifetime prevalence of psychiatric disorders in patients with alopecia areata. Compr Psychiatry 32, 245-251, PubMed: 1884604
96 Liakopoulou, M. et al. (1997) Children with alopecia areata: psychiatric symptomatology and life events. J Am Acad Child Adolesc Psychiatry 36, 678-684, PubMed: 9136503
97 Kavak, A., Yesildal, N. and Parlak, A.H. (2002) Effect of two consecutive earthquakes on outbreaks of alopecia areata. J Dermatol 29, 414-

Accession information: DOI: 10.1017/S146239940601101X; Vol. 8; Issue 14; 20 June 2006
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https://doi.org/10.1017/S146239940601101X Published online by Cambridge University Press

418, PubMed: 12184638
98 Ikeda, T. (1965) A new classification of alopecia areata. Dermatologica 131, 421-445, PubMed: 5864736
99 Penders, A.J. (1968) Alopecia areata and atopy. Dermatologica 136, 395-399, PubMed: 5662284
100 De Waard-van der Spek, F.B. et al. (1989) Juvenile versus maturity-onset alopecia areata—a comparative retrospective clinical study. Clin Exp Dermatol 14, 429-433, PubMed: 2605805
101 Weise, K. et al. (1996) Topical immunotherapy in alopecia areata: anamnestic and clinical criteria of prognostic significance. Dermatology 192, 129-133, PubMed: 8829494
102 Bigazzi, P.E. (1994) Autoimmunity and heavy metals. Lupus 3, 449-453, PubMed: 7704000
103 Elkayam, O., Yaron, M. and Caspi, D. (1999) Minocycline-induced autoimmune syndromes: an overview. Semin Arthritis Rheum 28, 392-397, PubMed: 10406406
104 Kissler, S., Anderton, S.M. and Wraith, D.C. (2001) Antigen-presenting cell activation: a link between infection and autoimmunity? J Autoimmun 16, 303-308, PubMed: 11334496
105 Holsapple, M.P. (2002) Autoimmunity by pesticides: a critical review of the state of the science. Toxicol Lett 127, 101-109, PubMed: 12052647
106 McElwee, K.J. et al. (2003) Dietary soy oil content and soy-derived phytoestrogen genistein increase resistance to alopecia areata onset in C3H/HeJ mice. Exp Dermatol 12, 30-36, PubMed: 12631244
107 McElwee, K.J. et al. (1999) Spontaneous alopecia areata-like hair loss in one congenic and seven inbred laboratory mouse strains. J Investig Dermatol Symp Proc 4, 202-206, PubMed: 10674366
108 Smyth, J.R., Jr. and McNeil, M. (1999) Alopecia areata and universalis in the Smyth chicken model for spontaneous autoimmune vitiligo. J Investig Dermatol Symp Proc 4, 211-215, PubMed: 10674368
109 McElwee, K.J. (2003) Spontaneous rat model of alopecia areata in the Dundee Experimental Bald Rat (DEBR). In Animal Models of Human Inflammatory Skin Diseases (Chan, L.S., eds), pp. 451-468, CRC Press
110 Michie, H.J. et al. (1990) Immunobiological studies on the alopecic (DEBR) rat. Br J Dermatol 123, 557-567, PubMed: 2147388
111 Michie, H.J. et al. (1991) The DEBR rat: an animal model of human alopecia areata. Br J Dermatol 125, 94-100, PubMed: 1911310
112 McElwee, K.J., Spiers, E.M. and Oliver, R.F. (1996) In vivo depletion of CD8+ T cells restores hair growth in the DEBR model for alopecia areata. Br J Dermatol 135, 211-217, PubMed: 8881662
113 McElwee, K.J. et al. (2005) Transfer of CD8(+) cells induces localized hair loss whereas CD4(+)/CD25(-) cells promote systemic alopecia areata and CD4(+)/CD25(+) cells blockade disease onset in the C3H/HeJ mouse model. J Invest Dermatol 124, 947-957, PubMed: 15854035
114 Tobin, D.J. et al. (1997) Autoantibodies to hair follicles in C3H/HeJ mice with alopecia areata-like hair loss. J Invest Dermatol 109, 329-333, PubMed: 9284100
115 McElwee, K.J., Pickett, P. and Oliver, R.F. (1996) The DEBR rat, alopecia areata and autoantibodies to the hair follicle. Br J Dermatol 134, 55-63, PubMed: 8745887
116 McElwee, K.J. et al. (1998) Experimental induction of alopecia areata-like hair loss in C3H/HeJ mice using full-thickness skin grafts. J Invest Dermatol 111, 797-803, PubMed: 9804341
117 Carroll, J.M. et al. (2002) Gene array profiling and immunomodulation studies define a cell-mediated immune response underlying the pathogenesis of alopecia areata in a mouse model and humans. J Invest Dermatol 119, 392-402, PubMed: 12190862
118 McElwee, K.J., Spiers, E.M. and Oliver, R.F. (1999) Partial restoration of hair growth in the DEBR model for Alopecia areata after in vivo depletion of CD4+ T cells. Br J Dermatol 140, 432-437, PubMed: 10233262
119 Gilhar, A. et al. (1998) Autoimmune hair loss (alopecia areata) transferred by T lymphocytes to human scalp explants on SCID mice. J Clin Invest 101, 62-67, PubMed: 9421466
120 Gilhar, A. et al. (2002) Mediation of alopecia areata by cooperation between CD4+ and CD8+ T lymphocytes: transfer to human scalp explants on Prkdc(scid) mice. Arch Dermatol 138, 916-922, PubMed: 12071819
121 Westgate, G.E., Craggs, R.I. and Gibson, W.T. (1991) Immune privilege in hair growth. J Invest Dermatol 97, 417-420, PubMed: 1714928
122 Paus, R., Christoph, T. and Muller-Rover, S. (1999) Immunology of the hair follicle: a short journey into terra incognita. J Investig Dermatol Symp Proc 4, 226-234, PubMed: 10674372
123 Paus, R. (1996) Control of the hair cycle and hair diseases as cycling disorders. Curr Opin

Accession information: DOI: 10.1017/S146239940601101X; Vol. 8; Issue 14; 20 June 2006
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https://doi.org/10.1017/S146239940601101X Published online by Cambridge University Press

Dermatol 3, 248-258
124 Parakkal, P.F. (1969) Role of macrophages in collagen resorption during hair growth cycle. J Ultrastruct Res 29, 210-217, PubMed: 5362393
125 Eichmuller, S. et al. (1998) Clusters of perifollicular macrophages in normal murine skin: physiological degeneration of selected hair follicles by programmed organ deletion. J Histochem Cytochem 46, 361-370, PubMed: 9487118
126 Weedon, D. and Strutton, G. (1981) Apoptosis as the mechanism of the involution of hair follicles in catagen transformation. Acta Derm Venereol 61, 335-339, PubMed: 6173989
127 Lindner, G. et al. (1997) Analysis of apoptosis during hair follicle regression (catagen). Am J Pathol 151, 1601-1617, PubMed: 9403711
128 McElwee, K.J. et al. (2003) Alopecia areata susceptibility in rodent models. J Investig Dermatol Symp Proc 8, 182-187, PubMed: 14582670
129 McElwee, K.J. et al. (1997) Topical FK506: a potent immunotherapy for alopecia areata? Studies using the Dundee experimental bald rat model. Br J Dermatol 137, 491-497, PubMed: 9390322
130 Freyschmidt-Paul, P. et al. (2001) Treatment of alopecia areata in C3H/HeJ mice with the topical immunosuppressant FK506 (Tacrolimus). Eur J Dermatol 11, 405-409, PubMed: 11525945
131 Price, V.H., Willey, A. and Chen, B.K. (2005) Topical tacrolimus in alopecia areata. J Am Acad Dermatol 52, 138-139, PubMed: 15627095
132 Oliver, R.F. and Lowe, J.G. (1995) Oral cyclosporin A restores hair growth in the DEBR rat model for alopecia areata. Clin Exp Dermatol 20, 127-131, PubMed: 8565246
133 Verma, D.D. et al. (2004) Treatment of alopecia areata in the DEBR model using Cyclosporin A lipid vesicles. Eur J Dermatol 14, 332-338, PubMed: 15358573
134 Ferrando, J. and Grimalt, R. (1999) Partial response of severe alopecia areata to cyclosporine A. Dermatology 199, 67-69, PubMed: 10449964
135 Phillips, M.A., Graves, J.E. and Nunley, J.R. (2005) Alopecia areata presenting in 2 kidney-pancreas transplant recipients taking cyclosporine. J Am Acad Dermatol 53, S252-255, PubMed: 16227102
136 Oliveira, V.D., Zankl, H. and Rath, T. (2004) Mutagenic and cytotoxic effects of immunosuppressive drugs on human lymphocyte cultures. Exp Clin Transplant 2, 273-279, PubMed: 15859941
137 Namazi, M.R. (2003) The potential efficacy of thalidomide in the treatment of recalcitrant alopecia areata. Med Hypotheses 60, 513-514, PubMed: 12615511
138 Baranda, L. et al. (2005) Severe and unresponsive HIV-associated alopecia areata successfully treated with thalidomide. Acta Derm Venereol 85, 277-278, PubMed: 16040426
139 Shohat, M. et al. (2005) In vitro cytokine profile in childhood alopecia areata and the immunomodulatory effects of AS-101. Clin Exp Dermatol 30, 432-434, PubMed: 15953089
140 Farina, C. et al. (2005) Glatiramer acetate in multiple sclerosis: update on potential mechanisms of action. Lancet Neurol 4, 567-575, PubMed: 16109363
141 McElwee, K.J. et al. (2003) The pathogenesis of alopecia areata in rodent models. J Investig Dermatol Symp Proc 8, 6-11, PubMed: 12894987
142 Ito, T. et al. (2004) Collapse and restoration of MHC class-I-dependent immune privilege: exploiting the human hair follicle as a model. Am J Pathol 164, 623-634, PubMed: 14742267
143 Paus, R., Nickoloff, B.J. and Ito, T. (2005) A 'hairy' privilege. Trends Immunol 26, 32-40, PubMed: 15629407
144 McElwee, K.J. et al. (2002) Resistance to alopecia areata in C3H/HeJ mice is associated with increased expression of regulatory cytokines and a failure to recruit CD4+ and CD8+ cells. J Invest Dermatol 119, 1426-1433, PubMed: 12485450
145 Zoller, M. et al. (2004) Apoptosis resistance in peripheral blood lymphocytes of alopecia areata patients. J Autoimmun 23, 241-256, PubMed: 15501395
146 Mayer, L. and Shao, L. (2004) Therapeutic potential of oral tolerance. Nat Rev Immunol 4, 407-419, PubMed: 15173830
147 Zoller, M. et al. (2002) Transient CD44 variant isoform expression and reduction in CD4(+)/CD25(+) regulatory T cells in C3H/HeJ mice with alopecia areata. J Invest Dermatol 118, 983-992, PubMed: 12060392
148 Huber, S. et al. (2004) Cutting edge: TGF-beta signaling is required for the in vivo expansion and immunosuppressive capacity of regulatory CD4+CD25+ T cells. J Immunol 173, 6526-6531, PubMed: 15557141
149 Tang, Q. et al. (2004) In vitro-expanded antigen-specific regulatory T cells suppress autoimmune diabetes. J Exp Med 199, 1455-1465, PubMed:

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https://doi.org/10.1017/S146239940601101X Published online by Cambridge University Press

15184499
150 McElwee, K.J. et al. (2005) What can we learn from animal models of Alopecia areata? Dermatology 211, 47-53, PubMed: 15983437
151 Price, V.H. (2003) Therapy of alopecia areata: on the cusp and in the future. J Investig Dermatol Symp Proc 8, 207-211, PubMed: 14582675
152 Ormerod, A.D. (2003) Alefacept. Biogen. Curr Opin Investig Drugs 4, 608-613, PubMed: 12833658
153 Leonardi, C.L. (2003) Efalizumab: an overview. J Am Acad Dermatol 49, S98-104, PubMed: 12894132
154 Klinkhoff, A. (2004) Biological agents for rheumatoid arthritis: targeting both physical function and structural damage. Drugs 64, 1267-1283, PubMed: 15200343
155 Sauder, D.N. and Mamelak, A.J. (2004) Understanding the new clinical landscape for psoriasis: a comparative review of biologics. J Cutan Med Surg 8, 205-212, PubMed: 16091996
156 Freyschmidt-Paul, P. et al. (2006) Interferon-gamma deficient mice are resistant to the development of alopecia areata. Br J Dermatol (in press)
157 Skurkovich, B. and Skurkovich, S. (2006) Inhibition of IFN-gamma as a method of treatment of various autoimmune diseases, including skin diseases. Ernst Schering Res Found Workshop 1-27, PubMed: 16329644
158 Freyschmidt-Paul, P. et al. (2000) Treatment with an anti-CD44v10-specific antibody inhibits the onset of alopecia areata in C3H/HeJ mice. J Invest Dermatol 115, 653-657, PubMed: 10998138
159 Yano, S. et al. (2002) Analysis of the expression of cutaneous lymphocyte-associated antigen on the peripheral blood and cutaneous lymphocytes of alopecia areata patients. Acta Derm Venereol 82, 82-85, PubMed: 12125957
160 Freyschmidt-Paul, P. et al. (2003) Fas-deficient C3.MRL-Tnfrsf6(lpr) mice and Fas ligand-deficient C3H/HeJ-Tnfsf6(gld) mice are relatively resistant to the induction of alopecia areata by grafting of alopecia areata-affected skin from C3H/HeJ mice. J Investig Dermatol Symp Proc 8, 104-108, PubMed: 12895005
161 Jantunen, E. and Luosujarvi, R. (2005) Stem cell transplantation in autoimmune diseases: an update. Ann Med 37, 533-541, PubMed: 16278166
162 Weissman, I. (2005) Stem cell research: paths to cancer therapies and regenerative medicine. Jama 294, 1359-1366, PubMed: 16174694
163 Freyschmidt-Paul, P. et al. (2003) Alopecia areata: treatment of today and tomorrow. J Investig Dermatol Symp Proc 8, 12-17, PubMed: 12894988
164 Walker, M.R. et al. (2005) De novo generation of antigen-specific CD4+CD25+ regulatory T cells from human CD4+CD25- cells. Proc Natl Acad Sci U S A 102, 4103-4108, PubMed: 15753318
165 Cotsarelis, G. and Millar, S.E. (2001) Towards a molecular understanding of hair loss and its treatment. Trends Mol Med 7, 293-301, PubMed: 11425637

Further reading, resources and contacts

A comprehensive text on hair biology and clinical diseases. Chapter 8 reviews alopecia areata:
Olsen, E.A. (ed.) (2003) Disorders of Hair Growth (2nd edn), McGraw-Hill Professional, ISBN: 0071364943

A comprehensive review of hair loss management including algorithms for patient management and treatment of alopecia areata and androgenetic alopecia:
Ross, E.K. and Shapiro, J. (2005) Management of hair loss. Dermatol Clin 23, 227-243

A review published by this journal on adrogenetic alopecia:
Ellis, J.A., Sinclair, R. and Harrap, S.B. (2002) Androgenetic alopecia: pathogenesis and potential for therapy. Exp. Rev. Mol. Med. 19 November, http://www.expertreviews.org/02005112h.htm

The National Alopecia Areata Foundation (NAAF) supports research to find a cure and acceptable treatments for alopecia areata, supports those with the disease, and educates the public about alopecia areata:
http://www.naaf.org/

A commercial web site with various articles on aspects of alopecia areata:
http://www.keratin.com/ad/

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Figures

Figure 1. Hair follicle cycle.
Figure 2. Model for pathogenesis of alopecia areata.

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