Alopecias in humans: biology, pathomechanisms and emerging therapies

Anneliese Willems* and Rodney Sinclair*†

*Sinclair Dermatology, Melbourne, Australia.
†Department of Medicine, University of Melbourne, Australia.

Abstract

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/VDE.13014

This article is protected by copyright. All rights reserved
Background – The hair follicle is a complete mini-organ with a complex biology. Recent discoveries have shed light on the pathogenesis and genetic basis of a number of hair loss conditions, offering novel treatment alternatives.

Objective – To explore the biology and physiology of hair growth, the pathomechanism behind alopecias and emerging therapies.

Conclusion and clinical importance – Hair growth is influenced by numerous physiological moderators. Greater understanding of the biology and physiology of the hair follicle and the pathomechanisms of hair disease facilitates development of targeted treatments. Sublingual minoxidil is a promising therapy in humans where optimised drug delivery enhances efficacy and reduces systemic adverse effects. Janice kinase inhibitors, which disrupt the inflammatory cascade, help maintain the hair follicle, preserve immune privilege, and regrow hair in alopecia areata. As the pathomechanisms of other forms of alopecia become better understood, new targeted therapies with greater efficacy will emerge.

Sources of Funding: This study was self-funded
Conflicts of Interest: No conflicts of interest have been declared

Introduction
Along with placental foetal development and lactation, hair is the defining characteristic of mammals. The earliest direct evidence of hair in mammals comes from fossilised casts and impressions in coprolites and pellets from the late Palaeocene beds of Inner Mongolia. Hairs in nonhuman hairy primates act as a thermoregulator, offering a survival advantage in climate extremes. While warm-blooded mammals owe much of their evolutionary success to the hair as a heat insulator, hair has no vital function in humans. However, hair serves other purposes and is concerned with sexual and social communication by constructing adornments such as the mane of the lion or the beard of the human male, or assisting in the dispersal of scents secreted by complexes of sebaceous or apocrine glands. Human hair can be red, blonde, brown or black, and straight, wavy or curly. These natural variations are an important part of our identity that can be manipulated according to the dictates of fashion or society.
Hair also is important to our self-confidence and psychological wellbeing. The loss of hair growth can result in profound emotional distress.\(^4\) Alopecia, derived from the Grecian word for “fox”, alope\(x\), an animal which commonly suffers from mange, refers to the loss of hair from any part of the body where it normally grows.\(^5\) Hair loss in humans is common and has numerous causes, including androgenetic hair loss, autoimmune disease, chemotherapy and psychiatric disorders.\(^6\)

Previously the growth of hair follicles and, as such, the pathomechanisms of hair loss, were uncertain. Recent research has shed light on the pathogenesis and genetic basis of hair loss.\(^4\) These findings better inform the pathomechanisms of alopecias, offering novel treatment avenues for exploration. In this review we will explore the biology and physiology of hair growth, the pathomechanisms of alopecias, and emerging therapies.

**The hair follicle**

The hair follicle (Figure 1) is a complex part of mammalian anatomy, the biology of which is understood only partially.\(^7,8\) The hair comprises cylindrical shafts of tightly compacted cells that grow from sac-like miniature organs called follicles.\(^3,7\) The human skin supports approximately five million hair follicles,\(^3\) of which only one hundred thousand are on the scalp.

In many mammals, follicles exist in follicular units with multiple hairs emerging from a single pore. In the merino sheep the hairs within the follicular unit are roughly equal in size (Figure 2).\(^9\) In other mammals there is considerable variation of follicle size, with the primary follicle producing guard hairs and the secondary follicles producing the undercoat (Figure 3). In humans, follicles exist only as follicular units on the scalp with multiple hairs exiting from a single pore (Figure 4).

Most follicles in humans produce vellus hairs that are cosmetically insignificant.\(^10\) Many never produce hairs long enough to protrude from the follicular ostium. On the scalp, however, the majority of hairs are terminal hairs that if uncut, may grow up to a metre long.

**The structure of the hair shaft**

This article is protected by copyright. All rights reserved
Pilosebaceous unit
Anatomically, the triad of the hair follicle, arrector pili muscle and sebaceous gland make up the pilosebaceous unit (Figure 1). The arrector pili muscle (APM) arises from the outer root sheath at the junction between the bulb and isthmus. It inserts into a bulge on the posterior wall, and some fibres insert circumferentially.

The sites of attachment of the APM and the sebaceous gland act as anatomical boundaries separating the hair follicle into three parts: the bulb, which extends from the base of the follicle to the insertion of the APM; the isthmus that extends from the insertion of the APM to the sebaceous duct; and the infundibulum, which runs from the entrance of the sebaceous duct to the follicular ostium.

The bulge contains a group of germinative cells that can be identified histochemically. The cells within the bulge are the immortal stem cells of the hair follicle, and destruction of the bulge will permanently destroy the follicle. Previously the APM was thought to be merely a bystander in hair disease, yet recent findings have established that the APM attachment to the hair follicle bulge may be necessary for reversal of hair follicle miniaturisation. The arrector pili muscle attaches to all follicles within a scalp follicular unit and also may insert into adjacent follicular units.

Cortex
All cell proliferation occurs in the hair bulb. Rapidly proliferating matrix cells produce the hair shaft. The bulk of the hair shaft is the cortex which forms the major part of the hair shaft, and contributes most to the colour and the mechanical properties of hair. The cortex consists of closely packed spindle cells containing cytoplasmic filaments that run parallel to the long axis of hair (Figure 5). These filaments are hard alpha keratin fibres. Each cell is separated by a narrow gap containing proteinaceous material that cements the cells together and contributes to the incredible strength of the hair shaft. Melanocytes are found only in the hair matrix at the base of the cortex and produce melanin granules that intersperse throughout the cortex producing hair pigment. Each hair shaft consists of three...
distinct types of cells: an outer cuticle that surrounds a central cortex which, in turn, may contain a central medulla.\textsuperscript{7}

**Cuticle**

The cortex is, in turn, encircled by the hair cuticle, a shield that protects the hair cortex and is responsible for the lustre and texture of hair.\textsuperscript{12} The function of the cuticle is to anchor the hair shaft in the follicle and to protect the interior fibres.\textsuperscript{7} The cuticle consists of a single layer of cells that overlap akin to roof tiles, with the free margin pointing towards the tip of the hair.

These cells are the first part of the emerging hair to harden by undergoing keratinisation and determine the shape of the emerging hair.\textsuperscript{17} If the cuticle is damaged the cortex will quickly degenerate resulting in broken hairs and split ends. The strength of the cuticle comes from the strong high sulfur protein present in the outer part of each cuticular cell. Absence of this protein which occurs in trichothiodystrophy produces weakened, fragile hairs that break off close to the root.\textsuperscript{12}

**Medulla**

If a hair has sufficient size and calibre, it will develop a central core, known as a medulla.\textsuperscript{17} If present, this central medulla, which arises from hair matrix cells, may occur intermittently along the hair. It is made up of a framework of spongy keratin supporting thin shells of amorphous material bounding air spaces of variable size. It is best seen on light microscopy of hair where, because of refraction of light, the air spaces appear dark.\textsuperscript{18} In some mammals the central air canal of hair provides an insulating effect crucial to thermoregulation; however, in humans the medulla is a vestigial structure.\textsuperscript{19}

**Dermal papilla**

The dermal papilla is located at the base of the follicle. The dermal papilla consists of an oval mass of spindle cells resting in a local environment rich in mucopolysaccharides. The papilla is surrounded by hair matrix epithelium from which it is separated by a thick basement membrane except where it sits on a dermal fibro elastic plate called the Arao-Perkins body.\textsuperscript{10} The papilla receives a rich neurovascular supply. It plays a vital role in stimulating

This article is protected by copyright. All rights reserved
embryological follicle formation and regulating the hair cycle. The size of the dermal papilla correlates closely with the size of the hair follicle.

Production of the hair fibre
The germinative epithelium gives rise to numerous distinct cell lineages that undergo terminal differentiation. The outer root sheath is continuous with the adjacent epidermis above and with the germinative layer of the hair matrix below. Outer root sheath keratinocytes keratinise with formation of keratohyaline granules. Inner root sheath cells keratinise with the formation of trichohyaline granules, while cortex cells keratinise without granule formation. In the cortex, interfilamentous matric proteins are actively transported into the follicle by the alanine/serine/cysteine/threonine transporter 1 (ASCT1), a sodium-dependant, neutral amino acid transporter, expressed in the outer root sheath and hair cortex of the keratogenous zone of the bulb. ASCT1 enables uptake of cysteine, which is the rate-limiting step in hair fibre production and directs the blood supply against the concentration gradient. Cells of the outer root sheath express different keratin markers to the cells of the medulla, cortex, cuticle and inner root sheath, which all express similar keratins.

Each hair arises from a follicle consisting of epidermis that has invaginated the dermis to form a sleeve-like structure. The base of the follicle is intimately associated with the dermal papilla, and hair is the product of interaction and communication between dermis and epidermis. The hair shaft consists of keratinocytes that are compacted and cemented together. The final product is remarkably strong and resistant to the extremes of nature.

The hair growth cycle
Hair growth occurs in life-long cycling and encompassing periods of growth (anagen), involution (catagen) and rest (telogen), after which the hair is shed (exogen) and the cycle continues. Each hair grows continuously until it achieves a maximum length, is retained for a period of time without further growth and is eventually shed and replaced. The duration of activity varies greatly from region to region, and subtle variation also occurs with age and between males and females.

This article is protected by copyright. All rights reserved
Anagen
Anagen is the period of active growth and in a human vellus follicle lasts between six and 12 weeks. In people, terminal hair anagen lasts 4–14 weeks on the moustache, 6–12 weeks on the arms, 19–26 weeks on the legs and 2–5 years on the vertex of the scalp.

Catagen
Catagen is the transitional phase that follows anagen and usually lasts two weeks.

Telogen
Telogen is the resting phase of the hair cycle. The club hair with its nonpigmented bulb is held in a sac and is retained in the follicle until the development of the next anagen hair is well-established. Telogen usually lasts three months on the scalp before the follicle spontaneously re-enters anagen; however, a premature anagen can be triggered by plucking the resting club hair.

In many animal species, the hair cycle is synchronised such that the entire pelage grows continuously through winter. When summer comes, growth abruptly ceases and a cephalocaudal moult ensues. In human hair this synchronised growth pattern only normally occurs in utero and becomes apparent with occipital alopecia of the newborn.

Types of hair
There are numerous physiological modulators behind the cycles of hair growth which include hormones, neuromediators, miscellaneous biomolecules, seasonal/environmental conditions, microinflammation and ageing. In particular, the type of hair produced by an individual follicle can change with age or under the influence of hormones. The three main recognised types of hair are:

1. *Lanugo hair* which is formed and shed during the seventh or eighth month in utero. It consists of fine, soft, nonpigmented hair that has no central medulla.
2. *Vellus hair* is the fine, unmedullated hair found on glabrous skin that is usually <2 cm long and nonpigmented.

This article is protected by copyright. All rights reserved
3. **Terminal hair** is the coarse, pigmented, long hair found on the scalp, eyebrows and eyelashes before puberty and additionally in the pubic, axillary, chest and beard areas of adults.

Intermediate or indeterminate forms of hair also exist on the scalp of infants at three months and last until the age of 2 years. They are coarser than lanugo hair and sparsely pigmented; however, they do not have a well-defined medulla like that found in terminal hair. Similar hair also appears on adult scalps in the context of androgenetic alopecia, a process that results in miniaturisation of terminal hairs and ultimate reversion into vellus hairs.

**Immunology of the hair follicle**

Placental foetal development and hair are two of the defining features of mammals. Placental development of a foetus requires that the foetal tissues, which are genetically different than maternal tissues, attach to the dam without triggering acute immune rejection. Mammalian pregnancy is therefore an example of a successful allo-transplant, the survival of which is permitted by placental immune privilege.

A vast array of immunological mechanisms underlie this phenomenon, such as downregulation of cell surface expression of classic (human leukocyte antigen (HLA)–A, HLA-B, HLA-C and HLA-D) and up-regulation of nonclassic (HLA-E, HLA-F and HLA-G) major histocompatibility antigens (MHC). Classical class I molecules are expressed constitutively on almost all cells except red blood cells. Significant allelic variation means that no two people (other than monozygotic twins) share the same MHC molecules. Human organ transplantations require donor and recipient matching of classical HLA antigens to avoid rejections. Cells with mismatched classical HLA antigens are vulnerable to attack by CD8+ T cells and MHC-Class I negative are vulnerable to NK T-cell attack. Upregulation of nonclassic (HLA-E, HLA-F and HLA-G) major histocompatibility antigens protects cells from NK T-cell attack. In particular, cell-surface HLA-G expression at the foetal–maternal interface has been more strongly implicated in maternal tolerance during pregnancy.
During anagen, hair follicle outer root sheath cells do not normally express classical HLA Class I or Class II antigens, yet do express nonclassical Class I antigens. Hair follicles demonstrate immune privilege in allogeneic transplantation and also xenotransplantation. Hair follicle immune privilege also serves to sequester highly immunogenic autoantigens from immune recognition during anagen, and to induce a state of peripheral tolerance against them whenever they may become exposed to the immune system.

Collapse of immune privilege occurs constitutively in catagen and also is fundamental to the development of alopecia areata (AA) and other autoinflammatory hair loss disorders.

**Hormonal influences on hair growth**

Circulating androgens increase both the rate of hair growth and the calibre of the hair (transforming vellus to terminal hairs) in androgen-dependent sites such as the beard. Paradoxically, in the scalp of a person genetically predisposed to androgenetic alopecia, androgens reduce both the rate of scalp hair growth and the calibre (transforming terminal to vellus hairs) of the hair, while antiandrogens partially restore it. It is not known why or how the same chemical can induce exactly opposite effects on different hair follicles. Despite these relatively site-specific changes, most hairs on the body are relatively uninfluenced by androgens. This insensitivity most likely is due to the differences in follicular metabolism of androgens, possible related to regional variation in the distribution of 5a-reductase isoenzymes.

Oestrogens reduce the rate of hair growth and prolong the duration of anagen. This is best seen during pregnancy when there is decreased hair shedding. Postpartum, large numbers of hairs enter catagen and subsequently telogen, which is followed by sometimes massive shedding approximately three months after the birth, known as telogen effluvium gravidarum.

Thyroxine hastens the onset of anagen in resting follicles and corticosteroids delay it. There also is a seasonal variation on the rate of hair growth in humana such that it grows faster in summer and more slowly during the winter. This effect is mediated through the pineal gland yet the exact mechanism is obscure.

This article is protected by copyright. All rights reserved
Alopecias in humans

Anything that interrupts any of the phases of the hair growth cycle may result in hair loss. Causes may be inflammatory, neoplastic, nutritional, infectious, endocrinological, stress-related or medication-related. \(^{12,24}\) Alopecias generally will target a given phase of the hair cycle, yet the anagen phase is the most vulnerable. \(^{25}\)

The pattern and time course of hair loss, especially whether it is focal or diffuse, may help guide diagnosis. \(^{26}\) Hair loss disorders also can be classified as scarring and nonscarring alopecias. \(^{27}\) In scarring alopecias, also known as cicatricial alopecias, there is irreversible destruction of the hair follicle resulting from destruction of stem cells in the bulge area of the outer root sheath. These stem cells are replaced by fibrous scar tissue resulting in permanent hair loss. \(^{28,29}\) By contrast, in nonscarring alopecias there is preservation of the follicle. \(^{30}\)

Two of the most common nonscarring alopecias are androgenetic alopecia (AGA) and AA. For both of these conditions, terminal hair follicle miniaturisation is the hallmark histopathological finding. \(^{15,25}\) The hair follicle which once produced healthy hairs begins to make fine hairs, with a fragile shaft that can easily fall out.

Androgenetic alopecia

Androgenetic alopecia is a patterned form of hair loss which is commonly associated with increased age. \(^{10}\) AGA is a complex polygenetic disorder. \(^{31,32}\) It can be found in both men and women, and in certain primates. \(^{33}\) The modern understanding of AGA was introduced in 1942 by Hamilton. \(^{34}\) He established that AGA in men is a physiologic process brought on by genetically predisposed hair follicles under the influence of androgens. \(^{35}\) Androgens’ role in male AGA has been well-established, yet the role of androgens in women suffering from AGA is less clear. \(^{36}\) It has been postulated that the influence of androgens is linked to higher levels of the 5α-reductase enzyme which converts testosterone to dihydrotestosterone, \(^{37}\) which is the most potent androgen that regulates hair cycling. \(^{38}\)
In AGA there is progressive miniaturisation of the hair follicles resulting in reduction in the number of hairs (Figure 6). Within this process, terminal hairs are replaced by fine short vellus-like hairs. The number of total hair follicles remains stable, yet there is a reduction in hair follicle size, depth and diameter of hair shaft. Men with AGA will commonly experience hair loss to the frontotemporal region with bitemporal recession initially. Women with AGA will frequently experience diffuse hair thinning over the midfrontal scalp and increased hair shedding.

AGA is most prevalent in Caucasian men and affects approximately 50% of men by the age of 50. In women, AGA varies significantly between populations and according to age. There are varied estimates as to its prevalence – it may affect 6–38% of women. AGA tends to become a medical problem when the hair loss has reached a stage of being excessive, premature or distressing.

Alopecia areata
The pathomechanism of AA is inflammatory and immune-mediated; the exact pathophysiology is unknown, yet there is a strong genetic and environmental bases for triggering the disease. AA is a type 1 inflammatory disease. Activated NKG2D+CD8+ cells produce the Th1 cytokine interferon-γ. In turn, this leads to the disruption of immune tolerance of hair follicles and the exposure to self-antigens. The result is a dense cell lymphocytic inflammatory infiltrate to the peri- and intrabulbar regions of the hair follicle with resultant apoptosis leading to hair loss.

AA is a relapsing and remitting condition, where natural history varies from individual to individual. Typically the first clinical signs are a small discrete patch of hair loss. Hair loss in AA can affect any part of the body. In alopecia totalis there is complete loss of hair to the scalp whilst in alopecia universalis there is complete loss of hair not only to the scalp, but also to other regions of the body, such as the eyebrows and eyelashes. In ophiasis alopecia there is a band of hair loss to the sides and lower back of the scalp.

Up to 70% of AA patients achieve a spontaneous and durable remission within 12 months (acute AA), while for others the disease course may be protracted with multiple relapses.
and remissions over many years (chronic AA). The psychological burden of AA for some individuals may be immense, and there are high rates of anxiety and depression. They also may experience reduced quality-of-life, lower self-esteem and poorer body image.

Treatment modalities – current and emerging

Hair loss treatments in AA and AGA seek to arrest miniaturisation, promote hair growth and prevent the initial factors that lead to the disease process itself. Choice of therapy is influenced by disease type, patient age, disease duration and disease extent.

Hair follicle miniaturisation is reversible in AA and not in AGA, as the miniaturised hairs maintain contact with the APM in AA and not in AGA. This loss of contact between the hair bulge and APM might explain irreversible miniaturisation seen in AGA. In particular, this may be caused by the fat infiltration seen in AGA that may cause the loss of contact between the bulge and APM. New evidence has established that preservation of the APM attachment to the hair follicle bulge may be an opportunity for preservation and reversal of the function of the hair follicle through the local stem cell repository.

Historically, therapies for AGA in men encompass topical minoxidil, oral finasteride and dutasteride. In women with AGA, antiandrogen agents include systemic therapies through spironolactone and cyproterone acetate. Procedural options include hair transplantation as well as emerging surgical treatments such as platelet-rich plasma injections, low-level laser therapy, microneedling or autologous fat transfers.

Minoxidil has long been used topically for the treatment of AGA. Minoxidil is a piperidine-pyrimidine derivative and a potent vasodilator, and historically has been used for the treatment of severe hypertension. The topical application of minoxidil has its limitations, however. The necessity for daily to twice daily application and resultant undesirable hair texture, presents barriers to long-term use. In addition, topical application only promotes hair growth in 50% of AGA cases given that maximal topical therapy produces subtherapeutic plasma levels. Minoxidil is a sulfate active metabolite which is metabolised by the sulfotransferase enzyme (SULT1A1). There are variations between individuals with
their metabolism of minoxidil via SULT1A1: those with higher levels of the enzyme will have a better response to topical minoxidil whilst those with low SULT1A1 have a lower response.

Topical application of minoxidil may cause local irritation, hypertrichosis of the temples and occasionally allergic contact dermatitis. However, owing to the rich capillary network surrounding the hair bulb there also is percutaneous systemic absorption which varies from individual to individual. Systemic adverse effects of minoxidil encompass postural hypotension, dizziness and lower limb oedema.

Oral minoxidil has recently been advocated in low doses. Oral minoxidil has a first-pass action through the liver where the SULT1A1 activity varies the blood level concentrations according to the SULT1A1 activity from individual to individual. For some individuals the haemodynamic adverse effects, as described above, from varied SULT1A1 activation can be significant. Sublingual minoxidil may help to circumnavigate this adverse effect profile through direct absorption to the blood stream, avoiding the gastric first pass. As sublingual minoxidil is almost fully systemically absorbed, the range of plasma concentration is narrow which results in the opportunity for more precise dosing. The role of systemic low-dose minoxidil is an emerging therapy which holds promise in treating AGA in both men and women. Its use is extending beyond AGA to other types of alopecias both in single and combination therapies. Unfortunately minoxidil has been demonstrated to be cardiotoxic in a number of common household pets. At this stage minoxidil therapy should not be considered in animals.

Changing treatment landscape for AA

Traditionally, there are no systemic therapies approved for managing moderate to severe AA. Local disease has treatment consensus, where for solitary patches, topical high-potency steroids or intralesional corticosteroids are first-line therapies. Historically, more complex disease has been challenging to manage. Reestablishment of hair follicle immune privilege is a prerequisite for hair regrowth. Immunosuppression has been widely attempted through systemic corticosteroids, ciclosporin, methotrexate and azathioprine. These therapies have had varied levels of success and their use carries significant potential for associated morbidities.
New immunotherapies have been trialled recently with promising results. In particular, Janice kinase (JAK) inhibitors are an emerging area of therapy for the treatment of AA (Figure 7). Known as DMARDs (disease-modifying antirheumatic drugs), these new therapies target the cytokine cascade. Altered cytokine production results in numerous inflammatory conditions. The JAK family is a group of receptor-associated molecules which play a significant role within the cytokine cascade. JAK inhibitors are antagonists of various members of the JAK enzyme family – consisting of JAK1, JAK2, JAK3 and tyrosine kinase-2 (TYK2). These medications block the binding and activation of the transducer and activator of transcription (STAT), ultimately disrupting the inflammatory cascade. JAK inhibitors with a role in the management of AA at the time of this publication include tofacitinib and baracitinib. Oral formulations have had hair regrowth in 67–75% of patients in several studies. Their role in treating AA is expected to continue to evolve.

Conclusions
As we continue to better understand the pathomechanism of hair loss, the array of therapies available will continue to evolve. Current therapeutic advances in AGA explore the role of reversing the loss of the attachment of the PAM. Sublingual minoxidil offers a novel approach to treatment, avoiding the complications of traditional topical and oral administration. JAK inhibitors are an emerging new line of treatment for autoimmune and inflammatory-based hair conditions.

References

This article is protected by copyright. All rights reserved

This article is protected by copyright. All rights reserved


This article is protected by copyright. All rights reserved


This article is protected by copyright. All rights reserved.
Figure Legends

Figure 1. Diagram of the hair follicle – a complex micro-organ.

Figure 2. Secondary follicle bundle in merino sheep.
In many mammals, follicles exist in follicular units with multiple hairs emerging from a single pore. Image adapted from Hardy & Lyne (1955).

Figure 3. The ferret hair follicle demonstrating primary follicle with secondary follicle.

Figure 4. Trichogram showing follicular units on the scalp.
Multiple hair shafts may exit from each follicular unit.

Figure 5. Surface view of cuticular scales in the proximal part of the hair shaft.
The cortex consists of closely packed stellate cells containing cytoplasmic filaments that run parallel to the long axis of hair.

Figure 6. Miniaturisation of the hair follicle in androgenetic alopecia (AGA).
In AGA, terminal hairs are replaced by fine short vellus-like hairs.

Figure 7. The evolution of remission of alopecia areata (AA).
Janus kinase inhibitors are an emerging therapy for treating AA.
Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:
Willems, A; Sinclair, R

Title:
Alopecias in humans: biology, pathomechanisms and emerging therapies

Date:
2021-08-25

Citation:

Persistent Link:
http://hdl.handle.net/11343/298878