ELSEVIER

Experimental Gerontology 37 (2002) 981–990

Experimental Gerontology

www.elsevier.com/locate/expgero

Mini-Review

Molecular mechanisms of androgenetic alopecia

Ralph M. Trüeb*

Department of Dermatology, University Hospital of Zurich, Gloriastr. 31, 8091 Zurich, Switzerland

Received 10 June 2002; received in revised form 17 June 2002; accepted 18 June 2002

Abstract

Androgenetic alopecia (AGA) is hereditary and androgen-dependent, progressive thinning of the scalp hair that follows a defined pattern. While the genetic involvement is pronounced but poorly understood, major advances have been achieved in understanding principal elements of the androgen metabolism involved: androgen-dependent processes are predominantly due to the binding of dihydrotestosterone (DHT) to the androgen receptor (AR). DHT-dependent cell functions depend on the availability of weak androgens, their conversion to more potent androgens via the action of 5alpha-reductase, low enzymatic activity of androgen inactivating enzymes, and functionally active AR present in high numbers. The predisposed scalp exhibits high levels of DHT, and increased expression of the AR. Conversion of testosterone to DHT within the dermal papilla plays a central role, while androgen-regulated factors deriving from dermal papilla cells are believed to influence growth of other components of the hair follicle. Current available treatment modalities with proven efficacy are oral finasteride, a competitive inhibitor of type 2 5α-reductase, and topical minoxidil, an adenosine-triphosphate-sensitive potassium channel opener which has been reported to stimulate the production of vascular endothelial growth factor in cultured dermal papilla cells. Since the clinical success rate of treatment of AGA with modulators of androgen metabolism or hair growth promoters is limited, sustained microscopic follicular inflammation with connective tissue remodeling, eventually resulting in permanent hair loss, is considered a possible cofactor in the complex etiology of AGA.

Keywords: Androgenetic alopecia; Androgen metabolism; Androgen receptor; Polygenic inheritance; Follicular microinflammation; Permanent hair loss

Androgenetic alopecia (AGA), also referred to as male-pattern hair loss or common baldness in men, and as female-pattern hair loss in women, affects at least 50% of men by the age of 50 years, and up to 70% of all males in later life (Norwood, 1975). Estimates of its prevalence in women have varied widely, though recent studies claim that six percent of women aged under 50 years are affected, increasing to a proportion of 30–40% of women aged 70 years and over (Norwood, 2001). The hair loss is heritable, androgen-dependent, and occurs in a defined pattern. It is assumed that the genetically predisposed hair follicles are the target for androgen-stimulated hair follicle miniaturization, leading to gradual replacement of large, pigmented hairs (terminal hairs) by barely visible, depigmented hairs (vellus hairs) in affected areas (Paus and Cotsarelis, 1999). The result is a progressive decline in visible scalp hair density. While male pattern AGA is characterized by its typical bitemporal recession of hair and balding vertex, female pattern AGA is set apart by its diffuse thinning of the crown and intact frontal hairline. While prerequisites are thus a genetic predisposition

* Tel.: +41-1255-3471; fax: +41-1255-4549.
E-mail address: ramitru@derm.unizh.ch (R.M. Trüeb).

0531-5565/02/$ - see front matter
PII: S0531-5565(02)00093-1

and androgens, clinical practice has shown us that simply blocking androgens does not result in the conversion of miniaturized follicles to terminal ones in advanced alopecia. On histologic examination of scalp biopsies, the miniaturization of terminal hairs is frequently associated with perifollicular lymphocytic infiltration, and eventually fibrosis (Jaworsky et al., 1992; Whiting, 1993). Therefore it is conceivable that the role of this microscopic follicular inflammation causing fibrosis below the shortened balding follicle has been underestimated, though it seems likely that this would prevent the follicle to reform a terminal hair follicle.

It is the aim of this paper to review the molecular mechanisms resulting in AGA, as far as androgens, genetics, and inflammatory phenomena are involved.

1. Hair-follicle cycling and signaling molecules controlling hair growth

The hair-growth cycle: The hair follicle is subject to constant turnover in the course of perpetual cycles through various stages of proliferation (*anagen*), involution (*catagen*), and resting (*telogen*), with regeneration in the successive hair cycle (Fig. 1). It is a major characteristic of anagen that not only the hair shaft is growing but that most epithelial hair follicle compartments undergo proliferation, with the hair matrix keratinocytes located around the dermal papilla showing the highest proliferative activity. Also, the newly formed hair shaft is pigmented by the follicle pigmentary unit (Paus and Cotsarelis, 1999). During the following catagen stage of the hair cycle, hair follicles enter a highly controlled process of involution that is characterized by a burst of programmed cell death (apoptosis) in the majority of follicular keratinocytes, termination of pigment production, substantial extracellular matrix-remodeling, and condensation of the dermal papilla (Paus and Cotsarelis, 1999). The resulting shortening of the regressing epithelial strand is associated with an upward movement of the dermal papilla within the connective tissue sheath of the follicle. In telogen the hair shaft matures into a club hair, which is held tightly in the bulbous base of the follicular epithelium, before it is eventually shed from the follicle, usually as a result of combing or washing. It is still unresolved whether shedding of the telogen hair (*teloptosis*) is also an active, regulated process or represents a passive event that occurs at the onset of subsequent anagen, as the new hair grows in (Paus and Cotsarelis, 1999; Pierard-Franchimont and Pierard, 2001). There are considerable variations in length of these stages depending on the body site location, with the duration of anagen determining the type of hair produced, particularly its length (Paus and Cotsarelis, 1999). On the scalp, hairs remain in anagen for a 2–7-year period of time, whereas that of telogen is 100 days, leading to a ratio of anagen to telogen hairs of approximately 9:1. On average the amount of new scalp hair formation essentially matches the amount that is lost due to shedding (approximately 100/day), thereby maintaining a consistent covering.

Hair growth control: The controls that underlie the hair cycle reside within the hair follicle itself, and are believed to result from changes in the intra- and perifollicular expression of specific regulatory molecules and their receptors (Paus et al., 1999). Much circumstantial evidence suggests that the dermal papilla which is composed of specialized fibroblasts located at the base of the follicle, determines hair follicle growth characteristics, especially the regulation of cell proliferation and differentiation of hair follicle matrix: without papilla fibroblasts and an intimate contact with hair matrix keratinocytes anagen cannot be sustained. Also, hair follicle morphogenesis can be induced by implanting dermal papilla cells under an appropriately receptive epithelium (Jahoda et al., 1984). Finally, it has been shown that implanting few cells of follicle dermal-sheath tissue from the scalp from an adult human male is sufficient to form new dermal papillae and induce new hair follicles in the skin of a genetically unrelated female (Reynolds et al., 1999). There is substantial evidence from bioassays that cultured dermal papilla cells can secrete a number of cytokines, growth factors and other, yet unidentified bioactive molecules that influence growth in other dermal papilla cells, outer root sheath cells, keratinocytes, and endothelial cells (Stenn et al., 1996). Finally, the hair cycle is subjected to cycle modulation by numerous extrinsic influences, such as androgens (Paus, 1996).

Pathobiology of AGA: AGA is characterized by progressive shortening of the duration of anagen with successive hair cycles, leading to decreased numbers

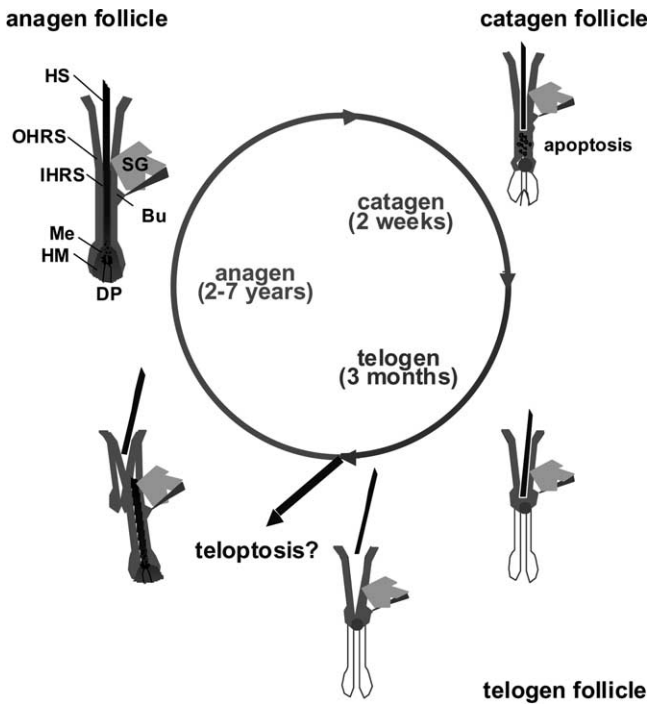


Fig. 1. The hair-growth cycle. Abbreviations: HS = hair shaft; OHRS = outer hair root sheath; IHRS = inner hair root sheath; SG = sebaceous gland; Bu = bulge; Me = Melanocytes; HM = hair matrix; DP = dermal papilla.

of hair in anagen at any given time, and progressive follicular miniaturization with conversion of terminal to vellus-like follicles (Paus and Cotsarelis, 1999). The result is increased shedding of short-lived telogen hairs (telogen effluvium), while the affected hair follicles produce shorter, finer hairs that cover the scalp poorly. Since AGA involves a process of premature termination of anagen associated with premature entry into catagen, it is critically important to dissect the molecular controls of the anagen–catagen transformation of the hair cycle (Paus, 1996). Catagen has been suggested to occur as a consequence of decreased expression of anagen maintaining factors, such as insulin-like growth factor 1 (IGF-1), basic fibroblast growth factor (bFGF), and vascular endothelial growth factor (VEGF), and increased expression of cytokines promoting apoptosis, such as transforming growth factor beta 1 (TGFβ 1), interleukin-1alpha (IL-1α), and tumor necrosis factor alpha (TNFα).

Responses to androgens are obviously also intrinsic to the individual hair follicle: not only does the response vary from stimulation to inhibition of hair growth depending on the body site, but androgen sensitivity also varies within individual areas, i.e. regression in AGA occurs in a patterned, progressive manner. Since many extrinsic hair growth-modulatory factors, such as androgens (Randall et al., 1992), apparently operate at least in part via the dermal papilla, research is currently also focused on identifying androgen-regulated factors deriving from dermal papilla cells.

Of the several factors that have been suggested to play a role in hair growth, so far only insulin-like growth factor (IGF-1) has been reported as altered in vitro by androgens (Itami et al., 1995), and stem cell factor (SCF) has been found to be produced in higher amounts by androgen-dependent beard cells than in control non-balding scalp cells, presumably also in response to androgens (Hibberts et al., 1996). Since SCF is the ligand for the cell surface receptor c-kit on melanocytes, this may also play a role for hair pigmentation.

2. Androgens, androgen metabolism, and the androgen receptor

Androgens: Of various hormones that affect hair growth, the most studied are the androgens, particularly as they pertain to AGA. Since Aristotle first noted that 'maleness' and sexual maturity were required for balding, it was not until 1942 that Hamilton's observations on men deprived of testicular androgens by castration established beyond doubt that androgens, in the form of testosterone or its metabolites, were prerequisites for development of common baldness. Hamilton observed that men who were castrated before puberty did not develop AGA, and that AGA can be triggered in castrated men by injecting testosterone (Kaufman, 1996).

Androgen metabolism: Androgen metabolism comprises glandular and extraglandular production, transport, target cell metabolism, and cellular response. While androgen biology in the adrenals and gonads, and the influence of the pituitary axis go beyond the scope of this review, androgen metabolism within the skin, as it pertains to hair growth and its disorders, is the focus (Kaufman, 1996). The androgen metabolism pathway begins with pregnenolone, a 21 carbon steroid substrate, converted from cholesterol. Following α-hydroxylation at the C-17 position, the action of the enzyme C_{17-20} lyase cleaves distal carbon moieties, leaving a C19 carbon steroid with a C-17 ketone in the distal ring. These '17-ketosteroids' make up a group of weak androgens, such as dehydroepiandrosterone (DHEA), defined by a low affinity for the androgen receptor. These weak androgens, however, can be enzymatically converted to more potent androgens with greater affinity for the androgen receptor, such as testosterone. Testosterone is the major circulating androgen. In women, systemic levels of testosterone are low compared with men, but the more abundant weak androgens serve as a source of precursors for potent androgens, which provide the physiologic or pathophysiologic androgen activity. Only a small fraction of androgens exists as free steroids in the circulation, with an equilibrium between free hormones and protein-bound androgens. The most important protein for androgen binding is sex-hormone binding globulin (SHBG). Normally 70% of testosterone is bound to SHBG, and 19% to albumin. The remainder is circulating unbound. In most target organs testosterone can be metabolized to DHT by the enzyme steroid 5α-reductase. Based on its affinity for the androgen receptor, DHT is fivefold more potent than testosterone. DHT is implicated in the pathogenesis of several disorders, including benign prostatic hyperplasia, prostate cancer, hirsutism, acne vulgaris, and AGA.

Androgen metabolism within skin: The skin and pilosebaceous unit are enzymatically equipped for local metabolism and conversion of sex steroids (Kaufman, 1996). The skin is capable of synthesizing active androgens from the systemic precursor DHEA-sulfate (DHEA-S). The first step is the desulfatation of DHEA-S by the enzyme steroid sulfate (STS). The principal pathways involved in conversion of weak androgens like DHEA to more potent androgens are through activity of the enzymes 3β-hydroxysteroid dehydrogenase-$\Delta^{5\rightarrow4}$-isomerase (3β-HSD), 17β-hydroxysteroid dehydrogenase (17β-HSD), and 5α-reductase. Once formed, potent androgens, such as testosterone and DHT, can be removed by conversion back to the weaker 17-ketosteroids, or are metabolized via other enzymatic pathways, including aromatase, which converts androgens to estrogens, and 3α-hydroxysteroid dehydrogenase to form androsterone and androstanediol. The latter can be glucuronidated to form androgen conjugates that are more rapidly cleared from the circulation. Remarkably, some target tissues, such as the hair follicle, show enhanced androgen metabolism and androgen sensitivity. The activity of enzymes involved in androgen metabolism within the skin has been studied in a variety of tissue preparations. The sebaceous glands in balding skin have been shown to express increased 3β-HSD activity when compared to non-balding scalp areas (Sawaya et al., 1988). Earlier it was shown that plucked human hair follicles or hair follicles from balding stumptailed macaques express considerable 17β-HSD activity (Takashima et al., 1970). In a study of plucked hair follicles from young adults not yet expressing AGA but with a strong family history of baldness, two populations were found, one with high 17β-HSD activity and one with low enzyme activity (Hodgins et al., 1985). The study suggested that low enzyme activity may be related to lesser degrees of balding. More recently, both men and women with AGA were shown to have higher levels of 5α-reductase enzyme activity in frontal

follicles than in their own occipital follicles, whereas higher levels of aromatase were found in their occipital follicles (Sawaya and Price, 1997).

Steroidogenic enzyme mutations: Since STS converts DHEA-S to DHEA that is eventually metabolized to more potent androgens in the periphery, and elevated plasma levels of DHEA-S and DHEA have been reported to correlate with balding in young men, the hypothesis was advanced, that men with genetic STS deficiency (X-linked recessive ichthyosis, XRI) do not or only develop minor forms of AGA. A survey of patients with XRI showed that this was not the case, since these men also showed advanced AGA (Trüeb and Meyer, 2000). In genetically determined deficiencies of the enzymes 3β-HSD, or 17β-HSD, respectively, the presence or absence of AGA has not been investigated so far (Hoffmann and Happle, 2000).

The description of an unusual form of incomplete male pseudohermaphroditism, due to a genetic deficiency of the type 2 steroid 5α-reductase by Imperato-McGinley et al. (1974), implicated DHT as principal mediator of androgen-dependent hair loss. Affected men, who are homozygous for mutation of the gene, do not develop AGA.

Mutations of the human gene encoding aromatase (CYP19) are rare and result in aromatase deficiency. Affected girls show pseudohermaphroditism at birth, and at puberty develop virilization and hirsutism due to an androgen excess, pubertal failure with no signs of estrogen action, hypergonadotropic hypogonadism, polycystic ovaries, and a tall stature. Males are rather tall with eunuchoid skeletal proportions. In theory, females and males might develop early onset of AGA (Hoffmann and Happle, 2000). Consistent with the role of aromatase in avoiding androgen-mediated effects on androgen-dependent hair follicles, is the observation that women taking aromatase inhibitors for the treatment of breast cancer often experience an AGA-like hair loss.

Androgen receptor (AR): Finally, the absence of balding in individuals with the androgen-insensitivity syndrome who lack functional AR clearly demonstrates the need for AR for AGA to occur (Quigley, 1998). All steroid hormones act by diffusing through the plasma membrane into the target cell and binding to specific intracellular receptors. The hormone-receptor complex undergoes conformational changes, exposing DNA-binding sites, and then bind to specific hormone response elements in the DNA, promoting the expression of specific hormone-regulated genes. The AR is believed to be responsible for determining the sensitivity of cells to androgens. Besides androgen insensitivity, various mutations have been described in the gene encoding the AR in a variety of diseases, including spinal and bulbar muscular atrophy (Kennedy's disease), and prostate cancer (Gottlieb et al., 1998). Some of these are associated with functional changes in AR expression. Expression of the AR has also been found to be increased in balding scalp (Randall et al., 1992; Sawaya and Price, 1997). Most recently, polymorphism of the AR gene has been found to be associated with male pattern baldness (Ellis et al., 2001).

3. Genetic involvement

The genetic involvement is pronounced, and the importance of genes concurs with marked racial differences in prevalence of AGA; non-Caucasians often exhibit significantly less balding. While major progress has been done in the understanding of androgen metabolism, the genetic predisposition to AGA remains poorly understood. A very high frequency of AGA has complicated attempts to establish a mode of inheritance. Moreover, it is not clear whether AGA is genetically homogeneous; some authorities suggest that female pattern hair loss is not the female counterpart of male AGA, and not androgen-dependent (Orme et al., 1999). The genes for type 1 and type 2 5α-reductase have been shown not to be associated with the inheritance of AGA (Ellis et al., 1998). Polymorphism of the AR gene is associated with male pattern baldness (Ellis et al., 2001), however, the AR gene is located on the X chromosome and does not explain the relatively strong concordance of the degree of baldness in fathers and sons. No specific gene has been identified so far, though single gene mutations, such as abnormality of the AR, might be necessary, but not sufficient for the phenotype (Ellis et al., 2001). We probably deal with a polygenic inheritance, dependent on a combination of mutations, e.g. in or around the AR gene affecting the expression of the AR, and

other genes controlling androgen levels. Interactions between such genes might account for the tissue-specific and developmental stage-specific expression of the AR that is necessary to explain the characteristic anatomic and temporal patterns of AGA. Other genes relevant to androgens, including those on the Y chromosome might also be examined (Ellis et al., 2001).

4. Hair follicle microinflammation

The limited success rate of treatment of AGA with hair growth promoters or modulators of androgen metabolism means that further pathogenic pathways may be taken into account. The implication of microscopic follicular inflammation in the pathogenesis of AGA has recently emerged from several independent studies (Jaworsky et al., 1992; Mahé et al., 2000; Whiting, 1993). An early study referred to an inflammatory infiltrate of activated T cells and macrophages in the upper third of the hair follicles, associated with an enlargement of the follicular dermal-sheath composed of collagen bundles (perifollicular fibrosis), in regions of actively progressing alopecia (Jaworsky et al., 1992). Horizontal section studies of scalp biopsies indicated that the perifollicular fibrosis is generally mild, consisting of loose, concentric layers of collagen that must be distinguished from cicatricial alopecia (Whiting, 1993). The term 'microinflammation' has been proposed, because the process involves a slow, subtle, and indolent course, in contrast to the inflammatory and destructive process in the classical inflammatory scarring alopecias (Mahé et al., 2000). The significance of these findings has remained controversial. However, morphometric studies in patients with male pattern AGA treated with minoxidil showed that 55% of those with microinflammation had regrowth in response to treatment, in comparison to 77% in those patients without inflammation and fibrosis (Whiting, 1993).

Inflammatory phenomena: An important question is how the inflammatory reaction pattern is generated around the individual hair follicle. Inflammation is regarded as a multistep process which may start from a primary event. The observation of a perifollicular infiltrate in the upper follicle near the infundibulum suggests that the primary causal event for the triggering of inflammation might occur near the infundibulum (Mahé et al., 2000). On the basis of this localization and the microbial colonization of the follicular infundibulum with *Propionibacterium* sp., *Staphylococcus* sp., *Malassezia* sp., or other members of the transient flora, one could speculate that microbial toxins or antigens could be involved in the generation of the inflammatory response. The production of porphyrins by *Propionibacterium* sp. in the pilosebaceous duct has also been considered to be a possible cofactor of this initial pro-inflammatory stress (Mahé et al., 2000). Alternatively, keratinocytes themselves may respond to chemical stress from irritants, pollutants, and UV irradiation, by producing radical oxygen species and nitric oxide, and by releasing intracellularly stored IL-1α. This pro-inflammatory cytokine by itself has been shown to inhibit the growth of isolated hair follicles in culture (Philpott et al., 1996). Moreover, adjacent keratinocytes, which express receptors for IL-1, start to engage the transcription of IL-1 responsive genes: mRNA coding for IL-1β, TNFα, and IL-1α, and for specific chemokine genes, such as IL-8, and monocyte chemoattractant protein-1 (MCP-1) and MCP-3, themselves mediators for the recruitment of neutrophils and macrophages, have been shown to be upregulated in the epithelial compartment of the human hair follicle (Mahé et al., 2000). Besides, adjacent fibroblasts are also fully equipped to respond to such a pro-inflammatory signal. The upregulation of adhesion molecules for blood-borne cells in the capillary endothelia, together with the chemokine gradient, drive the transendothelial migration of inflammatory cells, which include neutrophils through the action of IL-8, T cells and Langerhans cells at least in part through the action of MCP-1. After processing of localized antigen, Langerhans cells, or alternatively keratinocytes, which may also have antigen presenting capabilities, could then present antigen to newly infiltrating T lymphocytes and induce T-cell proliferation. The antigens are selectively destroyed by infiltrating macrophages, or natural killer cells.

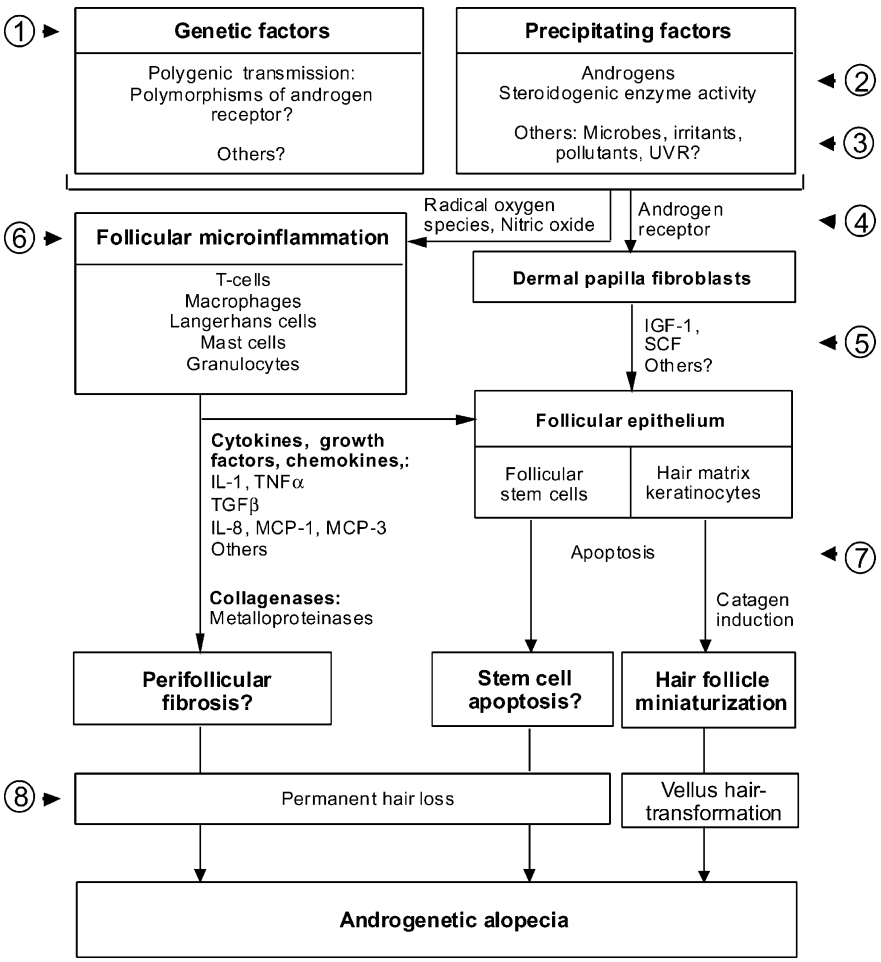
Perifollicular fibrosis: On the occasion that the causal agents persist, sustained inflammation is the result, together with connective tissue remodeling, where collagenases, such as matrix metalloproteinase (also transcriptionally driven by pro-inflammatory cytokines) play an active role (Mahé et al., 2000). Collagenases are suspected to contribute to the tissue changes in perifollicular fibrosis.

Permanent alopecia: Generally, permanent alopecia is the result of irreversible damage to the putative site of follicular stem cells in the 'bulge' area of the outer-root sheath in the superficial portion of the hair follicle (Lavker et al., 1993). In most of inflammatory scarring alopecias, e.g. *lichen planopilaris*, *lupus erythematosus*, and *pseudopelade (Brocq)*, the inflammation involves this area. In the recently described *fibrosing alopecia in a pattern distribution* (Zinkernagel and Trüeb, 2000), patients with AGA have additional clinical and histological features of inflammation and fibrosis limited to the area of androgenetic hair loss. A *lichen planopilaris*-type inflammation involving the bulge area presumably irreparably damages follicle stem cells. The preference of this site of the follicle for the immunologic attack may be related to the fact, that in contrast to the proximal hair follicle, the isthmus and infundibulum area do not bear any immune privilege (Paus, 1997).

5. Concluding remarks

Clinical and investigative advances have helped us to understand some of the pathogenic steps leading to androgenetic hair loss (Fig. 2). Besides androgens and genetic imbalance, additional pathogenic factors are suspected, such as microbial flora, endogenous and exogenous stress, microinflammation, and possibly others. While further suspects are likely to be exposed, individual diversity of causal agents, as well as of the sequence of events, or combined factors, must be kept in mind, when addressing the biological conditions contributing to AGA. The large number of therapeutic molecules currently claimed to be active and patented in this field and their limited efficacy in offering a definitive cure of AGA, confirm that the mechanism of AGA is highly complex.

Therapeutic challenges: The aim of therapy is to increase hair coverage of the scalp and to retard progression of hair thinning. Currently, two FDA approved drugs are available for this purpose, oral finasteride, at a dose of 1 mg per day, and topical solution of minoxidil (Price, 1999). Finasteride is a competitive inhibitor of type 2 5α-reductase and inhibits the conversion of testosterone to DHT. The rationale for the use of finasteride to treat AGA in men is based on the absence of AGA in men with congenital deficiency of type 2 5α-reductase, and the presence of increased 5α-reductase activity and DHT levels in balding scalp (Kaufman et al., 1998). Finasteride is contraindicated in women who are or may become pregnant, because 5α-reductase inhibitors may cause malformation of the external genitalia of male fetuses. Minoxidil promotes hair growth through increasing the duration of anagen. It causes hair follicles at rest to grow, and enlarges suboptimal follicles. While minoxidil was developed for treatment of hypertension, and this feature of the drug's action is best understood, its mechanism of action on hair growth is poorly understood. Minoxidil is a potassium-channel opener and vasodilatator, and has been reported to stimulate the production of VEGF in cultured dermal papilla cells (Lachgar et al., 1998). There is evidence that this effect is mediated by adenosine and sulfonylurea receptors, which are well-known target receptors for adenosine-triphosphate-sensitive potassium channel openers (Li et al., 2001). Topical solutions of 2 and 5 percent minoxidil are available for treatment of AGA in men and women. Unfortunately, the efficacy of minoxidil is variable and temporary, making it difficult to predict the success of treatment on an individual basis. Estrogens and antiandrogens are used in women with AGA, although no controlled studies have been done. When a combination of estrogen and a progestin is prescribed for oral contraception or hormonal replacement therapy in women with AGA, care should be taken to select a progestin with no androgenic, or preferably with antiandrogenic activity, e.g. cyproterone acetate. Women with this condition should also avoid androgens and their precursors, such as DHEA, since these may exacerbate hair loss (Price, 1999). So far, the inflammatory component has not been included in treatment protocols for AGA. Finally, it



Therapeutic strategies:

1. Gene therapy? (currently not available)
2. Modifiers of androgen metabolism: finasteride (available for men)
3. Antimicrobial shampoos?
4. Antiandrogens: cyproterone acetate (available for women)
5. Hair growth promoters: minoxidil (available for men and for women)
6. Antiinflammatory agents?
7. Apoptosis modulating agents? (currently not available)
8. Hair transplantation (available), implantation of dermal papilla cells or cells of follicle dermal-sheath (impending)

Fig. 2. Androgenetic alopecia: pathogenic mechanisms and therapeutic strategies.

has been proposed that gene therapy may offer yet another approach on condition that the genes responsible for alopecia are identified (Paus and Cotsarelis, 1999). Given the accessibility of the hair follicle and the availability of liposomal preparations that selectively target the follicle, the topical introduction of genes seems feasible (Li and Hoffman, 1995), though the large amounts of genetic material and the need to re-apply the agent at intervals on a continued basis would make commercial use very expensive and impractical (Sawaya and Shapiro, 2000).

References

Ellis, J.A., Stebbing, M., Harrap, S.B., 1998. Genetic analysis of male pattern baldness and the 5alpha-reductase genes. J. Invest. Dermatol. 110, 849–853.

Ellis, J.A., Stebbing, M., Harrap, S.B., 2001. Polymorphism of the androgen receptor gene is associated with male pattern baldness. J. Invest. Dermatol. 116, 452–455.

Gottlieb, B., Lehvaslaiho, H., Beitel, L.K., Lumbroso, R., Pinsky, L., Trifiro, M., 1998. The androgen receptor gene mutations database. Nucleic Acids Res. 26, 234–238.

Hibberts, N.A., Messenger, A.G., Randall, V.A., 1996. Dermal papilla cells derived from beard hair follicles secrete more stem cell factor (SCF) in culture than scalp cells or dermal fibroblasts. Biochem. Biophys. Res. Commun. 222, 401–405.

Hodgins, M.B., Murad, S., Simpson, N.B., 1985. A search for variation in hair follicle androgen metabolism which might be linked to male pattern baldness (abstract). Br. J. Dermatol. 113, 794.

Hoffmann, R., Happle, R., 2000. Current understanding of androgenetic alopecia. Part I: etiopathogenesis. Eur. J. Dermatol. 10, 319–326.

Imperato-McGinley, J., Guerrero, L., Gautier, T., Peterson, R.E., 1974. Steroid 5α-reductase deficiency in man: an inherited form of male pseudohermaphroditism. Science 186, 1213–1215.

Itami, S., Kurata, S., Takayasu, S., 1995. Androgen induction of follicular epithelial cell growth is mediated via insulin-like growth factor I from dermal papilla cells. Biochem. Biophys. Res. Commun. 212, 988–994.

Jahoda, C.A., Horne, K.A., Oliver, R.F., 1984. Induction of hair growth by implantation of cultured dermal papilla cells. Nature 311, 560–562.

Jaworsky, C., Kligman, A.M., Murphy, G.F., 1992. Characterisation of inflammatory infiltrates in male pattern alopecia: implication for pathogenesis. Br. J. Dermatol. 127, 239–246.

Kaufman, K.D., 1996. Androgen metabolism as it affects hair growth in androgenetic alopecia. Dermatol. Clin. 14, 697–711.

Kaufman, K.D., Olsen, E.A., Whiting, D., Savin, R., DeVillez, R., Bergfeld, W., Price, V.H., Van Neste, D., Roberts, J.L., Hordinsky, M., Shapiro, J., Binkowitz, B., Gormley, G.J., 1998. Finasteride in the treatment of men with androgenetic alopecia. Finasteride male pattern hair losss study group. J. Am. Acad. Dermatol. 39, 578–589.

Lachgar, S., Charveron, M., Gall, Y., Bonafe, J.L., 1998. Minoxidil upregulates the expression of vascular endothelial growth factor in human hair dermal papilla cells. Br. J. Dermatol. 138, 407–411.

Lavker, R.M., Miller, S., Wilson, C., Cotsarelis, G., Wei, Z.G., Yang, J.S., Sun, T.T., 1993. Hair follicle stem cells: their location, role in hair cycle, and involvement in skin tumor formation. J. Invest. Dermatol. 101, 16S–26S.

Li, L., Hoffman, R.M., 1995. The feasibility of targeted selective gene therapy of the hair follicle. Nat. Med. 1, 705–706.

Li, M., Marubayashi, A., Nakaya, Y., Fukui, K., Arase, S., 2001. Minoxidil-induced hair growth is mediated by adenosine in cultured dermal papilla cells: possible involvement of sulfonylurea receptor 2B as a target of minoxidil. J. Invest. Dermatol. 117, 1594–1600.

Mahé, Y.F., Michelet, J.F., Billoni, N., Jarrousse, F., Buan, B., Commo, S., Seint-Leger, D., Bernard, B.A., 2000. Androgenetic alopecia and microinflammation. Int. J. Dermatol. 39, 576–584.

Norwood, O.T., 1975. Male-pattern baldness. Classification and incidence. South Med. J. 68, 1359–1370.

Norwood, O.T., 2001. Incidence of female androgenetic alopecia (female pattern alopecia). Dermatol. Surg. 27, 53–54.

Orme, S., Cullen, D.R., Messenger, A.G., 1999. Diffuse female hair loss: are androgens necessary? Br. J. Dermatol. 141, 521–523.

Paus, R., 1996. Control of the hair cycle and hair diseases as cycling disorders. Curr. Opin. Dermatol. 3, 248–258.

Paus, R., 1997. Immunology of the hair follicle. In: Bos, J.D., (Ed.), Skin Immune System. Cutaneous Immunology and Clinical Immunodermatology, CRC Press, Boca Raton.

Paus, R., Cotsarelis, G., 1999. The biology of hair follicles. N. Engl. J. Med. 341, 491–497.

Paus, R., Müller-Röver, S., Botchkarev, V.A., 1999. Chronobiology of the hair follicle: hunting the 'hair cycle clock'. J. Invest. Dermatol. Symp. Proc. 4, 338–345.

Philpott, M.P., Sander, D.A., Bowen, J., Kealey, T., 1996. Effects of interleukins, colony stimulating factor and tumour necrosis factor on human hair follicle growth in vitro: a possible role for interleukin-1 and tumour necrosis factor-α in alopecia areata. Br. J. Dermatol. 135, 942–948.

Pierard-Franchimont, C., Pierard, G.E., 2001. Teloptosis, a turning point in hair shedding biorhythms. Dermatology 203, 115–117.

Price, V.H., 1999. Treatment of hair loss. N. Engl. J. Med. 341, 964–973.

Quigley, C.A., 1998. The androgen receptor: physiology and pathophysiology. In: Nieschlag, E., Behre, H.M. (Eds.), Testosterone: Action, Deficiency, Substitution, Springer, Berlin, pp. 33–106.

Randall, V.A., Thornton, M.J., Messenger, A.G., 1992. Cultured dermal papilla cells from androgen-dependent human hair follicles (e.g. beard) contain more androgen receptors than those from non-balding areas of the scalp. J. Endocrinol. 133, 141–147.

Reynolds, A.J., Lawrence, C., Cserhalmi-Friedman, P.B., Christiano, A.M., Jahoda, C.A., 1999. Trans-gender induction of hair follicles. Human follicle cells can be inducted to grow in an incompatible host of the other sex. Nature 402, 33–34.

Sawaya, M.E., Honig, L.S., Garland, L.D., Hsia, S.L., 1988. Delta 5-3 beta-hydroxysteroid dehydrogenase activity in sebaceous glands of scalp in male-pattern baldness. J. Invest. Dermatol. 91, 101–105.

Sawaya, M.E., Price, V.H., 1997. Different levels of 5alpha-reductase type I and II, aromatase, and androgen receptor in hair follicles of women and men with androgenetic alopecia. J. Invest. Dermatol. 109, 296–300.

Sawaya, M.E., Shapiro, J., 2000. Androgenetic alopecia. New approved and unapproved treatments. Dermatol. Clin. 18, 47–61.

Stenn, K.S., Combates, N.J., Eilertsen, K.H., Gordon, J.S., Pardinas, J.R., Parimoo, S., Prouty, S.M., 1996. Hair follicle growth controls. Dermatol. Clin. 14, 543–558.

Takashima, I., Adachi, K., Montagna, W., 1970. Studies of common baldness in the stumptailed macaque IV. In vitro metabolism of testosterone in the hair follicles. J. Invest. Dermatol. 55, 329–334.

Trüeb, R.M., Meyer, J.C., 2000. Male-pattern baldness in men with X-linked recessive ichthyosis. Dermatology 200, 247–249.

Whiting, D.A., 1993. Diagnostic and predictive value of horizontal sections of scalp biopsy specimens in male pattern androgenetic alopecia. J. Am. Acad. Dermatol. 28, 755–763.

Zinkernagel, M.S., Trüeb, R.M., 2000. Fibrosing alopecia in a pattern distribution. Patterned *lichen planopilaris* or androgenetic alopecia with a lichenoid tissue reaction pattern? Arch. Dermatol. 136, 205–211.