Molecular Basis of Androgenetic Alopecia

2

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Core Messages

- Androgenetic alopecia is a common, progressive, patterned loss of visible scalp hair.
- It causes psychological distress and negative effects on the quality of life.
- Adult levels of circulating androgens and functional intracellular receptors are essential prerequisites for the balding processes.
- Metabolism of circulating androgens, such as testosterone, to the more potent androgen, 5α-dihydrotestosterone, also appears necessary. This also acts via the androgen receptor.
- The current model for androgen action in the hair follicle focusses on the mesenchyme-derived, regulatory dermal papilla at the base of the follicle. This responds to the circulating hormones and coordinates the rest of the follicular cells by altering the paracrine signals it produces. These may be soluble growth factors or extracellular matrix components.
- There is also a strong genetic aspect to the incidence of androgenetic alopecia.
- Since the response to androgens occurs within the follicle, it can differ. Androgen responses vary from stimulation (e.g. beard), no effect (e.g. eyelashes) to inhibition on areas of the scalp (androgenetic alopecia). This paradoxical difference underpins the successful transplant of unaffected follicles from non-balding regions into the androgen-sensitive, balding areas during corrective surgery for androgenetic alopecia.

2.1 Introduction

Androgenetic alopecia, the most common form of hair loss in men, involves the progressive loss of visible, pigmented terminal hair on the scalp, in response to circulating androgens. It may also occur in women. Other names include: male pattern baldness, common baldness, male pattern alopecia, androgen-dependent alopecia, androgenetic alopecia or simply "balding". There are several other causes of hair loss such as the patchy baldness of the scalp and/or body of alopecia areata, generally believed to be an autoimmune disease [24]. These fall outside the scope of this book, but have been described elsewhere [10, 24, 94].

2.1.1 Patterns of Hair Loss

2.1.1.1 In Men

In men with androgenetic alopecia, the gradual replacement of long, pigmented, terminal hairs on the scalp

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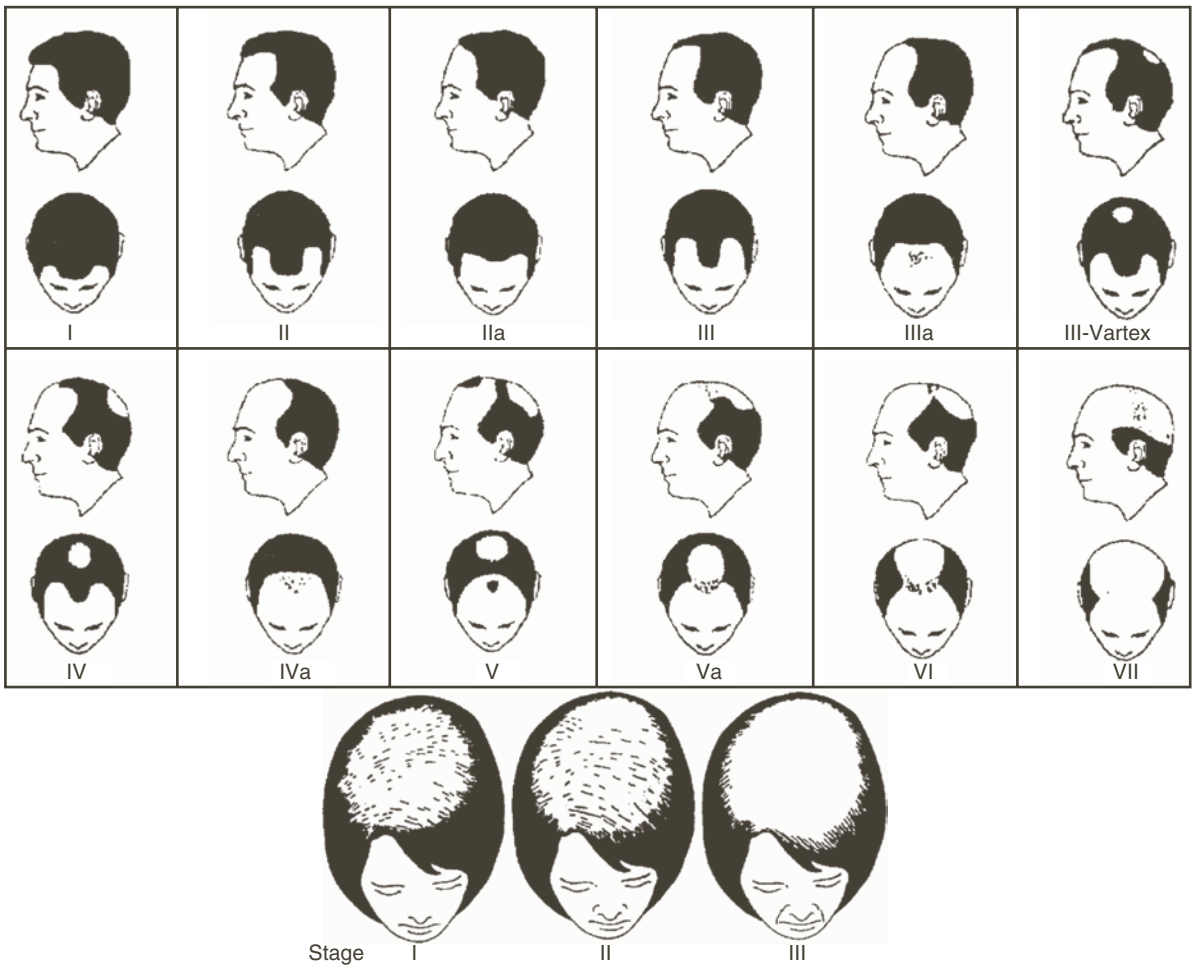

Fig. 2.1 Patterns of hair loss in androgenetic alopecia in men (*upper diagram*) and women (*lower diagram*). Androgens cause a gradual inhibition of hair growth on the scalp in genetically pre-disposed individuals. This is much more common in men than in women, and the pattern of the hair loss in men differs from women. In men, the first signs are generally temporal regression, which spreads backwards and joins thinning regions on the vertex to give a bald crown. In women, the front hairline is normally retained, and a general thinning on the vertex gradually becomes more pronounced until the vertex becomes bald (after Hamilton [4] and Ludwig [67])

by short, pale, *vellus* hairs normally occurs in a relatively precise pattern (Fig. 2.1). Hamilton graded this progression from type 1, pre-pubertal scalp with terminal hair on the forehead and all over the scalp, through gradual regression of the frontal hairline and thinning on the vertex, to type VII where the bald areas became fully coalesced to leave hair only around the back and sides of the head [51]. Norwood modified Hamilton's classification, including variations for the middle grades (see Fig. 2.1); this scale is used extensively during clinical trials [89].

2.1.1.2 In Women

Androgenetic alopecia is also reported in women, although androgen involvement is less established. Hamilton found post-pubertal recession to type II was common in Caucasian women with approximately 25% exhibiting the type IV pattern by age 50, although this did not develop further [51]. Although women can exhibit the "male" pattern, they usually show a different Ludwig pattern involving a progressive diffuse loss of hair from the crown while retaining the frontal hair line

(see Fig. 2.1) [80]. Venning and Dawber [137] found that 80% of pre-menopausal women had thinning in Ludwig stages I–III, while 13% had Hamilton types II–IV [7]; post-menopausally 37% exhibited the "male" pattern with some showing marked templar M-shaped recession, although not progressing beyond Hamilton stage IV.

2.1.2 Incidence

Although there are no precise statistics, the incidence in Caucasians is often quoted as approaching 100% [24]; others suggest that about half of men and women above 40 exhibit androgenetic alopecia [93]. There is a marked variation in other races, which often show much less balding. Most Chinese retain the pre-pubertal hairline after puberty, and baldness is less common, less extensive and starts later [51]. Japanese men also show a lower incidence, beginning balding about 10 years later than Caucasians [130]. Four times as many African-Americans also retain a full head of hair than Caucasians [121]. The reason for this racial variation is unclear, but is probably genetic because differences appear to be retained regardless of location.

2.1.3 Significance of Androgenetic Alopecia

Androgenetic alopecia is also seen in other primates, including the orangutan, chimpanzee and stump-tailed macaque [135]. This suggests a natural progression of a secondary sexual characteristic rather than a disease. In the past, when many men died young, marked androgenetic alopecia would have distinguished the surviving older male as a leader, like the silver-backed older male gorilla and larger antlers on older deer. Others have speculated that the bald patch of an angry older dominant male would flush and look very aggressive [43] or help in fighting because there was less hair to pull [28]. Whatever the potential benefit, the reduced incidence of baldness in African men [121] suggests evolutionary pressure to retain scalp hair for protection from strong sunlight.

Although androgenetic alopecia is common and neither life-threatening nor painful, it is a distressing disorder; Egyptian men's anxieties were recorded 4,000 years ago [40]! This reflects the important, although often underappreciated, roles of hair in human social and sexual communication, whatever the genetic background or culture. For example, the ritual head shaving of Christian and Buddhist monks and the short soldier haircuts are all designed to reduce individuality; these contrast with the religiously un-cut hair of Sikhs. In the youth-orientated culture of the industrialised nations, balding's association with ageing has very negative connotations and androgenetic alopecia often causes marked psychological distress and reduction in the quality of life in men [12, 36, 42, 81, 131, 139] and women [13, 136]. Patients report poor self-image, feelings of being older and loss of self-confidence. Similarly, other people report men with visible hair loss as older, less attractive, weaker and duller. Importantly, the same results were obtained in those who had never sought treatment [42]. Whatever may be its original biological role, androgenetic alopecia reduces the quality of life in the current industrialised world.

2.2 Changes During Androgenetic Alopecia

2.2.1 Altering the Type of Hair Produced Via the Hair Follicle Growth Cycle

The progressive loss of visible hair during patterned balding results from the gradual transformation of terminal follicles, producing the long, thick, pigmented hairs of youth, to smaller vellus follicles forming short, colourless, virtually invisible vellus hairs. This is a major change in cell biological terms; follicles possess a unique mechanism, the hair follicle growth cycle, which allows these changes [27, 73]. Each follicle normally undergoes a continual series of active, growing phases called *anagen*, alternating with periods of rest or *telogen*; these are separated at the end of anagen by a brief regression or *catagen* phase [27, 73] (see Fig. 2.2). This involves the destruction of the original lower follicle, and its total regeneration to form another follicle that can produce a totally new hair. The original hair is lost via active shedding called exogen [128]. In this way, the post-natal hair follicle appears to retain the ability to recapitulate the later stages of follicular embryogenesis throughout life.

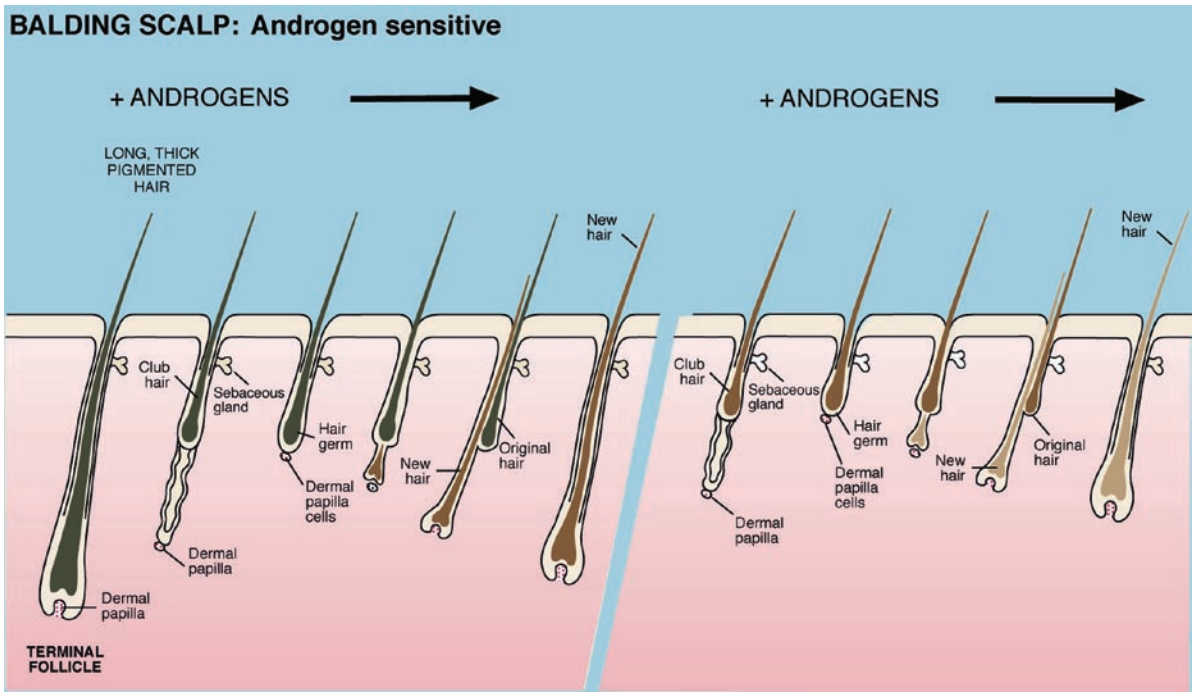

Fig. 2.2 Diagram representing the miniaturisation processes occurring in response to androgens in the scalp of a person with a genetic pre-disposition to androgenetic alopecia. Androgens inhibit scalp hair follicles in balding regions by inducing them to produce progressively smaller, finer and less pigmented hairs, until the terminal hairs of childhood and early adulthood are replaced by the vellus hairs of androgenetic alopecia and the area appears bald. Follicles themselves become shorter and finer, but must pass through a full hair cycle, probably a succession of cycles, to accomplish major changes. The white gap between the two parts of the diagram represents a space for at least one other cycle between the two shown to accommodate these changes in size

Many follicles will produce a new hair that is similar to the previous one, but the hair may differ in colour or size. It is unclear how much a hair can alter in size from the previous one, because many changes take place over several years e.g. developing a full beard [52]. The miniaturisation processes of androgenetic alopecia occur over many years with hair follicles reducing in size and depth in the skin and producing smaller and paler hairs (Fig. 2.2) [30, 119]. The type of hair produced by a follicle, particularly its length, depends greatly on the length of anagen. For example, long scalp hairs are produced by follicles with growing periods of more than 3 years [73, 119], whereas on the finger anagen may be only 1.5–3 months [119]. The cell biology and biochemistry of the local interactions involved in the control processes of the hair cycle are complex and not yet fully understood, but the size and length of the hair is controlled by the mesenchyme-derived dermal papilla situated at the base of the mainly epithelial hair follicle (see Fig. 2.2) [68, 92].

2.2.2 The Miniaturisation Processes

Scalp follicles pass through several cycles before the processes are complete (Fig. 2.2). Normally, scalp hair follicles are mainly in anagen; the average anagen of 2–3 years and telogen of approximately 100 days [73] gives an anagen-to-telogen ratio of about 9:1, although there is some seasonal variation in people living in temperate regions (see Sect. 2.3.1) [108]. While androgenetic alopecia develops, anagen shortens, increasing the proportion of telogen hairs [7, 97, 118, 140] which is detectable before any balding; it also results in shorter hairs. Follicle miniaturisation can be seen histologically [7, 74], indicating the hairs are also thinner [74, 118]. When scalp appears bald, most of the follicles are very short and small, with occasional resting terminal hairs.

Studies of androgenetic alopecia are complicated by senescent balding, the non-androgen-dependent hair thinning found in those more than 50 [28]. This also involves a progressive decrease in anagen follicles

[100] and hair diameter [28], but does not normally lead to baldness. Kligman suggested that both forms may occur together, proposing a pronounced inflammatory component in androgenetic alopecia, not seen in senescent baldness [74]. Recent observations have confirmed peri-follicular inflammation [30]. The sclerotic remains of the fibrous sheath are seen below the shortened follicles as "streamers" [74]; damage to the dermal sheath by chronic inflammation may prevent the reformation of terminal hair follicles in long-term alopecia, although this is debated.

During the miniaturisation processes of androgenetic alopecia, the follicle's associated arrector pili muscle reduces much more slowly than the follicle [82], while the androgen-dependent sebaceous gland becomes enlarged [74], often resulting in an oily, greasy scalp. Other changes include a reduced follicular blood supply [20, 111] and nerve networks twisting to form a type of encapsulated end organ below the follicle [41].

2.3 The Pathogenesis of Androgenetic Alopecia

Hair follicles are under hormonal regulation because of the importance of coordinating alterations in insulation properties and colour of an animal's coat to the environment [29, 107], and changes in the social and sexual communication aspects to the appropriate stage in the life cycle. In mammals, seasonal changes are coordinated to day length and, somewhat less, to temperature in the same way as seasonal breeding. Changes are translated to the follicle via the pineal and hypothalamus-pituitary route, involving gonadal, thyroid and corticosteroid hormones [29, 107].

2.3.1 Seasonal Changes in Human Hair Growth

Regular circannual changes in human hair growth were only fully recognised comparatively recently [19, 108]. In white Englishmen with indoor occupations, androgen-dependent beard and thigh hair growth increase significantly in the summer [108] and are lowest in January and February. This may reflect changes in circulating androgen levels, because these rise in European men in the summer [115, 125]. Scalp hair shows a single annual cycle with more than 90% of hairs growing in the spring, falling to about 80% in the autumn, paralleled by increased numbers of hairs being shed per day, which more than doubled [108]. Which hormones regulate this is unclear. As most people's scalp follicles will be in anagen for at least 2–3 years, such a marked seasonal effect is quite remarkable. Nevertheless, this effect has a major significance, as any new drug or treatment should be studied for at least a year to separate any effects from normal seasonal variations.

2.3.2 Paradoxical Effects of Androgens on Human Hair Growth

Androgens are the main regulator of human hair growth, although other hormones, including those of pregnancy, prolactin, melanocyte-stimulating hormone (MSH) and thyroid hormones, have effects in man and other species [105, 107]. One of the first signs of puberty is the gradual replacement of tiny vellus hairs with larger, more pigmented *intermediate* hairs in the pubis and later in the axillae [83, 84]; eventually, larger and darker terminal hairs are produced. These changes parallel the pubertal rise in plasma androgens that occurs earlier in girls than in boys [143, 144]. Similar changes occur in many areas in young men producing the beard, an extended pubic diamond, chest hair and greater hair on the limbs, which readily distinguish the mature adult man. These changes are gradual and often progress over many years. Beard growth increases rapidly during puberty, but continues to rise until the man is in his mid-30s [52], while terminal hair on the chest or ear canal may appear only years after puberty [50].

In marked contrast, androgens have no obvious effect on many follicles that produce terminal hairs in childhood, such as the eyelashes or many scalp follicles. Paradoxically, in individuals with a genetic pre-disposition, androgens promote the gradual transformation of large terminal scalp follicles to tiny vellus ones causing androgenetic alopecia [49, 51, 53]. Apart from the role of androgens, the precise mechanisms of these responses within the hair follicle are not well understood, although it is clear that the responses are intrinsic to the individual

follicle and dependent on body site. Not only do follicle responses range from stimulation to inhibition, but sensitivity to the androgens also varies within clearly defined patterns. Facial hair develops first above the mouth and centre of the chin in both young men and hirsute women, and regression in androgenetic alopecia occurs in a progressive manner, despite all follicles receiving the same circulating hormones [51]. Similarly, female circulating androgen levels are high enough to produce axillary and the female terminal pubic hair, but male patterns of body hair require normal male levels [4, 19, 49, 53, 58, 83, 84, 105, 115, 125, 143, 144]. Thus, androgens appear to promote and amplify an individual follicle's genetic programming. This end-organ response is the basis for hair transplant surgery [98]; when "non-balding" regions of the scalp are transplanted to the balding vertex, they retain their innate lack of androgen response and maintain terminal follicles, while miniaturisation progresses in the vertex follicles behind them.

2.3.3 Essential Requirement for Androgens

Androgens are essential for the development of androgenetic alopecia. It does not occur in men who have never entered puberty; men castrated after puberty show no further progression of their baldness, although they do not regain the frontal hairline, and testosterone replacements stimulate progressive balding, which halts during temporary withdrawal of the anagen [49, 52, 53].

Androgens, like other steroid hormones, pass through the plasma membrane and bind to specific intracellular proteins, inactive androgen receptors. This activates the receptors causing shape changes, which enable them to bind to specific hormone-responsive elements (HREs) in the DNA, often in association with other co-activating proteins, to initiate the translation of specific androgen-regulated genes and synthesis of their proteins (see Fig. 2.3, upper diagram).The essential role of androgens is confirmed by the absence of any post-pubertal changes in body or scalp hair growth in men without functional androgen receptors (i.e. with androgen insensitivity syndrome) [85]. Individuals with the complete form exhibit no pubic, axillary, chest or beard terminal hair and do not develop androgenetic alopecia.

Although testosterone is the main circulating androgen in men, in many tissues, it is metabolised intracellularly to the more potent androgen, 5α-dihydrotestosterone, by the enzyme 5α-reductase [17]. Both testosterone and 5α-dihydrotestosterone can activate the androgen receptor to alter the expression of androgen-sensitive genes. There are also various weaker androgens in the circulation, particularly in women, which can be metabolised to more active androgens such as testosterone and 5α-dihydrotestosterone (see Fig. 2.3). Deficiencies in 5α-reductase also reduce androgen effects on some hair follicles. Although all hair follicles require intracellular androgen receptors to respond to androgens, the necessity for 5α-reductase activity to produce intracellular 5α-dihydrotestosterone for the androgen response varies [54]. Individuals with 5α-reductase type 2 deficiency do not develop male patterns of body hair growth, despite their circulating androgens; they produce only female patterns of pubic and axillary hair, although their body shape masculinises [142]. They appear not to exhibit male pattern baldness, but this is more difficult to interpret; however, the re-growth of hair in young balding men given the 5α-reductase type 2 inhibitor, finasteride, strongly supports the role of both androgens and 5α-reductase in androgenetic alopecia [69].

Despite the widely held belief that baldness is an indicator of increased male sexuality, there is little scientific evidence for this other than the clear link with normal androgen parameters. There was no relationship between androgenetic alopecia and other androgen-regulated parameters, including muscle, bone, sebum excretion rate or body hair growth in adult men [9]. Normal male testosterone levels have been reported in balding men [101, 103] with higher urinary dehydroepiandrosterone [101] or dehydroepiandrosterone sulphate [113]; other studies showed raised serum-free testosterone, i.e. that are not bound to sex hormone-binding globulin [16, 26]. Overall, normal male androgen levels appear to be sufficient to produce androgenetic alopecia; the response obtained appears related to the intrinsic follicular response. In women, raised circulating androgens, particularly free androgens, appear to be related to hair loss, although the means from studies are often within the normal ranges for pre-menopausal women [8, 14, 25, 39, 79, 88, 129]. Women who present with androgenetic alopecia also often exhibit polycystic ovarian disease and hirsutism [14, 38, 91], even if presenting with alopecia without menstrual abnormalities [14]. Therefore, androgenetic alopecia requires circulating androgens, androgen receptors and intracellular 5α-reductase type 2.

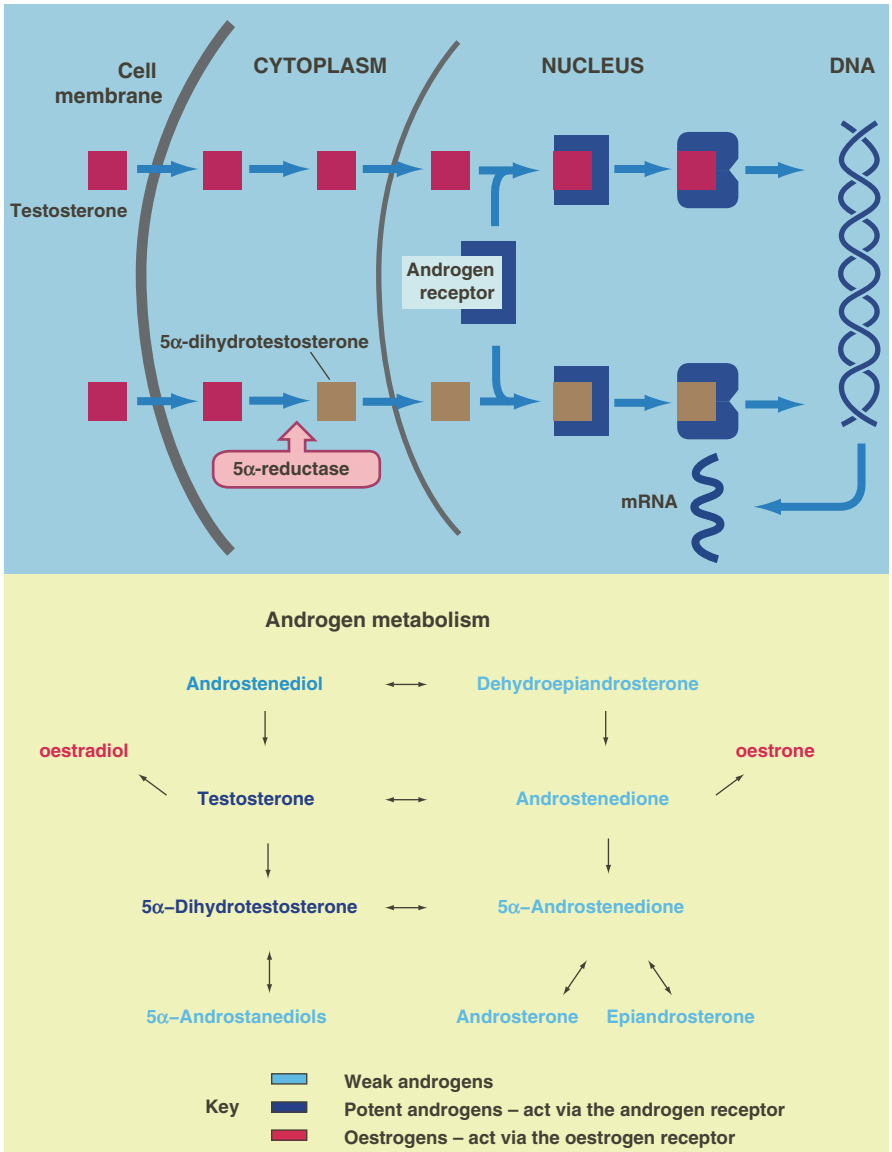

Fig. 2.3 The mechanism of action of androgens. *Upper diagram* – simple schematic of the general mechanism of androgen action. Androgens diffuse from the blood through the plasma membrane. Inside the cell, like other steroid hormones, testosterone may bind to specific androgen receptors. This occurs in many tissues such as skeletal muscle and axillary and pubic hair follicles. However, in certain tissues, particularly the secondary sexual organs such as prostate or beard and balding hair follicles, testosterone is metabolised to the more potent androgen, 5α-dihydrotestosterone (see *lower diagram*). If both are available in similar quantities, the receptor will bind 5α-dihydrotestosterone. Once hormone has bound, the receptor complex undergoes a conformational change exposing DNA-binding sites and the hormone-receptor complex, in conjunction with other co-activating proteins, will bind to specific hormone response elements (HREs) in the DNA altering the expression of specific androgen-dependent genes. *Lower diagram* – androgen metabolism. Circulating androgens such as testosterone from the testis in men and weaker androgens such as dehydroepiandrosterone and androstenedione from the adrenals and ovaries in women can be metabolised in many skin tissues. Some metabolism causes an increase in potency, e.g. from testosterone to 5α-dihydrotestosterone (DHT) as the androgen receptor binds DHT more strongly even than testosterone, another potent androgen. Other metabolisms form weaker androgens normally involved in excretion pathways, e.g. the androstanediols or steroids which act via the other steroid receptors i.e. the oestrogens

2.3.4 Genetic Influences

2.3.4.1 Incidence

The genetic involvement in androgenetic alopecia is also pronounced. It runs in families, and there are racial differences (see Sect. 2.1.2), while androgen replacement only stimulated balding in castrated men with a family history [49]. Although androgenetic alopecia has generally been accepted as an autosomal dominant trait with variable penetrance [5], this is based on a familial analysis in 1916 [99], and a more complex, polygenic inheritance is more likely [32, 76]. Interestingly, a very strong correlation in incidence was found in 54 sets of sons and fathers, with 81.5% of balding sons having balding fathers (Hamilton-Norwood scale III or higher) [32, 76]. This is greater than expected from an autosomal dominant inheritance and could implicate a paternally inherited gene, e.g. on the Y chromosome or the involvement of a gene that is capable of being paternally imprinted (i.e. preferentially inactivated by methylation of DNA, etc.).

2.3.4.2 Investigation of Specific Genes

Several genes have been investigated for association with androgenetic alopecia. No association was detected with neutral polymorphic markers for either type 1 (SRD5A1) or type 2 (SRD5A2) 5α-reductase genes in case–control association studies of Australian [32] or Korean (Asian) men [45]. A later study did find an association with a mutant allele (A49T) of type 2 5α-reductase, but this decreased the incidence of alopecia, although increasing that of prostate cancer [55]! Known dimorphic and polymorphic markers within the androgen receptor gene are more linked to balding in Caucasian men [34]. The *Stu* I restriction fragment length polymorphism (RFLP) in exon 1 was present in 98% of 54 young balding men and 92% of 392 older balding men but was also found in 77% of their older, non-balding controls. Analysis of triplet repeat polymorphisms, CAG and GAC revealed significantly higher incidence of short/short polymorphic CAG/GGC haplotypes in balding subjects and lower short/long, although no significance was provided. Interestingly, shorter triplet repeat lengths are associated with precocious puberty, i.e. appearance of pubic hair before eight [63] and androgen-dependent prostate cancer [127]. Whether this has functional significance, such as increased androgen sensitivity, or simply reflects linkage disequilibrium with a causative mutation is not clear. However, when the binding capacity for a range of steroids was compared between androgen receptors from balding and non-balding follicle dermal papilla cells, no differences were detected [58], and no link was seen with increased copy number variations of the androgen receptor gene [17].

Recently, genetic variability in a 1 Mb region within and centromeric to the androgen receptor gene was found to be associated with androgenetic alopecia [60] and strongest risk when associated with a variant in the flanking ectodysplasin A2 receptor gene (EDA2R) [61]. Links with a locus on chromosome 20 (20 pll) have also been reported in several populations [60, 117]. Other genes have also been implicated, including a link to one allele of the steroid metabolism gene, CYP17, to both women with polycystic ovaries and their brothers with early onset androgenetic alopecia [11]. An interesting connection is severe, early onset androgenetic alopecia in men with the x-linked gene for adrenoleukodystrophy who tend to have low testosterone levels [75]. The gene for *hairless*, which results in a complete loss of hair [1], also showed a marginally significant correlation with androgenetic alopecia with two mutations, but these became insignificant after correction for multiple testing [59]. The situation is still not fully clear at the moment, but moving forward rapidly.

2.4 Current Model for Androgen Action in the Hair Follicle

The mesenchyme-derived dermal papilla plays an important regulatory role in the follicle, determining the type of hair produced [68, 92]. Since hair follicles appear to partially recapitulate embryogenesis during the hair cycle (Fig. 2.2, Sect. 2.2.1) and steroids act via the mesenchyme in many developing steroid-dependent tissues [22], the author proposed that androgens would act on the other components of the follicle via the dermal papilla [105, 109]. In this hypothesis (Fig. 2.4), circulating androgens enter the dermal papilla via its own blood capillaries, binding to androgen receptors within the dermal papilla cells of androgen-dependent hair follicles [108, 106, 109]. Whether or not they are first metabolised intracellularly to 5α-dihydrotestosterone depends on the site of the follicle;

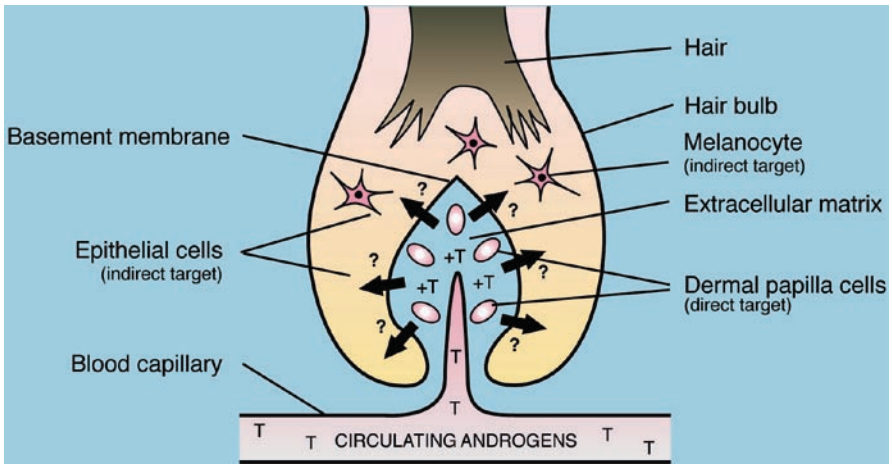

Fig. 2.4 Model of androgen action in the hair follicle. In the current hypothesis, androgens from the blood enter the hair follicle via the dermal papilla's blood supply. If appropriate, they are metabolised to 5α-dihydrotestosterone (see Fig. 2.3). They bind to androgen receptors in the dermal papilla cells causing changes in their production of regulatory paracrine factors; these then alter the activity of dermal papilla cells, follicular keratinocytes and melanocytes. *T* testosterone; *question mark* unknown paracrine factors. Reproduced from Randall [132]

for example, beard and balding-scalp follicle cells would first metabolise testosterone with 5α-reductase type 2, but axillary and pubic cells would not (Fig. 2.3). After androgens bind their receptors, the gene expression of the dermal papilla cells is altered so that they change their production of regulatory factors such as soluble growth factors or extracellular matrix proteins [105, 109]. Targets include the keratinocytes and melanocytes (pigment producing cells) and also the cells of the follicular connective tissue sheath, the dermal vasculature, and even dermal papilla cells themselves because all these would be altered in the formation of a differently sized or coloured hair; beard and scalp dermal papilla cells do produce autocrine stimulatory factors [47, 133]. Therefore, the direct androgen target cells would be the dermal papilla cells, and the other follicular components would be indirectly controlled by androgens. This seems a realistic model because androgens have such widely differing effects on follicles in different body sites, including whether or not 5α-reductase type 2 is necessary for stimulation of hair growth. It would be difficult for the follicle to be so well controlled if each follicular target cell had to respond to androgens directly.

This hypothesis has now received much experimental support. Androgen receptors are localised to the dermal papilla, but not keratinocyte cells by immunohistochemistry [15, 67] and cultured dermal papilla cells derived from androgen-sensitive beard and balding scalp follicles contain specific, saturable androgen receptors [2, 58, 110]. Important corroboration also comes from studies of androgen metabolism by cultured dermal papilla cells, because this reflects hair growth in 5α-reductase deficiency; beard cells produce 5α-dihydrotestosterone and express genes 5α-reductase type 2 [2, 65, 132] but pubic cells do not [48], corresponding to the presence of pubic but not beard hair in patients.

Although the key role of the dermal papilla in the induction of hair follicles and the regulation of the type of hair produced is well established [68], the lower part of the connective tissue sheath, or dermal sheath, which surrounds the hair follicle and isolates it from the dermis, has also been shown to form a new dermal papilla and human hair follicle development [116]. Cultured beard dermal sheath cells contain similar levels of androgen receptors to beard dermal papilla cells [86], and balding scalp dermal sheath expresses the mRNA for 5α-reductase type 2 like the dermal papilla [3]. Dermal sheath cells may respond directly to androgens to facilitate change in size of the sheath, or even the dermal papilla, in the development of a new anagen follicle; this would enable the new follicle to be larger or smaller depending on the follicle's androgen response. These results merit a modification of the model to include a direct action of androgens on the lower dermal sheath too.

Since the production of paracrine regulators by the dermal papilla is so important for normal follicle functions and androgen regulation (Fig. 2.4), it has been

investigated by several groups. Cultured dermal papilla cells retain hair growth-promoting ability [68] and secrete both extracellular matrix factors and soluble, proteinaceous growth factors [109]. Bioassays demonstrate that human cultured dermal papilla cells can secrete soluble, proteinaceous factors that promote growth in other dermal papilla cells [109, 132], outer root sheath cells [66] and transformed epidermal keratinocytes [56]. Importantly, testosterone in vitro alters the mitogenic capacity in line with its effect on hair growth in vivo. Testosterone stimulated beard, but not scalp, cells to increase their growth-promoting effects for beard dermal papilla cells [132], outer root sheath cells [66] and keratinocytes [56], while decreasing the capability of androgenetic alopecia scalp dermal papilla cells both from men [56] and the stump-tailed macaque [90]. Research is currently focussed on identifying androgen-regulated factors (reviewed [111]); androgens in vitro increase IGF-1 production by androgen-dependent beard cells [66] while stem cell factor (SCF) is produced in higher amounts by beard cells than control, non-balding scalp cells [57] and less by balding cells [114], presumably in response to androgens in vivo. Because SCF is the ligand for the cell surface receptor, c-kit, found on human follicular melanocytes, this may play a role in androgen-potentiated changes in hair pigmentation. In androgenetic alopecia where the hairs are paler than normal scalp hairs, the concentration of melanocytes per unit area of the hair bulb is the same in the paler, intermediate hair follicles of balding areas as in normal scalp follicles and they retain the same levels of the c-kit receptor protein. The only difference detected was the reduced SCF production by balding dermal papilla cells [114].

The expression of mRNA for the protease nexin-1 in dermal papilla cells is also altered by androgens [126]. This may play a role by altering the amount of extracellular matrix components produced [112] and therefore the size of the follicle and hair [6, 31]. Recently, dermal papilla cell conditioned media from balding scalp follicles has been shown to inhibit the growth of both human and rodent whisker dermal papilla cells in vitro and delay mouse hair growth in vivo [46], suggesting the active secretion of an inhibitory factor or factors. A possible candidate is transforming growth factor-β1 (TGF-β1), which has been induced by androgens in balding dermal papilla cells with transfected androgen receptors [64]. TGF-β also inhibits hair follicle growth in vitro [102] and a probable suppressor of TGF-β1 delayed catagen progression in mice in vivo [56]. Other candidates include dickkofp-1 (DDK-1) [87] and Wnt signalling [72] which are both induced by 5α-dihydrotestosterone in balding dermal papilla cells. Further study of such factors should lead to better treatments for androgen-dependent hair follicle disorders.

2.5 Treatment

Mainly because the pathogenesis mechanisms of androgenetic alopecia are not fully understood, the treatments available are limited and vary in effectiveness. Over the centuries, a wide range of remedies have been suggested for androgenetic alopecia [78] and currently treatments include wigs and hairpieces, surgery, hormone action modifiers, and non-hormonal therapy. Several of these are based on our understanding of the mechanisms of androgen action within the follicle.

2.5.1 Surgery

All surgical methods capitalise on the different intrinsic responses to androgens by spreading “non-balding”, i.e. occipital and parietal, terminal follicles over the androgen-sensitive scalp regions [98]. Originally involving the transplant of small biopsies with several follicles, this usually now involves micro-grafts with one or two follicles [134]. Once established, these expensive and painful treatments are long-lasting; however, the effect can be marred by the continual natural progression of balding, which may well require further transplants to avoid isolation of the transplanted region. Future modifications may include culturing dermal papilla cells to expand the non-balding follicular material before replanting into balding regions.

2.5.2 Hormonal Treatments

2.5.2.1 Anti-Androgens

Blocking the activation of androgen receptors by anti-androgens is a theoretically useful approach, but not really practical because anti-androgens block all

androgen actions, with unacceptable side effects on male masculinity and the potential to cause feminisation of a male foetus in a pregnant woman. Nevertheless, cyproterone acetate, an anti-androgen with pro-gestational effects, established for hirsutism and acne in Europe and Canada [37], is also used for androgenetic alopecia in women, generally in combination with oestrogen as oral contraception in pre-menopausal women; treatment appears to stabilise progression [138]. Similarly, spironolactone, an aldosterone antagonist with mild anti-androgenic effects, is often used in the USA [62].

2.5.2.2.5 α-Reductase Inhibitors

The most successful current therapeutic treatment in men is oral finasteride, a 5α-reductase type 2 inhibitor, which blocks the conversion of testosterone to 5α-dihydrotestosterone [122]. Finasteride, developed for benign prostate hypertrophy [141], slows hair loss progression and can promote hair growth in young men with below stage V hair loss (Fig. 2.1); it can also be useful in older men [44, 69–71]. Whether the inhibitor is working centrally or within the balding follicles is unclear because plasma 5α-dihydrotestosterone levels are reduced [69]. Unfortunately, finasteride was not effective in post-menopausal women [104], and its use in pre-menopausal women is restricted like anti-androgens (Sect. 2.5.2.1). Recently, a short trial of dutasteride, a dual inhibitor of 5α-reductase types 1 and 2 has shown similar, possibly better, effects [96].

2.5.2.3 Non-Hormonal Therapy

The most commonly used non-hormonal treatment, minoxidil, was initially devised as a vasodilator for use as an anti-hypertensive drug, but stimulated excessive hair growth as a side effect [23, 87, 123]. This provoked major interest in hair follicle biology because vellus follicles were stimulated to form terminal hairs, previously believed impossible; a reversal of the normal scheme where greater understanding leads to new approaches! Topical application of minoxidil is used in both men and women [23, 87, 123], stimulating re-growth in up to 30%, with only about 10% obtaining complete re-growth [95, 120]. Most success occurs with younger men and with the early stages of balding. Minoxidil probably acts as a potassium channel regulator of ATP-sensitive potassium channels [124].

2.5.3 Future Developments

Androgenetic alopecia is a common, progressive, androgen-dependent hair disorder with strong genetic links that often has marked negative effects on the quality of life. There is a great deal of interest among pharmaceutical companies ever since minoxidil demonstrated that terminal hair growth could be re-stimulated from balding follicles. The development of the 5α-reductase type 2 inhibitor, finasteride, has opened up the use of hormonal treatments in men. However, as the hormonal trigger and the follicle's ability to respond persist, treatment must be maintained.

Take Home Pearls

- Over the last 20 years, there have been great improvements in our understanding of hair follicle biology and the mechanism of androgen action in hair follicles, establishing the importance of local biochemical and cellular interactions within the follicle. This has highlighted the significant role of the dermal papilla, particularly in androgen regulation.
- Recently, dermal papilla cells have been shown to secrete autocrine and paracrine factors, which may play a role in the pathogenesis of androgenetic alopecia. These are currently a focus of investigation; IGF-1, SCF and TGF-β are implicated in androgen action.
- The significant role of inherited genetic predisposition to androgenetic alopecia is also being clarified, revealing strong associations with aspects of the androgen receptor gene and others on chromosome 20.
- Understanding the molecular mechanisms has led to treatments such as finasteride; as our knowledge deepens further, novel therapies should be developed.

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