Accepted Manuscript

Androgens and androgen receptor action in skin and hair follicles

Julieta María Ceruti, Gustavo José Leirós, María Eugenia Balañá

PII: S0303-7207(17)30492-6

DOI: 10.1016/j.mce.2017.09.009

Reference: MCE 10069

To appear in: *Molecular and Cellular Endocrinology*

Received Date: 9 March 2017

Revised Date: 28 August 2017

Accepted Date: 8 September 2017

Please cite this article as: Ceruti, Julieta.Marí., Leirós, Gustavo.José., Balañá, Marí.Eugenia., Androgens and androgen receptor action in skin and hair follicles, *Molecular and Cellular Endocrinology* (2017), doi: 10.1016/j.mce.2017.09.009.

Title:

Androgens and androgen receptor action in skin and hair follicles

Authors:

Julieta María Ceruti, Gustavo José Leirós and María Eugenia Balañá.

G. J. Leirós and J. M.Ceruti equally contributed to this work.

Affiliation:

Instituto de Ciencia y Tecnología Dr. César Milstein, Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET)

Saladillo 2468 (C1440FFX)

Ciudad de Buenos Aires- Argentina

Corresponding author:

María Eugenia Balañá

E-mail: mbalana@fundacioncassara.org.ar

Fundación Pablo Cassará, Instituto de Ciencia y Tecnología Dr. César Milstein, Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET)

Saladillo 2468 (C1440FFX)

Ciudad de Buenos Aires- Argentina

Tel. (+54 11) 4105-4126 / 4686-3687 / 4687-2542

Key words: skin steroidogenesis in health and disease, androgenetic alopecia, epithelial-mesenchymal interactions, dermal papilla, Wnt/β-catenin signalling

Conflict of interest: None

Abstract (143 words)

Beyond sexual functions, androgens exert their action in skin physiology and pathophysiology. Skin cells are able to synthesize most of active androgens from gonadal or adrenal precursors and the enzymes involved in skin steroidogenesis are implicated both in normal or pathological processes. Even when the role of androgens and androgen receptor (AR) in skin pathologies has been studied for decades, their molecular mechanisms in skin disorders remain largely unknown. Here, we go over recent studies of androgens and AR roles in several skin-related disorders, focusing in the current understanding of its molecular mechanisms in androgenetic alopecia (AGA). We review on the molecular pathophysiology of type 2 5α-reductase, AR coactivators, the paracrine factors deregulated in dermal papilla (such as TGF-β, IGF 1, WNTs and DKK-1) and the crosstalk between AR and Wnt signaling in order to shed some light on new promising treatments.

1-Introduction

Steroid sex hormones play an essential role in the maintenance of normal function of reproductive organs and in the sexual dimorphism among other physiological and pathological functions in different body tissues. Androgens and estrogens are steroid hormones, mainly synthesized in adrenal glands, ovaries, testis, placenta and brain that act through specific intracellular receptors. Beyond sexual functions, they also exert many effects on skin in different physiological and pathological processes.

The skin has the capability to produce androgens both *de novo* from cholesterol or using adrenal circulating precursors, such as dehydroepiandrosterone (DHEA), through specific enzymatic activities. Skin is a dynamic tissue that is renewed periodically, as well as is the hair follicle, which grows following a strict renewing cycle that is divided in defined phases. Androgens regulate many of these processes and others related to skin embryogenesis.

Androgen levels are under the control of enzymes catalyzing either its synthesis or destruction. These enzymes, as well as the binding to androgen receptor and coregulators, which are expressed in different skin regions in a specific spatial-temporal fashion, regulate androgen´s action.

In this review, we resume the current knowledge regarding the androgen´s functions on the skin, primarily focused on the pilosebaceous unit.

2-Role of androgens in skin physiology

In the skin, androgens regulate hair growth, sebum production and secretion, among other physiological effects as wound healing and cutaneous barrier formation.

Many long terminal hairs e.g. scalp hairs, eyelashes and eyebrows are developed from birth, maintained throughout life and have protective functions. Others hair types are secondary sexual characteristic and can be divided into two groups, adult axillar and pubic hairs in both sexes and beard and chest hairs in adult men [1-3]. They begin to growth to terminal hairs during puberty in response to the rise of plasma androgen levels [4, 5].

Sebum production by sebaceous glands is also under control of androgens. It was observed a significant rise in sebum production in both sex during the first days after birth, comparable to young adults, that is maintained until the second month of life, whereupon is observed a notably reduction [6]. This increase in sebum production correlates with the appearance of the so called genital crisis characterized by breast swelling, genital edema with hydrocele in boys and genital bleeding in girls that last two to three days. These results indicated that this sebum production rise would be related to androgen stimulation and correlated to the significant rise in plasma level of DHEA that is maintained through the first three month of life [7]. After the seventh year of life a new increase in DHEA secretion by adrenal glands (adrenarche) is observed in both sexes before any sign of puberty [7]. In this sense, it was observed a positive correlation of pre-pubertal acne, relative sebum secretion and urinary excretion of 17-ketosteroides in both sexes. Even though 17-ketosteroids are weak steroids, the sebaceous glands can respond to their stimulus at this stage of development [8]. It was also demonstrated that dihydrotestosterone (DHT) stimulation is sufficient to induce commitment of functional AR-expressive immature sebocytes into lipogenic differentiation process [9]. After puberty, the sebum production in men is significantly increased and is greater in men than in age-matched women [10, 11], men suffering complete androgen

insensitivity [12] or castrated men. In this last study group, oral administration of methyl testosterone increased significantly sebum production [13].

The apocrine sweat glands of the human axilla produce odor substances with pheromone functions whose nature corresponds to volatile steroids [14-17]. These functions only begin with the puberty indicating that sex hormones stimulation is required [18]. Indeed, it has been suggested by ligand binding assays, the presence of intranuclear and cytosolic androgen receptors in apocrine sweat glands from patients with osmidrosis of both sexes [19]. Immunohistochemistry studies demonstrated strong expression of androgen receptor (AR) and estrogen receptor-β (ER-β) in the apocrine secretor epithelium [20]. AR showed a higher expression correlated to the height of epithelium [20]. These results agree with the fact that the low epithelium is considered resting or inactive and therefore the secretory activity would be regulated by androgen action through AR. Likewise, androgens upregulate many enzymes involved in cholesterol synthesis [21] and given the role of cholesterol as pheromone precursor, then androgen would have an important role in the synthesis and secretion of these volatile hormones. Likewise, DHT showed to increase expression of Apoprotein D (Apo D) in apocrine gland cells, a protein that play a carrier role for axillar odor molecules [22]. On the other hand, it has been observed that isolated human apocrine sweat glands showed high levels of 5α-reductase activity [23-25] and a higher concentration of DHT than testosterone in axillary skin from patients suffering osmidrosis [19]. These results suggested an anabolic activity of 5α-reductase in apocrine sweat glands like happens in sebaceous glands, supported by the fact of the predominance of 5α-reductase type 1 in this kind of glands [26].

The regulatory roles of androgens and estrogens in skin wound healing were already extensively reviewed [27, 28].

Androgen receptor (AR) is expressed in keratinocytes, inflammatory cells (mainly macrophages) and fibroblasts involved in wound healing process in C57BL/6 wild type male mice [29]. This expression of AR during early wound healing associated both to epithelization and inflammatory cellular infiltrate, would involve this receptor in inflammation and/or repair processes. Castration of these animals resulted in a more rapid cutaneous wound healing associated to a reduced inflammatory response, as it was pointed by the reduction of TNF-α expression at wounded tissue. Therefore, endogenous testosterone could be inhibiting wound healing by upregulating proinflammatory cytokines secreted by macrophages. Similar results were observed with flutamide treatment in non-castrated animals [29].

Besides the effects on skin wound healing, androgens also demonstrated some role in cutaneous barrier formation [30]. Transepidermal water loss, as indicator of impaired barrier formation, was higher in male than female fetal rats and administration of the estrogen diethylstilbestrol to pregnant

mothers at estimated gestational day 14 to 16 accelerated fetal skin barrier development both morphologically and functionally. Otherwise dihydrotestosterone (DHT) delayed barrier fetal development when was administrated to pregnant mothers. Finally, the administration of AR antagonist flutamide in the same *in vivo* model avoided the gender differences in barrier formation. The effects of androgen on barrier homeostasis in both adult murine and human skin [31] were similar to what was exposed for fetal barrier formation. Hypogonadal mice showed faster skin barrier retrieval than normal animals and their treatment with testosterone displayed similar values to control. Similar results were observed in human hypopituitary patients treated with testosterone. The androgen mechanism underlying this effect appears to be related to epidermal lamellar body formation rather than differences in lipid synthesis [31].

3 Steroidogenesis in the skin

The synthesis of steroids hormones takes place in many tissues of which adrenal glands, ovaries, testis, placenta and brain are considered as classical steroidogenic organs. Nevertheless, skin constitutes an important peripheral steroidogenic tissue. Steroidogenesis pathway mainly focused in androgen synthesis is summarized in Figure 1 [32,33]. Human skin express key genes involved in the sex hormones synthesis such as CYP11A1, CYP17A1, 3β-hydroxysteroid dehydrogenase (3β-HSD), CYP19A1 (aromatase) among others [34-36] suggesting that skin has all the synthesis machinery to produce androgens *de novo* (Figure 1).

Although the skin can synthesize steroids *de novo* from cutaneous endogenous cholesterol, the main precursor used to produce steroids is adrenal DHEA-S. DHEA-S is hydrolyzed to DHEA by the steroid sulfatase located in sebaceous glands and dermal papilla cells (DPC) in terminal hair follicles [37, 38] whereas enzymatic activity of 3β-HSD1 converts DHEA into androstenedione, and 17β-HSD3 converts androstenedione in testosterone [39]. 17β-HSD is present in 5 different isoforms that function as a switch on/off mechanism for the production of the most potent sexual steroids. The isotypes 17β-HSD3 and 5 catalyze production of testosterone from androstenedione, while isotypes 17β-HSD2 and 4 catalyze the opposite reaction oxydizing testosterone into weak androgen androstenedione [39] (Figure 1). Fresh plucked anagen hair follicle showed high level expression of 17β-HSD2 both at inner root sheath (IRS) and outer root sheath (ORS) keratinocytes [40]. Similar expression pattern was observed in sebaceous glands with a predominant expression of 17β-HSD2 compared to the other isotypes probably by transcriptional regulation [41]. Moreover, a higher oxidative/reductive 17β-HSD ratio was seen in non-prone-acne skin compared to facial skin,

demonstrating a possible protective role of 17β-HSD in androgen effects on sebum over secretion [41].

Testosterone can be reduced to DHT by 5 α reductase enzyme. DHT is the most potent androgen for two reasons: 1) It cannot be aromatized to estrogen and 2) it has higher affinity for AR.

The enzyme 5α-reductase presents three isotypes: 5α-reductase type 1, 2 and 3 [42, 43] (Figure 1). Type 1 is predominantly expressed in skin and annexes (sebaceous glands, sweat gland and hair follicles), type 2 is expressed in the epididymis, the seminal vesicles, prostate, genital fibroblasts [44-46]. Finally, type 3 has shown to be expressed both in benign and neoplastic prostate tissue, but overexpressed and more broadly distributed in advanced prostate cancer [47].

5α-reductase activity in human growing and resting hair follicles plucked from male scalp was first identified in 1972 by Takayasu [48]. A subsequent study showed that only 5-α reductase 1 inhibitor suppressed 5-α reductase 1 activity in plucked hairs, indicating that this enzyme corresponded to isozyme type 1[49]. Other authors have shown that both 5α-reductase 1 and 2 activity were found in dissected scalp hair follicles, with a higher expression in balding than occipital hair follicles [50]. Furthermore, DPC from beard showed *in vitro*, a higher 5α-reductase 2 activity than DPC from occipital hair [51, 52]. It was also reported that 5α-reductase 1 mRNA is expressed in all scalp hair follicle, whereas 5α-reductase 2 mRNA is only expressed in DPC or dermal shealth obtained from scalp hairs [53].

In the same way, the pseudohermaphroditism consequence of 5α-reductase 2 deficiency, presented very strong evidence that beard hair growth and AGA hair loss could be related to activity of 5α-reductase 2 and not to activity of 5α-reductase 1 [54]. The 5α-reductase activity in hair follicles is mainly located at DPC: this activity is 14 and 80-fold higher in DPC from scalp and beard respectively than the rest the of hair follicles [55]. Even if controversial reports have been published, most of the results seem to indicate that 5α-reductase 1 activity is ubiquitously distributed in hair follicles, whereas 5α-reductase 2 is located at DPC from beard and AGA hair follicles, pointing out the dermal papilla as an androgenic target.

Testosterone can be converted into estrogens by aromatase action. Aromatase is encoded by CYP19, belongs to cytochrome P450 superfamily, and synthesizes estradiol (E2) and estrone (E1) from testosterone and androstenedione respectively (Figure 1). Aromatase is expressed in the ORS of anagen hair follicle and in sebaceous glands, but not in telogen hair follicles. Although, the expression was not uneven among body sites and gender, aromatase activity in women with AGA showed to be 2-fold higher in occipital compared to frontal hair follicles, and 6 to 3-fold higher in frontal and occipital sites, respectively, compared to men with AGA. Frontal follicles of women had almost twice aromatase activity than frontal hair follicles of men with AGA [50, 56]. Therefore

aromatase activity in the skin can serve as fine tune in the regulation of androgens and estrogens levels in target cells [57].

Given that DHT cannot be deviated to other non-androgenic pathway, it keeps its androgenic action unless it is degraded by another enzyme. This regulatory action is performed by 3α-HSD that catalyzes conversion of 5α-DHT into 3α-adiol (figure 1). This enzyme is mainly expressed in liver and regulates steroid hormone levels

4- Androgen receptor in skin

The action of androgens such as testosterone and DHT on skin is mainly mediated via the androgen receptor (AR), a ligand-dependent nuclear transcription factor and member of the steroid hormone nuclear receptor superfamily [58]. So, the lack of a functional AR results in severe alterations in the normal physiology of skin specially associated to development and physiology of skin appendages [59]).

The AR gene is located in X chromosome as a single copy so that males are hemizygote, and inactivating mutations results in testicular feminization syndrome [60].

The AR consists of three basic functional domains: the N- terminal transcription regulation domain, the DNA binding domain (DBD) and the ligand binding domain.

The N-terminal domain is the most variable, whilst the DBD is the most highly conserved region between the different members of the steroid hormone nuclear receptor family. Given the scarce variability between the DBDs, binding to selective androgen response elements (AREs) allows for the specific regulation of AR target genes [61]. The DBD is linked to the conserved ligand binding domain by a hinge region. The ligand binding domain allows physical association between the AR and heat shock proteins (HSP) in basal state. It also interacts with the N-terminus of the AR to stabilize bound androgens. Moreover, AR sequence includes: two transcriptional activating functions AF-1 and AF-2 [62, 63], a nuclear localization signal (NLS) and a nuclear export signal (NES) [64].

When AR interacts with its androgen ligand, it dissociates from HSPs, and the receptor-ligand complex translocates to nucleus and binds to AREs in the promoter region of androgen-regulated genes inducing their transcription in a DNA binding-dependent manner. On the other hand, androgens can exert their actions via the AR in a non-DNA binding-dependent manner, by initiating a rapid activation of second messenger signaling cascades. Moreover, ligand-independent actions of the AR have been identified recently (Reviewed in[65]).

Various coregulators can modulate AR function through binding to ligand binding domain or N-terminal domain, and there are more than 200 AR coregulators identified including transcriptional factors, kinases, chaperones, cytoskeletal proteins, among others [66].

AR is ubiquitously expressed in the body and display diverse functions, either stimulating or inhibiting cell growth, in different target organs or tissues. Localization of AR was widely studied in the human skin and its appendages. AR is expressed in epidermal keratinocytes, dermal fibroblasts and vascular endothelial cells in both neonatal foreskin and skin from adult men and women [67]. In eccrine sweat glands, only few secretory cells were observed to express AR, but in sebaceous gland AR is detected in both basal cells and sebocytes.

Most of latest works reported that in human hair follicle AR expression is restricted to DPC and is not found in the outer root sheath (ORS), hair bulb or bulge [68-72]. DPC derived from beard and balding scalp contain significantly greater levels of specific, low capacity, high affinity AR, as demonstrated with binding assays [73, 74], than those derived from relatively androgen-insensitive non-balding scalp follicles. This fact would suggest that androgens act on hair follicles via the dermal papilla *in vivo* (reviewed in [75]. Nevertheless, its expression in the ORS and medulla is controversial. Interestingly, AR mRNA was found to be expressed in dermal and epithelial portions of microdissected hair follicles from scalp [53]. Moreover, the type I hair keratin hHa7 and the AR are co-expressed in the medulla of male and female sexual hairs, and the expression of hHa7 appears to be directly regulated by androgens through three putative ARE motifs in its promoter [69]. Recently, the same group reported the *in vitro* androgenic regulation of this keratin in human occipital hair medulla, and a slight upregulation of AR expression in the nuclei of DPC and the cells of lower medulla of DHT-treated hair follicles [76].

On the other hand, it was shown that TR3, an orphan member of the steroid/thyroid/retinoid nuclear receptor superfamily, is localized to the stem cell compartment in the human hair follicles. Besides, androgen increases TR3 expression in cultured keratinocytes, suggesting that TR3 mediates at least part of the inhibitory effect of androgens on keratinocytes [77].

5-Role of androgens in skin pathologies

5.1 Acne vulgaris

Acne vulgaris is a multifactorial human skin disorder that occurs at the level of the pilosebaceous unit and it is mainly observed on face, shoulders, chest and back. The involvement of androgens in acne pathogenesis is supported by many experimental and clinical evidences, listed below:

1) One of the best predictors of severe acne are serum levels of DHEA-S and the onset of acne correlates with increased DHEA-S levels during adrenarche [78],

2) Severe acne observed in children suffering Congenital adrenal hyperplasia (CAH) [79] correlates with androgen excess due to the high levels of adrenocorticotrophic hormone (ACTH) induced by low cortisol levels.

3) Absence of acne in men with androgen insensitivity or castration before puberty [80],

4) Women with acne treated with antiandrogenic drugs reduced sebum production and improved mild to moderate acne [81, 82].

The major pathogenic factors involved in acne are infection by *Propinobacterium Acnes* which promotes perifollicular inflammation, hyperkeratinization that provokes obstruction of the infundibulum, stimulation of sebum production, seborrhea and excessive presence of androgens from local or systemic origin [83-86]. The activation of innate immunity begins with the interaction of surface proteins from *Propinobacterium Acne* with Toll Like Receptor-2 (TLR-2) present in sebocytes, keratinocytes and monocytes, inducing proinflammatory cytokines expression [87-90]. Moreover, DHT has been shown to be involved not only in sebum production but also in proinflammatory cytokine secretion by sebocytes [91].

A greater reductive activity of 17β-HSD indicative of a higher testosterone synthesis, was observed in sebaceous glands from acne-prone areas like facial skin, compared to non-acne-prone areas [41].Precisely, 17β-HSD 3 and 5 isozymes that catalyze the reduction of androstenedione to testosterone are preferentially expressed at sebaceous glands located in facial skin [36] (Figure 1). It is also interesting to note that the aromatase inhibitor MPV-2213 showed to produce acne as an adverse effect, suggesting the involvement of aromatase activity in the control of testosterone level associated to acne pathophysiology [92].

5.2 Hidradenitis suppurativa

Hidradenitis suppurativa (HS) is a chronic, inflammatory skin disease of the hair follicle affecting apocrine gland-bearing areas like axillary, inguinal and anogenital regions [93]. Exacerbation of HS in women was associated with menstruation (period normally characterized by low estrogen levels) and luteal phase of menstrual cycle (boost in ovarian androgens) indicating certain role of androgens in the pathogenesis of the disease [94, 95]. HS patients present normal androgens levels in serum suggesting that increased peripheral conversion of androgens rather than circulating levels could be involved in HA pathogenesis [94]. Nevertheless, in other studies, 5α-reductase enzyme that produces DHT from testosterone, and proposed as a pivotal factor in HS, showed similar levels

both in patients and healthy controls [25]. Neither androgen nor estrogen receptor expression showed differences between patients and healthy controls [96]. Beyond these results indicating the lack of association between androgen and/or AR with HA there exist reports showing illness improve after antiandrogen treatments [97, 98].

5.3 Androgenetic alopecia

The relationship between male gender condition and alopecia was suspected since very early human history. In 40' decade of the past century, Hamilton et al [99] showed that androgen stimulation is a prerequisite for common or androgenetic alopecia (AGA). Thus, androgens effects on human hair growth regulation vary depending on body sites. Even if androgens normally stimulate hair production in many sites of the body (e.g., the beard and the axillary regions), they can exert an opposite effect to suppress hair growth on genetically predisposed frontal and vertex scalp [100]. AGA is the most common form of hair loss in humans. AGA is caused by vellus transformation of scalp hairs, which corresponds to hair follicle miniaturization by repeated hair cycles with shortened anagen phase. AGA may begin during puberty and the prevalence rates in Caucasian population is approximately 50% among men between 40 – 49 years old and by the age of 80, over 90% of Caucasian men are affected to a various degree [101].

The important role of androgens and genetic factors in AGA has been confirmed. Hamilton [99] first demonstrated that this process is mediated mainly by androgen based on his clinical observation of androgen induction of AGA in men with testicular insufficiency. He also observed that eunuchoid and prepubertally castrated men do not develop baldness and had a reduced sebum secretion in areas which normally showed abundant sebum as happen in adult man facial skin and hairs [99]. Testosterone administration to these patients resulted in restoration of normal male developing scalp baldness and increased sebum secretion, demonstrating the importance of genetic factors in AGA indicating a close relationship between androgens and these two phenomena.

In males, AGA is characterized by a distinct pattern of androgen-dependent progressive hair loss from the scalp (male-pattern alopecia) that starts with a bi-temporal recession of the frontal hair line and follows by a thinning of the frontal and vertex scalp areas. This process eventually leads to complete baldness of the top of the scalp.

The prevalence of AGA among women is lower than in men [102]. As female scalp hair loss is clinically, etiologically and genetically different from the male baldness in many features [103], it is now designated as Female Pattern Hair Loss (FPHL). FPHL results from a progressive decrease in the ratio of terminal hairs to shorter, thinner vellus hairs. This follicular miniaturization is typically

presented as a diffuse reduction in hair density over the frontal and vertex areas, but parietal and occipital regions may be involved [104]. The mechanism through which this follicular transformation occurs in FPHL is not completely understood. Even if the roles of androgens and genetic susceptibility in male AGA are well accepted, the degree to which these factors contribute to FPHL is less clear [103]. In both men and women a higher expression of 5α-reductase 1 and 2 in frontal than in occipital hair follicles was observed; but in men its expression was approximately 3-fold higher than in women [50]. Estrogens may prolong hair follicle anagen growth phase [57, 105]. Moreover estradiol inhibits hair shaft growth in occipital hair follicles in women whereas stimulates frontal hair growth in men [106, 107] and 17α-estradiol stimulates aromatase activity in women hair follicles [108]. Therefore the conversion of androgen into estradiol by aromatase activity could be a regulatory mechanism to control androgen activity in hair follicles (Figure 1).

Men suffering AGA have normal levels of circulating androgens. However, testosterone and DHT can be synthesized in the pilosebaceous unit [36, 109, 110]through mechanisms that include one or more enzymes (Figure 1). The unwanted androgen metabolism at the hair follicle is the major factor involved in the pathogenesis of AGA. Elevated activity of 5α-reductase 2, which metabolizes circulating testicular testosterone into DHT in the genetically predisposed temporal and vertex follicles, is the most significant factor in men. The important role of 5α-reductase in AGA is supported by the absence of temporal regression and baldness in cases of 5α-reductase deficiency [111, 112].

3β-HSD activity in AGA patients is higher in frontal scalp hair follicles than in occipital scalp hair follicles [113]. Decreased aromatase activity (the enzyme that converts circulating ovarian testosterone into 17 beta-estradiol) leading to elevated local concentration of testosterone seems to be operative in women [114].

As no correlation between pattern of baldness and serum androgen has been found [115], the pathogenic action of androgens is likely to be mediated through the intracellular signaling of hair follicle target cells.

5.3.1 Androgen receptor in AGA

As mentioned before androgens/AR actions are involved in regulation of normal skin development and function as well as in some skin pathological events, as AGA.

DPC from androgen-sensitive follicles (beard, axilla, pubis and vertex/balding scalp) contained higher levels of AR than those derived from relatively androgen-insensitive non-balding occipital scalp follicles [68, 116-120], showing that DPC exhibit an altered phenotype in culture which

depends on the body site from which they were derived. As hair follicles from temporal and vertex areas of the scalp express large quantities of AR, binding of increased local levels of DHT is favoured, causing the shortening of anagen phase and progressive miniaturization of thick, pigmented terminal hair into thinner and non-pigmented vellus-like hair.

Normal testosterone levels are frequently observed in women with androgenetic alopecia (AGA), suggesting the involvement of androgen sensitivity in this condition. It was recently reported the increased AR messenger RNA expression in frontal-parietal hair follicles of women with AGA compared to controls [121] confirming the relation between androgen sensitivity and the AR mRNA production. Moreover, AR content in female frontal hair follicles is approximately 40% lower than in male counterparts. This difference may account for the particular clinical presentation of AGA in women and men [50].

5.3.1.1 Senescence in AGA

In an effort to elucidate the mechanisms implicated in the pathogenesis of AGA, a recent study indicated that balding DPCs undergo premature senescence *in vitro* denoted by senescence-associated β-galactosidase (SA β-gal) and p16INK4a protein expression, and markers of oxidative and DNA damage [122]. In the same line, it was reported that androgen/AR signaling accelerates premature senescence of human DPCs from frontal scalp, in association with DNA damage [123]. This fact is thought to reflect the irreversible cell growth arrest and may explain the miniaturization of hair follicles observed in AGA patients.

5.3.1.2 AR polymorphisms in AGA

The AR gene has three common polymorphisms. The two most important, CAG and GGN trinucleotide repeats in AR exon1, have been shown to be associated with prostate cancer risk [124-126]. They represent interesting AR activity markers because particular repeats alleles are associated with higher protein level or increased transactivity function [Ding, D 2004]. These polymorphisms were also associated with androgen-dependent skin disorders, but the overall results are still controversial. There are positive associations between shorter repeats alleles and skin disorders. CAG trinucleotide shorter repeats were shown to be related with acne, hirsutism and AGA [127-129] and patients with greater androgen sensitivity (<24 CAG repeats) were likely to have a significant response to finasteride treatment either in male [130]or female [131] AGA. However, other study showed that only GGN equally or less than 23 trinucleotide repeat alleles are truly associated with AGA [132]. Since both polymorphisms modulate AR activity, but only GGC

repeats showed to be associated with AGA, it is possible that cells from hair follicle lack certain cofactors that interact with CAG repeats. Taken together these results indicate that the main baldness factor is inherited from maternal family branch through X chromosome. Nevertheless, other genetic factors located at autosomal loci also could modulate AR functions and explain the similarity in AGA pattern observed in fathers and sons.

The third common polymorphism in the AR gene, is a StuI restriction-site polymorphism (E211 G>A). The E211 A allele is associated with a decreased risk of metastatic prostate cancer and androgenetic alopecia [133].

A meta-analysis from published data was recently conducted to determine whether the common AR gene polymorphisms confer susceptibility to AGA. These reviewers suggest that the G allele of AR StuI polymorphism might be a potential risk factor for AGA, especially in white populations. However, they did not find any obvious association between the CAG or GGC repeats polymorphisms of the AR gene and the risk for AGA [134].

5.3.1.3 AR methylation in AGA

The AR gene includes a ~1.5Kb CpG island encompassing the transcription start site and exon1. Differential methylation patterns have been linked with differential AR expression in various prostate cancer cell lines [135, 136].

AR gene promoter methylation is higher in occipital scalp hair follicles compared with those from vertex AGA scalp, pointing it as a mechanism that may influence the AR expression in hair follicle. AR promoter methylation may protect occipital hairs from miniaturization and hair loss [137]. Interestingly, it was recently demonstrated that DNA methylation regulates AR expression in developing prostate. This process may be a novel mechanism that controls androgen sensitivity and timing of mouse prostate ductal development. The authors propose that AR DNA methylation could represent a novel developmental checkpoint [138].

5.3.2 AR Coregulators in AGA

As mentioned above, DHT strongly binds to AR located in the cytoplasm of the target cells and the AR-DHT complex is translocated to the nucleus after dimerization. The interaction of the AR-DHT complex with the androgen responsive element (ARE) is modulated by a variety of proteins called coregulators. These AR coregulators are classified as coactivators when they activate transcription mediated by the AR or as corepressors when they suppress it [139].

Although many androgen receptor coactivators have been identified [61], their physiological and pathological significance is still not fully understood. It seems that the presence of different coregulators provides tissue specificity of androgen-elicited responses. Coregulators add another factor to the complexity of androgenic action on hair and could be involved in its paradoxical effect on scalp hair. A differential expression pattern of an AR coactivator in human hair follicles was first described by Lee et al. [140] suggesting its possible role in AGA. This study has shown a reduction of ARA70b/ELE1b expression in the dermal papilla and the hair bulbs from balding hairs. As ARA70b/ELE1b promotes cell growth [141], it is likely that this decrease of ARA70b/ELE1b contributes to the retardation of hair follicle growth and eventually leads to hair follicle miniaturization, major characteristics of AGA.

Another AR coactivator, Hic-5/ARA55 was found as a molecular regulator of androgen sensitivity in human hair follicle. It is highly expressed in DPC of hair follicles from androgen-sensitive sites such as AGA and beard, suggesting that Hic-5/ARA55 can enhance androgen sensitivity in dermal papilla [142]. The levels of Hic-5/ARA55 were found to correlate with previously reported levels of the androgen receptor in DPC from various sites [120, 143, 144].

These reports indicate that selective AR coactivators may be involved in the pathogenesis of AGA and therapeutic strategies targeting the action of coregulators might have an application in scalp hair loss.

Summarizing altogether the findings exposed above suggest that the sensitivity of hair follicles to androgens is mainly regulated through the 5α-reductase enzyme, AR, and AR co-activators.

5.3.3 Deregulation of DPC secreted factors

The observation that DPC derived from androgen sensitive sites (e.g., beard and frontal scalp) contain low capacity, high affinity AR[120] suggests that these cells are the main site of androgen action in the hair follicles. Embryonic induction of hair follicles and their regeneration during cycling is a process that implicates a crosstalk between epithelial precursor cells and the underlying mesenchymal dermal papilla, possibly through paracrine mediators [145]. These secreted factors from the DPC cause epithelial cells to proliferate and differentiate into the hair follicle cell lineages to produce the hair shaft [146, 147]. Androgen-driven alteration of the autocrine and paracrine regulatory factors produced by scalp DPC that influence self-growth or the growth of epithelial follicular components may be a key to AGA development. Researchers have been focused on identifying androgen-regulated factors and the signaling pathways involved in this crosstalk at different hair cycle stages. Many of them have been reported [147, 148].

Androgens were found to stimulate the synthesis and secretion of TGF-β from the dermal papilla isolated from the bald scalp, and this peptide factor may be responsible for androgen-induced growth inhibition in cocultured epithelial cells [75]. Both TGF-β1[149, 150], and TGF-β2 [151] have been identified as androgen-inducible negative mediators for AGA development .

IGF-1 was first identified as a testosterone-inducible positive paracrine mediator from beard DPC [68] that induced follicular epithelial cell growth using a coculture system of ORS cells and beard DPC. In addition, testosterone also induced autocrine stimulatory factors from beard DPC [152], which suggests that autocrine behavior is also involved in androgen regulation for beard growth

IL-6 was reported as upregulated in balding DPC compared with non-balding DPC and DHT-inducible IL-6 inhibits elongation of human hair shafts by suppressing matrix cell proliferation and promoting regression of hair follicles[153].

Moreover, the finding that DHT increases inducible nitric oxide (NO) synthase (iNOS) from DPC suggests that iNOS and NO are downstream effectors of AR in DPC [154].

Other reported findings that stem cell factor (SCF) is produced in higher amounts by beard than scalp DPC [155], and balding DPC produce less SCF than non-balding scalp DPC [156] 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 AGA, miniaturized hairs are paler than normal scalp hairs, however the concentration of melanocytes per unit area of the hair bulb does not change and they retain the same levels of the c-kit receptor protein. The reduced SCF production by balding DPC was the only detected difference.

Other diffusible factors that modulate papilla–epithelium interaction do exist, which include the Wnt (wingless-type MMTV integration site family) proteins [157]. The expression of the Wnt ligand antagonist dickkopf1 (DKK-1) has been found to be upregulated in response to DHT and reported to cause apoptosis in follicular keratinocytes co-cultured with DPC. Moreover, DKK-1 expression level is also elevated in the bald scalp of patients with AGA [158] .

5.3.4 Crosstalk between androgen and Wnt/β-catenin signaling in AGA

Hair follicle regeneration begins when signals from the mesenchyme derived DPC reach multipotent epidermal stem cells in the bulge region. Activation of the Wnt/β-catenin signalling pathway is important for the initiation and maintenance of hair morphogenesis [145, 159] and is critical for the maintenance of DPC inductive properties required for hair follicle regeneration and growth of the hair shaft [160-162]. The activation of Wnt signaling, especially Wnt10b is essential

for hair follicle development, hair cycling and hair growth [163]. Besides, the maintenance and growth of those hair follicles needs subsequent interaction of Wnt pathways between dermal and epidermal cells [161].

The importance of the Wnt/β-catenin pathway in AGA is emphasized by the demonstration of molecular cross-talk between androgens and the Wnt signaling in DPC. It was observed that in DPC from patients with AGA, the Wnt/β-catenin signaling pathway is negatively influenced by ligand-activated AR. Hacat keratinocyte proliferation and Lef/Tcf-mediated transcriptional activity stimulated by Wnt-3a were suppressed by DHT in a coculture of Hacat and DPC from AGA [157]. However, these phenomena could not be observed in DPC of non-AGA males. Moreover, we demonstrated that androgens regulate secreted factors involved in normal HF stem cell differentiation via the inhibition of the canonical Wnt signalling system in androgen-sensitive DPC [164]. We provided evidence that androgen activation of glycogen synthase kinase-3β (GSK-3β) appears to be responsible for the inhibition of Wnt/β-catenin signaling in androgen-sensitive DPC (Figure 2). Further studies will be necessary to elucidate the mechanism involved in the GSK-3β dephosphorylation mediated by androgens. In accordance with our findings, it has been reported previously that treatment of human DPC with a GSK-3β inhibitor resulted in an increased activity and expression of indicators of hair inductivity [165]. A functional cross-talk between the AR and Wnt signaling pathways has been described in target tissues [166]. It is becoming more evident that androgens deregulate DPC-secreted factors involved in normal HF stem cell differentiation via the inhibition of the canonical Wnt signaling pathway. Thus, the identification of these DPC-secreted factors would contribute to elucidating the regulation of epithelial–mesenchymal interactions that occur at the onset of hair regeneration and will lead to further understanding of the differentiation defects of hair follicle stem cells (HFSC) during AGA development. The observation that stem cells number was maintained in bald scalp whereas progenitor cells were markedly diminished supports this notion [167]. Understanding the signals responsible for stem cells differentiation would be the next step in developing new treatments for AGA. We have recently reported the role of Wnt agonists/antagonists as mediators of androgen inhibition of DPC-induced HFSC differentiation [168]. Wnt agonists/antagonists balance was analyzed after DHT stimulation of androgen-sensitive DPC and a downregulation of Wnt5a and Wnt10b was found while the Wnt antagonist Dkk-1 was upregulated. In addition, DKK-1 impaired HFSC differentiation mimicking androgens' action while the addition of WNT10b to DPC-medium conditioned with DHT, overcame androgen inhibition of HFSC differentiation. Our results identify DKK1 and WNT10b as paracrine factors which modulate the HFSC differentiation inhibition involved in androgen-driven balding (Figure 2)

The identification of more factors secreted by DPC responsible for differentiation of HFSC would contribute to elucidating the regulation of epithelial-mesenchymal interactions that occur at the onset of hair regeneration. It will lead to further understanding of the mechanisms involved in AGA development; thus opening a new option of targeted treatments for AGA through the modulation of the Wnt/β-catenin pathway.

There are already some studies showing that drugs that can act by activating Wnt signaling may be useful. Valproic acid (VPA), which activates the Wnt/β-catenin pathway and inhibitors of GSK-3β like lithium chloride and beryllium chloride, have been shown to induce hair regrowth through induction of anagen in murine model [169] and promote human hair growth in a phase II clinical trial that compared topical VPA (8.3 % sodium valproate) versus placebo for 24 weeks in 27 men with moderate AGA [170].

Another phase I trial revealed increased hair shaft thickness, hair density and number of total terminal hair without any significant adverse effects, compared with placebo at 12 weeks in subjects with AGA after intradermal administration of a 'Hair Stimulating Complex'(HSC). HSC is a bioengineered, non-recombinant, human cell-derived formulation containing Wnt7a protein, epidermal growth factors, and follistatin [171]. No relevant adverse effects were observed and phase II of this study is currently in progress with any published result available.

One more molecule that activates the Wnt pathway—SM04554— showed in a phase I clinical trial, to be safe, well-tolerated, and potentially efficacious for AGA treatment. According to a company report, in phase II trials the SM04554 topical solution (0.15 and 0.25 %) produced a statistically significant increase for both objective outcome measures: non-vellus hair count and hair density [172].

6- Conclusions and perspectives

The involvement of androgens and AR in many of the skin pathologies is well known and has been studied for decades; however, the molecular mechanisms by which androgens get involved in these skin disorders remain largely unknown.

Evidence has emerged of several other factors and processes which are able to contribute to the AR function.

The progressive elucidation of the distinct roles of androgens and AR or its downstream pathways in each skin disease is contributing to the development of better therapies that can specifically target AR (instead of androgens) to treat these disorders. Treatments targeting androgen metabolism in prostate cancer often result in undesirable side effects that are not acceptable in skin disorders,

taking into account the benefits they would cause to patients. The crucial aim in these androgenic skin disorders is to attenuate the pathological conditions more effectively, reducing side effects. A good approach to minimize the side effects is to develop topical reagents which could be efficiently delivered into the skin target cells and degraded before entering the circulation system.

In the case of the Androgenetic alopecia (AGA), the current understanding of the molecular mechanisms in androgen signaling pathway such as type 2 5α-reductase, AR, its coactivators, the deregulated paracrine mediators from dermal papilla (such as TGF-β, IGF 1, WNTs and DKK-1) and the crosstalk between AR and Wnt signaling pathways has opened the possibility of novel therapies. These new investigational treatments promise not only to stimulate hair growth, but also to induce formation of new hair follicles using bioengineering approaches and multiplication. Moreover, even if more studies are needed to prove their efficacy, new treatments targeting the Wnt signaling and others using stem cells have also shown to have a positive effect on hair regrowth.

Acknowledgements

G.J.L. is a researcher from Fundación Cassará. J.M.C and M.E.B. are members of CONICET (Consejo Nacional de Investigaciones Científicas y Técnicas).

This work was supported in part by a grant provided by CONICET (PIP 2015-2017 11220150100543) and by FONCyT -Agencia Nacional de Promoción Científica y Tecnológica (PICT 2014-2018)

FIGURE LEGENDS

Figure 1. **Steroidogenesis pathway focused in androgen synthesis and the regulation of androgen levels by different enzymes isotypes involved in this pathway**.

Figure 2. **Crosstalk between androgens and Wnt/β-catenin signaling in DPC. Effects on HFSC differentiation.** Black dashed line denote activation of Wnt/ β-catenin signaling in DPC and subsequent epithelial–mesenchymal Wnt pathways interactions, essential for hair growth and maintenance of hair follicles. Gray continuous line represent androgen signaling activation in sensitive DPC (p.e. from AGA patients), favouring the active form of glycogen synthase kinase-3β (GSK-3β) and consequent inhibition of Wnt ⁄β-catenin signaling (preventing LEF/TCF mediated gene transcription). Androgen/AR complex binding to AREs containing promoters of target genes disrupts Wnt agonists/antagonists (p.e.WNT10b; DKK1) balance involved in normal HFSC differentiation and in DPC inductive ability.

References

1. Randall, V.A., *Androgens and human hair growth.* Clin Endocrinol (Oxf), 1994. **40**(4): p. 439-57.
2. Marshall, W.A. and J.M. Tanner, *Variations in pattern of pubertal changes in girls.* Arch Dis Child, 1969. **44**(235): p. 291-303.
3. Marshall, W.A. and J.M. Tanner, *Variations in the pattern of pubertal changes in boys.* Arch Dis Child, 1970. **45**(239): p. 13-23.
4. Winter, J.S. and C. Faiman, *Pituitary-gonadal relations in male children and adolescents.* Pediatr Res, 1972. **6**(2): p. 126-35.
5. Winter, J.S. and C. Faiman, *Pituitary-gonadal relations in female children and adolescents.* Pediatr Res, 1973. **7**(12): p. 948-53.
6. Agache, P., et al., *Sebum levels during the first year of life.* Br J Dermatol, 1980. **103**(6): p. 643-9.
7. de Peretti, E. and M.G. Forest, *Unconjugated dehydroepiandrosterone plasma levels in normal subjects from birth to adolescence in human: the use of a sensitive radioimmunoassay.* J Clin Endocrinol Metab, 1976. **43**(5): p. 982-91.
8. Pochi, P.E., J.S. Strauss, and D.T. Downing, *Skin surface lipid composition, acne, pubertal development, and urinary excretion of testosterone and 17-ketosteroids in children.* J Invest Dermatol, 1977. **69**(5): p. 485-9.
9. Barrault, C., et al., *Androgens induce sebaceous differentiation in sebocyte cells expressing a stable functional androgen receptor.* J Steroid Biochem Mol Biol, 2015. **152**: p. 34-44.
10. Pochi, P.E. and J.S. Strauss, *Endocrinologic control of the development and activity of the human sebaceous gland.* J Invest Dermatol, 1974. **62**(3): p. 191-201.
11. Strauss, J.S.P., P.E., *The hormonal control of human sebaseous glands.*, in *Biology of Skin. The sebaceous glands.*, E.R. Montagna W, Silver AF, eds, Editor. 1963: Oxford: Pergamon Press. p. 220-254.
12. Imperato-McGinley, J., et al., *The androgen control of sebum production. Studies of subjects with dihydrotestosterone deficiency and complete androgen insensitivity.* J Clin Endocrinol Metab, 1993. **76**(2): p. 524-8.
13. Pochi, P.E., J.S. Strauss, and H. Mescon, *Sebum secretion and urinary fractional 17-ketosteroid and total 17-hydroxycorticoid excretion in male castrates.* J Invest Dermatol, 1962. **39**: p. 475-83.
14. Cowley, J.J. and B.W. Brooksbank, *Human exposure to putative pheromones and changes in aspects of social behaviour.* J Steroid Biochem Mol Biol, 1991. **39**(4B): p. 647-59.
15. Grosser, B.I., et al., *Behavioral and electrophysiological effects of androstadienone, a human pheromone.* Psychoneuroendocrinology, 2000. **25**(3): p. 289-99.
16. Sobel, N., et al., *Blind smell: brain activation induced by an undetected air-borne chemical.* Brain, 1999. **122 (Pt 2)**: p. 209-17.
17. Weller, A., *Human pheromones. Communication through body odour.* Nature, 1998. **392**(6672): p. 126-7.
18. Groscurth, P., *Anatomy of sweat glands.* Curr Probl Dermatol, 2002. **30**: p. 1-9.
19. Kurata, S., et al., *Intranuclear androgen and cytosolic receptor concentrations in the axillary skin of osmidrosis.* Arch Dermatol Res, 1990. **282**(1): p. 33-7.
20. Beier, K., I. Ginez, and H. Schaller, *Localization of steroid hormone receptors in the apocrine sweat glands of the human axilla.* Histochem Cell Biol, 2005. **123**(1): p. 61-5.

21. Swinnen, J.V., et al., *Coordinate regulation of lipogenic gene expression by androgens: evidence for a cascade mechanism involving sterol regulatory element binding proteins.* Proc Natl Acad Sci U S A, 1997. **94**(24): p. 12975-80.
22. Chen, H., et al., *Increased JNK1 activity contributes to the upregulation of ApoD in the apocrine secretory gland cells from axillary osmidrosis.* Mol Cell Biochem, 2011. **354**(1-2): p. 311-6.
23. Hay, J.B. and M.B. Hodgins, *Distribution of androgen metabolizing enzymes in isolated tissues of human forehead and axillary skin.* J Endocrinol, 1978. **79**(1): p. 29-39.
24. Takayasu, S., et al., *Activity of testosterone 5 alpha-reductase in various tissues of human skin.* J Invest Dermatol, 1980. **74**(4): p. 187-91.
25. Barth, J.H. and T. Kealey, *Androgen metabolism by isolated human axillary apocrine glands in hidradenitis suppurativa.* Br J Dermatol, 1991. **125**(4): p. 304-8.
26. Sato, T., et al., *Predominance of type I 5alpha-reductase in apocrine sweat glands of patients with excessive or abnormal odour derived from apocrine sweat (osmidrosis).* Br J Dermatol, 1998. **139**(5): p. 806-10.
27. Fimmel, S. and C.C. Zouboulis, *Influence of physiological androgen levels on wound healing and immune status in men.* Aging Male, 2005. **8**(3-4): p. 166-74.
28. Gilliver, S.C., F. Wu, and G.S. Ashcroft, *Regulatory roles of androgens in cutaneous wound healing.* Thromb Haemost, 2003. **90**(6): p. 978-85.
29. Ashcroft, G.S. and S.J. Mills, *Androgen receptor-mediated inhibition of cutaneous wound healing.* J Clin Invest, 2002. **110**(5): p. 615-24.
30. Hanley, K., et al., *Hormonal basis for the gender difference in epidermal barrier formation in the fetal rat. Acceleration by estrogen and delay by testosterone.* J Clin Invest, 1996. **97**(11): p. 2576-84.
31. Kao, J.S., et al., *Testosterone perturbs epidermal permeability barrier homeostasis.* J Invest Dermatol, 2001. **116**(3): p. 443-51.
32. Miller, W.L., *Molecular biology of steroid hormone synthesis.* Endocr Rev, 1988. **9**(3): p. 295-318.
33. Miller, W.L. and R.J. Auchus, *The molecular biology, biochemistry, and physiology of human steroidogenesis and its disorders.* Endocr Rev, 2011. **32**(1): p. 81-151.
34. Slominski, A., et al., *Steroidogenesis in the skin: implications for local immune functions.* J Steroid Biochem Mol Biol, 2013. **137**: p. 107-23.
35. Slominski, A., G. Ermak, and M. Mihm, *ACTH receptor, CYP11A1, CYP17 and CYP21A2 genes are expressed in skin.* J Clin Endocrinol Metab, 1996. **81**(7): p. 2746-9.
36. Zouboulis, C.C., et al., *Sexual hormones in human skin.* Horm Metab Res, 2007. **39**(2): p. 85-95.
37. Milewich, L., R.D. Sontheimer, and J.H. Herndon, Jr., *Steroid sulfatase activity in epidermis of acne-prone and non-acne-prone skin of patients with acne vulgaris.* Arch Dermatol, 1990. **126**(10): p. 1312-4.
38. Hoffmann, R., et al., *Steroid sulfatase in the human hair follicle concentrates in the dermal papilla.* J Invest Dermatol, 2001. **117**(6): p. 1342-8.
39. Chen, W., D. Thiboutot, and C.C. Zouboulis, *Cutaneous androgen metabolism: basic research and clinical perspectives.* J Invest Dermatol, 2002. **119**(5): p. 992-1007.
40. Courchay, G., et al., *Messenger RNA expression of steroidogenesis enzyme subtypes in the human pilosebaceous unit.* Skin Pharmacol, 1996. **9**(3): p. 169-76.
41. Thiboutot, D., et al., *Oxidative activity of the type 2 isozyme of 17beta-hydroxysteroid dehydrogenase (17beta-HSD) predominates in human sebaceous glands.* J Invest Dermatol, 1998. **111**(3): p. 390-5.

42. Andersson, S. and D.W. Russell, *Structural and biochemical properties of cloned and expressed human and rat steroid 5 alpha-reductases.* Proc Natl Acad Sci U S A, 1990. **87**(10): p. 3640-4.
43. Uemura, M., et al., *Novel 5 alpha-steroid reductase (SRD5A3, type-3) is overexpressed in hormone-refractory prostate cancer.* Cancer Sci, 2008. **99**(1): p. 81-6.
44. Thiboutot, D., et al., *Immunolocalization of 5alpha-reductase isozymes in acne lesions and normal skin.* Arch Dermatol, 2000. **136**(9): p. 1125-9.
45. Eicheler, W., et al., *Immunohistochemical evidence for differential distribution of 5 alpha-reductase isoenzymes in human skin.* Br J Dermatol, 1995. **133**(3): p. 371-6.
46. Nikolakis, G., et al., *Skin steroidogenesis in health and disease.* Rev Endocr Metab Disord, 2016. **17**(3): p. 247-258.
47. Godoy, A., et al., *5alpha-reductase type 3 expression in human benign and malignant tissues: a comparative analysis during prostate cancer progression.* Prostate, 2011. **71**(10): p. 1033-46.
48. Takayasu, S. and K. Adachi, *The conversion of testosterone to 17 -hydroxy-5 -androstan-3-one (dihydrotestosterone) by human hair follicles.* J Clin Endocrinol Metab, 1972. **34**(6): p. 1098-101.
49. Gerst, C., et al., *Type-1 steroid 5 alpha-reductase is functionally active in the hair follicle as evidenced by new selective inhibitors of either type-1 or type-2 human steroid 5 alpha-reductase.* Exp Dermatol, 2002. **11**(1): p. 52-8.
50. Sawaya, M.E. and V.H. Price, *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, 1997. **109**(3): p. 296-300.
51. Itami, S., et al., *Characterization of 5 alpha-reductase in cultured human dermal papilla cells from beard and occipital scalp hair.* J Invest Dermatol, 1991. **96**(1): p. 57-60.
52. Itami, S., S. Kurata, and S. Takayasu, *5 alpha-reductase activity in cultured human dermal papilla cells from beard compared with reticular dermal fibroblasts.* J Invest Dermatol, 1990. **94**(1): p. 150-2.
53. Asada, Y., et al., *5 alpha-reductase type 2 is constitutively expressed in the dermal papilla and connective tissue sheath of the hair follicle in vivo but not during culture in vitro.* J Clin Endocrinol Metab, 2001. **86**(6): p. 2875-80.
54. Inui, S. and S. Itami, *Androgen actions on the human hair follicle: perspectives.* Exp Dermatol, 2013. **22**(3): p. 168-71.
55. Eicheler, W., R. Happle, and R. Hoffmann, *5 alpha-reductase activity in the human hair follicle concentrates in the dermal papilla.* Arch Dermatol Res, 1998. **290**(3): p. 126-32.
56. Sawaya, M.E. and N.S. Penneys, *Immunohistochemical distribution of aromatase and 3B-hydroxysteroid dehydrogenase in human hair follicle and sebaceous gland.* J Cutan Pathol, 1992. **19**(4): p. 309-14.
57. Ohnemus, U., et al., *The hair follicle as an estrogen target and source.* Endocr Rev, 2006. **27**(6): p. 677-706.
58. Chang, C., et al., *Androgen receptor: an overview.* Crit Rev Eukaryot Gene Expr, 1995. **5**(2): p. 97-125.
59. Zouboulis, C.C. and K. Degitz, *Androgen action on human skin -- from basic research to clinical significance.* Exp Dermatol, 2004. **13 Suppl 4**: p. 5-10.
60. Quigley, C.A., et al., *Androgen receptor defects: historical, clinical, and molecular perspectives.* Endocr Rev, 1995. **16**(3): p. 271-321.
61. Heinlein, C.A. and C. Chang, *Androgen receptor (AR) coregulators: an overview.* Endocr Rev, 2002. **23**(2): p. 175-200.

62. Wilson, E.M., *Analysis of interdomain interactions of the androgen receptor.* Methods Mol Biol, 2011. **776**: p. 113-29.
63. Callewaert, L., N. Van Tilborgh, and F. Claessens, *Interplay between two hormone-independent activation domains in the androgen receptor.* Cancer Res, 2006. **66**(1): p. 543-53.
64. Tan, M.H., et al., *Androgen receptor: structure, role in prostate cancer and drug discovery.* Acta Pharmacol Sin, 2015. **36**(1): p. 3-23.
65. Davey, R.A. and M. Grossmann, *Androgen Receptor Structure, Function and Biology: From Bench to Bedside.* Clin Biochem Rev, 2016. **37**(1): p. 3-15.
66. van de Wijngaart, D.J., et al., *Androgen receptor coregulators: recruitment via the coactivator binding groove.* Mol Cell Endocrinol, 2012. **352**(1-2): p. 57-69.
67. Liang, T., et al., *Immunocytochemical localization of androgen receptors in human skin using monoclonal antibodies against the androgen receptor.* J Invest Dermatol, 1993. **100**(5): p. 663-6.
68. Itami, S., S. Kurata, and S. Takayasu, *Androgen induction of follicular epithelial cell growth is mediated via insulin-like growth factor-I from dermal papilla cells.* Biochem Biophys Res Commun, 1995. **212**(3): p. 988-94.
69. Jave-Suarez, L.F., et al., *Androgen regulation of the human hair follicle: the type I hair keratin hHa7 is a direct target gene in trichocytes.* J Invest Dermatol, 2004. **122**(3): p. 555-64.
70. Kariya, Y., et al., *Sex steroid hormone receptors in human skin appendage and its neoplasms.* Endocr J, 2005. **52**(3): p. 317-25.
71. Pelletier, G., et al., *Localization and estrogenic regulation of androgen receptor mRNA expression in the mouse uterus and vagina.* J Endocrinol, 2004. **180**(1): p. 77-85.
72. Thornton, M.J., et al., *The distribution of estrogen receptor beta is distinct to that of estrogen receptor alpha and the androgen receptor in human skin and the pilosebaceous unit.* J Investig Dermatol Symp Proc, 2003. **8**(1): p. 100-3.
73. Hibberts, N., A. Howell, and V. Randall, *Balding hair follicle dermal papilla cells contain higher levels of androgen receptors than those from non-balding scalp.* J Endocrinol, 1998. **156**(1): p. 59-65.
74. Randall, V.A., M.J. Thornton, and A.G. Messenger, *Cultured dermal papilla cells from androgen-dependent human hair follicles (e.g. beard) contain more androgen receptors than those from non-balding areas of scalp.* J Endocrinol, 1992. **133**(1): p. 141-147.
75. Inui, S. and S. Itami, *Molecular basis of androgenetic alopecia: From androgen to paracrine mediators through dermal papilla.* Journal of dermatological science, 2011. **61**(1): p. 1-6.
76. Yoshida, H., et al., *Keratins of the human occipital hair medulla: androgenic regulation of in vitro hair keratin K37 expression.* Br J Dermatol, 2013. **169**(1): p. 218-21.
77. Xie, L., et al., *TR3 is preferentially expressed by bulge epithelial stem cells in human hair follicles.* Lab Invest, 2016. **96**(1): p. 81-8.
78. Lucky, A.W., *A review of infantile and pediatric acne.* Dermatology, 1998. **196**(1): p. 95-7.
79. New, M.I., *An update of congenital adrenal hyperplasia.* Ann N Y Acad Sci, 2004. **1038**: p. 14-43.
80. Imperato-McGinley, J., *5alpha-reductase-2 deficiency and complete androgen insensitivity: lessons from nature.* Adv Exp Med Biol, 2002. **511**: p. 121-31; discussion 131-4.
81. Zouboulis, C.C. and J. Piquero-Martin, *Update and future of systemic acne treatment.* Dermatology, 2003. **206**(1): p. 37-53.
82. van Vloten, W.A. and V. Sigurdsson, *Selecting an oral contraceptive agent for the treatment of acne in women.* Am J Clin Dermatol, 2004. **5**(6): p. 435-41.

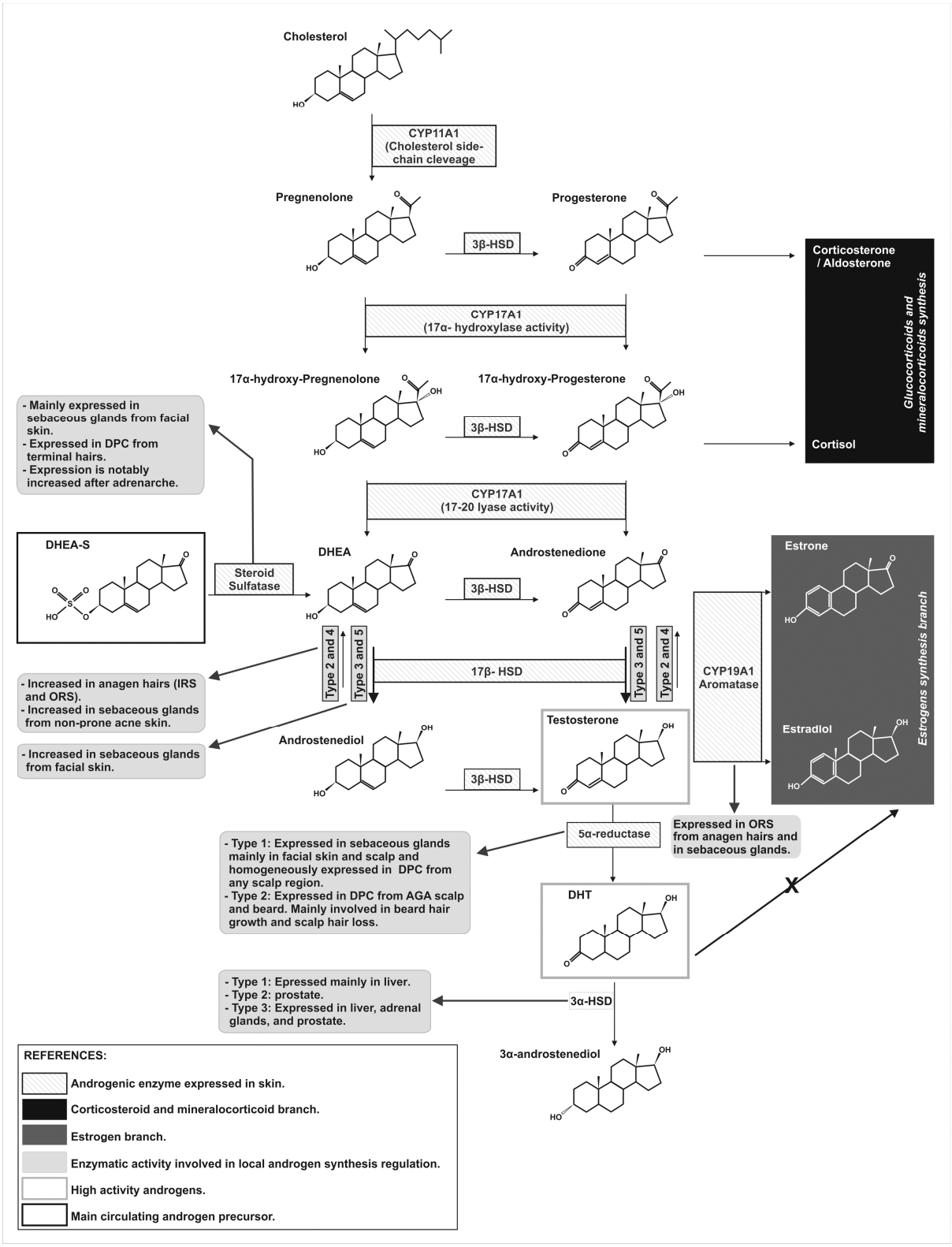
83. Zouboulis, C.C., et al., *What is the pathogenesis of acne?* Exp Dermatol, 2005. **14**(2): p. 143-52.
84. Zampeli, V.A., et al., *New pharmaceutical concepts for sebaceous gland diseases: implementing today's pre-clinical data into tomorrow's daily clinical practice.* Curr Pharm Biotechnol, 2012. **13**(10): p. 1898-913.
85. Beylot, C., et al., *Propionibacterium acnes: an update on its role in the pathogenesis of acne.* J Eur Acad Dermatol Venereol, 2014. **28**(3): p. 271-8.
86. Suh, D.H. and H.H. Kwon, *What's new in the physiopathology of acne?* Br J Dermatol, 2015. **172 Suppl 1**: p. 13-9.
87. Huang, Y.C., et al., *Cell-free extracts of Propionibacterium acnes stimulate cytokine production through activation of p38 MAPK and Toll-like receptor in SZ95 sebocytes.* Life Sci, 2015. **139**: p. 123-31.
88. Graham, G.M., et al., *Proinflammatory cytokine production by human keratinocytes stimulated with Propionibacterium acnes and P. acnes GroEL.* Br J Dermatol, 2004. **150**(3): p. 421-8.
89. Grange, P.A., et al., *Nicotinamide inhibits Propionibacterium acnes-induced IL-8 production in keratinocytes through the NF-kappaB and MAPK pathways.* J Dermatol Sci, 2009. **56**(2): p. 106-12.
90. Vowels, B.R., S. Yang, and J.J. Leyden, *Induction of proinflammatory cytokines by a soluble factor of Propionibacterium acnes: implications for chronic inflammatory acne.* Infect Immun, 1995. **63**(8): p. 3158-65.
91. Lee, W.J., et al., *Effect of dihydrotestosterone on the upregulation of inflammatory cytokines in cultured sebocytes.* Arch Dermatol Res, 2010. **302**(6): p. 429-33.
92. Ahokoski, O., et al., *Hormonal effects of MPV-2213ad, a new selective aromatase inhibitor, in healthy male subjects. A phase I study.* Br J Clin Pharmacol, 1998. **45**(2): p. 141-6.
93. Kurzen, H., et al., *What causes hidradenitis suppurativa?* Exp Dermatol, 2008. **17**(5): p. 455-6; discussion 457-72.
94. Harrison, B.J., G.F. Read, and L.E. Hughes, *Endocrine basis for the clinical presentation of hidradenitis suppurativa.* Br J Surg, 1988. **75**(10): p. 972-5.
95. Mortimer, P.S., et al., *Mediation of hidradenitis suppurativa by androgens.* Br Med J (Clin Res Ed), 1986. **292**(6515): p. 245-8.
96. Buimer, M.G., et al., *Immunohistochemical analysis of steroid hormone receptors in hidradenitis suppurativa.* Am J Dermatopathol, 2015. **37**(2): p. 129-32.
97. Kraft, J.N. and G.E. Searles, *Hidradenitis suppurativa in 64 female patients: retrospective study comparing oral antibiotics and antiandrogen therapy.* J Cutan Med Surg, 2007. **11**(4): p. 125-31.
98. Goldsmith, P.C. and P.M. Dowd, *Successful therapy of the follicular occlusion triad in a young woman with high dose oral antiandrogens and minocycline.* J R Soc Med, 1993. **86**(12): p. 729-30.
99. Hamilton, J.B., *Male hormone stimulation is prerequisite and an incitant in common baldness.* Am J Anat, 1942. **71**: p. 451-480.
100. Randall, V.A., et al., *Androgens and the hair follicle. Cultured human dermal papilla cells as a model system.* Ann N Y Acad Sci, 1991. **642**: p. 355-75.
101. Hamilton, J.B., *PATTERNED LOSS OF HAIR IN MAN: TYPES AND INCIDENCE.* Annals of the New York Academy of Sciences, 1951. **53**(3): p. 708-728.
102. Norwood, O., *Incidence of Female Androgenetic Alopecia (Female Pattern Alopecia).* Dermatologic Surgery, 2001. **27**(1): p. 53-54.

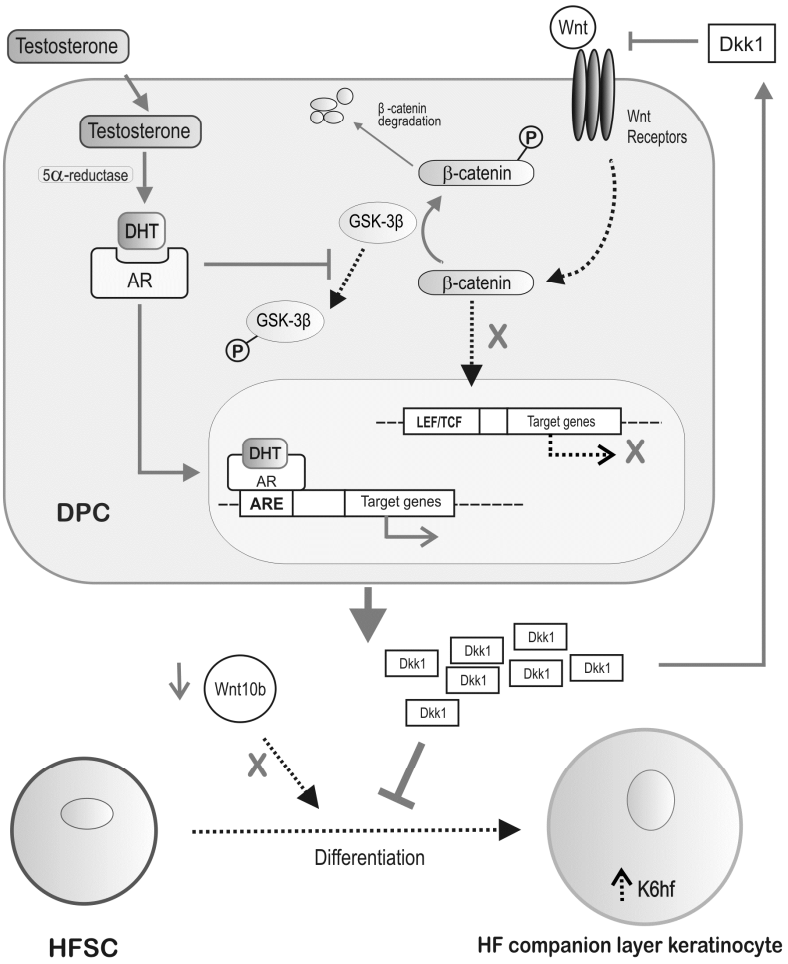
103. Vujovic, A. and V. Del Marmol, *The Female Pattern Hair Loss: Review of Etiopathogenesis and Diagnosis.* BioMed Research International, 2014. **2014**: p. 767628.
104. Price, V.H., *Androgenetic Alopecia in Women.* Journal of Investigative Dermatology Symposium Proceedings, 2003. **8**(1): p. 24-27.
105. Conrad, F. and R. Paus, *Estrogens and the hair follicle.* J Dtsch Dermatol Ges, 2004. **2**(6): p. 412-23.
106. Thornton, M.J., *Oestrogen functions in skin and skin appendages.* Expert Opin Ther Targets, 2005. **9**(3): p. 617-29.
107. Conrad, F., et al., *Estrogens and human scalp hair growth-still more questions than answers.* J Invest Dermatol, 2004. **122**(3): p. 840-2.
108. Hoffmann, R., et al., *17alpha-estradiol induces aromatase activity in intact human anagen hair follicles ex vivo.* Exp Dermatol, 2002. **11**(4): p. 376-80.
109. Chen, W.C. and C.C. Zouboulis, *Hormones and the pilosebaceous unit.* Dermatoendocrinol, 2009. **1**(2): p. 81-6.
110. Zouboulis, C.C., *The skin as an endocrine organ.* Dermatoendocrinol, 2009. **1**(5): p. 250-2.
111. Peterson, R.E., et al., *Male pseudohermaphroditism due to steroid 5-alpha-reductase deficiency.* Am J Med, 1977. **62**(2): p. 170-91.
112. Trueb, R.M., *Molecular mechanisms of androgenetic alopecia.* Experimental Gerontology, 2002. **37**(8â€“9): p. 981-990.
113. Sawaya, M.E., *Steroid chemistry and hormone controls during the hair follicle cycle.* Ann N Y Acad Sci, 1991. **642**: p. 376-83; discussion 383-4.
114. Happle, R. and R. Hoffmann, *Current understanding of androgenetic alopecia. Part I: etiopathogenesis.* European Journal of Dermatology, 2000. **1**(10): p. 319-327.
115. Faydaci, G., et al., *Baldness, benign prostate hyperplasia, prostate cancer and androgen levels.* Aging Male, 2008. **11**(4): p. 189-92.
116. Ando, Y., et al., *Expression of mRNA for androgen receptor, 5alpha-reductase and 17beta-hydroxysteroid dehydrogenase in human dermal papilla cells.* Br J Dermatol, 1999. **141**(5): p. 840-5.
117. Kwon, O.S., et al., *Expression of androgen receptor, estrogen receptor alpha and beta in the dermal papilla of human hair follicles in vivo.* J Dermatol Sci, 2004. **36**(3): p. 176-9.
118. Nakanishi, S.I., S; Adachi, K; et al, *Expression of androgen receptor, type I and type II 5 a-reducase in human dermal papilla cells*, in *Hair research for the next millenium*, D.R. Neste, V.A.; eds., Editor. 1996, Elsevier Publishers: Amsterdam. p. 333-337.
119. Randall, V.A., et al., *Mechanism of androgen action in cultured dermal papilla cells derived from human hair follicles with varying responses to androgens in vivo.* J Invest Dermatol, 1992. **98**(6 Suppl): p. 86S-91S.
120. Randall, V.A., M.J. Thornton, and A.G. Messenger, *Cultured dermal papilla cells from androgen-dependent human hair follicles (e.g. beard) contain more androgen receptors than those from non-balding areas of scalp.* J Endocrinol, 1992. **133**(1): p. 141-7.
121. Richeti, F., et al., *Increased androgen receptor messenger RNA in frontal-parietal hair follicles of women with androgenetic alopecia.* Genet Mol Res, 2013. **12**: p. 1834-1840.
122. Bahta, A.W., et al., *Premature senescence of balding dermal papilla cells in vitro is associated with p16(INK4a) expression.* J Invest Dermatol, 2008. **128**(5): p. 1088-94.
123. Yang, Y.C., et al., *Androgen receptor accelerates premature senescence of human dermal papilla cells in association with DNA damage.* PLoS One, 2013. **8**(11): p. e79434.
124. Chang, B.L., et al., *Polymorphic GGC repeats in the androgen receptor gene are associated with hereditary and sporadic prostate cancer risk.* Hum Genet, 2002. **110**(2): p. 122-9.

125. Hsing, A.W., et al., *Polymorphic CAG and GGN repeat lengths in the androgen receptor gene and prostate cancer risk: a population-based case-control study in China.* Cancer Res, 2000. **60**(18): p. 5111-6.
126. Stanford, J.L., et al., *Polymorphic repeats in the androgen receptor gene: molecular markers of prostate cancer risk.* Cancer Res, 1997. **57**(6): p. 1194-8.
127. Pang, Y., et al., *Combination of short CAG and GGN repeats in the androgen receptor gene is associated with acne risk in North East China.* J Eur Acad Dermatol Venereol, 2008. **22**(12): p. 1445-51.
128. Sawaya, M.E. and A.R. Shalita, *Androgen receptor polymorphisms (CAG repeat lengths) in androgenetic alopecia, hirsutism, and acne.* J Cutan Med Surg, 1998. **3**(1): p. 9-15.
129. Yang, Z., et al., *Relationship between the CAG repeat polymorphism in the androgen receptor gene and acne in the Han ethnic group.* Dermatology, 2009. **218**(4): p. 302-6.
130. Sato, A.A., Y; Kojima, Y.; et al, *Correlation between polymorphic CAG-repeats in the androgenreceptor gene and therapeutic efficacy of finasteride in androgenetic alopecia.* Skin Surgery, 2008. **17**: p. 80-86.
131. Keene, S. and A. Goren, *Therapeutic hotline. Genetic variations in the androgen receptor gene and finasteride response in women with androgenetic alopecia mediated by epigenetics.* Dermatol Ther, 2011. **24**(2): p. 296-300.
132. Hillmer, A.M., et al., *Genetic variation in the human androgen receptor gene is the major determinant of common early-onset androgenetic alopecia.* Am J Hum Genet, 2005. **77**(1): p. 140-8.
133. Hayes, V.M., et al., *The E211 G>A androgen receptor polymorphism is associated with a decreased risk of metastatic prostate cancer and androgenetic alopecia.* Cancer Epidemiol Biomarkers Prev, 2005. **14**(4): p. 993-6.
134. Zhuo, F.L., et al., *Androgen receptor gene polymorphisms and risk for androgenetic alopecia: a meta-analysis.* Clin Exp Dermatol, 2012. **37**(2): p. 104-11.
135. Jarrard, D.F., et al., *Methylation of the androgen receptor promoter CpG island is associated with loss of androgen receptor expression in prostate cancer cells.* Cancer Res, 1998. **58**(23): p. 5310-4.
136. Kinoshita, H., et al., *Methylation of the androgen receptor minimal promoter silences transcription in human prostate cancer.* Cancer Res, 2000. **60**(13): p. 3623-30.
137. Cobb, J.E., et al., *Evidence of increased DNA methylation of the androgen receptor gene in occipital hair follicles from men with androgenetic alopecia.* Br J Dermatol, 2011. **165**(1): p. 210-3.
138. Keil, K.P., et al., *Androgen receptor DNA methylation regulates the timing and androgen sensitivity of mouse prostate ductal development.* Dev Biol, 2014. **396**(2): p. 237-45.
139. Thakur, M.K. and V. Paramanik, *Role of steroid hormone coregulators in health and disease.* Horm Res, 2009. **71**(4): p. 194-200.
140. Lee, P., et al., *Expression of androgen receptor coactivator ARA70/ELE1 in androgenic alopecia.* J Cutan Pathol, 2005. **32**(8): p. 567-71.
141. Li, P., et al., *Heterogeneous expression and functions of androgen receptor co-factors in primary prostate cancer.* Am J Pathol, 2002. **161**(4): p. 1467-74.
142. Inui, S., et al., *Androgen receptor co-activator Hic-5/ARA55 as a molecular regulator of androgen sensitivity in dermal papilla cells of human hair follicles.* J Invest Dermatol, 2007. **127**(10): p. 2302-6.
143. Hibberts, N.A., A.E. Howell, and V.A. Randall, *Balding hair follicle dermal papilla cells contain higher levels of androgen receptors than those from non-balding scalp.* J Endocrinol, 1998. **156**(1): p. 59-65.

144. Itami, S., et al., *Interaction between dermal papilla cells and follicular epithelial cells in vitro: effect of androgen.* Br J Dermatol, 1995. **132**(4): p. 527-32.
145. Millar, S.E., *Molecular Mechanisms Regulating Hair Follicle Development.* Journal of Investigative Dermatology, 2002. **118**(2): p. 216-225.
146. Blanpain, C., et al., *Self-renewal, multipotency, and the existence of two cell populations within an epithelial stem cell niche.* Cell, 2004. **118**(5): p. 635-648.
147. Botchkarev, V.A. and J. Kishimoto. *Molecular control of epithelialâ€"mesenchymal interactions during hair follicle cycling*. in *Journal of Investigative Dermatology Symposium Proceedings*. 2003: Elsevier.
148. Roh, C., Q. Tao, and S. Lyle, *Dermal papilla-induced hair differentiation of adult epithelial stem cells from human skin.* Physiological genomics, 2004. **19**(2): p. 207-217.
149. Inui, S., et al., *Androgen-inducible TGF-beta1 from balding dermal papilla cells inhibits epithelial cell growth: a clue to understand paradoxical effects of androgen on human hair growth.* FASEB J, 2002. **16**(14): p. 1967-9.
150. Inui, S., et al., *Identification of androgen-inducible TGF-beta1 derived from dermal papilla cells as a key mediator in androgenetic alopecia.* J Investig Dermatol Symp Proc, 2003. **8**(1): p. 69-71.
151. Hibino, T. and T. Nishiyama, *Role of TGF-beta2 in the human hair cycle.* J Dermatol Sci, 2004. **35**(1): p. 9-18.
152. Thornton, M.J., et al., *Androgen-dependent beard dermal papilla cells secrete autocrine growth factor (s) in response to testosterone unlike scalp cells.* Journal of Investigative Dermatology, 1998. **111**(5): p. 727-732.
153. Kwack, M.H., et al., *Dihydrotestosterone-inducible IL-6 inhibits elongation of human hair shafts by suppressing matrix cell proliferation and promotes regression of hair follicles in mice.* J Invest Dermatol, 2012. **132**(1): p. 43-9.
154. Wolf, R., et al., *Nitric oxide in the human hair follicle: constitutive and dihydrotestosterone-induced nitric oxide synthase expression and NO production in dermal papilla cells.* Journal of molecular medicine, 2003. **81**(2): p. 110-117.
155. Hibberts, N.A., A.G. Messenger, and V.A. Randall, *Dermal papilla cells derived from beard hair follicles secrete more stem cell factor (SCF) in culture than scalp cells or dermal fibroblasts.* Biochemical and biophysical research communications, 1996. **222**(2): p. 401-405.
156. Randall, V.A., et al., *Stem cell factor/c-Kit signalling in normal and androgenetic alopecia hair follicles.* Journal of Endocrinology, 2008. **197**(1): p. 11-23.
157. Kitagawa, T., et al., *Keratinocyte growth inhibition through the modification of Wnt signaling by androgen in balding dermal papilla cells.* The Journal of Clinical Endocrinology & Metabolism, 2009. **94**(4): p. 1288-1294.
158. Kwack, M.H., et al., *Dihydrotestosterone-inducible dickkopf 1 from balding dermal papilla cells causes apoptosis in follicular keratinocytes.* J Invest Dermatol, 2008. **128**(2): p. 262-9.
159. Andl, T., et al., *WNT signals are required for the initiation of hair follicle development.* Dev Cell, 2002. **2**(5): p. 643-53.
160. Ito, M., et al., *Wnt-dependent de novo hair follicle regeneration in adult mouse skin after wounding.* Nature, 2007. **447**(7142): p. 316-320.
161. Kishimoto, J., R.E. Burgeson, and B.A. Morgan, *Wnt signaling maintains the hair-inducing activity of the dermal papilla.* Genes Dev, 2000. **14**(10): p. 1181-5.
162. Shimizu, H. and B.A. Morgan, *Wnt signaling through the B-catenin pathway is sufficient to maintain, but not restore, anagen-phase characteristics of dermal papilla cells.* Journal of Investigative Dermatology, 2004. **122**(2): p. 239-245.

163. Fu, J. and W. Hsu, *Epidermal Wnt controls hair follicle induction by orchestrating dynamic signaling crosstalk between the epidermis and dermis.* Journal of Investigative Dermatology, 2013. **133**(4): p. 890-898.
164. Leiros, G.J., A.I. Attorresi, and M.E. Balana, *Hair follicle stem cell differentiation is inhibited through cross-talk between Wnt/beta-catenin and androgen signalling in dermal papilla cells from patients with androgenetic alopecia.* Br J Dermatol, 2012. **166**(5): p. 1035-42.
165. Yamauchi, K. and A. Kurosaka, *Inhibition of glycogen synthase kinase-3 enhances the expression of alkaline phosphatase and insulin-like growth factor-1 in human primary dermal papilla cell culture and maintains mouse hair bulbs in organ culture.* Archives of dermatological research, 2009. **301**(5): p. 357-365.
166. Grisouard, J. and D. Mayer, *Specific involvement of glycogen synthase kinase-3 in the function and activity of sex steroid hormone receptors reveals the complexity of their regulation.* The Journal of steroid biochemistry and molecular biology, 2009. **117**(4): p. 87-92.
167. Garza, L.A., et al., *Bald scalp in men with androgenetic alopecia retains hair follicle stem cells but lacks CD200-rich and CD34-positive hair follicle progenitor cells.* The Journal of clinical investigation, 2011. **121**(2): p. 613-622.
168. Leiros, G.J., et al., *Androgens modify Wnt agonists/antagonists expression balance in dermal papilla cells preventing hair follicle stem cell differentiation in androgenetic alopecia.* Mol Cell Endocrinol, 2017. **439**: p. 26-34.
169. Lee, S.-H., et al., *Valproic acid induces hair regeneration in murine model and activates alkaline phosphatase activity in human dermal papilla cells.* PLoS One, 2012. **7**(4): p. e34152.
170. Jo, S.J., et al., *Topical valproic acid increases the hair count in male patients with androgenetic alopecia: a randomized, comparative, clinical feasibility study using phototrichogram analysis.* The Journal of dermatology, 2014. **41**(4): p. 285-291.
171. Zimber, M.P., C. Ziering, and F. Zeigler, *Hair regrowth following a Wnt- and follistatin containing treatment: safety and efficacy in a first-in-man phase 1 clinical trial.* J Drugs Dermatol, 2011. **10**(11): p. 1308-1312.
172. Yazici Y. and L. Samumed, *A phase 2, multicenter, randomized, double-blind, vehicle-controlled study of the safety, tolerability, and efficacy of 0.15 % and 0.25 % concentrations of topical SM04554 solution in male subjects with androgenetic alopecia.* https://clinicaltrials.gov/ct2/show/study/NCT02275351, 2015.


Cholesterol
CYP11A1
(Cholesterol side-chain cleveage
Pregnenolone
3β-HSD
Progesterone
Corticosterone / Aldosterone
Glucocorticoids and mineralocorticoids synthesis
Cortisol
CYP17A1
(17α- hydroxylase activity)
17α-hydroxy-Pregnenolone
17α-hydroxy-Progesterone
3β-HSD
- Mainly expressed in sebaceous glands from facial skin.
- Expressed in DPC from terminal hairs.
- Expression is notably increased after adrenarche.
CYP17A1
(17-20 lyase activity)
DHEA-S
Steroid Sulfatase
DHEA
Androstenedione
3β-HSD
Estrone
Estradiol
Estrogens synthesis branch
CYP19A1 Aromatase
Type 2 and 4
Type 3 and 5
17β- HSD
Type 3 and 5
Type 2 and 4
- Increased in anagen hairs (IRS and ORS).
- Increased in sebaceous glands from non-prone acne skin.
- Increased in sebaceous glands from facial skin.
Androstenediol
Testosterone
3β-HSD
5α-reductase
Expressed in ORS from anagen hairs and in sebaceous glands.
- Type 1: Expressed in sebaceous glands mainly in facial skin and scalp and homogeneously expressed in DPC from any scalp region.
- Type 2: Expressed in DPC from AGA scalp and beard. Mainly involved in beard hair growth and scalp hair loss.
DHT
- Type 1: Epressed mainly in liver.
- Type 2: prostate.
- Type 3: Expressed in liver, adrenal glands, and prostate.
3α-HSD
3α-androstenediol
REFERENCES:
Androgenic enzyme expressed in skin.
Corticosteroid and mineralocorticoid branch.
Estrogen branch.
Enzymatic activity involved in local androgen synthesis regulation.
High activity androgens.
Main circulating androgen precursor.


Testosterone
Testosterone
5α-reductase
DHT
AR
β -catenin degradation
β-catenin
GSK-3β
GSK-3β
β-catenin
Wnt
Dkk1
Wnt Receptors
LEF/TCF
Target genes
DHT
AR
ARE
Target genes
DPC
Dkk1
Dkk1
Dkk1
Dkk1
Dkk1
Dkk1
Dkk1
Wnt10b
Differentiation
K6hf
HFSC
HF companion layer keratinocyte

Highlights

Androgens have physiological and pathological effects on skin.

Skin has the enzymes necessary to synthesize androgens *di novo* or from precursors.

The enzymes regulate the level of the most potent androgens, testosterone and DHT.

Crosstalk between androgen and Wnt signalling in DPC influences progression of AGA.

DHT blocks normal HFSC differentiation deregulating DPC-secreted factors.