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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 5 α -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 grow 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 5 α -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 5 α -reductase in apocrine sweat glands like happens in sebaceous glands, supported by the fact of the predominance of 5 α -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, 3 β -hydroxysteroid dehydrogenase (3 β -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 3 β -HSD1 converts DHEA into androstenedione, and 17 β -HSD3 converts androstenedione in testosterone [39]. 17 β -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 17 β -HSD3 and 5 catalyze production of testosterone from androstenedione, while isotypes 17 β -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 17 β -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 17 β -HSD2 compared to the other isotypes probably by transcriptional regulation [41]. Moreover, a higher oxidative/reductive 17 β -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 5α 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 5α -reductase 1 inhibitor suppressed 5α -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 sheath 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 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 3 α -HSD that catalyzes conversion of 5 α -DHT into 3 α -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 *Propionobacterium 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 *Propionobacterium 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 17 β -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, 17 β -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, 5 α -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 17β -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- β 1 [149, 150], and TGF- β 2 [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. Hacaat keratinocyte proliferation and Lef/Tcf-mediated transcriptional activity stimulated by Wnt-3a were suppressed by DHT in a coculture of Hacaat 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-3 β (GSK-3 β) 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-3 β dephosphorylation mediated by androgens. In accordance with our findings, it has been reported previously that treatment of human DPC with a GSK-3 β 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-3 β 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.

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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-3 β (GSK-3 β) 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.

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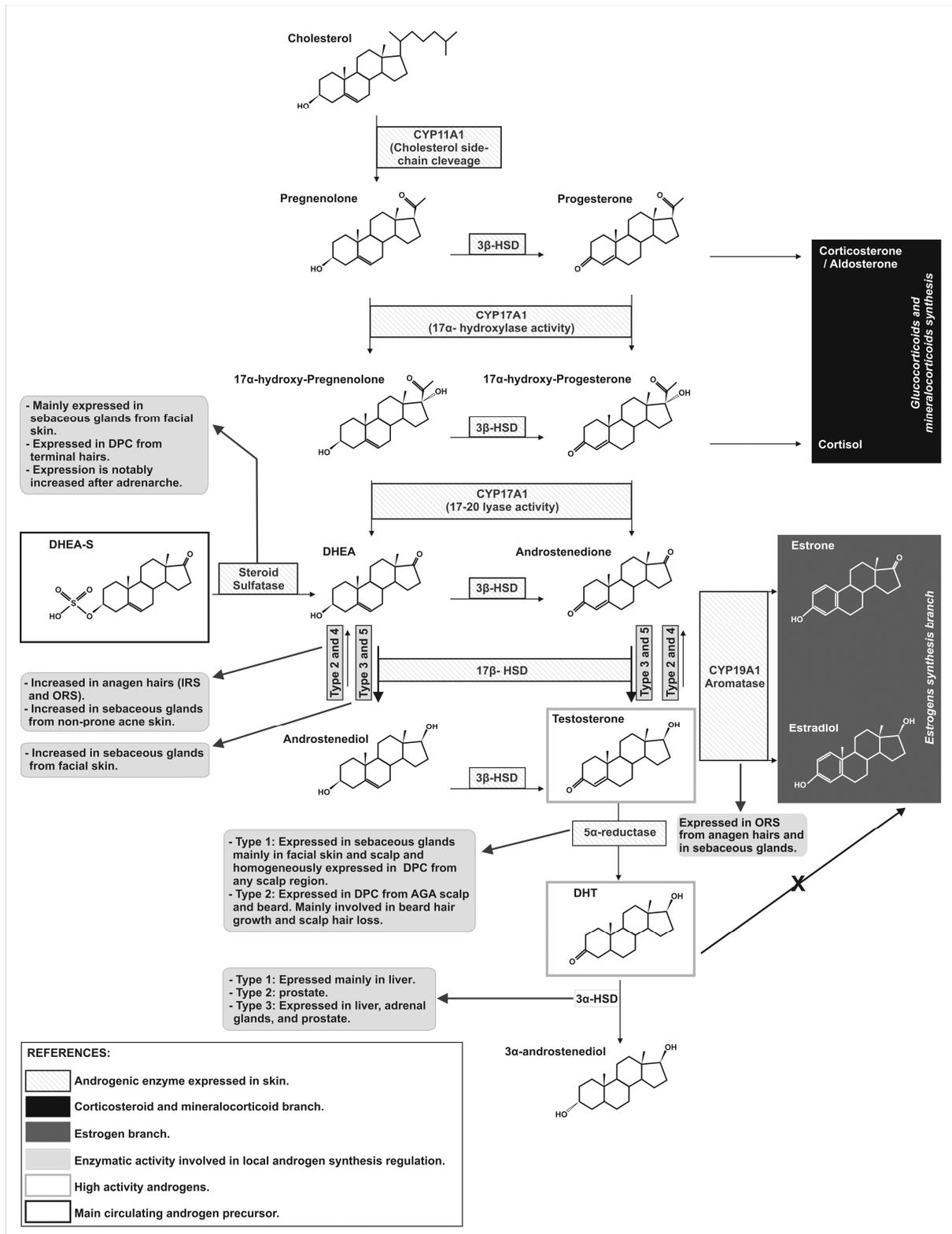
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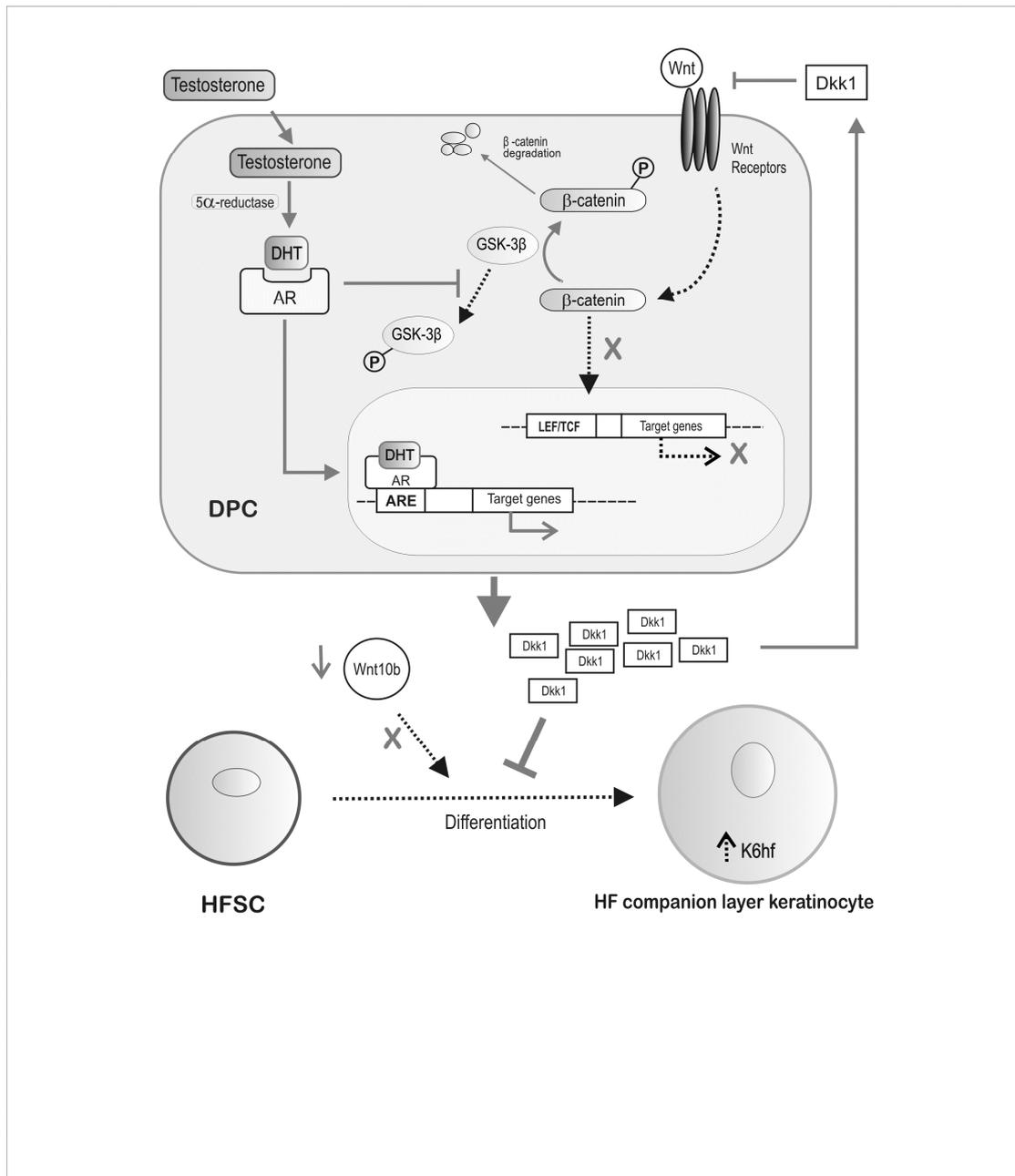
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Highlights

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.