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The Role of Androgen and Androgen Receptor in the Skin-Related Disorders

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Abstract

Androgen and androgen receptor (AR) may play important roles in several skin related diseases, such as androgenetic alopecia and acne vulgaris. Current treatments for these androgen/AR-involved diseases, which target the synthesis of androgens or prevent its binding to AR, can cause significant adverse side effects. Based on the recent studies using AR knockout mice, it has been suggested that AR and androgens play distinct roles in the skin pathogenesis, and AR seems to be a better target than androgens for the treatment of these skin diseases. Here we review recent studies of androgen/AR roles in several skin-related disorders, including acne vulgaris, androgenetic alopecia, and hirsutism, as well as cutaneous wound healing.

Keywords

androgen; androgen receptor; wound healing; androgenetic alopecia; acne vulgaris; hirsutism

Introduction

The role of androgen/androgen receptor (AR) has been implicated in the skin physiology and pathogenesis based on the facts that AR and many androgenic steroidogenesis enzymes expressed in skin, and the presence of sexual dimorphism in the architecture and diseases of skin [35,55,117]. Recent progress using animal models and conditional AR knockout (ARKO) mice resulted in several important and interesting findings regarding how androgen/AR signals play roles in the skin-related diseases [61]. In this review, we will focus on the role of androgen/AR in several skin disorders, including acne vulgaris, androgenetic alopecia, hirsutism and cutaneous wound healing. The accumulated evidences and new findings suggest that AR, but not androgens, may become a potential target for more effective treatment of these androgen/AR-related skin disorders.

Androgen and androgen receptor

Androgens are well known to control the development and functions of the reproductive system in both male and female [56,114]. The major circulating androgen is testosterone, which is mainly produced by Leydig cells in the male testis; while adrenal glands are also capable of secreting testosterone, but at a much lesser degree. Testosterone can be

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metabolized by 5 α -reductases into a more potent androgen, 5 α -dihydrotestosterone (DHT). Both testosterone and DHT can bind to AR, but DHT has ten-fold higher affinity to AR compared to testosterone [16]. While skin is not the major source of androgen synthesis, in sebocytes, sweat glands, and dermal papilla cells, the circulating androgenic pro-hormones, dehydroepiandrosterone (DHEA) and androstenedione, can be converted into testosterone and DHT. These potent androgens subsequently regulate dermal physiology through intracrine or paracrine manners [117].

AR belongs to the nuclear receptor superfamily and contains a ligand-binding domain, a DNA-binding domain, and a N-terminal regulatory domain. Upon binding to its ligand (i.e. DHT or testosterone), AR translocates from the cytosol into the nucleus and serves as a transcriptional factor to regulate the expression of its target genes, such as prostate specific antigen (PSA). In addition to androgen-dependent activation, AR function can also be modulated by interaction with various coregulators through binding the AR N-terminal domain or ligand-binding domain. There have been more than 200 AR coregulators identified, including transcriptional factors (eg. ER α and AP-1), kinases (eg. ERK and MAK), chaperones (eg. HSP70 and HSP90), cytoskeletal proteins (eg. actin and filamin), and histone modifiers (eg. HDAC and SRC) [47,107], etc. Such complexity implicates AR serves as an important hub to converge and reflect multiple cellular functions and signals. The *AR* gene locates on the X chromosome; therefore, there is only one copy of *AR* gene in males, and its defect (naturally occurring mutant) in males results in testicular feminization syndrome (Tfm) [88].

As long ago as the 4th century BC, Aristotle saw a relationship between androgenetic alopecia and gender/sexual maturity. In 1942, Hamilton et al showed that prepubertal castration prevents sebum production and androgenetic alopecia. However, conditions were reversed with the addition of testosterone [45], suggesting that androgenetic alopecia is androgen-dependent. Indeed, it has been found that inherited 5 α -reductase-II deficiency caused lower DHT levels and resulted in decreased facial and body hair [52]. The effects of androgens in the skin are mainly dependent on binding to AR. The lack of functional AR in skin prevents androgen action in skin appendages [118]. The AR gene has a polymorphism of glutamine repeats (polyQ) within exon 1, which when shortened may augment AR transactivation. It has been found that shorter polyQ polymorphisms in AR genes are more prevalent in people with androgenetic alopecia, hirsutism, and acne [27,86,94,112].

Due to the lack of a proper animal model, the detailed function of AR in the associated pathological roles remained difficult to elucidate until the conditional AR deficient mice became available [114]. Male ARKO mice were infertile with 80% smaller testes and lower testosterone levels than wild type males in addition to impaired prostate development [114]. It was also determined that a deficiency of AR in mice resulted in insulin resistance, a potential cause of type II diabetes [64]. The conditional ARKO strategy also plays a very important role in the research of the androgen/AR effects in skin-related diseases and will be discussed in the later sections of this review.

Androgen/AR in cutaneous wound healing

It has been suggested that sexual hormones are involved in cutaneous wound healing. Although there was no significant difference in the healing rate of young adults, the cutaneous wounds in elderly men heal more slower than those in elderly women; in addition, the serum testosterone level was negatively correlated to the healing rate in elderly men [3,31]. In the rodent models, AR has been detected in the keratinocytes, dermal fibroblasts, and infiltrating macrophages of healing wounds [3]. Castration of mice accelerates wound healing with attenuated inflammation, especially TNF α mRNA expression. Similarly,

systemic flutamide (an antiandrogenic compound that can block the interaction between androgens and AR) treatment promotes wound closure as well [3]. Therefore, androgens seem to suppress cutaneous wound healing through binding to AR. In another study, Ashcroft and colleagues further suggested that DHT is important to suppress wound healing by modulating inflammatory responses [36]. Systemic inhibition of 5 α -reductase enhances cutaneous wound healing in rats with less inflammatory cell infiltration, less interleukin-6 (IL-6) and TNF α expression, while TGF β 1-expressing cell number was increased in the wound sites. These findings imply that testosterone and DHT play distinct roles to suppress repair and DHT has more potent effects compared to testosterone [36]. Smad3 is downstream of TGF β receptor signaling. Upon binding to its ligands, TGF β receptor transduces signals to activate smad3 or smad2, which subsequently bind to smad4 and regulate gene expression [24]. Unlike in wild type (WT) mice, the effect of castration in enhancing wound healing is diminished in smad3 null mice, suggesting that androgen effects on wound healing suppression might be mediated by smad3 [4]. However in both castrated and ARKO mice, TGF β 1 levels were not significantly changed in wounds while healing rate was accelerated as compared to WT mice, indicating that this smad3 effect might be TGF β 1-independent [3,61]. It is noteworthy as well that cutaneous wound healing in smad3 null mice was already accelerated to the extent similar to that in castrated mice [5], so there might not be the further capacity for the effect of castration to be seen in the smad3 null mice. Castration of mice also accelerates collagen deposition in the healing wounds, and the concurrent increase of matrix metalloproteinase (MMP)-1 and MMP-13 suggests that androgen might suppress collagen deposition by modulating the expression and/or activation of collagenases [37].

Using conditional knockout strategy to study AR function in individual cell types, we found that, in general ARKO (total body ARKO) mice, cutaneous wound healing was accelerated with faster re-epithelialization, attenuated inflammation, and increased collagen deposition [61]. Interestingly, myeloid-specific ARKO mice showed a similar acceleration in wound healing, suggesting that AR in the inflammatory cells, especially macrophages, plays an important role to suppress wound repair. On the other hand, while AR in keratinocytes and fibroblasts was dispensable for regulating the overall wound healing rate, keratinocyte AR promoted but fibroblast AR suppressed re-epithelialization [61]. There is some controversy regarding the role of AR in keratinocyte functions. *In vitro* DHT treatment inhibited keratinocyte migration [38]; however, *in vivo* data showed that re-epithelialization was delayed in keratinocyte-specific ARKO mice without influencing keratinocyte proliferation, suggesting that keratinocyte AR might actually promote keratinocyte migration to hasten re-epithelialization [61]. Such controversy may be due to the fact that *in vitro* culture systems do not take into account the possible cross-talk among different cell types (such as fibroblasts and keratinocytes). In addition, the inhibitory effect on keratinocyte migration following *in vitro* DHT treatment only became obvious at higher doses (100 nM), which was higher than the physiological levels of DHT (1-10 nM). Therefore, the decrease in keratinocyte migration might be caused by cytotoxicity rather than through physiological DHT signaling.

TNF α , which is mainly expressed by the infiltrating macrophages, was reduced in the ARKO mice wounds compared to WT mice wounds, while local restoration of TNF α could reverse the acceleration of wound healing in ARKO mice, implicating that TNF α was critical in mediating AR function in wound healing suppression [61]. Further studies suggest that AR enhances local TNF α expression through multiple mechanisms, including increasing inflammatory monocyte population in the bone marrow and peripheral blood, promoting chemotaxis of monocytes by enhancing chemokine (C-C motif) receptor-2 (CCR2) expression, and enhancing TNF α expression in macrophages [61]. In addition to directly activating TNF α transcription [61], there are evidences showing that androgen/AR

activates mTORC2, which subsequently activates Akt/SKG1 to phosphorylate FOXO1 and FOXO3a [30]. Upon phosphorylation, FOXO1/FOXO3a are released from the nucleus and degraded through the proteosome pathway [22]. Interestingly, dendritic cells deficient of FOXO3 showed increased TNF α and IL-6 production [22], implicating an indirect mechanism by which androgen/AR enhances TNF α production.

In terms of therapeutic purposes, blocking AR activation by using traditional antiandrogen (flutamide) or the AR degradation enhancer, 5-hydroxy-1, 7-bis (3,4-dimethoxyphenyl)-1,4,6-heptatrien-3-one (ASC-J9®) could suppress TNF α activity and hasten wound healing rate, suggesting the feasibility to promote healing by selectively targeting AR [3,61].

While AR plays a negative role in cutaneous wound healing, it might play an opposite role in mucosal wound healing, with men able to heal mucosal wounds faster than women. The possible explanation was the fundamental difference, including lower levels of neutrophils, macrophages, and their associated factors, in mucosal wounds compared to cutaneous wounds. Additionally, the mucosal epithelium has a quicker turnover rate, with more vascularization [28].

Androgen/AR in acne vulgaris

Acne is a disorder of the pilosebaceous unit in the face, neck, and upper trunk. It has been known that sebaceous glands are androgen target tissues. Castration could prevent sebum production, while testosterone replacement could reverse this condition [87]. AR has been detected in the epithelial cells of sebaceous glands by immunohistochemistry and biochemical binding assays [18].

In addition, sebaceous glands contain most of the steroidogenic enzymes for the conversion of DHEA/DHEAS (DHEA sulfate) into testosterone and DHT [15,32]. There are three isoforms of 5 α -reductase, and their expression patterns vary across species and tissues [105]. Type I 5 α -reductase mainly express in the sebocytes, keratinocytes, and dermal fibroblasts; type II 5 α -reductase is mainly detected in the seminal vesicles, epididymis, prostate, and fibroblasts from adult genital skin, as well as the inner root sheath of the hair follicle; while the newly found type III 5 α -reductase is detected in the prostate cancer and sebocyte cell lines [17,93]. In addition to its steroidogenic activity, type III 5 α -reductase is critically involved in N-linked glycosylation [11]. Intriguingly, the sebum production rate in patients with the deficiency of type II 5 α -reductase was similar to that of normal males [52], suggesting that DHT produced locally by type I 5 α -reductase enhances sebum production. However in the clinical and in vitro studies, selective inhibitors for type I 5 α -reductase did not significantly reduce sebum production and improve acne vulgaris [62,97], indicating that suppression of 5 α -reductase alone might not be sufficient to improve acne. There are several possibilities to explain this. First, suppression of an individual type of 5 α -reductase might not be sufficient to completely block DHT synthesis due to the redundancy between different types of 5 α -reductase, and the sebaceous glands might be sensitive to even tiny amounts of DHT. Second, the newly found type III 5 α -reductase might play a more important role in regulating sebum production. Third, in addition to the difference in their potency, testosterone and DHT do not act the same way on AR activation [36], suggesting that testosterone, rather than DHT, could be a more important regulator in sebum production. Additionally, the participation of AR coregulators might compensate for the deficit in DHT production.

Hormonal treatment is not usually the first option to treat female acne. However, some acne patients (30-80%) showed various degree of hyperandrogenemia [48,100]. Although there was no positive correlation between the severity of acne and markers of androgenicity [20],

it is still possible to treat these patients by decreasing serum androgen levels or by inhibiting the action of androgens in the sebaceous glands. Flutamide is a nonsteroidal antiandrogen that inhibits the binding of DHT to AR but has no progestational effects [25]. The effects of flutamide on acne were observed mainly in patients with hirsutism and satisfactory results were observed for both conditions [95]. Although topical inocoterone treatment can reduce the size of sebaceous glands in the experimental animals [66], the clinical studies did not show significant effect to improve acne [66]. However, inocoterone indeed reduces the inflammatory acne lesions [66], likely due to suppression of AR function to dampen the inflammatory response [36,61]. Although in vitro studies with human SZ95 sebocytes and HaCaT keratinocytes, cyproterone acetate did not show significant effect on the testosterone-induced proliferation [97], but both topical and oral cyproterone acetate treatments improve acne lesions. Interestingly, the serum cyproterone level is much lower with topical treatment compared to oral treatment [42], suggesting that topical antiandrogen treatments of acne is practical and an important approach to consider, potentially with less risk of adverse effects compared to the systemic treatment [34]. Other AR blockers, e.g. spironolactone, also show certain levels of therapeutic effect on acne, but their applications are rather limited by significant side effects such as menstrual irregularity, birth defects, and hepatotoxicity [34]. Isotretinoin (13-cis-retinoic acid), a retinoid acid derivative, is a very effective sebum suppressive anti-acne agent. And there are evidences showing that Isotretinoin can modify AR signaling [8,9,72]. Human acnes are usually accompanied by excessive inflammation and infection [14]. Tetracycline is one of the antibiotics commonly used to treat acne. In addition to its antimicrobial activity, tetracycline can also inhibit inflammatory responses through regulating NF κ B activation [81].

The characteristic of human acne is a multifaceted condition involving keratinization, androgens, sebum production, infections, and genetics. Evidences also showed the association between the western diet (especially diets with high glycemic load and high amounts of dairy proteins) and acne [21,68,71,101]. Unfortunately, none of the currently available animal models recapitulates all of these properties [76,83]. Among them, fuzzy rats are a mutant strain exhibiting androgen-dependent hyperplasia of sebaceous glands. Male fuzzy rats have increased secretion of sebum, and therefore, the dorsal skin shows a dark brownish seborrheic appearance. After castration, the seborrheic appearance of the skin becomes clean and whitish, the size of sebaceous glands decreases to female size, and sebum secretion is reduced as well (Fig. 1). Upon topical treatment with the AR antagonist (RU58841) or 5 α -reductase inhibitors (finasteride and MK386) on the dorsal skin of male fuzzy rats, the inhibition of sebocytes proliferation, sebum production, and the size of sebaceous glands was observed, although with varying degrees of acne suppression [113]. The AR degradation enhancer, ASC-J9, has been shown effective on enhancing cutaneous wound healing following topical treatment [61], and the Phase II clinical studies of its topical application on acne vulgaris is on the way. Interestingly, the preliminary experiments on fuzzy rats show topical ASC-J9 treatment reduces sebum production and the size of sebaceous glands (Fig. 1). Another animal model for human acne uses Syrian golden hamsters, in which the growth of hamster flank organ is androgen dependent. After topically treating the animal with liposome-based 5 α -reductase inhibitor (4-MA), the size of sebaceous gland is reduced and apoptosis is induced in flank organ [63]. The rhino mouse (hr^{rh}/hr^{rh}) is another mutant mouse strain of hairless mice to study the sebaceous gland activity related to human acneic comedones [83]. In spite of the advantages in handling the treatment conditions and genetic manipulations, it is noteworthy that animal models for acne treatments do not always mirror the effects in clinical studies [66].

The mechanisms by which androgen/AR regulate sebocyte activity in acne vulgaris are still unclear, and several possibilities have been suggested. For example, AR might enhance the activities of fibroblast growth factor receptor 2 (FGFR2), which has been shown critical in

sebaceous gland development and homeostasis [69]. Second, AR might enhance lipogenesis in sebocytes through increasing the expression of sterol regulatory element binding proteins (SREBPs) [70]. Third, androgens might cross talk with insulin-like growth factor-1 (IGF-1) activities in regulating acne development [6,70]. IGF-1 has been shown able to induce SREBP-1 expression and lipogenesis in sebocytes [102,108]. In addition, IGF-1 can enhance AR activity through multitude mechanisms that will be discussed later in more details [70,74]. And fourth, androgens/AR have been suggested able to enhance inflammatory responses of macrophages and neutrophils [19,61]. As a result, androgen/AR might enhance not only the sebaceous gland activity, but also the inflammation that promotes acne formation and progression. Therefore, suppressing AR function by treating with antiandrogens alone, or in combination with antibiotics (i.e., to reduce bacterial infection) might be a potential therapeutic approach to treat acnes more effectively (Fig. 2). However, since most of these studies were carried out in animal models or in vitro, as mentioned above, it is necessary to further verify these mechanisms in clinical studies.

IGF-1, the growth hormone of puberty, induces synthesis of androgens and enhances 5 α -reductases activity in the skin [74]. In addition, IGF-1/PI3K/Akt activity stimulates phosphorylation of FOXO1, an AR co-repressor. Upon phosphorylation, FOXO1 translocates from the nucleus into the cytosol and releases its inhibition on AR transactivation [29,67,70]. In patients with Laron syndrome, who are deficient in IGF-1, the development of acne or hirsutism is absent, even though they have functional AR [6]. Higher FOXO proteins concentration is detected in the nucleus of these patients [43]. Once overdosed with IGF-1 treatment, Laron patients developed acne and hirsutism with hyperandrogenism [58,73].

It is noteworthy that AR is actually regulated by both androgens and AR coregulators, and the outcome of AR function is the convergence/balance of these signals [47]. In the case of acne regulation, AR activity, at least in part, is determined by androgens and insulin/IGF-1/FOXO signals. Both high glycemic-load diet and milk/dairy proteins increase the insulin/IGF-1 signaling, which in turn has substantial influence on AR activities. This might explain in part the effect of diet in acne pathogenesis [68].

Recent studies in prostate cancer cells showed that DHT could stimulate the mTORC2/Akt/FOXO1 pathway, which is important in promoting cell growth [30]. It merits further studies to examine if androgens also promote sebocyte growth through similar pathways.

Androgen/AR in androgenetic alopecia

Androgenetic alopecia (AGA), also known as “male pattern baldness”, is the most frequent type of hair loss in males [85]. This clinical condition affects ~50% of the Caucasian male population by middle age. By age 80, over 90% of Caucasian males are affected at various degrees. This pathophysiology is resultant from hair follicle miniaturization in the predisposed scalp. As in men, hair thinning and loss are commonly found in females. The prevalence of female pattern hair loss (FPHL) is ~12% among females at 20-29 years of age and ~50% for females over 80 years old [26]. The hallmark of FPHL, like that of AGA, is hair follicle miniaturization, manifested as a diffuse thinning (the so called “Christmas tree”) pattern in the mid-frontal scalp region. Although the relationship between FPHL etiology and androgen or AR is less clear, a subset of affected females displays hyperandrogenism; perturbations of the androgen/AR pathway could be an underlying cause for their suffering.

Androgens, which normally stimulate terminal hair production in many sites of the body (e.g. the beard and the axillary regions), exert an opposite effect to suppress hair growth on genetically predisposed frontal and vertex scalp [90]. In the hair follicle, the circulating male hormone, testosterone, is converted by 5 α -reductase enzyme into DHT. The DHT level is

increased in balding scalp and thus is the more relevant androgen for AGA pathogenesis. The role of AR in AGA disorder has been supported by: (i) no balding is seen in individuals lacking a functional AR (for example, in patients with androgen insensitivity syndrome) [41]; and (ii) AR expression in the scalp of AGA patients is site specific—elevated in the frontal and vertex regions but normal in the parietal and occipital regions [49]. The gene association studies highlighted the AR gene as the only risk gene confirmed to date for AGA phenotypes [51]. It has been accepted that an AR gene variant or variant(s) are the primary culprit responsible for AGA onset and development, likely through an aberrant expression of the AR protein in the scalp follicle. A recent gene association study found that men with Kennedy's Disease (or spinal bulbar muscular atrophy), a mortal neuron disease caused by mutant AR gene, had significantly thicker hair than normal men. Kennedy's Disease is associated with limited androgen sensitivity because of a dysfunctional AR, with longer polyQ repeats or polymorphism in their AR gene; therefore, this discovery suggests that active AR function is a risk factor for androgenetic alopecia [99]. However, balding may be inherited in a polygenic mode [59]. Genome-wide studies of phenotypic identical siblings have been initiated to study new susceptible genes for AGA and have discovered a link between this skin disorder and loci located at chromosomes 20p11 [92] and 3q26 [50]. It is possible that genes present in these loci increase the risk for AGA, although signaling pathways associated with this hair disorder have not been identified. Recent meta-analysis results identified a significant association between the G allele of the AR StuI polymorphism and the risk for AGA especially in the white populations, but no association was found between the CAG or GGC polymorphism and the risk for AGA [116].

In animal studies, spontaneous hair growth in mice is at least partly regulated by the AR activation pathway; gonadectomy induced a wave of hair regrowth in male mice [2] and the anagen phase of the second hair cycle was longer in ARKO mice than in their WT littermates [82].

The dermal papilla is considered to be the main site of androgen action in the hair follicles, because dermal papilla cells derived from androgen sensitive sites (e.g. beard and frontal scalp) contain low capacity, high affinity AR [91]. However, the molecular action of androgens on the dermal papilla remains largely unclear. The current hypothesis suggests that the androgen/AR complex alters the production of autocrine and paracrine regulatory factors in the dermal papilla to influence self growth or the growth of epithelial components of the follicle. Using co-culture techniques, 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 co-cultured epithelial cells [53]. Other diffusible regulatory factors modulating papilla-epithelium interaction may exist, which likely include the Wnt (Wingless-type MMTV integration site family) proteins [57].

Minoxidil is the only topical therapy approved by the US Food and Drug Administration (FDA) to treat AGA. This drug is available as 2% (also, the only drug approved for FPHL) and 5% solution preparations, and a 5% foam formulation. Minoxidil, a peripheral vasodilator, stimulates the growth of follicle keratinocytes and prolongs the anagen phase [75]; it is recommended for individuals whose hairs have not been completely miniaturized. Topical twice per day dosing of Minoxidil could take 4-6 months to produce a therapeutic effect and the maximal effect is reached after approximately one year of use. In clinical trials, the 2% or 5% solution was found to arrest hair loss on the vertex and frontal scalp for a majority of patients, but stimulated mild to moderate hair regrowth in only 30%-45% of the recruits [85]. Minoxidil treatment, if effective, is a life-long therapy, because hair growth would stop and the retained hair would fall once the treatment is discontinued. The therapeutic target for Minoxidil in AGA is still elusive, while potassium channels and

prostaglandins are among the suggested ones, there is yet conclusive evidence to prove this [75]. Recent studies suggested the increased prostaglandin D₂ (PGD₂) level in the hair follicles is one of the major causes for AGA [33]. The effect of Minoxidil in increasing Prostaglandin E₂ (PGE₂) [60] warrants further studies to determine if the treatment of Minoxidil reduces the production of PGD₂, possibly due to competing for the common upstream substrates of PGD₂ and PGE₂. Given that prostaglandin D₂ synthase (PTGDS), the key enzyme to generate PGD₂, is one of the androgen-responsive genes [104,115], it might explain at least in part the mechanism behind androgen/AR effects in AGA.

Finasteride is a systemic medicine approved in 1997 by the FDA to treat AGA. This compound is an inhibitor of the type II 5 α -reductase, which converts testosterone to DHT and is abundantly expressed in the scalp [54]. With the approved dose of 1 mg per day, finasteride stabilized hair loss in most subjects, but induced mild to moderate hair regrowth in only 37-61% of the sufferers. Improvement in hair density may not be perceived until after 6-12 months of treatment, and 2 years of use are required to achieve a maximal effect [85]. Finasteride, similar to minoxidil, is not curative. Research interest has been focused on the development of dual type I and type II 5 α -reductase inhibitors, such as dutasteride [84], in hopes of finding a more satisfactory drug to replace finasteride.

Since currently available treatments for AGA are very limited and face the problems of a slow onset of beneficial effects, high individual variability in efficacy, and unwanted sexual side effects, it is important to find a novel approach to treat AGA. Based on the more updated understanding of AGA pathogenesis, AR may serve as a better target than DHT to tackle this hair loss disorder. Classic antiandrogens are undesirable, because they are ineffective through dermal dosing and their long-term systemic use raises the risks of gynaecomastia and impotence. A new approach to treat AGA safely and effectively is to develop a topical anti-AR therapy to specifically silence the AR protein in the scalp, but not elsewhere in the body.

Androgen/AR in hirsutism

Overproduction of androgens or increased sensitivity of hair follicles to androgens has been the common cause of hirsutism in females. There are two major paths for treating hirsutism. The first is cosmetic treatment, which includes plucking, shaving, waxing, and laser removal of unwanted hairs. The second is hormonal treatment that usually comes in forms of antiandrogens or AR blockers. While these antiandrogen treatments may have adverse side effects in men, the side effects for women who have hirsutism may be averted through a variety of ways, making these the preferred treatment methods. Because hair growth is a very slow cyclical process, it may take several months for drug effects to appear.

Spironolactone is an AR blocker that competes with androgens to bind with the AR without activating the AR's transcriptional functions. However, there are several detrimental side effects to this drug, including menstrual irregularities, breast tenderness, fatigue, gastritis, and headaches. This may be an option for treating androgenetic alopecia, but is more often used to treat hirsutism, as most of the side effects may be evaded with the use of a contraceptive pill [12]. Studies have shown that spironolactone treatment of 100 mg/day reduces serum testosterone levels. The treatment with spironolactone is dose-dependent, but most physicians do not recommend taking more than 100 mg/day [65]. Whereas it may cause nausea and the other side effects stated above, the treatment also resulted in a significant reduction in hair growth [13].

Cyproterone acetate is another AR blocker that directly competes with androgens to bind to the AR. It is a progestin derivative, and therefore has antigonadotropic action and also blocks androgen secretion. Although it is internationally used as a drug for hirsutism

treatment, it is not allowed in the United States because it increased the occurrence of liver tumors in rats [96], as well as the report of several cases of liver cancer in women who used cyproterone acetate [98].

Flutamide is also an AR blocker that may be used to treat hirsutism. Women taking flutamide 125 mg three times a day experience lower serum levels of androgens after a year. Treatment with flutamide also results in significant recovery from hirsutism conditions. Blocking the AR most likely resulted in reduced androgen levels, which in turn slowed hair growth [78]. However, while it is an effective treatment, there is also concern for liver toxicity which may occur after several months of continuous use [109].

Finasteride is currently used in clinics for male androgenetic alopecia. Studies have shown that finasteride treatment was as effective in reducing hirsutism as spironolactone or flutamide. This is most likely due to the ability of finasteride to block the conversion of testosterone to the much more potent DHT [80]. However, in another study, flutamide was shown more effective than finasteride in treating hirsute women [106]. The efficacy of finasteride as compared to flutamide needs further verification. Aside from the efficacy, there is concern about using finasteride during pregnancy as it may cause birth defects.

Eflornithine is a relatively new topical treatment that seems to have a very favorable effect in treating hirsutism. It is an irreversible inhibitor for ornithine decarboxylase, which is normally affected by androgens to regulate cell proliferation in the hair follicle. Because eflornithine blocks this enzyme, the reduced enzyme activity results in little or no hair growth. However, like most topical treatments, the effect is only temporary and the reduction of hair growth is reversed shortly after treatment is discontinued [79]. Eflornithine can also improve the efficiency of standard laser hair removal [46,110].

Chlormadinone acetate is a steroidal progestin with antiandrogen and antigonadotropic effects. There are also reports showed its beneficial effect for hirsutism treatment in women, although the detailed mechanism remains elusive [39,44].

Future direction and potential impact to the skin-related disorders

The involvement of androgen/AR in skin pathogenesis has been studied for decades; however, the molecular mechanisms of how androgen/AR participates in these skin disorders remain largely unknown. The establishment of the conditional ARKO mouse model could provide a useful tool to dissect AR function in the individual cells or tissue types in skin pathogenesis and lead to insights/mechanistic explanations concerning these diseases. For example, ARKO mice under the rhino mouse background could be used to test the effects of androgens/AR in the sebaceous gland activity related to acneic comedones [7]. ARKO mice under the B6CBAF1 background might be used for studying androgenetic alopecia [103]. More and more studies could be expected in the near future to reveal the underlying mechanisms. From the conventional point of view, androgens and AR rely on each other to execute their physiological functions; however, a new concept has been emerging lately which discriminate between the roles of androgens and AR [19,61,89]. Increasing evidence suggest that several other factors, such as estrogens, antiandrogens and kinases, are able to activate the AR function in the absence of testosterone and DHT. Even growth factor (eg. insulin/IGF-1) signaling can modulate AR activities. On the other hand, androgens also have AR-independent effects [77,89]. To take these “non classic” androgen and AR functions into consideration, conditional ARKO models will provide very useful tools to distinguish the roles of androgens from the roles of AR. In addition, using the *Cre-loxP* system to generate female ARKO mice, it is also feasible to study the AR functions in female mice.

Current treatments targeting androgens (such as in the patients with prostate cancer) employ either surgical or chemical castration and usually result in considerable side effects, such as impotence, loss of libido, osteoporosis, and fatigue [111]. Due to the profound adverse effects over the benefits for patients, these treatments are not to be used to treat skin disorders. Since the distinct roles of androgens and AR has been implicated, it is therefore very interesting and possible to develop better therapies that can specifically target AR (instead of androgens) or its downstream pathways to treat these disorders. Topical treatments with antiandrogens or AR degradation enhancers could be a better approach over systemic treatments to minimize the side effects, providing that these topical reagents can be efficiently delivered into the target cells and degraded before they can enter the circulation system at a significantly detrimental concentration. Indeed, an AR degradation enhancer has been demonstrated effective in the topical treatment of wound healing and acne with minimized adverse effects [61].

From the clinical point of view, advantages rise from using AR degradation enhancers or other small molecules to target AR in therapies. For example, in the clinical situation, impaired wound healing is prevalent in patients with diabetes mellitus, which is usually associated with prolonged and excessive inflammation in the wound tissues. In diabetic animal models, systemic anti-TNF α antibody treatment promotes cutaneous wound healing [40], suggesting that TNF α plays a critical role in impairing the healing of diabetic mice. Therefore, directly targeting AR might be a potentially better therapeutic approach for diabetic wounds, with the following advantages over TNF α neutralizing antibody treatment: First, although TNF α critically mediates the effects of AR on wound healing suppression, it does not encompass all functions of AR [61]. Therefore, directly targeting AR will promote wound healing on a more general scale than will targeting TNF α . Second, the cost of using synthetic small molecules is significantly less than the cost of using neutralizing antibodies. Finally, chemical-based therapeutics are more stable and flexible in terms of drug delivery than protein-based therapeutics.

Many skin diseases, such as acne and psoriasis, involve abnormal or excessive inflammatory responses. It has been demonstrated that AR in macrophages can promote inflammation, especially via up-regulation of TNF α expression, to suppress wound healing [3,61]. Therefore, it would be of great interest to examine if AR is also involved in the regulation of other (skin) diseases showing dysregulation of inflammatory responses [1,10]. For example, in the autoinflammatory pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome, the symptoms include acne at puberty (with increased androgen and IGF-1 signaling) as well as pyoderma gangrenosum, a chronic autoinflammatory problem with impaired wound healing. Treatment with a TNF α blocker could improve the pathology of PAPA syndrome [23]. It is therefore conceivable that reduction in AR activities might be beneficial for the disease. The ultimate goal is to attenuate the disease states of these androgen/AR-involved diseases more efficiently with minimized side effects.

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Fig. 1. ASC-J9® treatment alleviates seborrhea symptoms in male fuzzy rats. Starting from 28 days of age, male fuzzy rats were separated into 3 groups. One group was castrated (Cas), another was treated topically with ASC-J9® cream on the dorsal skin 5 days a week (ASC-J9®), and the other group was left untreated (Non). **(A)** Eight weeks after castration or ASC-J9® treatment, the dorsal skin was photographed to compare the seborrhea between groups. **(B)** The skin tissues were dissected and treated with 17 mM EDTA/PBS buffer for 2 hours at 37°C. Then the epidermis was separated from the dermis by forceps and fixed with 4% paraformaldehyde/PBS solution. The sebaceous glands were observed under a dissecting microscope at a magnification of 50X and photographed. Circles indicate the sebaceous ducts, and **(C)** the diameter of the ducts was measured using Image J software (NIH). Data are presented as mean $\pm$ S.E. *, $p < 0.01$

Fig. 2.

The role of androgens/AR in acne formation/progression. Acne formation in human results from excessive sebum formation and is usually accompanied by excessive inflammation and infections in the hair follicle. Macrophages and neutrophils are recruited to the inflamed follicles and secrete cytokines and other mediators to promote the inflammation and infection clearance. However the inflammatory response also damages the normal tissues in the follicles. AR can promote the inflammatory response mediated by macrophages and neutrophils, and androgens/AR can also directly promote sebum production that plugs the follicle pore. The IGF-1/FOXO1 pathway can enhance AR activity and subsequently promote sebum production. Current treatments for acne include antibiotics for infection clearance and therefore reducing the subsequent inflammation. Some antibiotics (eg. tetracycline) possess both antimicrobial and anti-inflammatory effects. Retinoid (and its derivatives, eg. isotretinoin) suppresses sebum production and promotes extrusion of the plugged material in the follicles. Antiandrogens reduce androgen levels, and AR degradation enhancers (ADEs) directly target AR to regulate the AR-mediated activities during acne formation/progression, such as reducing sebum production and suppressing the function of macrophages and neutrophils to dampen the inflammatory response.