



Androgen modulation of Wnt/ β -catenin signaling in androgenetic alopecia

A. Premanand¹ · B. Reena Rajkumari¹

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Abstract

Androgenetic alopecia (AGA) is a dermatological disorder of scalp hair loss characterized by a progressive miniaturization of hair follicles with shortened anagen phase leading to a decreased number of hairs on the scalp. It is a complex polygenic trait prevailing around two-thirds of the male population. Elevated expressions of 5 α -dihydrotestosterone and androgen receptor are the causal factors for AGA. This review describes recent studies on the role of androgens and androgen receptor (AR) transactivation activity in modulating the Wnt/ β -catenin signaling in the dermal papilla cells of the balding scalp in androgenetic alopecia. Here, we analyse the androgen-induced dermal papilla secreted factors on stimulating catagen entry in hair follicles and the molecular cross-talk between AR and Wnt/ β -catenin signaling with a brief mention on alternative treatment strategy targeting Wnt/ β -catenin signaling for promoting hair growth.

Keywords Androgenetic alopecia · Androgen · Androgen receptor · Dihydrotestosterone · Dermal papilla · Wnt · β -catenin

Introduction

Alopecia or hair loss is a dermatological disorder in which the hair abnormally sheds from the skin where it is normally present [76]. It is caused by many factors and, in most instances, inflammatory, hormonal, genetic, or environmental factors either variably dominate or interact with each other in the development of alopecia [4]. Hair loss can take place anywhere on the body, but mostly it affects the scalp. Scalp hair loss provokes serious psychological issues in humans and affects their quality of life. The common types of scalp hair loss are androgenetic alopecia, telogen effluvium, anagen effluvium, alopecia areata, tinea capitis, and cicatricial alopecia, etc [73]. Scalp hair loss mediated by androgens is called androgenetic alopecia; and it is the most common form of hair loss in humans [73].

Androgenetic alopecia (AGA), also known as androgenic alopecia, hereditary baldness, and pattern baldness, is

characterized by a progressive loss of visible terminal hair on the scalp via hair follicle miniaturisation [63]. AGA is a unisex disorder and manifests in both sexes, but the hair loss pattern established is different. Male pattern baldness is characterized by a defined M pattern starting with the bi-temporal recession of the frontal hairline to form a characteristic M shape. Concurrently hair also starts thinning at the vertex which eventually leads to a bald patch that finally widens and joins with the receding frontal hairline [18]. On the other hand, a diffuse hair loss pattern occurs in females. The hairline does not recede in women, and very rarely, it will lead to complete baldness [10]. Male pattern baldness develops in 30–100% of men with increasing age from 17 to 80 years [7], whereas only 12–40% of women exhibit female pattern baldness by the age of 30–70 years [58]. Patterned hair loss commencing in the adolescent period leading to well-established bald appearance before 30 years of age is called as adolescent AGA or premature AGA or early onset AGA [66].

✉ B. Reena Rajkumari
b.reenarajkumari@vit.ac.in

A. Premanand
anandprem1792@gmail.com

¹ Department of Integrative Biology, School of Bio Sciences and Technology, Vellore Institute of Technology, Vellore 632014, Tamil Nadu, India

Human hair dynamics

The human scalp hair growth follows a mosaic pattern of hair follicle (HF) activity unlike most mammals in which synchronous or wave pattern is present [74]. A typical

human head has approximately 100,000–150,000 HFs and each follicle has the ability to grow about 20 single hairs way through hair cycle during a person's lifetime [69]. The hair follicle is a dynamic mini-organ made up of different cell populations linked to ectodermal, mesodermal, and neural crest origin. The outer root sheath (ORS), matrix, inner root sheath (IRS), and hair shaft are derived from epithelium, while the dermal sheath and dermal papilla (DP) are derived from mesenchyme [40]. Each HF is a regenerating system and physiologically undergoes continuous cycles of anagen (growth phase), catagen (regression/involution phase), telogen (resting phase), and exogen (hair shedding or loss of telogen club hair—which may not occur always) [1]. The hair cycle relies on the cyclic activation and suppression of hair follicle stem cells (HFSC) which regulates the proliferation, differentiation, and apoptosis of a variety of cells in the HF niche [34]. Many reciprocal signaling cascades such as Wnt/ β -catenin, Sonic Hedgehog (SHH), bone morphogenetic protein (BMP), notch, transforming growth factor- β 2 (TGF- β 2), NF- κ B, and fibroblast growth factors (FGFs) between the epithelial and mesenchymal cells in the HF are involved in the HF morphogenesis and regeneration during hair cycle [38, 52, 65]. During embryonic HF development, the induction, organogenesis, and cytodifferentiation stages of the HF are formed by direct interactions between the epithelium (keratinocytes) and mesenchyme (dermal fibroblasts) [48, 65]. However, during hair regeneration in adult hair cycle, the DP stimulates the growth, differentiation, replication, and fates of the epithelial cells. The epithelial cells sequentially regulate the growth of neighbouring mesenchymal cells. The epithelium and mesenchyme collaborate together to construct the HF mini-organ again [48]. Therefore, DP plays a vital role in the HF regeneration during hair cycle and any abnormality in adult HFs should start with distortions in the dermal papilla cells (DPCs).

Androgenetic alopecia: conceptualization

The hypothesis on male pattern baldness started as long ago as fourth century BC when Aristotle observed that “eunuchs do not go bald” and advocated the relationship between baldness and gender/sexual maturity [43]. Then, in 1942, James B. Hamilton, through his studies on eunuchs and eunuchoids, demonstrated that male hormone substances (androgens) along with genetic predisposition are the prerequisite and incitant for common baldness [17]. He observed that in men, after puberty with increasing age, androgens stimulate facial hair growth (beard), axillary, and pubic hair, but suppress hair growth at the temples and vertex in individuals with appropriate genetic background. However, prepubertal castration prevents this change in hair growth. Furthermore, in a subsequent study

in 1951, Hamilton observed that testosterone administration does not develop baldness in eunuchs and eunuchoids without appropriate genetic predisposition and emphasized the importance of genetic factors in AGA pathology [19]. Thus, the term “androgenetic” describing the underlying factors of pattern baldness is coined a decade later by Ludwig (1962) by fusing the words androgen and genetic [53].

In AGA, thick pigmented terminal hairs were transformed into thin non-pigmented vellus hairs through miniaturization of hair follicles by repeated hair cycles with diminished anagen phase [27]. Subsequent studies in the next decade revealed that testosterone (T), the major circulating androgen, passes easily through the cell membrane and is metabolized into a more potent 5 α -dihydrotestosterone (5 α -DHT or DHT) by the cytoplasmic 5 α -reductase (5 α -R) enzymes. While both T and DHT can bind to the androgen receptor (AR) resulting in a receptor-ligand complex, 5 α -DHT has five times higher binding affinity to AR than T. The complex is then translocated to the nucleus, binds, and regulates the androgen-responsive elements (AREs) in the chromatin [29, 43]. However, 5 α -DHT has ten-fold higher potency than T in AR signaling, and thus, DHT ligand bounded AR strongly regulates the AREs [27, 29]. Since there is no correlation between the levels of serum, free and bioavailable testosterone, the pathogenic basis of androgens in AGA is generally presumed to be mediated by intracellular signaling inside the target cells [13]. Findings that reported heightened expressions of AR and DHT in the balding DPCs than non-balding DPCs implied that AR-5 α -DHT complexes and their transactivation activity are responsible for the miniaturization of hair follicles in AGA [27].

Molecular mechanism

Androgen: the incitant

Androgens are an important regulator of hair growth and their effects vary depending on the body site and precisely to the HF itself [62, 64]. The action of blood circulating androgenic steroid hormones (T and 5 α -DHT) inside the cell is mediated by the androgen binding receptor [43]. In the hair follicle, AR is located in the DPCs and not in the surrounding epithelial cells [27, 28], indicating that DP is the target for androgens in the HF niche [27]. Though men with AGA have normal levels of circulating androgens, the amount of 5 α -DHT in the DPCs of the HF is increased due to the activity of 5 α -R type 2 enzymes. Since androgen is the principal incitant in AGA [17], it is believed that the role of androgen in AGA starts with the AR activity of DPCs.

Polymorphisms in androgen receptor: the necessary prerequisite

Androgen receptor, a member of nuclear receptor superfamily, is considered to play a vital role in AGA as (1) there is no balding seen in individuals with non-functional AR (e.g.: patients with androgen insensitivity syndrome) and (2) site-specific expression of AR in the scalp of AGA patients with elevated expression in frontal and vertex regions but normal in parietal and occipital regions [22, 43]. Moreover, gene association studies have highlighted AR as the most plausible candidate gene for AGA phenotypes [20]. The human AR is reported to have two polymorphisms glutamine (CAG) repeats and glycine (GGC) repeats of varying length and a *StuI* restriction site single-nucleotide polymorphism (SNP) on exon 1 [9, 67]. AR gene with shorter polymorphisms of glutamine (polyQ) repeats which augment AR transactivation function [5, 31] has been associated with AGA [12, 68]. In addition, the presence of thicker hair than normal in men with Kennedy's disease (dysfunctional AR due to longer polyQ repeats) [71] supports the notion that heightened AR transactivation may be responsible for AGA. However, another study associated glycine (GGN) repeats in AR with AGA [23]. Though glycine repeats do not confer any androgen-dependent AR transactivation, the AR protein levels were found to be high in cells with shorter glycine repeats [9]. A 2012 meta-analysis on eight studies identified *StuI* polymorphism (rs6152, G > A) as the significant risk for AGA [80] which is further substantiated by a separate study on patients with prostate disease recently [39]. Exon 1 resides in the N terminal domain of AR which performs major transactivation function. The three polymorphisms in exon 1 of AR, which are associated with AGA, give rise to increased AR activity, AR protein levels, and AR transactivation of genes. These studies imply that either increased AR transactivation or increased AR protein or levels or both factors in the DPCs are responsible for AGA.

AR co-activators are proteins that modulate the activity of AR by binding to one or more regions on it [8]. In balding DPCs, the co-activator ARA70 β /ELE1 β is expressed less when compared to normal DPCs from occipital areas [44]. Whereas another study reported that co-activator Hic-5/ARA55 is found to be increased in androgen sensitivity DPCs of beard and balding DPCs but not in occipital areas [24]. The selective expression of AR co-activators in the balding DPCs in AGA may answer the question on "why the growth of HFs remains normal elsewhere in the body when stimulated by the same ligand 5 α -DHT?" [20]. Additional works on the analysis of co-activators between balding DPCs and beard DPCs are necessary to understand the selective role of androgen in DPCs.

The dynamic interaction of AR with its target gene sites or AREs in the chromatin strongly depends on the nature of

the ligand. The ligand nature determines the type of co-activators recruited by AR by inducing conformational changes in the ligand-binding domain of AR. In addition, mutation in AR confers different transcription activity. Consequently, the factors such as AR gene polymorphisms, ligand nature, and co-activators significantly affect the dynamics of AR interactions with chromatin resulting in different AR function on the transcription of genes [37]. AGA has been associated with both AR polymorphisms and different co-activators expression in balding DPCs. As 5 α -DHT is expressed more in the DP of AGA, studies on the dynamics of 5 α -DHT-AR complex and their selective recruitment of co-activators are required to understand their activation of target genes in the balding DPCs.

Androgen-induced DPC secretion of factors and catagen entry of HF

In AGA patients, the duration of anagen phase in HFs of the frontal and vertex regions is decreased and more hairs than usual are in the catagen phase of the hair cycle [70]. The decreased anagen length implies that the hair follicles are being pushed out of growth phase by driving them into the resting phase. Studies have shown that DHT induces DPCs of AGA phenotype to secrete paracrine factors that are responsible for catagen induction in HFs.

In a co-culture study of DPCs with outer root sheath keratinocytes (KCs), DHT treatment induced the DPCs to secrete Dkkopf-related protein 1 (DKK-1) which inhibited the growth of ORS cells [42]. DKK-1 is a catagen inducer and regulates the anagen-to-catagen transition of HFs [41]. Since DKK-1 is one of the most DHT up-regulated genes in balding DPCs, it is evident that DHT drives the HFs in the balding scalp to enter into catagen phase through the paracrine factor DKK-1 [42].

DHT also up-regulate interleukin-6 (IL-6) secretion in balding DPCs. In addition, IL-6 was shown to suppress the proliferation of KCs and inhibit hair shaft elongation. In mice, IL-6 injection caused premature onset of catagen. Hence, IL-6 is another paracrine factor secreted by balding DPCs induced by DHT that promotes regression phase in HF [40].

Furthermore, a previous co-culture model study of AR overexpressing human DPCs (mimicking balding DPCs) and KCs reported that androgen induces the DPCs to secrete transforming growth factor- β 1 (TGF- β 1) which, in turn, suppressed the growth of epithelial KCs [25, 26]. In addition, TGF- β 1 is also reported to be a catagen inducing molecules [65].

In addition to this, a recent study found that the enzyme prostaglandin D₂ synthase (PTGDS) and its product prostaglandin D₂ (PGD₂) were at high levels in the bald scalp when compared to the haired scalp [15]. Since gene expression and

protein-level studies in the mouse have shown that PTGDS and PGD₂ were at peak levels in the late anagen imminent to catagen phase. It was inferred that elevated levels of PGD₂ in the balding scalp drive the hair follicles to an early catagen phase [15, 56]. Besides, there is a hypothesis that increase in androgen receptor activity could increase PGD₂ concentrations on the scalp [3, 79]. Conclusively, it is apparent that DHT drives the HF in the balding scalp to enter into catagen phase through secretion of factors such as DKK-1, IL-6, TGF-β1, and PGD₂.

Androgen interference of Wnt signaling and impaired HFSC differentiation

Wnt signals are generally active and participate in early development, growth, and maintenance of various tissues. They have many unique properties out of which (1) short-range action and (2) mediating local signaling between neighbouring cells are predominant [6]. The current Wnt/β-catenin pathway model in cell signaling is described as follows. In the absence of a Wnt, a complex of protein inclusive of axin, adenomatous polyposis coli (APC), glycogen synthase kinase-3β (GSK-3β), casein kinase 1 (CK1), protein phosphatase 2A (PP2A), and the E3-ubiquitin ligase (β-TrCP) residing in the cytoplasm binds β-catenin. The complex specifies a β-TrCP recognition site on β-catenin by phosphorylation and ubiquitinates it. After phosphorylation and ubiquitination, the β-catenin is degraded by the proteasome. Binding of Wnt to its frizzled receptor on cell surface induces the association of axin with phosphorylated lipoprotein receptor-related protein (LRP). Disheveled (Dvl) protein acting downstream of frizzled receptors is also required in Wnt pathway activation. The destruction complex gets inactivated and ubiquitination by β-TrCP is blocked resulting in accumulation of newly synthesized β-catenin in the cytoplasm. In the nucleus when Wnt is off, the T cell factor (TCF) is repressed by Groucho and when Wnt is on β-catenin binds to TCF leading to up-regulation of target genes [6, 57].

Wnt/β-catenin signaling plays a pivotal role in the embryonic hair follicle morphogenesis, development, and regeneration during hair cycle [33, 65]. In hair cycle, the telogen-to-anagen transition of HF is driven by balanced interactions between Wnt/β-catenin signaling and BMP pathways [2]. In the hair follicle bulge and secondary hair germ, the epidermal stem cells and melanocyte stem cells interact with each other and jointly undergo activation plus differentiation to regenerate hair by activating Wnt signaling [61]. Thus, any aberrant regulation in Wnt signaling leads to disordered hair growth and evidently, studies have associated Wnt inhibition with reduced hair growth [33, 47].

Dihydrotestosterone suppression of Wnt3a-mediated proliferation keratinocytes was the first study to emphasize the

molecular crosstalk between androgen and Wnt signaling in AGA [36]. Wnt 3a is secreted from hair epithelium and it is shown to maintain anagen gene expression in DP cells [35, 36]. Observation of DHT suppression of Wnt signal-mediated transcription only in DP of AGA suggested that Wnt signaling is aberrated.

Leiros et al., in 2012, revealed that DHT and AR signaling activate glycogen synthase kinase-3β (GSK-3β) in DPC which inhibits canonical Wnt pathway [49] by phosphorylating β-catenin leading to its degradation by the proteasome [51]. GSK-3β activity is enhanced in the presence of DHT through inhibition of its phosphorylation at Ser-9. The study concluded that GSK-3β activation in DPC inhibited HFSC differentiation in AGA [49]. Interestingly, a previous study reported that GSK-3β inhibition in DPCs leads to insulin-like growth factor-1 secretion promoting hair growth [78]. A subsequent study by the team in 2017 found that DHT stimulation in DPCs down-regulates the WNT agonists WNT5a and WNT10b while up-regulating the Wnt antagonist DKK-1 [50]. DKK1 is a natural Wnt inhibitor and it disrupts the Wnt-induced frizzled-LRP complex formation [6]. These two studies clearly show that the impaired HFSC differentiation in AGA [16] is mediated by androgen modulation of Wnt agonists and antagonists expression balance in DPCs [49, 50] (Fig. 1).

The Wnt activity in bald scalp DP is also found to inhibited by negative regulator of Wnt CXXC-type zinc-finger protein 5 (CXXC5). CXXC5 interacts with the disheveled protein [45] and inhibits the Wnt pathway [6]. The mechanism for the increased expression of CXXC5 is not yet identified and further studies are warranted [33, 45].

Conclusively in androgenetic alopecia, it is substantiated that aberrant regulation of Wnt leads to hair loss. Wnt is externally inhibited by the paracrine mediator DKK-1, and inside the cells, the Wnt signaling is inhibited through CXXC5 and increased GSK-3β activity. AR signaling is responsible for dephosphorylation of GSK-3β and secretion of paracrine factors DKK-1, IL-6, TGF-β1, and PGD₂, which inhibits the keratinocytes growth and promotes the HF into catagen phase (Fig. 1). Reduced anagen phase results in short hair length; and in successive hair cycles, the new anagen hair is shorter than the previous one. Shedding of telogen hairs and delay in anagen regrowth results in a reduced number of hairs in the scalp giving a bald appearance [70].

Treatment and management

Although AGA is not a life-threatening disease, it affects the self-esteem and life quality of the affected men. Presently, minoxidil 2–5% solution is available to promote hair growth through topical applications, while 5α-R inhibitors finasteride and dutasteride are the oral synthetic drugs approved

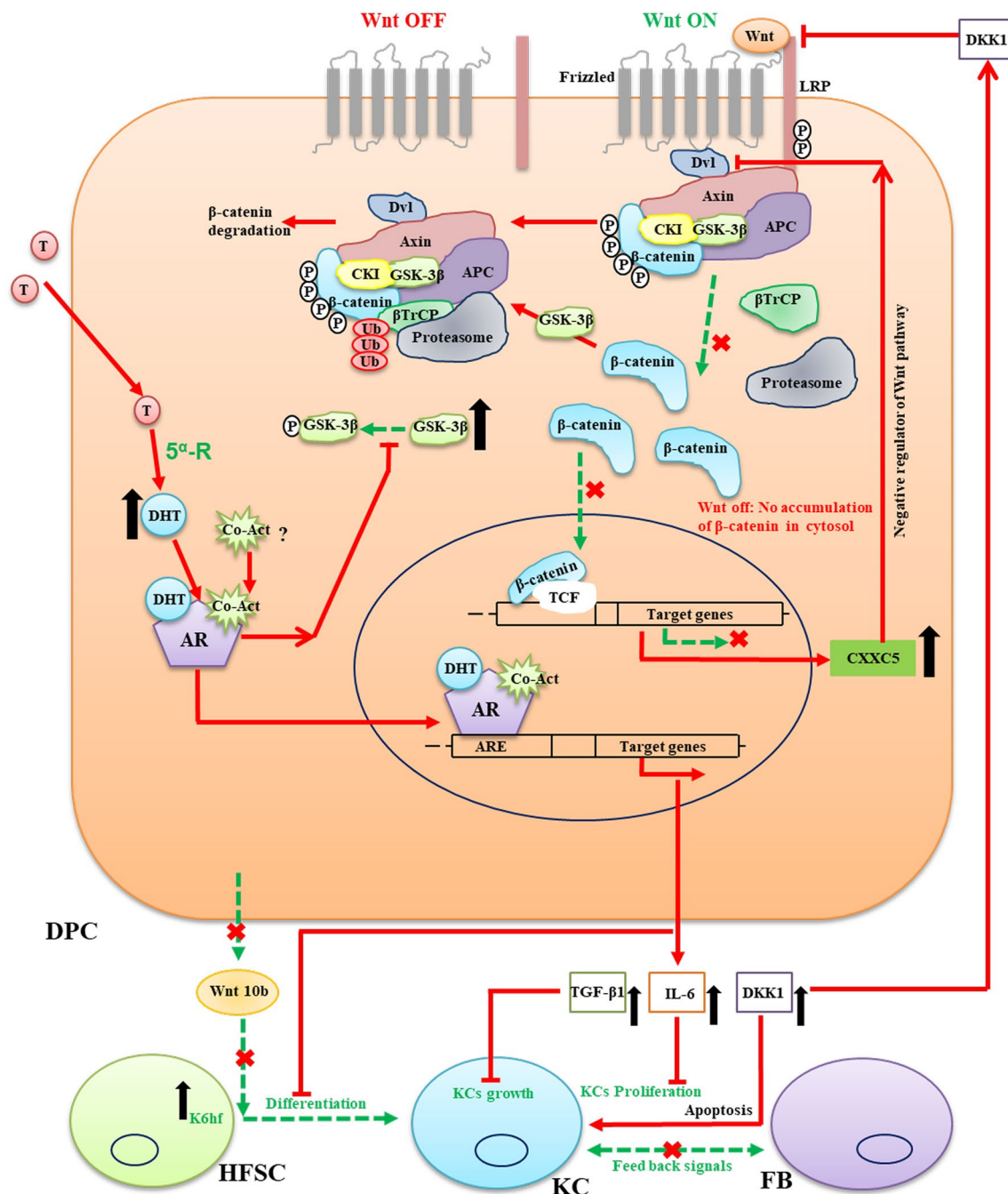


Fig. 1 Androgen modulation of Wnt/β-catenin signaling in DPC and its effect on hair growth. The green dashed line represents the normal activated Wnt/β-catenin signaling in the DPC and subsequent interactions between the epithelium and mesenchyme leading to hair regeneration in hair cycle. The red continuous line denotes the molecular cross-talk between androgen and Wnt/β-catenin signaling in the androgen sensitive DPC of balding scalp. The androgen ligand-androgen receptor (DHT-AR) complex inhibits the dephosphorylation of GSK-3β resulting in β-catenin degradation and up-regulates paracrine factors such as TGF-β1, IL-6, and DKK1 while down-

regulating Wnt agonists Wnt 10b. DKK1 is a natural Wnt inhibitor and blocks the binding of Wnt to frizzled receptor. CXXC5 a negative Wnt regulator is also elevated in balding DPCs which disrupts the binding of Dvl to Frizzled receptor. DPC dermal papilla cell, HFSC hair follicle stem cell, KC keratinocyte cell, FB fibroblasts, DHT dihydrotestosterone, AR androgen receptor, GSK-3β glycogen synthase kinase-3β, TGF-β1 transforming growth factor-β1, IL-6 interleukin-6, DKK1 Dkkopf-related protein 1, Dvl Disheveled, CXXC5 CXXC-type zinc-finger protein 5

by medical agencies available to treat AGA [29]. However, these drugs have limited efficacy with side effects and must be continued for the lifetime [11, 54, 59, 77]. Hair transplantation and low-level laser light are the other options available with varied treatment efficiency and only recommended for patients whose medication regimen has failed [14]. New emergent therapies like topical androgens, prostaglandins, latanoprost, antibiotics and antifungal, growth factors, stem cell therapies, scalp micro-needling, and platelet-rich plasma therapy are available and practiced off-label [7, 32, 75].

Alternative treatment strategy

Considering that aberration in Wnt signal pathway leads to the disordered state of HF in AGA. Modulating Wnt signals through (1) adjusting the Wnt ligands secretion, (2) altering the ligand–receptor binding, (3) obstructing β -catenin translocation, or (4) by regulating extra-follicular dermal Wnt agonists and Wnt antagonists should have translational value in hair development [47]. In the case of AGA, the HF has a diminished anagen phase due to unstable β -catenin. Stabilizing β -catenin through amplifying Wnt signals would extend the anagen phase and delay the onset of catagen phase in HF.

One such strategy was tested in mice using R-spondin 2 which prevents β -catenin degradation by stabilizing Wnt receptors. In addition, significantly R-spondin 2 injection repressed catagen onset and extended the anagen phase resulting in longer hair shaft growth [72].

Administration of single intradermal injection of a bioengineered hair stimulating complex (HSC) containing follistatin, Wnt 7a, and growth factors demonstrated improved hair growth in AGA patients for a clinical phase 1 study [81].

Valproic acid (VPA), a GSK-3 β inhibitor, that activates Wnt/ β -catenin activity induced hair regeneration in murine models and activated alkaline phosphatase activity in human DPCs [46]. In addition, the topical application of VPA (sodium valproate, 8.3%) in men with AGA showed significant hair growth [30].

Interestingly, natural products from herbs such as *Aconiti Ciliare*, *Malva verticillata*, *Thuja orientalis*, and *Acanthopanax koreanum* are shown to treat hair loss by promoting Wnt/ β -catenin activity [21, 60].

Conclusion

The bald scalp in AGA patients preserves quiescent hair follicle stem cells to a larger extent but lacks the progenitor cells [16]. It is evident that the diminished conversion of hair follicle stem cells to progenitor cells is attributed to the aberration in Wnt/ β -catenin activity mediated by androgens [55].

Modulating the AR transactivation and stabilizing Wnt/ β -catenin signaling pathway would cure, reverse, and prevent hair loss in AGA with minimized side effects. Besides new treatments, targeting Wnt pathway has shown a promising effect on hair growth.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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