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The Pathogenesis and Treatment Progress of Androgenic Alopecia

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Abstract

Androgenic alopecia, also known as seborrheic alopecia, is the most common hair loss disorder in dermatology clinics, mainly characterized by hair follicle miniaturization and progressive hair loss. The etiology and pathogenesis of androgenic alopecia are not clear, but may be related to heredity and androgen metabolism. Currently, minoxidil and finasteride are the only two drugs approved by the U.S. Food and Drug Administration (FDA) for AGA treatment, other treatments include oral minoxidil, hair transplantation, low energy laser therapy (LLLT), platelet-rich plasma (PRP), Chinese medicine microneedles, and combination therapy. With the development of medicine and science, we have ushered in the era of biologics and targeted therapy. In recent years, a variety of signaling pathways for androgenic alopecia have been found, which may provide a basis for targeted therapy for androgenic alopecia.

Keywords

Androgen Alopecia, Pathogenesis, Gene Expression, Signal Transduction, Treatment Progress, Targeted Therapy

1. Overview of Androgenic Alopecia

Androgenic alopecia (AGA) is a common non-cicatricial alopecia, with more than 50% of the general population suffering from androgenic alopecia. AGA often occurs during and after puberty and is characterized by progressive hair follicle miniaturization and hair loss. The incidence of the disease increases with age. The etiology and pathogenesis of androgenic alopecia are still unclear, but it is believed that it is mainly due to genetic factors, hair follicle microecology

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dominated by androgen metabolism, and stress factors. Some androgenic alopecia may be associated with comorbidities, such as hyperlipidemia and polycystic ovary syndrome. There are a variety of methods to inhibit the progression of hair loss, such as topical minoxidil, oral 5α reductase inhibitors (such as finasteride, commonly used in male patients), spironolactone (often used in female patients), hair transplantation, low energy laser therapy (LLLT), platelet-rich plasma (PRP), hair transplantation, traditional Chinese medicine microneedles, and combination therapy. However, the existing non-surgical treatment methods not only have a long treatment period, but also have no obvious effect on improving moderate and severe hair loss, while hair transplantation is expensive, invasive and cannot inhibit the development of the disease. In recent years, it has been found that androgenic alopecia is a genetic disease with multiple signaling pathways such as Wnt/β-catenin, ZAK-STAT, HIF-1, etc., which regulate hair growth, and the Wnt/β-catenin pathway is the most significant. Therefore, based on these signaling pathways and regulatory factors, it is possible to target drugs for androgenic alopecia, and provide new treatment progress for androgenic alopecia (**Figure 1**).

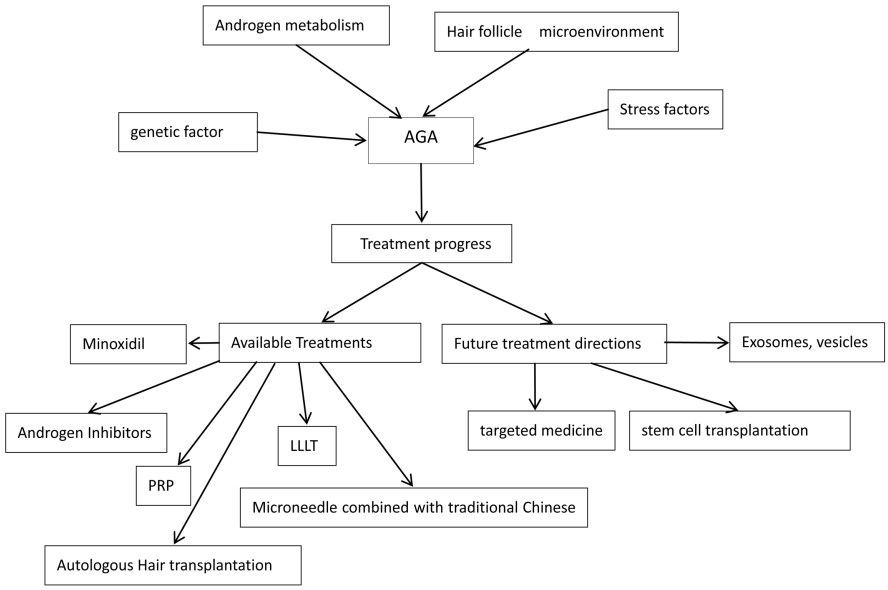

Figure 1. The pathogenic mechanism and treatment progress of AGA.

2. Etiology and Pathogenesis

2.1. Genetic Factors

Androgenetic alopecia may be a polygenic disease, and more than 50% of the patients have a family history of heredity, and paternal inheritance is a great influence. Several genetic susceptibility loci of AGA have been identified, such as WNT10A gene on chromosome 2q35 and APCDDI gene polymorphism located on chromosome 18 p11.2, which are also associated with androgenetic alopecia [1].

2.2. Androgen Metabolism and Various Signaling Pathways

2.2.1. Androgen Metabolism

Androgen metabolism Hair growth is related to the induction of hair follicle microecological signaling pathways and growth factors. Studies have shown that the activity of 5A-reductase type II in hair follicles in alopecia AGA region is significantly higher than that in non-alopecia region, and the 5α-reductase in the tissue can convert testosterone into 5α-dihydrotestosterone (DHT) with a stronger effect. In addition, androgen levels in the blood circulation are normal in some patients, while AR expression in the hair follicles is increased, causing the hair follicles to be sensitive to androgens. DHT plays a biological role after binding with androgen receptors on hair follicle cells, which makes hair follicles minuscule and fine hair become thinner in the growing period and shortens the hair growth cycle. Fine hair, which was originally thick and black, will gradually become light fine hair. Finally, hair follicles will shrink and fall away, leading to baldness on the forehead, from the coronal area to the top of the head. Androgens have a negative effect on the length of the hair shaft, the size of the hair follicle, and the duration of the hair cycle, miniaturizing it and gradually transferring it to the superficial dermis. Androgen blocking is still an effective treatment for AGA.

2.2.2. Various Signaling Pathways and Growth Factors

However, some studies have found that even if the effect of androgens is blocked, the hair cycle will not return to normal, and it may be necessary to promote the hair growth cycle. With the in-depth study of the mechanism of hair loss, people found that in addition to androgens, there are many growth regulators to regulate the hair growth cycle. The Wnt/β-catenin signaling pathway has been shown to be critical in the regulation of hair growth. P.Vasserot *et al.* found that FGF (fibroblast growth factor) 18 and BMP (bone morphogenetic protein) produced by hair follicles in the early stage kept hair follicles in a resting state. When hair follicles transition from resting to growth, and FGF-7 and FGF-10 production together with an increase in BMP antagonists activate Wnt/β-catenin signaling, promoting hair follicle decline growth and hair stem production. Liu *et al.* found that HIF-1 pathway-related genes (EGLN1 and EGLN3) and Wnt/β-catenin pathway inhibitors (SFRP2 and PEDF) may play an important role in DPC activity, hair growth and hair cycle. In vitro HF studies have shown that down-regulation of EGLN1/EGLN3/PEDF can promote HF growth and prolong HF growth period, suggesting that these genes may be used as therapeutic targets for AGA [2] [3]. Dkk1, a negative regulator of Wnt signaling, is overexpressed in hair loss dermal papilla cells (DPC). TGF-β1 production is up-regulated in DPC and can inhibit keratinocyte proliferation [3]. In DHT-induced secreted DKK1 diabetic mice, the increase of miR-29a was positively correlated with β-catenin level and negatively correlated with DKK1 level, indicating that miR-29a is a regulator of DKK1 and therefore of Wnt/β-catenin signaling pathway. Elevated levels of miR-29a inhibit androgen receptor (AR)

expression in the body, and inhibiting DKK1 levels in bald areas of the scalp may prevent further progression of this disease. In addition, DKK1 has been hypothesized as a potential biomarker for obesity [4]. Platelet-derived growth factor (PDGF) stimulates stem cell mitogenesis, converts growth factor-B to activate the dermal papilla and inhibits apoptosis in the cell cycle [5]. Roenigk *et al*. found that PGE2 and PGF2αpromote hair growth [6]. Cell-free fat extract (CEFFE) can inhibit DHT-induced AR expression in mice, thereby reducing hair loss [7]. Androgens may promote the production of TGF-β, reduce the level of IGF-1, and inhibit hair growth. In addition, prostaglandin F2 (PGF2) and PGE2 cause hair growth and prolong the hair growth period, while PGD2 inhibits hair growth, and TGF-β2, Foxp1, and tumatin M signaling pathways have also been shown to regulate the hair cycle. However, the relationship level of the above factors is still unclear.

Some studies have shown that the adhesion signal is another important factor in the development of AGA. Zyxin (ZYX) is an actin interacting protein that is essential for cell adhesion and migration. Some studies have found that ZYX gene is highly expressed in frontal HF, and in mouse experiments, ZYX gene knockout can promote hair growth. Polymerase chain reaction (RT-PCR) analysis showed that ZYX regulates the growth cycle of hair follicles and the proliferation and induction of DPC through ITGB1 and HIF-1 signaling pathways. Therefore, ZYX may be a therapeutic target for AGS [8]. In addition, genes associated with immune response were up-regulated in AGA hair follicles, suggesting that, similar to alopecia areata, autoimmune hair follicle inflammation may also be involved in Aga. The JAK-STAT pathway regulates the quiescence of hair follicles during the resting period, and JAK inhibitors, as targets for the treatment of alopecia areata, have also been used in androgenic alopecia in recent years [9].

2.3. Hair Follicle Microecology

The vast majority of AGA patients are prone to seborrheic alopecia. Pathological perspective: studies have shown that Malazzia is positively correlated with the incidence of androgenic alopecia [10], and early studies have shown that using 2% ketoconazole shampoo can increase hair density [11].

2.4. Stress Factors

Life pressure, tension, lack of sleep, etc., can make scalp capillaries continue to shrink; Oxidative stress accelerates the aging process of hair follicles.

3. Clinical manifestations of AGA

The main manifestations are progressive hair reduction and thinning after puberty. Androgenic alopecia is characterized by a gender-specific distribution. Male pattern alopecia (MPHL) is characterized by a gradual receding hairline and progressive thinning and thinning of hair at the top of the head, culminating

in baldness. Female pattern hair loss (FPHL) is characterized by diffuse hair loss and thinning, affecting the frontal and crown of the scalp, the hair seam is constantly widening, in a typical "Christmas tree"-like change, and the general hairline is not affected.

4. Treatment Progress

4.1. Androgen Inhibiting Drugs

1) Finasteride Finasteride is a type II 5α-reductase inhibitor, which can inhibit the reduction of testosterone by type II 5A-reductase to DHT. Continuous medication is taken for 6 to 12 months or more, and long-term maintenance treatment is required. Finasteride is only used in male patients and may cause serious side effects on other androgen-dependent tissues, such as sexual dysfunction and breast hyperplasia [12]. In recent years, many local preparations of androgen inhibitors have been developed, and microneedle introduction technology has been used for local administration, but microneedle introduction is an invasive operation, which may lead to local infection, redness, erythema and other risks [13]. Thus, Vora *et al.* proposed the concept of dissolved microneedles (DMNs) transdermal drug delivery systems to improve the efficiency of delivery to hair follicles [14]. 2) Amperolactone Amperolactone is a potassitic-holding diuretic and antiandrogenic drug that reduces testosterone production by inhibiting 17-alpha hydroxylase and lyase. It is commonly used in female patients with side effects including postural hypotension, electrolyte imbalance, breast tenderness, and menstrual irregularities. Clascoterone (clastone) is a novel topical androgen receptor inhibitor, which competes with the androgen dihydrotestosterone to bind the androgen receptors in sebaceglands and hair follicles to weaken the signaling required for acne onset. In 2020, 1% clastone cream was approved for the first time in the United States for the topical treatment of acne vulgaris in patients 12 years of age or older. Studies have shown that clascoterone is more effective than cyproterone acetate or 17-alpha estradiol, and that patients using clastone have faster hair growth compared to topical minoxidil. In vitro studies have shown that clascoterone binds androgen receptors with high affinity and inhibits DHT-stimulated signaling [4]. Clinical studies of higher concentrations of clastone for the treatment of androgenic alopecia are ongoing [15] [16].

4.2. Minoxidil Drug Therapy

Minoxidil is the main topical hair growth promotion drug, with the role of dilating blood vessels and promoting resting hair follicles into the growth phase. The drug concentration is generally 5% for men and 2% for women. The effective time is about 3 months, and the maintenance time is generally from half a year to 2 years. The common adverse reactions are contact dermatitis, dandruff, and hypertrichosis. Hui Xing *et al.* constructed a novel transdermal drug delivery system for NO and minoxidil using hyaluronic acid liposomes as carrier (HL@Mi/NONNATIOATE). Nitric oxide (NO) is a signaling molecule in a variety of physiological processes,

including vasodilation, immune response, and cell proliferation. The system has good effect of transdermal and hair regeneration. NO can reduce inflammatory immune response, promote cell proliferation and angiogenesis, prolong the residence time of minoxidil in the skin, and effectively improve its bioavailability. The system has efficient osmotic and synergistic therapeutic effects and alleviates local adverse reactions, and can be used to treat AGA [17].

In addition, low-dose oral minoxidil (OM) has been used clinically with improvement in more than 60% of patients, and studies have shown that low-dose (5 mg/day) oral minoxidil for AGA treatment is not associated with clinically significant changes in systolic or diastolic blood pressure in any sex or in any age group [18].

4.3. Promote Hair Regeneration

Mesenchymal stem cells (MSCS) are stromal cells capable of self-renewal and differentiation into various types of specialized cells that serve as hair follicle reserves. The concept of MSC-derived exosomes or extracellular vesicles (EVs) is relatively new and is growing in practice as a means of combining the regenerative capacity of MSCS with cell-cell communication mediated by exosomes. Msc-exosomes are currently used to treat a variety of medical conditions, reduce inflammation and reduce external hair loss [19]. There is increasing evidence that extracts of adipose stem cell components (ADSC-CE) contribute to hair regeneration in patients with androgenic alopecia. Mesenchymal stem cells (MSCS) are immature precursor cells derived from mesoderm with self-renewal potential and multidirectional differentiation ability. MSCS are found in abundance in adipose tissue and are relatively easy to obtain, and recent studies have attempted to determine the medicinal effects of MSCS and apply them to regenerative medicine. Adipose tissue-derived stem cells (ADSCs), a type of MSC, secrete a variety of growth hormones that help cells develop and proliferate [20] [21].

4.4. Related Treatment with Other Metabolic Disease

1) The prevalence of FPHL in PCOS patients was about 28%; Most patients with PCOS have hyperandrogenemia, and the effect on hair growth may be mediated by androgen activity. Metformin is an oral hypoglycemic agent used to treat diabetes and metabolic syndrome due to its ability to increase insulin sensitivity, increase glucose utilization, and lower serum triglyceride levels. Due to its ability to reduce over-production of ovarian androgens, it is used in PCOS to treat acne, weight gain, and hirsutism. Although there is no reliable data to describe the effects of metformin on FPHL, the anti-androgenic effects of the drug are thought to be beneficial [22].

2) Dyslipidemia was the most common co-existing systemic disease in this study [23]. AGA is more common in obese patients [4]. Studies have shown that long-term aerobic moderate to high intensity exercise can help delay the progression of androgenic alopecia [24].

4.5. Targeted Drugs Based on Signaling Pathways

Changes in WNT3 and HSD17B6 gene expression in AGA were confirmed by studying differences in gene expression and methylation patterns in hair follicles in the bald and occipital regions of AGA patients. We identified 53 differentially expressed genes (DEG), including WNT3 and BMP8, in bald and non-bald occipital scalp. WNT3 plays an important role in cell-cell signaling during morphogenesis and is expressed in developing and mature hair follicles. We found overexpression of WNT3 in Aga. Overexpression of WNT-3 in transgenic mice produces a short-hair phenotype due to altered differentiation of hair stem cells. The HSD17B6 gene encodes 3α-hydroxysteroid dehydrogenase in the human prostate, which catalyzes the reverse conversion of 3α-diol to DHT. Variants of this gene have been linked to hyperandrogenemia and polycystic ovary syndrome, a condition characterized by hair loss, as well as acne and obesity. This study confirmed the importance of androgen metabolism and Wnt pathways in the pathophysiology of AGA and may be a new target for the treatment of AGA, but this study was only for men [25]. In addition, miR-221 was found to inhibit hair growth and proliferation of dermal papilla cells (DPC) and dermal sheath cells (DSCs) in AGA patients. Studies have shown that AR (androgen receptor) promotes the transcription of miR-221, and miR-221 is significantly upregulated in balding hair follicles, thereby inhibiting the expression of IGF-1 (insulin-like growth factor 1), resulting in the inactivation of the MAPK pathway of DPC and the PI3K/AKT pathway of DSC, thereby inhibiting hair growth. In AGA patients, the expression of miR-221 was positively correlated with the expression of AR and IGF-1. These findings highlight the potential value of miR-221 as a novel biomarker and therapeutic target for AGA. Therefore, miR-221 can be used as a direct target of AR, and IGF-1 may also be a target for the treatment of alopecia [26].

5. Summary and Prospect

Since microfollicles retain stem cell populations, it may be possible to reactivate stem cells by improving the growth environment of hair follicles [27]. Delaying the growth stage in the early stage and reversing the miniaturized hair follicles in the middle and late stage may become our future treatment directions, such as targeted drugs and gene regulation. In addition, the use of exosomes, vesicles and other pathogenic factors in the signaling pathway, the use of transdermal drug delivery preparations, such as liposomes, can improve drug bioavailability, reduce the frequency of administration and improve patient compliance, providing a promising strategy for long-term clinical alopecia treatment. It is worth noting that although the Wnt/β-catenin pathway is crucial in the regulation of hair growth, and some miRNAs can regulate the Wnt pathway to promote hair growth, the Wnt/β-catenin pathway is involved in many extremely complex biological processes, and Wnt is a proto-oncogene in many types of tumors [2] [28]. Therefore, more precise targeted drugs for androgenic alopecia are needed.

In short, androgenic alopecia is not currently curable, but it can be controlled or delayed by a variety of treatments.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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