

The Progress of Common Treatments and Research for Androgenetic Alopecia

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Abstract

Androgenetic alopecia (AGA) is the most common type of hair loss, in which patients mostly present with a state of a receding hairline on the forehead. It brings a great mental burden to the patient. Androgenetic alopecia is caused by the combination of dihydrotestosterone (DHT) and androgen receptors (AR), disrupting the hair follicle cycle and minimizing hair follicles. The major treatments currently available include finasteride, minoxidil, hair transplantation, Platelet-rich plasma (PRP), stem cell therapy, etc. This article reviews the mechanism of AGA and the existing major treatments. The author suggested that androgen receptor degrader drugs have good prospects for application among those of various therapeutic options.

Keywords: androgenetic alopecia, finasteride, androgen receptor degrader drugs, research advances

1. Introduction

With the increasing social pressure and changes in lifestyle and eating habits, more and more people are suffering from hair loss (Marks et al., 2019), and the trend of hair loss is more serious: the average age of hair loss is 20 years earlier than that of the previous generation, and the proportion of people with hair loss before the 30s is as high as 84% (Katsoulis et al., 2021; Ohn et al., 2022). Hair loss has become another social disease besides obesity. Among all hair loss types, androgenetic alopecia accounts for the largest proportion of cases. Androgenetic alopecia is an androgen-dependent polygenic genetic disease of hair loss, accounting for about 90% of the total number of people with hair loss (Desmond J. Tobin, 2005). The onset of hair loss does not damage the physical health of the patient, but it brings serious mental stress and

psychological burden to the patient (D Williamson, 2001; THOMAS F. CASH, 2001). Currently, there are many drugs and treatments for androgenetic alopecia. This article reviews the pathogenesis of androgenetic alopecia and the current major treatments in the hope of providing patients with more information on treatment to find the appropriate treatment for patients.

2. Mechanism of Androgenetic Alopecia

In 1942, James Hamilton of Yale University found that castrated men were less susceptible to hair loss than ordinary men, identifying androgens as the major contributor to androgenetic alopecia (Hamilton, 1942). However, the results of an American twin study showed that only 20% of the fraternal identical twins showed co-occurring hair loss

characteristics (Gatherwright et al., 2013). This suggests that the genetic factor is the same but it presents differently due to different environments. It has been shown that the onset of androgenetic alopecia is regulated by a combination of various factors. The main elements include genetics, hormonal abnormalities (thyroid disease, diabetes, etc.), immune abnormalities and mental status, and age.

Androgenetic alopecia is associated with the miniaturization of hair follicles and the gradual softening and thinning of hair until it is lost completely (Deng et al., 2022). Miniaturization of the hair follicle is mainly led by the regression of the blood vessels around the hair follicle which leads to insufficient supply of nutrients to the hair follicle, thus resulting in a continuous shortening of the hair follicle cycle. Each hair follicle perpetually goes through three stages: growth (anagen), involution (catagen), and rest (telogen) (Chen et al., 2016; RALF P AUS, 1999). In healthy individuals, about 84% of hair follicles are in the anagen phase, 1% to 2% are in the regression phase, and 10% to 15% are in the resting phase (James L. Ross, 2021), while in patients with androgenetic alopecia, the resting phase of hair follicles becomes longer and the anagen phase is shorter. The blood flow in AGA patients is significantly lower than that in non-alopecia areas and normal people.

Free testosterone binds to serum sex hormone-binding globulin receptors on the surface of hair follicle cells and transports testosterone into the cells, where it is reduced intracellularly by 5 α -reductase to DHT (Ryan & Chan, 2015). DHT, a competitive inhibitor of heat shock protein (HSP), has a higher affinity for AR, and thus separation of AR from HSP occurs upon induction of DHT. The complex of DHT and AR is modified by phosphatase and binds to form a dimer, which is bound to the Androgen response elements (ARE) in the promoter region of target genes by the input protein- α across the nuclear membrane under the action of nuclear localization signal, with the participation of nuclear related factors, and regulates the expression of downstream genes (Li Dan, 2018).

Hair follicle miniaturization is closely linked to testosterone (T). Testosterone is a major androgen in human body, which can be converted to dihydrotestosterone (DHT) by 5 α -reductase in vivo. DHT binds to the

androgen receptor (AR) in the hair follicle cells and exerts its biological effects, which guide the transcription and translation of the downstream related genes, altering the mesenchymal stem cell-epithelial cell interaction in the hair follicle by regulating the Wnt/ β -catenin, Shh, TGF β , BMP and other signaling pathways, thereby regulating the hair growth cycle and the activity of hair papilla cells, keratinocytes, and melanocytes, which leads to hair loss (Ceruti et al., 2018; Shigeki Inui, 2002). Although DHT is recognized as a major trigger of androgenetic alopecia (AGA). However, the regulation of the hair growth cycle is complicated and includes various cytokines, hormones, neurotransmitters, growth factors and underlying epigenetic modifications (Ustuner, 2013). Therefore only interrupting testosterone is not a perfect cure for hair loss.

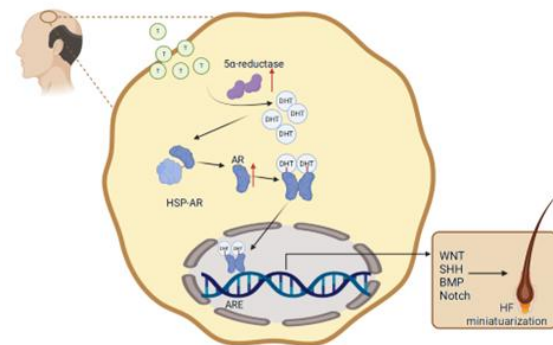


Figure 1. DHT in the pathogenesis of androgenetic alopecia

DHT regulates WNT, Shh, BMP, and nortch signaling pathways leads to miniaturization of hair follicles, clinically defined as vellus hair.

3. 5-Alpha Reductase Inhibitor

Finasteride is one of two FDA approved drugs for the treatment of androgenetic alopecia, which is a type II 5-alpha reductase (5- α R) selective inhibitor that reduces the effect of androgens on hair loss by decreasing the production of DHT (Areej Adil, 2017). Finasteride must be taken for more than one year, and if it is not effective after 6 months, it should be discontinued. The drug can cause side effects such as abnormal sexual function, reduced sperm, and abnormal gynecomastia (Ion G. Motofei, 2019). Finasteride can often be used combined with ketoconazole, which provides an anti-inflammatory effect and a better scalp environment. The two drugs work better in combination (Yi Zhou, 2020).

Dutasteride is a more potent 5-alpha reductase inhibitor than finasteride, and has a more obvious inhibitory effect than finasteride, reducing systemic DHT levels by 95% (compared to about 71% for finasteride), but its side effects are also more obvious, and patients are more likely to suffer from impotence and other sexual function problems (Upreti et al., 2014; Wu, 2019).

4. Minoxidil

Minoxidil, a type of piperidine-pyrimidine derivative, is a potential potassium channel opener, which mainly acts as a vasodilator and can enhance the blood flow around the hair follicle, shorten the resting phase of the hair follicle and make the resting hair follicle enter the anagen phase permanently to promote hair growth, but the exact mechanism of action is not clear (Paulo Müller Ramos, 2020). Minoxidil alone usually works in about 3 months, and it usually takes 6 months to show significant effects. Some of the common adverse reactions include irritant dermatitis, hypersensitivity, hypotension, and changes in heart rate and pulse rate (Michael Randolph, 2020).

5. Androgen Receptor Degraders

In recent years, due to the technology maturation of Proteolysis Targeting Chimeric (PROTAC), AR degraders have become popular drugs in near years, and AR degraders designed based on the PROTAC technology are most likely to have effective therapeutic effects on drug resistance generated by AR antagonists, but no AR degraders have been available on the market yet (Zhenyi Hua, 2021). In 2022, Pioneer Pharmaceuticals'GT20029 androgen degradation agent for the treatment of androgenetic alopecia has entered clinical trials. phase I of GT20029 has shown excellent androgenetic alopecia treatment effects. In January 2023, a research team from Zhejiang University developed a protein hydrolysis-targeted chimeric androgen receptor degradant, TJA107 (Ruxuan Wang, 2023), which is effective in the treatment of AGA at the animal level with significant effects.

6. Hair Transplantation

Hair transplantation is the surgical procedure of redistributing a portion of the hair from the back of the scalp to the scalp or other areas of the body where hair loss has occurred, so that the transplanted hair retains all of its original growth characteristics and continues to grow in the new transplanted area. The results are

usually long-lasting. Hair transplantation is one of the most effective techniques to improve the appearance of permanent hair loss, but more clinical studies have shown that hair transplantation is not long lasting, it is expensive and carries certain surgical risks due to the physical requirements of the patient (Nestor et al., 2021).

7. Low-Level Laser Therapy

Low-Level Laser Therapy (LLLT) is a recent phototherapy technique used to cure androgenetic alopecia (Gentile Pietro, 2020). Low-Level Laser is a low-energy, short-wavelength laser that has been used in early studies for the treatment of androgenetic alopecia because of its hair growth-promoting effects. In low-power laser therapy, the hair follicles are irradiated with low energy laser to reduce the inflammatory response of hair follicles and to promote cellular metabolism, thus causing the resting hair follicles to revive and achieve the effect of promoting hair growth. However, the mechanism of Low-Level Laser Therapy is unclear, it may be that red light absorption by cytochrome c oxidase (CCO) in mitochondria leads to inhibition of nitric oxide (NO) photodissociation, causing ATP accumulation, reactive oxygen species regulation and induction of transcription factors, leading to protein synthesis and NO-related vasodilation. Its advantages are that it has no side effects, is painless, does not require long-term use, and is suitable for patients with all types of hair loss. Its disadvantages are that the treatment effect is relatively slow, requires a relatively long treatment cycle, and the price of the treatment equipment is higher and cannot be promoted on a large scale (Avci Pinar, 2013).

8. Platelet-Rich Plasma

Platelet-rich plasma (PRP) is a concentrated mixture of platelets and plasma extracted from autologous blood by centrifugation (Nestor et al., 2021). PRP therapy has been reported to induce the proliferation of dermal papilla cells, thereby increasing the survival rate of hair follicle cells, and possibly prolonging the hair follicle cycle by regulating the growth phase, and has become one of the recommended treatments by many doctors because of its autologous origin, minimally invasive, no serious adverse effects and low price. Platelet-rich plasma is typically used to treat patients with AGA who have intact hair follicles, mostly in patients with grade 4 or

less hair loss (Natalie Justicz, 2020). The most common negative reactions of PRP are temporary pain and erythema at the injection site of appearances. Although it still has promising application as a method of AGA, the standard for the preparation method and the amount of PRP required for the injection is not yet unified, and still needs more researches for it.

9. Adipose Stem Cells

Adipose stem cells (ADSCs) are widely appreciated in the cosmetic field because of their restorative effects and easy accessibility. Existing studies have found that adipose stem cells are also effective in the treatment of AGA. Festaet et al. found that patients transplanted with adipose tissue rich in Stromal Vascular Fraction (SVF) had an increase of 31 hairs/cm², while another group transplanted with adipose tissue alone (without SVF) had an increase of 14 hairs/cm². This study suggests that both adipose tissue and SVF have a stimulating effect on hair regrowth. The effect was more obvious with the presence of SVF. In addition to directly transplanting ADSCs, ADSCs exocrine secretion is also useful for the treatment of AGA. Fukuoka et al. found that 22 patients injected with adipocyte cultures (ADSCs-CM) 3-5 times per week and treated for a total of six weeks, ultimately increased the hair by 1.54 hairs/cm² (Tak Young Jin, 2020). There was no significant difference between men and women. Won et al. found that ADSC-CM acted on human hair papilla cells cultured in vitro and found that their proliferation rate was more than 30% higher than that of the control group after 48h. Park et al. injected ADSC-CM subcutaneously into C3H/NeH mice and found that it activated the hair follicle anagen phase and promoted hair regeneration. All these studies showed that ADSCs-CM also have significant effects in the treatment of AGA, and the protein injection is safer than directly transplanting cells and more convenient for storage (Chong Hyun Won, 2010). Therefore, injection of cellular exosomes is more promising than direct cell injection

10. Prostaglandin Medication

Prostaglandins (PGs) are a class of lipid mediators that play an important role in the regulation of the hair follicle cycle. Prostaglandins that are involved in the regulation of androgenetic alopecia are divided into two main categories based on their type of

action: prostaglandin D₂, which inhibits hair growth, and prostaglandin E₂, which promotes hair growth. Levels of prostaglandin E₂ are elevated at the onset of orthogenesis and prostaglandin E₂ analogs are able to increase hair density. Prostaglandin D₂ is synthesized by prostaglandin D₂ synthase (PTGDS) that is present at the site of the outer root sheath below the bulge, and its binding to GPR44, the receptor for PTGDS, induces miniaturization of the hair follicle, prevents the maturation of stem cells into progenitor cells, and prevents the maturation of filiform hairs into terminal hairs. High levels of prostaglandin D₂ are detected in the scalp of patients who develop androgenetic alopecia, while prostaglandin E₂ expression is relatively low. Thus the use of prostaglandin drugs can be effective in improving hair loss (Shangxuan Jiang, 2023).

11. Conclusion

The incidence of androgenetic alopecia is gradually increasing due to the stress of modern life and changes in lifestyle habits, and increased mental work and a diet high in oil and salt, which is very detrimental to the image of modern people. At present, the mechanism of androgenetic alopecia is still unclear, and the types of cytokines and growth factors involved in the relevant signaling pathways and the androgen-mediated downstream genes still need to be studied. There are many treatments for hair loss, and the main FDA-approved drugs are finasteride and minoxidil, but both require up to a year of treatment time and have more significant side effects. For the huge demand of treating AGA, there are many non-drug treatments available, including hair transplant, stem cell therapy, PRP and other means. However, there are still shortcomings in these treatments, such as hair transplantation, which requires patients to bear the risk of surgery and is expensive and applicable to a small population. Stem cell therapy and PRP mainly play a role in the treatment of hair loss through the interaction between growth factors and regulatory cells, but there is no standardized implementation of such biological treatments, and their treatment mechanisms still need further research to determine. The novel androgen receptor inhibitors have not yet been marketed as drugs for AGA. However, AR degraders are small molecule compounds, which are cheaper, have good patient compliance, and have fewer side effects than

finasteride and dutasteride. The author believes that they have great prospects for development. In this paper, we summarized several important factors involved in androgenetic alopecia, the mechanism of androgenetic alopecia, and the research progress of related therapeutic drugs through literature search, which further clarified the ideas and clues for the research and treatment of alopecia process.

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