Abstract: In most of mammals, hair plays a very important role and protects them against physical forces, defends them against parasites and UV rays, provides heat conservation, and acts as a sensory organ. During the process of evolution, human hair lost these essential life-supporting functions. Human hair is now viewed as an object of aesthetic interest. However, androgenetic alopecia (male pattered hair loss) has been a source of distress for many men since ancient times. Hair loss due to the side effect of anticancer agents and extensive alopecia areata often drastically impair the QOL of affected persons. Recent rapid progress in molecular biology has clarified the molecular mechanisms for hair generation and regeneration. The pathogenetic mechanism of androgenetic alopecia, reported to affect about one-third of all men in their 40’s, and the nature of alopecia areata (as an autoimmune condition), have recently been clarified. New therapies based on these findings are expected to emerge.

Key words: Hair cycle; Male pattern alopecia; Alopecia areata

Introduction

The hair follicle is one of the smallest organs in the body. In many mammals, hair plays a very important role and protects the animal against physical forces, defends it against parasites and UV rays, provides heat conservation, and acts as a sensory organ. For human beings, hair has lost these essential life-supporting functions, and it is now viewed as an object of aesthetic interest that only serves to enhance physical attractiveness and to provide camouflage. However, unexpected hair loss causes serious psychological trauma in the affected persons, and it is sometimes described as a life-altering disease.

This paper reviews new topics on androgenetic alopecia and alopecia areata, which are classic types of hair loss.

Hair Cycle

Biologically, the hair follicle is a unique organ in the body where the process of tissue regeneration and involution is repeated throughout the lifespan. This process is called the hair cycle...
(from anagen to catagen to telogen) (Fig. 1). Because the regulation of the hair cycle involves many factors, various pathological conditions result in alopecia.¹)

**Effects of Androgen on Hair Cycles in Humans**

Interestingly, most of the steroid receptor family affect hair cycles in humans, as exemplified by hypertrichosis due to glucocorticoids, alopecia due to thyroid hormone, retinoid, and vitamin D abnormalities, and hirsutism and male pattern alopecia due to androgen. While many of these abnormalities are caused by the action to epithelial cells of the hair follicle, the difference in androgen sensitivity is defined by dermal papilla cells, which are mesenchymal cells of hair follicles.

The dermal papilla is the only part of a hair follicle that has androgen receptors and type-II 5α-reductases (known isozymes of 5α-reductase), which are needed for the action of androgen in male sexual organs.²) Strong male phenotype expressions, such as beards and male pattern alopecia, require both androgen receptors and type-II 5α reductase. Because epithelial cells of hair follicle lack androgen receptors, hair growth seems to be controlled by the androgen-dependent release of signals from dermal papilla cells.

To find out the signals, we established an *in vitro* co-culture system using epithelial cells and dermal papilla cells from hair follicles. In the growth of sexual hair during puberty, we found that insulin-like growth factor I (IGF-I) is the hair growth factor released from beard dermal papilla cells (paracrine growth factor) in an androgen-dependent manner. In androgenic alopecia in humans, we found that dermal papilla cells release transforming growth factor (TGF) β1 in an androgen-dependent manner. TGF-β1 suppressed the growth of keratinocytes in hair follicles and shortened the duration of anagen in male pattern alopecia (Fig. 2).³,⁴)

For the treatment of this common disease affecting 30% of Japanese males in their 40's, a 1% minoxidil solution was marketed in Japan several years ago, which generated great interest. Minoxidil was originally developed as a K channel opener to treat hypertension. Because this agent was found to cause the adverse effect of hypertrichosis, it is used as a topical medication for alopecia. Although the mode of action has not been clarified, minoxidil is suspected to promote hair growth because it activates prostaglandin endoperoxide synthase-I in hair papilla cells and enhances PGE₂ synthesis.⁵)

In Western countries, a type-II 5α reductase inhibitor called finasteride is currently prescribed.⁶) A clinical trial of this agent is ongoing in Japan, it will probably be marketed in Japan before next year. While this agent causes

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**Fig. 1 Hair cycle**

**Fig. 2 Action mechanism of androgen in hair follicle**

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hypogonadism among a few percent of the males, oral administration of finasteride is contraindicated in females, because it causes feminization of male fetuses. We expect the development of new therapeutic agents targeted at TGF-β in the future.

Alopecia Areata

Alopecia areata is a common disease representing 2% to 5% of all new patients visiting dermatology departments. According to statistics in the U.S., the prevalence is about 2,000 per 100,000 persons, and the lifetime risk is reported to be 1.7%. This disease is characterized by clearly defined patches of hair loss chiefly on the head. Alopecia areata is classified into 4 types: single, multiple, totalis, and universalis (i.e., total body hair loss). Usually, the disease appears as a single or a few coin-shaped patches of hair loss, but a total loss of hair on the head and body occurs in 7% of all cases. No differences between the sexes are observed. While this disorder develops in a wide range of ages, about 25% of all cases develop before the age of 15. About 20% of the patients have a family history of this disease. As noted above, alopecia areata is often regarded as a trivial problem, but it may cause serious psychological trauma in the affected persons. In the case of minors, it can be a cause of school truancy, and the patient may become the target of bullying by classmates. In adults, this disease can result in limited employment choices.

The pathogenesis of this disorder was explained by various theories in the past, including infection, nutritional disturbance, neurological (stress), and endocrine theories. Nowadays, it is considered an organ-specific autoimmune disease with a genetic background, because about 20% of patients are positive for antinuclear antibodies, thyroglobulin, and microsome antibodies. Human leukocyte antigen (HLA) DQB1*03 (DQ3) is commonly detected in this disease, and the presence of DQB1*1104 (DR11) and DQB1*0301 (DQ7) has been shown to cause extensive development and prolongation of the disease.

In the affected area of the skin, CD4 lymphocyte infiltration is observed around the anagen hair roots, CD8 lymphocytes invade into hair roots, and matrix cells undergo apoptosis. However, no lymphocyte infiltration is seen in the vicinity of the hair bulge, where hair follicle stem cells are believed to be located. For this reason, permanent hair loss does not occur in alopecia areata. When an alopecic scalp skin from a patient is transplanted to a SCID mouse (an immunodeficient mouse), hair will regenerate. When T lymphocytes isolated from the affected skin are stimulated by a homogenate of hair follicles and introduced locally into the transplanted site, the disease is reproduced. These results indicate that alopecia areata is an autoimmune disease in which T lymphocytes recognize and attack autoantigens in hair follicles.

Local immunotherapy is the most effective treatment for intractable multiple alopecia areata at present (Fig. 3). Though details of the mode of action have not been clarified, this therapy uses local application of hapten to induce allergic contact dermatitis aimed at stimulating hair generation. When the expression of cytokine mRNAs in locally infiltrating lymphocytes was compared before and after
local immunotherapy, the T_{H1} type was seen before treatment, and an increase in IL-10 and a decrease in IL-1β were observed after treatment.10)

Systemic administration of steroids has long been criticized because the life prognosis of this disease does not warrant such treatment. However, this therapy is attracting new attention as understanding and recognition of this disease as an autoimmune condition and as a life-altering disease have grown. The efficacy of steroid pulse therapy has been reported in patients with multiple alopecia areata within one year of its onset.11)

**Conclusion**

Alopecia is often disregarded as a minor disease, but the distress of affected persons is serious. This article focuses on the mode of onset of male pattern alopecia and alopecia areata, which have been elucidated recently. The mechanism of the hair cycle is being clarified rapidly, since molecular biologists, in addition to dermatologists, have become interested in hair as an ideal tissue regeneration model.

Based on such findings, promising results have been reported from animal experiments to prevent chemotherapy induced alopecia. In addition, the study of the hair follicle, the smallest organ in the body, is expected to provide new information that may contribute to the progress of regenerative medicine of other organs.

**REFERENCES**