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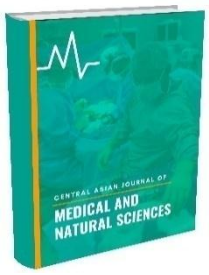

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Molecular Aspects of the Pathogenesis of Androgenetic Alopecia

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Abstract: The main regulators of the anagen phase of the hair follicle are dermal papillae and their sources - dermal fibroblasts of the extracellular matrix. Epithelial-mesenchymal interactions of the extracellular matrix are carried out by a number of proteinases, of which matrix metaloproteinases play an important role. Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases that can be produced by various types of skin cells, including fibroblasts, keratinocytes, macrophages, endothelial cells, mast cells, and eosinophils. Matrix metalloproteinases are composed of at least 19 cloned membranes, including type IV collagenases (such as MMP-2 and MMP-9), metalloelastase, interstitial collagenase, stromelysins, matrilisins, and membrane-type MMPs. In addition, growing evidence demonstrates that Matrix metalloproteinases can influence signaling pathways associated with various factors, such as insulin-like growth factor binding protein-3, tumor necrosis factor-α (TNF-α), fibroblast growth factor receptor 1, and angiogenic factors. We examined 85 males with androgenic alopecia aged 18 to 41 years. The distribution of patients with androgenic alopecia, depending on the duration of the pathological process, showed that the main number of those who seek advice from a dermatologist are patients with a disease duration from 1 to 5 years - 51.6%, as well as up to 1 year - 24.8% and from 5 to 10 years - 23.6%. The study of the concentration of inhibitors of matrix metalloproteinases (TIMP1) in patients with androgenic alopecia showed a significant decrease in its level compared to the same indicators in the control group.

Key words: Alopecia, androgenic hair loss, bald patches, scalp, cytokines.

Thus, with the M3 type, the TIMP1 concentration was 2.01 ± 0.18 pg / ml (P <0.001), with the C2-C3 type - 1.49 ± 0.022 pg / ml (P <0.001), with the U1 type - 0.88 ± 0.054pg / ml (P <0.001). In the control group, the same indicator was 3.7 ± 0.09pg / ml. In our study, reliably low TIMP1 values in

androgenic alopecia are associated, on the one hand, with the observed oxidative stress in the extracellular matrix and the inflammatory process, in which the release of reactive oxygen species occurs in parallel with a decrease in the TIMP1 level and, accordingly, an increase in the level of matrix metalloproteinases. The studies have proved the important role of the parameters of the activity of the extracellular matrix and apoptotic factors in androgenic alopecia, which lead to the inflammatory process and subsequent atrophy of the hair follicles.

Introduction

Recent advances in molecular and cellular biology have led to a deeper understanding of hair formation, hair growth, and their cyclical nature. Follicular pigmentation processes, neuroendocrine regulation, immune status and follicular stem cell research, in addition to the development of methods for targeting the hair follicle, will help advance new therapeutic approaches to the treatment of hair diseases.

So, one of the common forms of alopecia is androgenic alopecia - progressive baldness, caused by the action of androgens on hair follicles. The main reason for the development of androgenetic alopecia is genetic - activation of the androgen receptor, as a result of which the anagen or growth phase in the normal hair growth cycle is shortened. In addition to genetic predisposition, various environmental factors such as exposure to ultraviolet radiation, decreased sleep duration, increased stress, high body mass index, circulatory disorders due to smoking, arterial hypertension and hyperinsulinemia, causing chronic microinflammation, oxidative stress and decreased circulation (malnutrition) of the follicles cause worsening of androgenic alopecia, which was clearly demonstrated in previous studies of population. It has been proven that dihydrotestosterone, penetrating into follicular cells, triggers a cascade of reactions that lead to an increase in the production of cytokines, mainly TGF β 1 and 2. Cytokines promote the onset of the telogen phase and the generation of aging signals for hair papillary cells (7). As a result, dystrophy of hair follicles occurs and, as a result, dystrophy of the hair they produce (Goryachkina V.L., Ivanova M.Yu. et al. 2015). Hair becomes thin, short, colorless. 10-12 years after the onset of alopecia, the orifices of the follicles are replaced by connective tissue, and they can no longer produce even vellus hair (Zaborova V.A., Arzumanyan V.G., Gurevich K.G. 2013).

The main regulators of the anagen phase of the hair follicle are dermal papillae and their sources - dermal fibroblasts of the extracellular matrix. Epithelial-mesenchymal interactions of the extracellular matrix are carried out by a number of proteinases, of which matrix metaloproteinases play an important role. Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases that can be produced by various types of skin cells, including fibroblasts, keratinocytes, macrophages, endothelial cells, mast cells, and eosinophils. Matrix metalloproteinases are composed of at least 19 cloned membranes, including type IV collagenases (such as MMP-2 and MMP-9), metalloelastase, interstitial collagenase, stromelysins, matrilisins, and membrane-type matrix metalloproteinases. In addition, growing evidence demonstrates that matrix metalloproteinases can influence signaling pathways associated with various factors, such as insulin-like growth factor binding protein-3, tumor necrosis factor-α (TNF-α), fibroblast growth factor receptor 1, and angiogenic factors. (2-6). Consequently, in the processes of hair growth, the extracellular matrix is of great and decisive importance, as mentioned above, and it is also interesting because it takes an active part in the formation of niches for stem cells "containing the necessary pool of stem cells. In androgenic alopecia, androgens, by binding to receptors in the hair follicle papillae, increase the activity of matrix metalloproteinases. As an important component of the hair follicle, the extracellular matrix is regulated by matrix metalloproteinases (MMPs) and their inhibitors (tissue matrix metalloproteinase inhibitors; TIMPs). The activity of Matrix metalloproteinases is regulated by their specific inhibitors known as tissue inhibitors of metalloproteinases (TIMPs). The activities of MMP-2 and MMP-9 are

specifically inhibited by TIMP-2 and TIMP-1, respectively, which may be vital for HF regulation. Indeed, it has been shown that fluctuations in the expression levels of MMP-2 and MMP-9 occur throughout the hair growth cycle. MMP-2 and TIMP-2 were found in all HF structures, while MMP-9 and TIMP-1 are restricted to specific regions of HF, such as the sebaceous gland and inner root sheath (9).The relevance of studying the activity of tissue inhibitors of matrix metalloproteinases in androgenic alopecia is also due to their regulating effect on perifolicular inflammation and microfibrosis of the hair follicle orifices, which reduces the effectiveness of therapy and the quality of life of patients. Also, the inhibition of proliferative processes in the dermal papilla and the transition of the hair follicle to the telogen stage in patients with androgenic alopecia is influenced by the factor of apoptosis (FasL). One of the external factors triggering apoptosis in the cell is the Fas protein ligand - Fas ligand (FasL). FasL is naturally produced by enzymatic degradation involving metalloproteinases.

Purpose of study: to study the activity of matrix metalloproteinase and apoptotic factors as the leading factors in remodeling the extracellular matrix of the hair follicle in androgenic alopecia.

Materials and Methods

We examined 85 males with androgenic alopecia aged 18 to 41 years. The distribution of patients with androgenic alopecia, depending on the duration of the pathological process, showed that the main number of those who seek advice from a dermatologist are patients with a disease duration from 1 to 5 years - 51.6%, as well as up to 1 year - 24.8% and from 5 to 10 years - 23.6%.The results of a hormonal test for testosterone showed an increase in blood concentration in only 4% of patients with androgenic alopecia. The patients noted stressful situations (62%), chronic diseases of the nose and throat (43%), and the use of hormonal drugs (28%) as provoking factors for hair loss. The control group consisted of 20 healthy people, representative of gender and age. All patients with androgenic alopecia underwent videotrichodermatoscopic examination of the scalp using an Aramo-SG video camera (Korea) with X60 and X200 lenses and the Trichoscience diagnostic program. A characteristic feature of the phototrichogram of patients with androgenic hair loss, carried out in the parietal zone, was an increased amount of velus hair and thinned hair (more than 45%). According to the clinical specific classification (BASP) of androgenic alopecia, 36 (42.3%) patients had type C2-C3, in which there was hair loss in the frontal and temporal areas of the scalp. In 26 (30.5%) patients with androgenic alopecia, type M3 was observed, in which there were pronounced bald patches in the frontal-parietal region, and in 23 (27.2%) patients, U1 was recorded, in which the fusion of bald patches in the frontal and parietal regions was observed, remained only intact hair of the occipital region of the scalp.

The activity of matrix metalloproteinase was determined by the study of the concentration of inhibitors of matrix metalloproteinase (TIMP1), as well as the factor of apoptosis (FasL) in patients with androgenic alopecia in the blood was carried out by an automated enzyme-linked immunosorbent assay on a Human reader Single apparatus. Method for the study of the concentration of inhibitors of matrix metalloproteinase TIMP1:

Twist the timp 1 Standard vial, prepare the 50 ng / ml timp1 Stock Standard by adding 400 µl of 1X Sample Dilution Buffer to the vial. The powder dissolves thoroughly, mixing gently. Tube Label # 1-8. Prepare standard # 1 by adding 20 µl of 50 ng / ml stock standard to 980 µl of 1X Sample Buffer Diluent # 1. Mix thoroughly and gently. Pipette 400 µL Sample Buffer Diluent into each tube. Prepare standard # 2 by transferring 200 µl from tube # 1 to # 2, mix thoroughly. Prepare standard # 3 by transferring 200 µl from tube # 2 # 3, mix thoroughly. Using the table below as a guide, further serial dilutions are prepared. Sample Diluent buffer serves as a zero standard (0 pg / ml). Analysis Procedure: Equilibrate all materials and ready-to-use reagents to room temperature (18-25 ° C) prior to use. Recommended for the analysis of all standards, controls and samples in duplicate - add 100 µl of each standard (section of the standard preparation 10) and sample to the appropriate wells. Incubate for

2.5 hours at room temperature or overnight at 4 ° C with gentle shaking; washed 4 times with 1X wash solution. Wash by filling each well with 1X wash solution (300 µl) using a multichannel pipette. After the last wash, remove the remaining 1X wash buffer by aspiration or decantation. Turn the tablet over and blot with clean paper towels. Add 100 µl of 1X biotinylated timp1 for antibody detection (Section 9 Reagent Preparation) to each well. Incubate for 1 hour at room temperature with gentle shaking. Repeat washing as in step 2. Add 100 µl of 1X HRP-streptavidin solution to each well. Incubate for 45 minutes at room temperature with gentle shaking. Repeat washing as in step 2. Add 100 µl of One-Step TMB Substrate Reagent to each well. Incubate for 30 minutes at room temperature in the dark with gentle shaking. Add 50 µl of stop solution to each well at 450 nm.

Results And Discussion

Blood tests of the apoptosis factor showed that with androgenic alopecia C2-C3 and U1 types, there was a significant increase in FasL - 0.26 ± 0.083 pg / ml (P <0.05) and 0.38 ± 0.014 pg / ml (P <0.001) in comparison with similar indicators of the control group - 0.036 ± 0.01pg / ml (Table 1). But with the M3 type of androgenic alopecia, there was only a tendency to an increase in this indicator - 0.04 ± 0.005pg / ml.

Таблица 1. Concentration of apoptosis factors and inhibitors of matrix metalloproteinases in the blood of male patients with androgenic alopecia

Biological molecules (pg / ml)	Control group (n = 20)	types of androgenic alopecia		
		M3 (n=36)	C2-C3 (n=26)	U1 (n=23)
Apoptosis factor (FasL)	0,036±0,01	0, 04±0,005	0,26±0,083*	0,38±0,014***
Matrix metalloproteinase (TIMP) inhibitors	3,7±0,09	2,01±0,18***	1,49±0,022***	0,88+0,054***

Note * - differences relative to the data of the control group are significant (* - P <0.05, *** - P <0.001)

The study of the concentration of inhibitors of matrix metalloproteinases (TIMP1) in patients with androgenic alopecia showed a significant decrease in its level compared to the same indicators in the control group. Thus, with the M3 type, the TIMP1 concentration was 2.01 ± 0.18 pg / ml (P <0.001), with the C2-C3 type - 1.49 ± 0.022 pg / ml (P <0.001), with the U1 type - 0.88 ± 0.054pg / ml (P <0.001). In the control group, the same indicator was 3.7 ± 0.09pg / ml. In our study, reliably low TIMP1 values in androgenic alopecia are associated, on the one hand, with the observed oxidative stress in the extracellular matrix and the inflammatory process, in which the release of reactive oxygen species occurs in parallel with a decrease in the TIMP1 level and, accordingly, an increase in the level of matrix metalloproteinases. On the other hand, an increase in the receptor sensitivity of cell membranes to steroids, which occurs with an increase in the level of heat shock proteins, is accompanied by a change in the level of growth factors, as a result of which there is a decrease in the concentration of their inhibitors - TIMP1, and, as a consequence, an increase in matrix metalloproteinases, which alter the metabolism of the connective tissue of hair. follicle and leading, subsequently, to the atrophy of the latter. he study of the activity of matrix metalloproteinases has been studied by many scientists. In particular, French scientists have established that cytokine- and EGF-induced activation of MMP-9 (10) in the lower epithelial part of the human hair follicle is the main mechanism by which the involution of the hair follicle observed in alopecia can occur. Scientists in California found that the β-catenin-independent wnt pathway stimulates the polarization of newly adherent T cells to the basement membrane surface, while signaling of the β-catenin-dependent wnt

pathway regulates MMP expression. In the absence of a wnt signal, T cells cannot activate MMP expression and therefore cannot cross the basement membrane and enter inflammatory tissues. Therefore, manipulation of wnt signaling by T cells can be further used to control the activity of matrix metalloproteinases and the inflammatory process (11)

Conclusion

The studies have proved the important role of the parameters of the activity of the extracellular matrix and apoptotic factors in androgenic alopecia, which lead to the inflammatory process and subsequent atrophy of the hair follicles. Therefore, the therapy of androgenic alopecia should be aimed at finding methods of influencing the above parameters in order to effectively treat that improves the quality of life of patients.

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