

RESEARCH ON POLYMORPHISM OF MATRIX METALLOPROTEINASES AND GROWTH FACTOR GENES IN PATIENTS WITH PHOTO AGING AND WITH MELASMA

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Abstract: *In patients with a genetic predisposition, associations of the mutant variants Arg25Pro of the TGFβ1 gene, A-8202G of the MMP9 gene and MMP1 1607G (9.6%), associations of the mutations of the Arg25Pro gene of the TGFβ1 gene, and A-8202G of the MMP9 gene (5.8%) are mainly detected, associations of mutations of Arg25Pro genes of TGFβ1 and MMP1 1607G (3.8%), associations of mutations of A-8202G genes of MMP9 and MMP1 1607G (15.4%) of the examined patients with photo-aging.*

Keywords: *Gene polymorphism, fibroblasts, melasma, photoaging.*

Introduction. Aging of skin is an actual problem of modern dermatology and cosmetology [2]. Photo-aging is a complex of biological processes that cover various layers of the skin [1; 3]. Their clinical effects can occur at any age and the degree of manifestation depends on the total dose received throughout life. The resulting damage to proteins by UV irradiation provoke the formation of cross-links in collagen molecules, inactivation of antioxidant enzymes [4]. Mutations in DNA molecules can lead to carcinogenesis and cell death due to the avalanche-like growth of free radicals and other toxic molecules [3; 5]. Degenerative changes in the dermal intercellular substance are associated with increased activity of metalloproteinases, and the activation of proinflammatory cytokines in keratinocytes contributes to the development of inflammation and tissue damage [3]. Collagen is one of the main building blocks of human skin, providing much for the strength of the skin. Dermal fibroblasts synthesize procollagen, which are converted to collagen. There are two important regulators of collagen production: the transforming growth factor (TGF) -β, which provokes collagen synthesis, and the transcription factor (AP) -1, which inhibits collagen production and regulates collagen breakdown by over-regulating the activity

of matrix metal-loproteinases (MMPs) [7]. The literature data indicate the multifactorial nature of the pathogenesis of photoaging, and the conducted numerous studies do not cover all the links of disorders associated with the development of this disease. Objective: to study the Arg25Pro polymorphism of the TGF β 1 gene, the A-8202G polymorphism of the MMP9 gene, and the MMP1 1607G polymorphism in patients with photo-aging of the Uzbek nationality. Material and research methods. 107 patients (19 men and 88 women) with photo-aging of skin of various types and 38 (8 men and 30 women) of practically healthy people aged from 21 to 68 years old were under observation at the inpatient and outpatient treatment in the clinic of RSNPMTSDV and K MH RUz. The study included patients with the first, the second and the third type of photosensitivity. All patients received anamnesis on admission, identified provoking factors, evaluated the skin condition, conducted general clinical hematological and biochemical studies. Studies of the Arg25Pro polymorphism of the TGF β 1 gene, the A-8202G polymorphism of the MMP9 gene and the MMP1 1607G polymorphism were carried out in the laboratory of the Department of Molecular Medicine and Cell Technologies of the Research Institute of Hematology and Blood Transfusion under the guidance of Dr. med. Professor Babayev KT mutations (polymorphism) in the human genome were detected using the SNP-express system. Results and its discussion. Anamnesis collection revealed only the presence of hereditary predisposition in only 30.7% of the examined patients. The main provoking factors were pro-longed exposure to the sun (66%), 25.5% of patients could not indicate any factor, in 8.4% of patients the provocative factor was the administration of oral contraceptives. Photo-aging was more frequently observed in patients with type 2 skin (47.6%), and mainly the lesions were located symmetrically on the face. It should be said that the clinical manifestations in patients with photo-aging depended on skin type. So, the SPF-factor was mainly characteristic of FS1 (40%), FS2 (31.4%) and FS3 (51.8%); epidermal formations in the form of freckles, telangi-ectasia, seborrheic and actinic keratosis; Dermal lesions in the form of wrinkles, cross-striation, a violation of the general skin tone, skin roughness, atrophy and a million were also characteristic of the above-mentioned skin types. As noted earlier, the regulators of collagen metabolism are: TGF- β , which induces collagen synthesis, and collagen regulating collagen MMPs. In this regard, we have studied the genes of these regulators. A study of the possible association of allelic and genotypic variants of the Arg25Pro polymorphism

Medical science 200 of the TGF β 1 gene with the development of photoaging showed a decrease in the frequency of arginine alleles by 1.45 times and an increase in the proline allele by 4.1 times relative to the frequencies of the above-mentioned alleles in healthy individuals (Table 1). A significant increase in the frequency of the proline allele indicates the protective effect of this allele in the development of photoaging. The frequency of the Arg /; Arg, Arg/Pro and Pro/Pro genotypes was calculated according to the odds ratio. In the population group, we did not reveal the presence of the Pro/Pro mutant genotype, whereas in patients with photo-aging, its frequency increased to 23.1%. At the same time, there was a significant decrease in the detection rate of the homozygous form of Arg/Arg by 1.7 times and an increase in the heterozygous (Arg/Pro) form by 1.56 times, i. e. with the presence of the heterozygous form, the risk of photo aging increases by 1.56 times, and with the carriage of the mutant Pro/Pro genotype TGF β 1—by 23.1 times, and such differences were statistically significant.

Thus, a significant association was found between the “un-favorable” genotypic variant of Arg/Pro and, especially, the Pro/Pro allele of the Arg25Pro polymorphism of the TGF β 1 gene and the development of photoaging. Dermal fibroblasts synthesize procollagen, which are converted to collagen. There are two important regulators of collagen production: TGF- β and protein activator (AP) –1. TGF- β is a cytokine that stimulates collagen synthesis. AP-1 is a transcription fac-tor inhibiting collagen production. TGF- β targets are also diverse

cells, since the expression of its high-affinity receptor is widespread. The effect of TGF- β on the immune system is dominated by inhibitory effects, it enhances the synthesis of extracellular matrix proteins, promotes wound healing, and has an anabolic effect. Turning off the TGF- β gene leads to the development of a fatal generalized inflammatory pathology and impaired formation of mature collagen, and, as a result, the clinical manifestations of photoaging. Normally, there is a balance of collagen due to the regulation of its synthesis and decomposition under the action of matrix metalloproteinases (MMP-9 and MMP-1). In this regard, we further studied the A-8202G polymorphism of the MMP9 gene. A comparative analysis of the frequency distribution of alleles and genotypes of the A-8202G polymorphism of the MMP9 gene in a group of patients with photo-aging and the total population sample revealed statistically significant differences (table 2). The frequency of occurrence of the A and G alleles was 37.5 and 62.5% in patients with photo-aging, 60.5 and 39.5% in the control group. As can be seen, a significant decrease in the frequency of allele A was revealed in the group of patients by 1.61 times, an increase in the frequency of allele G by 1.58 times compared with the control group. In patients with photo-aging, the frequency of A/A, A/G and G/G genotypes differed significantly from the population sample. We found a significant decrease in the frequency of occurrence of the AA allele 2.13 times, and an increase in the mutant G/G allele 2.66 times. These data indicate the association of this polymorphism with the development of photoaging.

Thus, a significant association was revealed between the “unfavorable” genotypic variant G/G of the A-8202G polymorphism of the MMP9 gene and the development of photoaging. MMP-9 is secreted as a zymogen, its substrates are

denatured type I collagen and native collagens. It takes part in the processes of inflammation, tissue remodeling and repair, mobilization of matrix-bound growth factors and cytokine processing [7]. Consequently, mutations in its gene can lead to disruption of the metabolism of collagen and the formation of skin aging, especially under the influence of ultraviolet rays. However, MMP-1 also plays an important role in the regulation of collagen metabolism. When comparing the frequencies of alleles and genotypes of the MMP1 1607G polymorphism between the general group of patients with photo-aging and the population sample, statistically significant differences were also found.

The frequency of occurrence of the M and G alleles was 48.1 and 51.9% in the main group of patients and 64.5 and 35.5% in the control group. As can be seen, a significant increase in the frequency of the G allele in the group of patients was detected 1.46 times as compared with the control group. We found that the risk of photo-aging increased by 1.82 times with the carriage of the mutant G/G genotype, and this difference was statistically significant. Thus, a significant association has been revealed between the “unfavorable” genotypic variant of the G/G allele of the MMP1 1607G polymorphism and the development of photo-aging. It should be said that MMP-1 is synthesized by fibroblasts, chondrocytes, keratinocytes, macrophages, endothelial cells, osteoblasts, and is involved in the degradation of collagen filaments in the remodeling of the extracellular matrix. In this regard, it can be assumed that the presence of mutations in the gene of this protein may contribute to photo-aging of the skin. It was of interest to study the association of Arg25Pro gene mutations of the TGF β 1 gene, A-8202G of the MMP9 gene and MMP11607G gene in patients with photo-aging. The analysis showed the presence of the association of all three genes in 5 of 52 (9.6%) of the examined patients, the association of mutations of the Arg25Pro gene of the TGF β 1 gene and the A-8202G of the MMP9 gene—in 3(5.8%) patients, the association of mutations of the Arg25Pro genes TGF β 1 and MMP1 1607G—in 2(3.8%) patients, mutation associations of the A-8202G genes of the MMP9 and MMP1 1607G—in 8(15.4%) of the examined. It should be said that such associations of mutations in the genes were mainly observed in patients with hereditary predisposition, severe course of pathology. Thus, a

significant association has been revealed between the “unfavorable” genotypic variant of the genes listed above and the development of photo-aging, this is especially pronounced in patients with hereditary predisposition. In our opinion, the identification of a functionally unfavorable genetic marker in patients with photo-aging allows us to predict the risk of early aging of the skin and determine the further tactics of therapeutic and preventive measures. Summarizing the above, we can say that UV irradiation leads to the generation of ROS and the induction of AP-1 [12], which cause the production of MMPs with consistently increasing collagen decay, and also leads to a decrease in TGF- β and, as a result, slowing down the production of collagen, which together are the main mechanism of skin photoaging.

Repeated UV damage throughout life leads to the development of a visible “sun scar”, showing a visible wrinkle. In addition, under the influence of ultraviolet ray disrupted the process of maturation of keratinocytes, the appearance of atypical keratinocytes, manifested by dryness and peeling of the skin—xerosis. Ultraviolet damage to Langerhans cells, which are located mainly in the spinous layer of the epidermis, which have an antigen-presenting function and carry out immune surveillance, leads to a violation of the mechanisms of immunological protection of the skin. In addition, dark-pigmented subjects cause less collagen breakdown and less DNA damage than light-pigmented subjects [3; 6]. Analysis of the assessment of the functional significance of the polymorphism of the Arg25Pro genes of the TGF β 1 gene, A-8202G of the MMP9 gene, and MMP1 1607G gene in patients with photo-aging made it possible to draw the following conclusions: 1. A statistically significant difference was found between patients with photo-aging and healthy donors in the frequencies of allelic variants of the Arg25Pro polymorphism of the TGF β 1 gene, manifested by a high relative risk of skin photo-aging and genotypic heterozygous Arg/Pro and mutant Pro/Pro variants.

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