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Collagen synthesis in the skin: genetic and epigenetic aspects

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ABSTRACT

One of the most important functions of the skin, mechanical, is provided by collagen fibers and their interaction with other elements of the extracellular matrix. Synthesis of collagen fibers is a complex multistep process. At each stage, disturbances may occur, leading, as a result, to a decrease in the mechanical properties of the connective tissue. In clinical practice, disorders of collagen synthesis are manifested through increased skin laxity and looseness and premature aging. In addition to the clinical presentation, it is important for the cosmetologist and dermatologist to understand the etiology and pathogenesis of collagenopathies. The present review summarizes and systematizes available information about the role of genetic and epigenetic factors in the synthesis of collagen fibers in the skin. Understanding the etiology of collagen synthesis disorders can allow doctors to prescribe pathogenetically grounded treatment with the most effective results and minimize adverse reactions.

Keywords: skin collagen, collagen synthesis, collagenopathy, gene polymorphism

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Синтез коллагена в коже: генетические и эпигенетические аспекты

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РЕЗЮМЕ

Одна из важных функций кожи, механическая, обеспечивается коллагеновыми волокнами и их взаимодействием с другими элементами внеклеточного матрикса. Синтез коллагеновых волокон – это сложный многоэтапный процесс. На каждом этапе может возникнуть нарушение, приводящее в итоге к снижению механических свойств соединительной ткани. Клинически нарушения коллагенообразования проявляются в виде повышенной дряблости, рыхлости кожи, раннего проявления признаков старения лица. Кроме клинической картины, врачу косметологу и дерматологу важно понимать этиологию и патогенез коллагенопатий. В нашем обзоре мы обобщили и систематизировали имеющуюся информацию о роли генетических и эпигенетических факторов в процессе синтеза коллагеновых волокон кожи. Понимание патогенеза нарушения коллагенообразования может позволить врачам назначать патогенетически обоснованное лечение с достижением наиболее эффективных результатов и минимизацией нежелательных реакций.

Ключевые слова: коллаген кожи, синтез коллагена, коллагенопатия, полиморфизм генов

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

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INTRODUCTION

In order to prescribe pathogenetically grounded therapy for aesthetic skin imperfections, it is important to understand the physiological and pathological processes in the skin and, based on this, prescribe a set of measures aimed at restoring its physiological properties [1]. To do this, it is necessary to perform in-depth study on synthesis of collagen fibers, including the genetic aspects of collagen synthesis. Uniting fragmented data about genes encoding key proteins, including enzymes, at all stages of collagen synthesis in the skin can help to develop new predictive strategies in medical cosmetology (aesthetic medicine).

Collagen accounts for up to 25% (in dry weight) of all proteins in the human body, providing structural support for connective tissue, including the skin [2]. A large number of modern methods of aesthetic medicine are aimed at improving and stimulating collagen synthesis in the skin [3]. At the same time, some companies have undertaken clinical trials, and histologic studies and have suggested that particular techniques bring significant results. However,

in clinical practice, we are far from achieving consistent clinical effects in all patients. In the context of diverse results in our patients, we most often talk about the "individual characteristics" of a particular person. So, what underlies these individual characteristics?

There are two groups of factors that can influence collagen synthesis in the skin: external and internal ones [4]. External factors include nutrition (the completeness of intake of nutrients necessary for collagen synthesis) and the impact of environmental factors. Internal factors include the hormonal status, the inherent genetic code for the structural elements of the skin, and epigenetic regulation of the activity of genes encoding key proteins and enzymes of collagen synthesis [5]. The genetic aspects of collagen fiber turnover (synthesis, function, degradation), as well as their role under normal conditions and in pathology are being actively studied. The largest number of studies are devoted to the collagen of bone tissue and internal organs. The number of studies concerning genetic predictors of collagen synthesis in the skin has been increasing in recent years, but there is a need to systematize the existing data.

THE STRUCTURE OF THE COLLAGEN MOLECULE

n the extracellular matrix, two main classes of macromolecules are distinguished: glycoproteins (fibronectin, proteoglycans, and laminin) and fibrous proteins (collagen and elastin). The extracellular matrix proteins are called "matrisomes" [6]. A collagen molecule is a fibrillar glycoprotein characterized by versartility in the construction of various tissues. The natural form of the collagen fiber provides necessary mobility during skin stretching, but in scar tissue, fibers are straighter and thinner, and, consequently, the tensile strength of the collagen fiber decreases [7]. Depending on the type of collagen, its supramolecular structure can be fibrillar and non-fibrillar. Among the 28 types of collagens in the skin, type I, III, and V fibrillar collagens are of the greatest importance for the skin, while non-fibrillar collagens (type IV collagen located in the basement membrane and type VI, VII, XIV, and XVII collagens) are less important.

All collagens, at least partially, are supercoils twisted in a left-handed fashion consisting of three polypeptide chains [8]. These polypeptide chains can have the same sequence of amino acid residues (in this case, the collagen molecule is known as homomeric) or a different sequence (heteromeric collagen molecule) [9]. So, the dominant form of type I collagen is a heterotrimer. The homotrimeric can be found in fetal tissues, tumors, and some fibrous lesions in various tissues; it is more resistant to the action of collagenases [10]. In contrast, the dominant form of type III collagen is a homotrimer. Its fiber diameter is smaller than that of type I collagen. However, when type I and III collagen appear together, the latter regulates the diameter of the collagen fiber [11]. The collagen molecule consists of repeating triads of (X-Y-Gly)n, where Gly is the amino acid glycine. The X and Y positions may be attributed to any other amino acids, but quite often they are filled by proline or hydroxyproline [12]. Glycine is the smallest of the amino acids, and its lateral hydrogen is always in the center of the helix. This amino acid contributes to the coiling of the three helices and provides tight packing of collagen into the helix [13, 14]. Mutations in genes that lead to replacement of glycine with another amino acid, lead to a change in the structure of the helix and thus a disruption in the protein function. For example, more than 650 mutations in the *COL3A1* gene encoding the pro-alpha 1 chain of type III collagen have been identified, among which missense mutations replacing glycine with a bulkier amino acid are the most common. Most glycine substitutions lead to the formation of a more thermolabile protein with greater susceptibility to proteinases [15]. Most patients with such mutations are heterozygous and can produce both normal and abnormal α-chains of type III procollagen, so they can have both normal and mutant homotrimers and triple chains containing one or two abnormal chains [16].

COLLAGEN SYNTHESIS

The main producers of extracellular matrix components, including collagen, are fibroblasts. Collagen fiber synthesis is a complex multi-stage process that begins with transcription of the gene encoding collagen in the cell nucleus and ends with the assembly of the collagen fiber in the extracellular space [17]. At each stage, it is possible to identify genes that contribute to the fiber formation. At the initial stage, these are genes that contain the structure code for the polypeptide chain. Also, at this stage, the role of epigenetic regulation can be noted. At the next

stages of the assembly (post-translational changes), the role of genes responsible for spatial arrangement of collagen fibers affecting the functionality of the fiber is important [18].

The assembly of the collagen polypeptide chain occurs in ribosomes, where information is read from the messenger ribonucleic acid (mRNA), and the polypeptide chain is assembled (translated) from amino acids with the participation of transfer RNA (tRNA). The primary collagen polypeptide chain consists of three domains: N-propeptide, triple-helical (makes up 95% of the molecule), and C-propeptide. These domains are transported to the endoplasmic reticulum, where they undergo subsequent post-translational modification [19]. A key step in the collagen formation is formation of a triple supercoil, or trimerization, which begins at the C-terminal end at the site of disulfide bonds and proceeds at a lightning speed to the N-terminal end of the molecule. Each individual polypeptide chain is folded into a left-handed helix. Then all three chains are folded together into a right-handed helix. Before the assembly of the supercoil, post-translational changes occur in each of the chains, such as hydroxylation, glycosylation, and oxidative deamination. All these changes occur inside the cell [20]. For subsequent thermal stability of collagen, prolyl residues in the triple-helical domain are hydroxylated to 4-hydroxyproline by prolyl-4-hydroxylase encoded by the genes *P4HA1, P4HA2, P4HB,* and *P4HA3* (Table) [21]. For subsequent collagen reticulation, some of the lysine residues are hydroxylated by procollagen-lysine, 2-oxoglutarate-5-dioxygenase encoded by the *PLOD* gene and then glycosylated [22, 23]. As seen from the Table, under physiological conditions, *PLOD1* and *PLOD3* are highly expressed in the skin. Hydroxylation requires the presence of oxygen, vitamin C (for reduction of iron ions in the composition of enzymes), and α-ketoglutarate [24]. Ascorbic acid (vitamin C) is a cofactor of prolyl hydroxylases and lysyl hydroxylases, which are involved in collagen biosynthesis [25].

Table

Genes encoding enzymes involved in post-translational changes in the collagen fiber [26]

Gene, encoded protein / enzyme	Localization on the chromosome	Clinical manifestations of mutation / polymorphism	Expression in the skin (RPKM)
P4HA1 (α-subunit of the prolyl 4-hydroxylase)	10q22.1, 17 exons	Poor prognosis in malignant neoplasms	7.129 ± 2.121
P4HA2 (α-subunit of the prolyl 4-hydroxylase)	5q31.1, 17 exons	Poor prognosis in malignant neoplasms, risk of myopia	4.6 ± 0.816
P4HB (β-subunit of the prolyl 4-hydroxylase)	17q25.3, 10 exons	Poor prognosis in malignant neoplasms	89.377 ± 8.824
PLOD1 (LH1) (lysyl hydroxylase (procollagen lysine, 2-oxoglutarate 5-dioxygenase 1))	1p36.22, 20 exons	Ehlers – Danlos syndrome type VI	11.061 ± 2.249
PLOD2 (LH2) (lysyl hydroxylase (procollagen lysine, 2-oxoglutarate 5-dioxygenase 2))	3q24, 23 exons	Ehlers – Danlos syndrome type VIB, Brook's syndrome	0.988 ± 0.202
PLOD3 (LH3) (lysyl hydroxylase (procollagen lysine, 2-oxoglutarate 5-dioxygenase 3))	7q22.1, 19 exons	Ehlers – Danlos syndrome type VIB, Stickler-like syndrome	7.062 ± 2.361
LOX (lysyl oxidase)	5q23.1, 8 exons	Aortic aneurysms, vascular disorders	4.234 ± 1.207
ADAMTS1 (disintegrin and metalloprotease with thrombospondin motif 1)	21q21.3, 9 exons	Impaired growth, fertility, and organ morphology	2.796 ± 0.682
ADAMTS2 (disintegrin and metalloprotease with thrombospondin motif 2)	5q35.3, 23 exons	Ehlers – Danlos syndrome type VIIC	1.395 ± 0.248
ADAMTS10 (disintegrin and metalloprotease with thrombospondin motif 10)	5q35.3, 23 exons	Disruption of growth and development of the skin, lens, and heart, Weil – Marchesani syndrome	1.485 ± 0.952
BMP1 (bone morphogenetic protein 1)	8p21.3, 21 exons	Osteogenesis imperfecta, disruption of morphogenesis and tissue regeneration	5.382 ± 1.39
BMP2 (bone morphogenetic protein 2)	20p12.3, 3 exons	Impaired development of bone and cartilage tissue	2.551 ± 0.444
BMP4 (bone morphogenetic protein 4)	14q22.2, 6 exons	Dental system pathology, orofacial cleft, microphthalmia, cardiovascular pathology	2.207 ± 0.446
BMP7 (bone morphogenetic protein 7)	20q13.31, 7 exons	Pathology of the skeletal system, kidneys, and brown adipose tissue	7.722 ± 0.536

Other lysine and hydroxylysine residues undergo oxidative deamination using lysyl oxidase (LOX), thus forming reactive aldehydes that are capable of forming covalent intramolecular and intermolecular cross-links [27]. Trimerization occurs in the endoplasmic reticulum and is facilitated by chaperone proteins. The folding of the procollagen molecule begins only after the translation of the entire protein molecule is completed, with the autonomous folding of the C-propeptide domain on each monomer strand. After the folding, cysteine-rich C-propeptide is stabilized by disulfide bonds. After the folding, C-propeptide domains "recognize" each other and assemble together; in fibrillar proteins this process is mediated by Ca^{2+} and intermolecular disulfide bonds [28]. The assembled C-propeptide trimer then initiates almost instantaneous folding of the triple-helical domain, which is rich in proline and glycine, with preliminary isomerization of proline peptide bonds into a trans configuration [10]. In the resulting triple helix, further hydroxylation of procollagen is weakened and preparation for protein secretion begins (in a non-canonical way). After the formation of the supercoil, large globular domains are removed from both sides of the molecule to produce tropocollagen. Then, collagen reticulation occurs – cross-links are formed between some lysine and hydroxylysine residues [29].

Regulation of the displacement and orientation of various collagen chains occurs by additional globular non-collagen domains. After the formation of the triple helix, N-terminal propeptides are removed by zinc-dependent proteases belonging to the ADAMTS group (A disintegrin and metalloproteinase with thrombospondin motifs). The C-terminal propeptides of collagen are cleaved off by a group of metalloproteases belonging to BMP-1 (bone morphogenetic protein 1) (Table) [30]. As seen from the Table, the expression of the *ADAMTS1, ADAMTS2,* and *ADAMTS10* genes in the skin under physiological conditions is approximately the same, whereas the remaining enzymes of the ADAMTS group have only low-level gene expression in the skin. However, the key enzyme involved in the cleavage of the N-terminal propeptide is the N-protease encoded by the *ADAMTS2* gene. In the group of *BMP* genes, *BMP7* and *BMP1* have the greatest expression in the skin under physiological conditions, but the key role in the cleavage of the C-terminal propeptide in the skin belongs to BMP-1 [31].

The assembly of a collagen molecule is spatially arranged depending on the type of collagen and is enzymatically supported by additional molecular organizers, such as fibronectin, integrins, and minor collagens [32]. First, supramolecular structures of 4–5 protofibrils are assembled from a tropocollagen molecule; then, microfibrils are formed, from which a fibril (with a diameter from 10 to 300 nm) is produced with the participation of proteoglycans [33]. Proteoglycans on the surface of fibrils form a kind of a shell. Then, during the autogenesis, fibrils form a collagen fiber, which also includes glycosaminoglycans, glycoproteins, and non-collagen proteins. Fibrillogenesis is a spontaneous process (self-assembly), which is evidenced by spontaneous formation of fibrils by collagen fibers *in vitro*. However, *in vivo*, fibrillogenesis of type I collagen is controlled by cellular mechanisms – it occurs only in the presence of type V collagen, fibronectin, and integrins (fibronectin-binding and collagen-binding) [34]. At the same time, it is believed that type V collagen is important for the nucleation of type I collagen fibrils, while fibronectin and integrins are important during its assembly.

The tissue specificity of the collagen fiber is determined by the final composition of various collagens in heterotypic fibrils, and this composition is influenced by various signaling molecules involved in the fibrillogenesis [35]. In the collagen molecule, there are intrahelical and interhelical bonds. Reticulation is carried out by two mechanisms: specific (enzymatically controlled) and non-specific (spontaneous). According to the first mechanism, lysine is oxidized by lysyl oxidase with subsequent formation of aldimines. Then the reaction with histidine occurs to form chemically stable histidinohydroxylysino-norleucine [36]. Lysyl oxidase, which hydroxylates the lysyl residues of type I and II collagens, is encoded by the *LOX* gene [37]. The second mechanism may include multiple non-specific reactions with glucose and its oxidation products, resulting in the formation of advanced glycation end-products. This mechanism is especially important in aging and in diseases, such as diabetes mellitus. Carbohydrates and oxidized carbohydrates react with arginine, lysine, and hydroxylysine to form a glycated protein. Reticulated collagen is resistant to enzymatic and chemical degradation.

REGULATION OF COLLAGEN SYNTHESIS

The synthesis and assembly of the collagen fiber are influenced by many signaling molecules and proteins. Some of the most important of these are N-propeptides of type I collagen; fibronectin; lysyl oxidase; tenascin-X; thrombospondin; matrillins; perlecan; decorin; biglycan; fibromodulin; and lumican. Thus, a mutation of the gene encoding tenascin-X leads to the development of Ehlers – Danlos syndrome. In this syndrome, collagen fibrils of the usual size and shape are detected, but with a lower packing density. As a result, the total collagen content in the skin is reduced by 30% [38]. In addition, collagen and N-propeptides inhibit further synthesis of procollagen through negative feedback regulation. One of the most common glycoproteins of the extracellular matrix is fibronectin, which plays an important role in the development, cell growth, differentiation, adhesion, and cell migration through integrin-mediated signaling [39].

The formation of type I collagen fibrils requires the presence of type V collagen, as type V collagen acts as a central nucleus in the formation of type I collagen fibers. Transforming growth factor β1 (TGFß1), Wnt / β-catenin, and p38 mitogen-activated protein kinase (MAPK) also play a role in regulating the expression of collagen genes [40]. TGFß also binds to the extracellular matrix through binding to latent TGFß-binding protein 1, which is associated with fibronectin 1 and fibrillin microfibrils [41]. TGFß1 stimulates the differentiation of myofibroblasts, resulting in pathological fibrosis (scarring) during tissue regeneration. An additional factor in the differentiation of myofibroblasts is mechanical tension (stiffness) of the tissue that supports profibrotic activation [42]. Various cytokines, including interferon-gamma (IFNy), interleukin (IL)-1, and basic fibroblast growth factors (bFGF, FGF-2), may participate in the suppression of TGFß1 activity. As a result of their action, collagen deposition decreases, and apoptosis is induced [43]. Hypoxia can lead to a decrease in the level of mRNA and type III collagen in chondrocytes and, on the contrary, to their increase in the lungs, resulting in alveolar fibrosis. In the skin, adenosine and purine, which are formed from ATP and ADP, are released in response to hypoxia, trauma or metabolic stress. In fibroblasts, adenosine, acting through its receptors, activates the expression of the *COL3A1* gene [44]. Epidermal growth factor (EGF) and basic fibroblast growth factor (bFGF) also enhance the expression of *COL3A1* mRNA and protein in human skin fibroblasts through MAPK signaling [45].

EPIGENETIC REGULATION

Epigenetics studies inherited changes in protein synthesis that are not determined by changes in the nucleotide sequence. Typically, such changes are caused by the action of protein synthesis regulators (de-/methylation of DNA, de-/acetylation of histones, de-/phosphorylation of transcription factors, the action of regulatory microRNA (miRNA)) and other intracellular mechanisms. Modification of DNA and histones (involved in DNA packaging in the cell nucleus) alters the histone – histone and histone – DNA interactions, regulating the availability of transcription factors and influencing gene transcription [46]. Among other factors, modification of epigenetic mechanisms underlies the mechanisms of aging of the skin and collagen fibers. The role of DNA and histone methylation, as well as histone acetylation, is the most studied [47]. In particular, DNA methylation results in transcription repression and long-term maintenance of genome stability. However, in some sporadic cases, DNA methylation leads to gene activation in several types of cells [48]. Demethylation of DNA is facilitated by the influence of some external and internal factors. Maintenance of methylated DNA is important for the preservation of progenitor cells and self-renewal of the skin [49].

With aging of the skin, the so-called epigenetic drift accumulates, as a result of which both hypomethylated and hypermethylated DNA regions accumulate. At the same time, ultraviolet (UV) radiation makes a great contribution to DNA hypomethylation, and the degree of hypomethylation is correlated with clinical parameters of skin photoaging [50]. An example of epigenetic changes is a decrease in the regulation of the gene encoding LOX in old fibroblasts, resulting in a decrease in the mechanical properties of the skin [51]. Methylation of histones, depending on the modified site, can lead to activation or suppression of transcription. Acetylation (deacetylation) of histone tails has the opposite effects of methylation (demethylation): acetylation leads to chromatin relaxation and transcription activation; deacetylation, on the contrary, leads to tighter chromatin coiling and transcription inhibition.

Specific NAD^+-dependent enzymes (sirtuins (SIRT)), due to their participation in histone acetylation, play a key role in epigenetic regulation and facilitate transcription. Moreover, they participate in the control over energy metabolism and oxidative stress, cell survival, response to UV damage, DNA repair, tissue regeneration, and inflammation [52]. In the dermis, SIRT can inhibit collagen degradation, regulate DNA repair, and increase the activity of type I collagen synthesis by fibroblasts. The activity of SIRT decreases with age and under conditions of oxidative stress [53].

CONCLUSION

A large number of genetic and epigenetic factors affect the functioning of collagen fibers and, consequently, the mechanical properties of the skin. Gene mutations leading to various collagenopathies may be associated with one of the genes encoding collagen proteins, enzymes involved in post-translational collagen modifications, MMP or glycosaminoglycans [10]. In Russian medicine, the terms differentiated and undifferentiated hereditary connective tissue dysplasias were previously proposed. The introduction of modern methods of molecular genetic diagnosis indicates that the most common hereditary ("differentiated") collagenopathies include osteogenesis imperfecta, Ehlers – Danlos syndrome, Caffey disease, and Marfan syndrome [25], which should be taken into account by doctors of aesthetic medicine. These are monogenic syndromes of Mendelian inheritance caused by causal (pathogenic) gene mutations, in which the contribution of the environment is minimal or absent. For example, the genes involved in the development of Ehlers – Danlos syndrome include *COL5A1, COL5A2, COL3A1, PLOD1, COL1A1, COL1A2, ADAMTS2, TNXB, FMNA, CHST14, SLC39A13, B4GALT7,* and *FKBP14* [54].

On the other hand, the number of associative genetic studies on multifactorial collagenopathies is increasing. In these diseases, both the carriage of polymorphisms in candidate collagen genes and the influence of external environmental factors are important. This is due to higher incidence of multifactorial collagenopathies in the population compared with monogenic collagenopathies, many of which are rare (orphan). The study of the contribution of single nucleotide polymorphisms (SNPs) to the development of multifactorial connective tissue diseases, in general, and to the development of human skin collagen pathology, in particular [55], is relevant. Yet, associative genetic studies on the genes responsible for collagen fiber function are currently insufficient to compile a complete and clear personalized algorithm for the management of such patients by cosmetologists and dermatologists. Therefore, doctors, to a greater extent, focus on the clinical presentation: increased flabbiness, hyper-elasticity, early manifestations of aging, and other signs indirectly indicating collagen pathology. Based on the clinical presentation, a treatment plan is designed aimed at protecting and improving synthesis of collagen fibers. Such recommendations, based on external and internal factors, may include lifestyle changes, additional intake of vitamins and minerals, and mesotherapy (biorevitalization) with amino acids and co-factors necessary for collagen synthesis. Taking into account the results of molecular genetic diagnosis of monogenic and multifactorial collagenopathies and transferring them into real clinical practice are very important. It can improve the effectiveness and safety of local and general therapy for normal and pathological skin aging.

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