The Use of Collagens and Fibroblasts in Modern Medicine (Literature Review)

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ABSTRACT

The work is devoted to a review of the options for the use of collagen and collagen-based materials in medicine and the pharmaceutical industry. The problem of effective impact on the local manifestation of the wound process and at the present stage of development of medicine remains unresolved, despite the emergence of various drugs and techniques. Among the many types of cells that can have a clinical effect, dermal fibroblasts are of particular interest, which are a heterogeneous population of cells of the mesenchymal series and play a key role in the processes of regulating cellular interactions and maintaining skin homeostasis. Currently, there are more than 60 modern cell or tissue preparations for the treatment of wounds, which makes it difficult to choose the appropriate, safe and effective adjuvant therapy. A review of the world literature on the role of collagen in the process of wound healing is presented. The problems of epidemiology of chronic wounds and ulcers of various origins, physiology and pathophysiology of wound healing phases are considered. The pathogenetic role of different types of collagen, as well as the mechanisms of collagen, macrophages, fibroblasts, matrix metalloproteinases and other cytokines in the healing of ulcers are discussed.

Keywords:	Collagen, "collost", biomaterial, allogeneic fibroblasts, human fibroblasts in the form of a skin substitute, repair of damaged tissues, chronic wounds.

Under management

Collagen is a fibrillar protein that forms the basis of the connective tissue of the body and ensures its strength and elasticity. Connective tissue contains from 1 to 9% collagen. Collagen belongs to the class of proteins called scleroproteins. A feature of proteins of this class is their phylogenetic relationship in different species of animals and humans. The term "collagen" refers to specific monomeric protein molecules and aggregates of these molecules, which form fibrillar structures in the extracellular matrix of connective tissue (Fig. 1.). In the collagen molecule, every third amino acid is glycine. Collagen is also characterized by amino acids that are not found in other proteins, such as oxyproline and oxylysin, the content of which is 23% of the total amino acid composition of the collagen molecule [1].

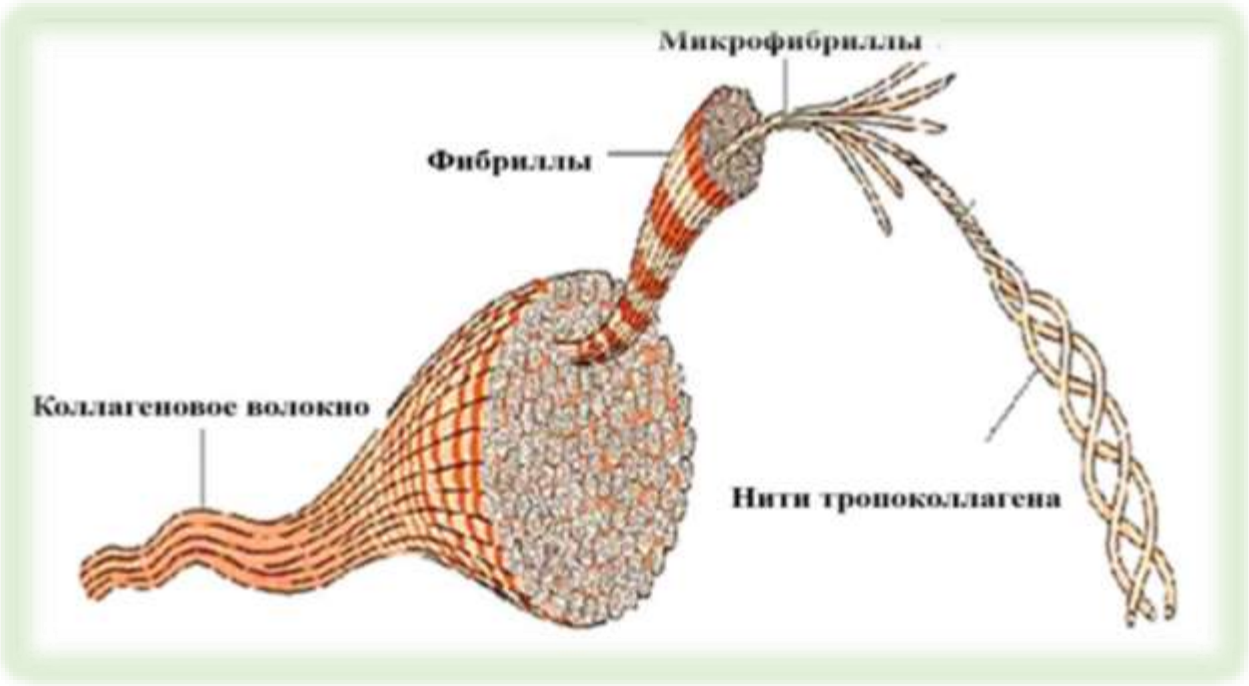

Figure 1 – Structure of collagen fiber

In the pharmaceutical and medical industries, collagen has found wide application. On its basis, various dosage forms (soft and liquid), special patches and sponges (hemostatic collagen sponge, collagen sponge with methyluracil, collagen sponge with sanguiritrine, etc.), as well as a variety of means for quickly stopping bleeding (local hemostasis agents), medical products for the treatment of wounds, burns, trophic ulcers, pressure sores and other defects of soft tissues of various genesis have been developed [2]. The complex three-helix molecule is ordered in such a way that the free side chains of the glycine of each polypeptide chain are inside the common helix, and the rings of proline, oxyproline, and the side groups of amino acids protrude outwards. 2.). The unique physicochemical, physico-mechanical and biological properties of collagen make it widely used as an auxiliary substance in the production of prolonged dosage forms, as a hemostatic agent and matrix for directed tissue regeneration in the form of membranes, sponges, coatings, as well as a component of complex combined drug systems, including a collagen-based depot matrix, a medicinal substance (or combination of substances) and a release modulator. In addition, collagen itself, due to its "typical" specificity as a high molecular weight compound, has a high potential for pharmaceutical development [2,3]. To date, scientists have identified more than 40 genes that collectively encode 28 types of collagen. They are designated by the Roman numerals I–XXVIII. Such a pronounced variety of collagen types is necessary to provide different physiological roles in various tissues and organs [9].

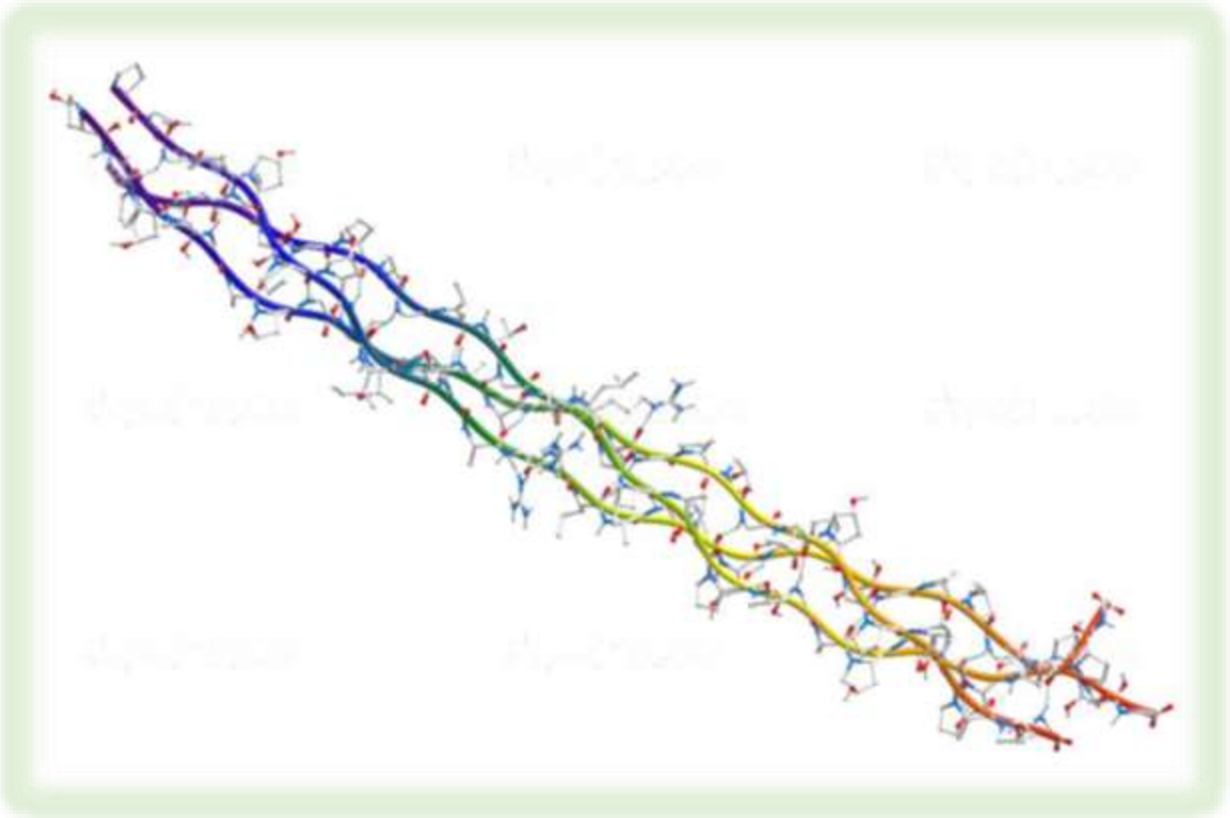

Figure 2 – Ternary-helical model of collagen molecule

Biomaterial "Collost" was implanted starting from the 2nd phase of the wound process. "Collost" is a bioplastic material based on native unreconstructed bovine collagen with a fully preserved structure. To close planar wounds and ulcerative defects, the Biomaterial "Collost" in the form of membranes was used. A membrane pre-soaked in a warm (38 ° C) sterile physiological solution was applied to the sonically treated wound for 15 min. When the wound defect was localized on the plantar surface, the membrane was fixed with 3-4 Tisorb 00 ligatures. Upon completion of the manipulation, a gel dressing was applied (Hydrosorb, Gelepran) [4]. "Collost" is a sterile bioplastic collagen material with a fully preserved fibrous structure that provides tissue regeneration. The mechanism of action of "Collost" is due to the fact that its basis is type I collagen, which acts as an extracellular matrix and provides guided contact of epithelial cells and fibroblasts, creating their optimal migration and orientation, as well as binding cells to form new tissue. Optimizationof ultrasonic cavitation and bioplastic material "Collost" helps to accelerate the processes of wound cleansing from devitalized tissues and microbial contamination of wounds, and also prevents secondary infection. The use of ultrasonic and bioplastic material "Collost" significantly improves the cytologic picture of wounds, affecting the acceleration of reparative processes and epithelialization periods. [5].

Fibroblasts are one of the main secretory cells of the body, involved in the formation of the extracellular matrix, repair of skin damage, stimulation of the growth of keratinocytes and blood vessels. In accordance with their location in the tissues and the functions performed, fibroblasts are able to produce procollagen, fibronectin, glycosaminoglycans, proelastin, nidogen, laminin, chondroitin-4-sulfate, tenascin [6]. Transplantation of cultured allogeneic fibroblasts improves the clinical indicators of the course of the wound process, significantly reducing the healing time of wounds compared to traditional methods of treatment by an average of 7-8 days, which significantly reduces the duration of treatment, mortality, as well as the cost of victims. For the current level of care for seriously ill patients, transplantation of allogeneic fibroblasts

cultured in vitro is the most acceptable. Dermal fibroblasts are a heterogeneous population of mesenchymal cells and play a key role in regulating cellular interactions and maintaining skin homeostasis [7,10]. The connective tissue framework of the heart, lungs, gastrointestinal tract, muscles and other organs contain fibroblasts that perform specialized functions. Differences in gene expression between the fibroblasts of the dermis and skin derivatives are shown, fibroblasts obtained from various anatomical sites have tissue-specific cytophysiological differences [19].

The regeneration of periodontal tissues involves: transforming growth factor alpha (affects angiogenesis), beta growth foctor (stimulates the synthesis of type 1 collagen, fironectin and osteonectin) and the main fibroblast growth factor (affects the growth of all types of cells in tissues). In experimental studies, a pronounced effect of FRF (common fibroblast growth factor) on the acceleration of angiogenesis processes was also established (it enhances the proliferation of endotheliocytes of capillaries, smooth muscle cells and pericytes, which play an important role in the formation of blood vessels). Also, OFGF is a powerful mitogenic factor for cells of mesenchymal origin, it significantly reduces the time of their doubling [8]. An experimental model of the wound process was formed in male rats of the Wistar line against the background of alloxan diabetes. Studies of the cellular structures of wounds demonstrate a positive dynamics of the course of reparative processes in experimental animals with alloxan diabetes with local administration of the sorbent - the drug Beta-Beta. This was manifested in the improvement of angiogenesis processes, the development of granulation tissue and the epithelialization of wound surfaces. An experimental model of alloxan diabetes was formed to study the therapeutic reparative effects of the drug Beta-Beta with its topical application in conditions of purulent-necrotic wounds of soft tissues of rats [12].

Treatment of chronic wounds is a continuously developing direction. Problems of excessive mechanical forces, infection, inflammation, reduced production of growth factors and, of course, lack of collagen will affect the results of treatment. Numerous studies have shown that collagen preparations are bioactivators and promote their own tissue regeneration, integrating into the surrounding natural tissues. Their main advantages are the regulation of the biochemical environment of the wound, stimulation of chemotaxis and angiogenesis. They have the properties of a thin layer of natural skin, but are devoid of the shortcomings inherent in foreign cellular elements that contribute to the rejection of the skin graft [9].

Foot ulcers in patients with diabetes occur and often lead to amputation of the lower extremities unless an operative, rational interdisciplinary approach to therapy is adopted. The main components of treatment that can ensure successful and rapid healing of diabetic foot ulcers include training, blood sugar control, wound debridement, extended dressing, unloading, surgery, and advanced treatments, which are used in clinical practice. These approaches should be used whenever possible to reduce the high incidence and risk of serious complications resulting from foot ulcers [18].

Tissue damage is accompanied by trauma to microvessels and activation of the coagulation cascade aimed at stopping bleeding and the formation of a platelet clot. The latter contains fibrin, fibronectin, vitronectin, von Willebrand factor, thrombospondin, which form a matrix for cellular migration. Immediately after damage, collagen begins to contact the blood of the wound surface, which contributes to platelet aggregation and activation of a number of chemical factors [17].

The problem of treatment of long-term non-healing wounds is one of the most urgent in medicine due to the wide variety of possible causes of their occurrence, the difficulties of selecting treatment. The article presents the results of a study of possible causes of impaired wound healing, among which one of the most significant is a violation of the synthetic function of fibroblasts. In this case, there is a change in the spectrum of expressed cytokines and growth factors, including an increase in the expression of pro-inflammatory cytokines.

These factors lead to the impossibility of forming a full-fledged extracellular matrix, which means the impossibility of fibroblast migration, impaired cellular differentiation and wound healing. Thus, long-term non-healing wounds are characterized by stereotyped changes, regardless of their etiology and localization [13].

Currently, a rapidly developing direction of medicine is regenerative medicine, where cell technologies are applied using cultured human cells. The proposed innovative method of treatment is the complete closure of the ulcer after the implantation of the cell product. As a result, the frequency and duration of medical examinations are significantly reduced, the quality of life and social activity of the patient improves. At least a hundred patients who received such treatment between 2000 and 2015 in the process of clinical trials did not have ovre appeals. The use of this method is extremely important for that part of the patients in whom the existing open ulcer of a small area does not allow to perform a surgical operation for the underlying disease. According to some reports, at least 2,000 patients a year in St. Petersburg need treatment for trophic ulcers [11]. In addition, the high activity in long-term non-healing wounds of proteolytic enzymes, primarily serine, and matrix metalloproteinases in combination with a lack of their inhibitors can cause increased utilization of various cytokines and growth factors, thereby causing their deficiency and in combination with other factors leading to the development of a long-term, functioning on the principle of a vicious circle of pathological process. morphological and immunohistochemical studies can be said that long-term non-healing wounds are characterized by the presence of chronic inflammation, a feature of which is the predominance of monocytic-macrophage cells in the infiltrate in combination with increased expression of pro-inflammatory cytokines and a violation of their normal ratio. In addition, there is an increase in proteolytic activity in the wound area in combination with a decrease in the activity of inhibitors. Proteases. The expression of fibrogenic growth factors decreases. Violation of the formation of normal connective tissue is manifested by a decrease in the content of type III collagen, the accumulation of tenascin and the plasma form of fibronectin in the stroma, the redistribution of laminin, a decrease in the number of myofibroblasts in the wound. These changes are stereotyped for most long-term non-healing wounds, regardless of their etiology and localization [13,14,15].

In patients with trophic ulcers of venous etiology, skin fibroblasts retain the ability to form collagen with the stimulating effect of biological growth factors. Autologous platelet-rich plasma stimulates the synthesis of collagen by culture of skin fibroblasts of patients with trophic ulcers of venous etiology, which may be an experimental justification for the use of platelet concentrates in clinical practice [16].

Thus, in recent decades, significant progress has been made in understanding the molecular mechanisms of the main phases of the normal and complicated wound process. Fibroblasts provide a universal biological model for in *vitro* study of the dynamic molecular regulatory processes underlying cell growth and proliferation, intra-metabolism and transduction, and extracellular signals. A new step towards an effective solution to the socially significant problem of closing extensive wound defects may be the further study of the processes of direct intercellular interaction and the choice of connexin proteins as indicators of the state of the healing process and the target for pathogenetic effects. Given the above data, the treatment of chronic ulcers and other ulcers complicated by diabetes mellitus remains unresolved and requires further study.

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