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Research Article

THE MECHANISM OF ACTION OF THE GEL FORM OF COLLAGEN IN DIABETIC WOUNDS

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ABSTRACT

The work is devoted to a review of the options for the use of collagen and materials based on collagen in medicine and the pharmaceutical industry. Tissue engineering is a medical science dealing with the reproduction of biological tissues and organs. This area of medicine opens avenues for the creation of organs and tissues using biomaterials and nanostructures to sustain their development, maintenance, and function repair in a living organism. Among the many types of cells that can have a clinical effect, of particular interest are dermal fibroblasts, which are a heterogeneous population of mesenchymal cells and play a key role in the regulation of cell interactions and maintaining skin homeostasis. Currently, there are more than 60 modern cellular or tissue drugs for the treatment of wounds, which makes it difficult to choose an appropriate, safe, and effective adjuvant therapy. Recent years have witnessed a major leap in 3D technology for the reproduction of biological structures. Increasing attention is being paid to the controlled design and production of 2D–3D structures consisting of biological materials and viable cells, the procedure defined as bioproduction or bio-prototyping. Skin substitutes obtained with the bio-prototyping technology possess a wide range of medical applications, primarily to compensate for resident skin deficiency in wound healing.

KEYWORDS

Collagen, "Collost", biomaterial, allogeneic fibroblasts, human fibroblasts as a skin substitute, repair of damaged tissues, chronic wounds.

INTRODUCTION

The term "tissue engineering" itself was introduced into the scientific community in 1960 due to the widespread use of tissue cells in combination with various other materials. Under this term, it was customary to understand an interdisciplinary science, located at the intersection of biology and engineering, whose task is to recreate living tissues to replace or improve the functioning of organs [1, 2]. The main goal of tissue engineering is to artificially recreate the most accurate tissue structure. To solve this problem, it is necessary to have a source (donor) of cells, an artificial extracellular matrix (ECM), and a growth factor. To create a biological surrogate that would take root in the body during the process of skin regeneration, cells, and ECM are used, as well as cellular structures that could be used in the cell therapy procedure [3].

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 a class of proteins called scleroproteins. A feature of proteins of this class is their phylogenetic relationship with different species of animals and humans [4]. 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 hydroxyproline and oxylipin, the content of which is 23% of the total amino acid composition of the collagen molecule [5]. In the pharmaceutical and medical industries, collagen has found wide applications. On its basis, various dosage forms (soft and liquid), special plasters and sponges (hemostatic collagen sponge, collagen sponge with methyl-uracil, collagen sponge with sanguirythrin, etc.), as well as various means for quickly stopping bleeding (local hemostasis agents), medical products for the treatment of wounds, burns, trophic ulcers, bedsores and other soft tissue defects of various origins [6].

Review of modern wound healing technologies. Within the framework of tissue engineering technology, natural polymers such as gelatin or agar became one of the first materials for cell cultivation [7]. Currently, "hydrogels" (alginate, methylcellulose, agarose, gelatin, fibrin, collagen, pluronic, tropoelastin, matrigel, silk fibroin, etc.) can serve as potential biological materials for skin regeneration. Their hydrophilic function ensures the concentration of water in the skin. Thus, collagen is often used as a basis for cell culture, but it can be used, like hyaluronic acid, for the treatment of wound surfaces. Also, recent studies have shown the possibility of using minor proteins taken from natural bone tissue (for example, fibronectin and osteocalcin) in tissue engineering [8].

In addition to biomaterials, some synthetic materials can also be used in tissue engineering. These technologies are being introduced to increase the body's ability to regenerate by planting synthetic material on cell materials to form "neo-skin". Synthetic polymers have several advantages. First, their composition is completely known and predictable. Second, they are designed to minimize the immune response. Biomaterial "Kollost" was implanted starting from the 2nd phase of the wound process. Collost is a bioplastic material based on native non-reconstructed bovine collagen with a completely preserved structure. To close planar wounds and ulcerative defects, the biomaterial "Kollost" was used in the form of membranes. A membrane pre-soaked in warm (38°C) sterile saline for 15 min was applied to the wound treated with ultrasound. When the wound defect was localized on the plantar surface, the membrane was fixed with 3–4 Tisorb 00 ligatures. After the manipulation was completed, a gel dressing (Hydrosorb, Gelepran) was applied [9]. "Kollost" accelerates the processes of wound cleansing from devitalized tissues and microbial contamination of

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wounds, and also prevents secondary infection. The use of ultrasound and bioplastic material "Kollost" significantly improves the cytological picture of wounds, which affects the acceleration of reparative processes and the timing of epithelialization [10]. Fibroblasts are one of the main secretory cells of the body involved in the formation of the extracellular matrix, repair of skin lesions, and stimulation of the growth of keratinocytes and blood vessels. By their location in tissues and their functions, fibroblasts can produce procollagen, fibronectin, glycosaminoglycans, proelastin, nidogen, laminin, chondroitin-4-sulfate, and tenascin [11].

One of the breakthroughs in the field of tissue engineering was the creation of modern thin tissues, which have already been successfully transplanted more than once into recipients with acute deficiency of the latter. However, recreating thicker tissues (e.g., muscle or liver tissue) can be complicated by the limitation of oxygen diffusion inside the created cell arrays, which forces researchers to resort to simulating a vasculature inside an artificial tissue, which already complicates the technology itself.

In recent years, there has been a significant leap in the technology of 3D production of biological structures. Researchers have begun to pay great attention to technology that allows the creation of controlled design and production of 2D–3D structures consisting of biological materials and viable cells. This process is called biomanufacturing or bio-prototyping. The main goal of further development of this technology is to improve the 3D printer and the system of observation, as well as the control of the production of organs and tissues using an ink-like liquid called "bio-ink" [12,13]. The apparatus for biological modeling itself consists of three adjusting actuators of angular displacement and a medical syringe that releases bio ink. The initial information for bio-prototyping of organs or tissues is a digital three-dimensional model, for the design of which data obtained using computed tomography or magnetic resonance imaging can be used. Such a digital model contributes to a more accurate match to the structure of the surrogate material [14].

However, despite all the advantages that tissue engineering began to have with the advent of 3D bio-modeling, there were still many unresolved issues that researchers still had to solve. One such difficulty was recreating the exact hierarchy within the newest fabric itself. Thus, the invention of laser-mediated bioprinting turned out to be a solution to this problem, since this technology allows the printing of high-quality compounds by combining various lines of cellular structures. As part of the experiment, the skin recreated using this technology was implanted into some animals, and the new cover confirmed the ability to mimic the behavior of natural cellular structures. As a result of this study, laser-mediated bioprinting has shown itself to be one of the best ways to generate artificial skin [15, 16].

Transplantation of cultured allogeneic fibroblasts improves the clinical indicators of the course of the wound process, significantly reducing the time of wound healing by an average of 7-8 days compared to traditional methods of treatment, which significantly reduces the time of treatment, mortality, and costs for the victims. For the current level of care for seriously ill patients, the most acceptable is the transplantation of in vitro cultured allogeneic fibroblasts. Dermal fibroblasts are a heterogeneous population of mesenchymal cells and play a key role in the regulation of cell interactions and maintenance of skin homeostasis [17,18]. The connective tissue frame of the heart, lungs, gastrointestinal tract, muscles, and other organs contain fibroblasts that perform specialized functions. Differences in gene expression between fibroblasts of the dermis and skin derivatives are shown. Fibroblasts obtained from different anatomical sites have tissue-specific cytophysiological differences [19].

Studies of the cellular structures of wounds demonstrate the positive dynamics of the course of reparative processes in experimental animals with alloxan diabetes with local administration of the sorbent, 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 has been formed to study the therapeutic reparative effects of Beta-Beta when applied topically to purulent-necrotic wounds of soft tissues in rats [20].

There is also an alternative way to transplant printed tissue models. This is in vivo bioprinting, in which cell structures are printed directly on the surface or inside the recipient's body. This technique has already been actively used in some experimental studies, for example, inside wound or burn surfaces, as well as in areas of damage to the skull in mice. If a higher speed and resolution of a 3D bioprinter is achieved, this technique can be applied immediately after an injury and even become a common part of medical operations to restore wound or burn surfaces. Thus, an interesting and promising direction within this approach is the introduction of bioprinters into surgical instruments [21].

The treatment of chronic wounds is a continuously evolving area. Problems of excessive mechanical forces, infection, inflammation, decreased production of growth factors, and of course lack of collagen will affect treatment outcomes. Numerous studies have shown that collagen preparations are bioactivators and promote their tissue regeneration, integrating into the surrounding natural tissues. Their main advantages are regulation of the biochemical environment of the wound, stimulation of chemotaxis, and angiogenesis. They have the properties of a thin layer of a natural skin but are free from the disadvantages inherent in foreign cellular elements that contribute to skin graft rejection [22].

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 and the difficulties in choosing a treatment. The article presents the results of a study of possible causes of impaired wound healing, among which one of the most significant is the 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 the formation of a full-fledged extracellular matrix, and hence the impossibility of fibroblast migration, disruption of cell differentiation, and wound healing. Thus, long-term non-healing wounds are characterized by stereotypical changes regardless of their etiology and localization [23].

Currently, a rapidly developing area of medicine is regenerative medicine, where cellular technologies are used using cultured human cells. The proposed innovative method of treatment is the complete closure of the ulcer after implantation of the cell product. As a result, the frequency and duration of medical examinations are significantly reduced, and the quality of life and the patient's social activity improve. At least 100 patients who received such treatment between 2000 and 2015 during clinical trials had no follow-up visits. The use of this method is also extremely important for the part of patients in whom

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the existing open ulcer of a small area does not allow performing 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 [24].

CONCLUSION

Thus, the study showed that collagen-containing dressings can be effectively used in the complex therapy of patients with a neuropathic form of diabetic foot syndrome. The effect of Promogran is based on its ability to reduce the activity of wound proteolytic enzymes, thereby preventing the lysis of protein structures, primarily collagen. The research results proved that the applied tissue equivalents have a long shelf life and are relatively easy to use, which puts them among the advanced technologies of modern medical science. A new step towards an effective solution to the socially significant problem of closing extensive wound defects may be 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 a target for pathogenetic influence. Given the above data, the treatment of chronic and other ulcers as complications of diabetes mellitus remains unresolved and requires further study.

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