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Prospects And Disadvantages the Use of Collagen and Other Biotechnologies in The Treatment of Burn Wounds (Literature Review)

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Annotation. In recent decades, new methods of treating burn wounds based on biotechnologies have emerged. The review presents the main materials for the treatment of burns that were created using tissue engineering-biological wound coatings and skin substitutes.

Key words: biological wound coverings, decellularized dermis, "live skin equivalent", skin substitutes, collagens, keratinocytes, fibroblasts.

Introduction. One of the most important tasks of treating patients with burns is to restore the skin as quickly as possible, which, unfortunately, is not always accompanied by complete structural and functional restoration of the original tissue. Often, after treatment of burns, the patient's quality of life decreases due to cosmetic defects and limited joint mobility due to the formation of scar tissue.

Principles of skin restoration. Skin restoration in case of superficial burns (I, II degrees) Just as physiological regeneration, occurs at the expense of preserved stem cells of the basal layer of the epidermis. In third-degree burns (so-called borderline burns), when the basal layer of the epidermis is destroyed, the skin is restored due to the presence of stem and/or progenitor cells in the wound (epithelial cells in the skin appendages and dermal cells in the micro vessel wall) [1]. The functioning of such cells ensures the restoration of the epidermis and skin, as well as cellular and non-cellular components of the dermis, the interaction of which determines the percentage of scarring in the regenerating skin [2]. In case of deep burns (III-B, IV degrees), autodermoplasty is necessary to restore the skin, the main disadvantage of which is an additional skin wound at the site of flap removal, and in case of extensive lesions-a shortage of donor resources [3-6]. Current research is aimed at finding methods that speed up the wound healing process, reduces car formation, and develop skin substitutes that can be used as functional equivalents of skin autotransplant.

Overview of the main products created using tissue engineering. The initial stage of research aimed at creating modern wound coverings and skin substitutes included studying the possibility of enzymatic separation of the epidermis and dermis [7] and in vitro keratinocyte cultivation vitro [8]. The first successful transplantation of autologous keratinocytes from primary culture to wounds was performed by M.Karasek and M.Charlton in 1971 during experiments on rabbits [9]. The authors used collagen gel as a substrate for keratinocyte cultivation. In 1975, J.. Rheinwald and H.. Green [10] succeeded in growing primary epidermal cells in serial culture on a layer of mouse fibroblasts that were lethally irradiated with 3T3. The results of studies performed by these authors indicated that the size of the epidermal graft can be increased by more than 500 times over 3-4 weeks compared to the initial one. After the first clinical application [11], the effectiveness of using cultured dermal autografts was confirmed in almost all leading burn centers in different countries [12-19]. However, in the course of research, negative results were also noted, manifested by a high variability in the effectiveness of using epidermal graft cells, which depended on the location and condition of the wound, the patient's age, and the qualifications of specialists [16, 20]. In 1981, E.Bell et al. [21] created a graft containing elements of the dermis and epidermis, the so-called "living skin equivalent", and tested it on an animal model. Later, this technology was transformed into Apligraf® product, which consists of allofibroblasts on a collagen gel matrix and keratinocytes grown on a pre-formed dermal layer. There are mixed opinions in the literature about the "living equivalent of skin" [22, 23]. According to some authors, the reasons for not always successful results of using coatings containing collagen are:: a decrease in the proliferative activity of fibroblasts in contact with collagen; an increase in the level of collagenase

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synthesis; and the instability of such coatings to the effects of enzymes and infection [23-25]. It should be noted that such constructs use both allo-and autocells, as well as their combination [12, 16, 26-28].

Further significant progress was achieved by creating a two-layer "artificial skin", the upper layer of which consisted of a thin silicone film, and the lower layer consisted of a biodegradable porous membrane, which included collagen and chondroitin-6-sulfate [29]. Artificial skin was applied to deep burn wounds after necrectomy. Within 2-3 weeks, fibroblasts and endothelial cells of the patient penetrated the pores of the lower lay broke through the vessels, and at the same time the lowest layer was biodegraded. The result was a tissue that looked more like a dermis than a scar. After neoderma formation, the upper silicate layer was removed and autodermoplasty was performed with a thin graft about 0.1 mm thick. This cell-free collagen glycosaminoglycandermal substitute is now available as a material called "Integra Artificial Skin®. Integra®" was created in the 80s of the XX century, and its commercial release began in the USA in 1996. The hypothesis of a possible combination of cultured keratinocytes with Integra® became the basis for planning a new series of studies, as a result of which there was hope to get the dermis and laboratory-grown epidermis, which would save the patient from the need to use donor resources. However, in practice, it turned out that cultured epidermal autografts do not take root on the dermis formed by Integra® [30, 31].

The invention of Integra® was an important step in the development of a skin replacement. However, to skin substitute with improved functional and cosmetic results, further research in this area was required. Several commercial products have been created in the last 30 years. They contain cells of various origins (auto-, allo -) and materials degradable by microorganisms (natural or synthetic polymers),which form the basis for cell transfer, and also provide a better fit to the wound. They can be divided into skin substitutes containing cells of the epidermis (epidermal), dermis (dermal), and elements of both the dermis and epidermis (dermo-epidermal) [32].

Epidermal substitutes contain autogenic keratinocytes, which are often grown in the presence of mouse fibroblasts. Most products belong to the category of " cultured epidermal autografts"(Epicel®, Epidex™, Myskin™), for which keratinocytes are grown in the form of a multi-layered cell layer [33, 34]. From the moment of a patient's skin biopsy to the creation of the final product, it takes about 3 weeks. During thisetime, burn wounds are treated with bandages. A "cultured epidermal autograft" can only be placed on a well-prepared wound bed. The results of multicenter SV studies indicate wide range of engraftment outcomes with an average value of 50% or less [33, 35, 36]. The disadvantages of this method include mainly the long duration of the preparation period, the low frequency of engraftment, and the high cost.

Cultured autogenic keratinocytes can also be used as a suspension (Re Cell®) [37-39]. In this method, keratinocytes are "sprayed" onto the wound. Despite the fact that the results of using this method indicated a somewhat faster epithelialization and maturation of the epidermis in wound modeling [40], it is not suitable for the treatment of deep burns.

Since the above-described methods lack dermal component, the low degree of epidermal connection and the high frequency of scar formation cause extremely high requirements for wound preparation [41].

The created dermal substitutes restore the dermis, causing the formation of new tissue, and create optimal conditions for healing a burn wound [42]. After application, they are covered with a permanent epidermal coating or its substitute. Some derma substitutes consist of a cell-free base and bind to the wound bed for a long time (AlloDerm®, Integra®, Matriderm®) [43-49]. In the wound, the manufactured dermal analog is populated by the main dermal cells and as cularized in the wound [50]. When an autogenic neodermis isc formed and vascularized, usually 2-3 weeks after the dermal analog is applied, a split skin flap can be applied to it [51].

It should be noted that the use of a dermal analog and an epidermal graft is possiblено both simultaneously [38, 45, 46, 52, 53], and in two stages [47].

Созданы также Dermo-epidermal substitutes for temporary wound closure have also been developed, in which human neonatalгенные allogeneic keratinocytes and fibroblasts are combined with wound coatings (Apligraf®, Orcel®). They are used mainly for the treatment of chronic wounds [42, 50, 54, 55]. The results of studies indicate the effectiveness of their use [56, 57], including in burned patients [58].
To producean autogenic dermo-epidermal analog [42], keratinocytes and allofibroblasts were taken from the burned patient and added to the collagen-glycosaminoglycan substrate [59] and hyaluronic acid [26]. The

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production time of such a graft was about 4 weeks. Few similar clinical trials have been performed so far, but they have shown more favorable results interms of scar formation compared to the use of allocells [42].

Studies to evaluate the effectiveness of the use of bone marrow mesenchymal stromal cells are also ongoing [60-62]. Such cellular materialл is autologous, easily cultivated and differentiated.

Biological wound coatings for the treatment of superficial burns in the practice of the Burn Center of the N.V.Sklifosovsky Research Institute of Joint Ventures

The N. V. Sklifosovsky Research Institute of Joint Ventures uses allofibroblasts on an organosilicon substrate for the treatment of grade IIIA burns. A type I collagen-based bandage with platelet факто-derived growth factor (PDGF-BB), which has a pronounced stimulating effect on burn wound healing, has also been developed and successfully used [63]. The use of both methods accelerates epithelialization of superficial burns (I–II–IIIA degrees) by at least 2 times, as well их as promotes their healing with a good cosmetic effect. However, as independent methods, they cannot be used to restore the skin in burns of stage IIIB and IV , because of the lack of dermis, which is the main problem with deep burns. For these purposes, it is necessary to create an analog of human skin that would be close to the skin in anatomical and functional characteristics; subsequently, such an analog could be vascularized.

Prospects for the use of wound coatings for the treatment of deep burns.

For the local treatment of deep burns, necrotic tissue excision (necrectomy) and skin restoration by autotransplantation of a split skin flap are traditionally used. A promising direction in the treatment of deep burns is the use of decellularized (cell-free) cadaver skin. The main advantages of such biological material include the compliance of the composition and organization of the dermis used with the characteristics of the patient's own dermis, as well as the possibility of preserving the basement membrane. However, this method has a number of significant drawbacks. The allogeneic nature of such structures can lead to the development of rejection due to the remaining cells, which are often difficult to remove. In addition, there is a risk of infection of the recipient through natural biological material sob tained from cadaveric material. That is why they are often used as temporary biological dressings, rather than permanent skin substitutes.

Conclusion. Cadaveric skin is a good biological coating, but it is subject to immune rejection 10-21 days after applying it to a burn wound. In order touse this skin as a substitute, it is necessary to carefully remove all immunogenic factors that can lead to rejection of the donor material. At the same time, it is necessary to preserve the native structure and composition of the skin. Methods used to achieve these goals usually have opposite effects: excessive removal of immunogenic components can destroy the structure and composition of the tissue, while more gentle methods can preserve the immunogenicity of the tissue [64]. Currently, physical and chemical methods of decellularization have been proposed to preserve the structure and properties of allogeneic grafts [65, 66]. The results of these studies indicate that the cell-free skin matrix supports fibroblast penetration, neovascularization, and epithelialization in the absence of an immuneresponse [67]. There was also evidence that cosmetic and functional results after the use of allogeneic dermal graft sin the area of deep burns significantly exceed the results after autodermoplasty with a perforated flap, and also contribute to faster healing of donor wounds due to the fact that this requires the use of thinner autodermografts [68].

AlloDerm® Companyand LifeCelltm are virtually the only commercial product on the market based on cell-free collagen dermis. Its price per 100 sm^2 reaches 300 USD. There are no Uzbek analogues of this product. Thus, the development of a domestic drug based on decellularized allogeneic dermis-collagen-seems to be a very relevant and promising area of research.

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