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ABSTRACT

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PROBLEMS OF HEALING SOFT TISSUE INJURIES

Introduction. Wound healing is one of the key physiological processes that ensure human survival, and at the same time, it is an urgent medical problem. This literature review presents modern ideas on the repair of soft tissue injuries in normal and in various pathological conditions.

Methods. The literature review was based on published scientific studies using the information retrieval systems PubMed, Web of Science, Scopus, Google Scholar, and ResearchGate. We mainly reviewed the studies that were published in the last 5 years. 77 scientific papers were selected for the article.

Results. The structure and cellular composition, the role of stem cells of the skin and muscle tissue in the regenerative aspect were analyzed. The histological characteristics of the stages of healing, as well as the effect of some pro-inflammatory and anti-inflammatory interleukins, growth factors, are given. Scientific data indicate that repairing acute wounds is a strictly coordinated process in time and space of the interaction of various cell pools and bioactive molecules. Analysis of experimental and clinical studies also reflects the sensitivity of the healing process to the action of both local and systemic factors. The influence of such factors leads to the transition of acute wounds into chronic ones. Mechanisms of disorders arising from excessive inflammation and synthesis of the extracellular matrix, delay of re-epithelialization are given in the review. The influence of infection, hypoxia, hormonal and dietary disorders, hyperglycemia, venous hypertension, kidney diseases, and tissue compression is highlighted.

Conclusions. The skin and underlying muscles are often exposed to injuries and have significant regenerative and repair capabilities. Acute wounds go through a series of successive stages in their healing process, which ensure the restoration of the morphological and functional properties of tissues. Under the influence of various factors acute soft tissue injuries can turn into chronic, long-term wounds. Such wounds are

characterized by disturbances in the sequence and duration of healing stages, intercellular and cell-matrix interactions, and the dynamics of regulatory cytokines. Further scientific research on the pathogenesis of chronic wounds will contribute to their more successful treatment.

Keywords: skin and muscle injuries, wound healing, reparative processes, chronic wounds.

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ПРОБЛЕМИ ЗАГОЄННЯ УШКОДЖЕНЬ М'ЯКИХ ТКАНИН

Вступ. Загоєння ран є одним з ключових фізіологічних процесів, що забезпечує виживання людини, і водночас актуальною медичною проблемою. В даному огляді літератури представлено сучасні уявлення щодо репарації ушкоджень м'яких тканин у нормі та при різних патологічних станах.

Методи. Огляд літератури створено на основі аналізу опублікованих наукових досліджень з використанням інформаційно-пошукових систем PubMed, Web of Science, Scopus, Google Scholar та ResearchGate. В основному ми розглядали дослідження, опубліковані за останні 5 років. До статті відібрано 77 наукових праць.

Результати. Проаналізовано будову і клітинний склад, роль стовбурових клітин шкіри та м'язової тканини у регенераційному аспекті. Наведено гістологічні характеристики етапів загоєння, а також дію деяких прозапальних і протизапальних інтерлейкінів, факторів росту. Наукові дані вказують на те, що репарація гострих ран являє собою суворо скоординований у часі і просторі процес взаємодії різноманітних клітинних пулів та біоактивних молекул. Аналіз експериментальних і клінічних досліджень також віддзеркалює чутливість процесу загоєння до дії як локальних, так і системних факторів. Вплив таких чинників призводить до переходу гострих ран у стан хронічних. В огляді наведені механізми порушень, що виникають при надлишковому запаленні та синтезі екстрацелюлярного матриксу, затримці реепітелізації. Висвітлено вплив інфекції, гіпоксії, гормональних і аліментарних порушень, гіперглікемії, венозної гіпертензії, хвороб нирок, компресії тканин.

Висновки. Шкіра та м'язи часто піддаються травмам і мають значні регенеративні та репараційні можливості. Гострі рани в процесі загоєння проходять ряд послідовних стадій, які забезпечують відновлення морфофункціональних властивостей тканин. Під впливом різноманітних чинників гострі ушкодження м'яких тканин можуть переходити в хронічні рани, що довго не гояться. Для таких ран характерні порушення послідовності та тривалості етапів загоєння, міжклітинних і клітинно-матриксних взаємодій, динаміки регуляторних цитокінів. Подальші наукові дослідження щодо патогенезу хронічних ран сприятимуть більш успішному їх лікуванню.

Ключові слова: ушкодження шкіри та м'язів, загоєння ран, репаративні процеси, хронічні рани.

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INTRODUCTION / ВСТУП

The skin is the largest complex human organ that performs many functions. One of the most important is the protective function, which is realized in many ways and protects the human body from mechanical and physical damage, infections, fluid loss, etc. The multilayered structure of the skin, together with the underlying muscle tissue, serves as a protective barrier for internal organs and large vascular and nerve bundles. According to current data, soft tissue injuries in Ukraine account for 49.4% of peacetime polytrauma and 66.7% of combat injuries [1].

Wounds are mechanical damage to the entire skin thickness with penetration into fatty tissue, muscles, and sometimes deeper (into cavities, internal organs, etc.). Their healing is a universal mechanism that manifests biological adaptation and ensures the survival of humans and animals. Without the ability to close wounds, multicellular organisms would not have been able to emerge in the course of evolution [2]. Therefore, the process of wound healing is essential for restoring the normal vital activity of the body. The physiological regulation of skin wound healing is a complex process that depends on many cell types, extracellular matrix, and mediators interacting in a temporal and spatial sequence. An imbalance of these interactions can occur under the influence of local or systemic factors, leading to disruptions in wound repair mechanisms [3]. The damage repair processes are characterized histologically, but a complete understanding of the biochemical and cellular events that control normal and especially pathological wound healing is lacking [4].

THE AIM OF THE STUDY

To analyze modern views on the reparative ability of soft tissues and possible disorders in the healing process with the help of available scientific sources.

MATERIALS AND METHODS

The literature review was based on published scientific studies using the information retrieval systems PubMed, Web of Science, Scopus, Google Scholar, and ResearchGate. Key search terms included “wound healing”, “reparative processes in the skin and muscles”, “chronic wounds”. We mainly reviewed the studies that were published in the last 5 years, including literature reviews that tracked the fundamental data of previous years. 77 scientific papers were selected for the article.

RESULTS AND DISCUSSION

Structure and cellular composition of skin and muscle tissue in the regenerative aspect. The skin is a complex organ comprising different tissues that work in concert to protect against daily wear and tear, environmental hazards, and trauma. When this barrier is disrupted by injury, a carefully coordinated response between different cell types, signaling factors, and interactions in the extracellular matrix is required to restore tissue integrity and function. The key to this process is tissue-resident stem cells, which can self-renew and maintain their population during homeostasis and create one or more specialized cell types to maintain and restore skin functions [5]. Under homeostatic conditions, each stem cell population tends to contribute only to the differentiation program at a particular site. However, after injury, when the systemic and local environment changes dramatically, these stem cell populations demonstrate plasticity in response to physiological cues [6]. Even if their niche is not disturbed, neighboring stem cells respond to wound-induced stimuli by leaving their niche and participating in the re-epithelialization of the damaged tissue. In some cases, this requires them to change their tissue regeneration program, which can be temporary or permanent, depending on the specific type of wound [7].

The skin consists of three main layers: epidermis, dermis, and hypodermis. The epidermis is a stratified squamous keratinized epithelium that primarily provides the skin's barrier function. Only the inner basal layer, separated from the dermis by the basement membrane, is proliferative. When the basal cells are detached, they stop proliferating and begin an upward differentiation pathway, forming the stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum. During this passage, due to the deployment of special transcriptional programs, keratinocytes undergo a programmed series of morphological and biochemical changes that end in the formation of corneocytes (dead scales) [8]. Each scale is a shadow cell that has lost all its organelles, including the nucleus, and consists of a strong protein sac (cornified membrane), bonded with γ-glutamyl-ε-lysine, filled with insoluble bundles of keratin filaments [9]. Groups of corneocytes are connected by lipid double layers (fatty acids, cholesterol, and cholesterol esters) produced in the last stages of terminal differentiation. The result is a highly hydrophobic barrier that prevents the penetration of harmful microbes and protects against excessive fluid loss [10]. To continuously rejuvenate the epidermis, scales are exfoliated (the process of desquamation) from the skin surface and replenished with internally

differentiated cells that move outward. In addition to keratinocytes, the epidermis contains dendritic cells (Langerhans cells), melanocytes, Merkel cells and epidermotropic lymphocytes. A collection of epidermal cells produces numerous active catabolic enzymes: lipases, phosphatases, esterases, nucleotidases, and proteases [11].

The basement membrane provides the physical boundary between the epithelium and the dermis. The dermis also provides the epidermis with growth-stimulating factors, enzymes, and structural components. The structural composition of the dermis is rich in nerves, blood vessels, hair follicles, and sebaceous and sweat glands. The presence of different dermal fibroblast lines is important for the production and maintenance of collagen and elastin fibers, which are part of the extracellular matrix. This structure provides the elasticity of the dermis. Regulation of hair growth is provided by stem cells of hair follicles, and pigmentation is provided of melanocytes [6].

The last layer, the hypodermis, is composed mainly of fat (adipocytes) and mesenchymal stem (stromal) cells. Numerous studies show that adipose tissue influences the microenvironment by secreting a wide range of bioactive factors with a diverse set of functions, including lipid metabolism, energy balance, insulin sensitivity, regulation of angiogenesis, immunomodulation, and inflammatory response. Adipose tissue secrets can affect the homeostasis of tissues and organs at the autocrine, paracrine, and/or endocrine levels, as well as at the level of gene expression [12]. It has been established that one gram of hypodermis contains 500 times more mesenchymal stem cells than bone marrow [13]. A complex relationship between hematopoietic cells, fibroblasts, and keratinocytes is involved in skin homeostasis has been show [14]. Functional analysis of rodent models shows that fat depots are involved in the coordination and control of keratinocyte and fibroblast proliferation and migration to ensure epidermal and dermal repair [15]. Thus, resident mesenchymal stem cells are able not only to heal injuries directly through proliferation but also to secrete numerous pro-regenerative, anti-fibrotic, and anti-apoptotic signaling mediators, cytokines and growth factors necessary for endogenous repair processes: homeostasis, regeneration, and restoration of all skin layers [12, 15].

Skeletal muscle is the most abundant tissue in the human body, accounting for about 40% of body weight. In everyday life, muscles are sensitive to various injuries, such as mechanical trauma, thermal stress, myotoxic agents, ischemia, neurological disorders, and other pathological conditions. Muscle regeneration is driven by the presence of muscle stem cells - satellite cells. These cells, myosatelliocytes, are located in a niche between the sarcolemma (plasma membrane) and the basal lamina surrounding the muscle fibers and remain dormant under normal conditions [16]. In response to exercise, muscle growth, injury, or other stimuli, muscle stem cells are activated, initiate a cell cycle, rapidly proliferate and differentiate into new myotubes, or connect to damaged myofibers to repair the symplast. After activation and proliferation, some muscle stem cells can return to a quiescent state and replenish the *in vivo* stem cell pool to prepare for the next regeneration process. Thus, damaged myofibers can be regenerated, and muscle functions such as strength, contraction, and metabolism can be restored [17].

Histological characteristics of the healing stages of acute wound in soft tissues. Classification of wounds by types of healing includes healing by primary tension, secondary tension and under scab [2].

Healing by primary tension occurs in superficial cut wounds, or when suturing surgical wounds. At the same time, the edges of the wound are located at a small distance and are first connected by fibrin, and then by collagen fibers and vessels, while rapid epithelization occurs. Provided there is no infection, necrosis, foreign bodies, and the general satisfactory condition of the patient, such wounds heal within 5-10 days.

Healing under the scab is observed in superficial, small wounds. After injury, such wounds are covered with a crust (scab) of clotted blood, lymph, and tissue fluid. Without inflammatory factors, the epidermal layer quickly regenerates, healing occurs within 5-7 days and the scab falls off.

Healing by secondary tension is a more complex and long-term process. It occurs with deep and significant soft tissue injuries, often infected. At the same time, the wound cavity has a significant amount of necrotized tissue, its healing always takes place through the process of inflammation and the formation of granulation tissue [2]. In the process of repair of acute soft tissue wounds of this type, four phases are distinguished: hemostasis, inflammation, proliferation, and remodeling. The hemostasis phase begins immediately after the injury and ensures the cessation of bleeding and the formation of a fibrin clot. This occurs in three stages: vasoconstriction, primary hemostasis, and secondary hemostasis. When tissue is injured, the immediate response is vasoconstriction of the vessel walls, which prevents excessive blood loss. However, the initial reflex contraction only temporarily reduces bleeding. This is because increased hypoxia and acidosis of the wound lead to passive muscle relaxation and cause renewed blood leakage [18]. Primary (platelet-vascular) hemostasis includes platelet aggregation and platelet plug formation, which occurs

under the influence of collagen in the subendothelial matrix [19]. Secondary hemostasis refers to the activation of the coagulation cascade when soluble fibrinogen is converted into insoluble filaments that form a fibrin network. The platelet plug and the fibrin network join together to form a blood clot, which stops bleeding, forms a barrier against invading microorganisms, and serves as a temporary framework for the migration of leukocytes, keratinocytes, fibroblasts, and endothelial cells. In addition, platelets release growth factors and chemokines, which are important mediators for the subsequent phases of wound healing [20].

The inflammation phase can be divided into the early phase with neutrophil accumulation and the late phase with the appearance and transformation of monocytes in the wound [21]. Within a few hours after an injury, the bulk of neutrophils migrate through the endothelial cell wall of blood capillaries to the site of injury. The work of neutrophils is crucial during the first days after injury, as their ability to phagocytose and secrete protease kills bacteria and promotes the degradation of necrotic tissue [22]. They also release pro-inflammatory mediators and act as chemoattractants for other cells involved in the inflammatory phase. In the absence of appropriate stimuli, neutrophil infiltration into the wound stops in a few days [23]. Within 48-72 hours, circulating monocytes enter the injury area and differentiate into mature tissue macrophages that phagocytose pathogens and cellular debris. Under the influence of proinflammatory cytokines, interferons, molecular fragments of the extracellular matrix, lipopolysaccharides, or other microbial products, macrophages become proinflammatory or "classically activated" [24]. After activation, proinflammatory macrophages themselves produce a large number of proinflammatory mediators and cytokines, inducible nitric oxide synthase, and chemokines that attract additional leukocytes [25]. *In vitro* studies show that macrophages can switch from a proinflammatory to an "alternatively activated" or reparative phenotype [26]. The alternative phenotype is characterized by the expression of anti-inflammatory mediators and the production of growth factors. An important condition for the creation of a reparative phenotype of a macrophage is successful efferocytosis - phagocytosis of apoptotic neutrophils [27]. Macrophages are able not only to recognize and actively engulf neutrophilic granulocytes but can also induce their apoptosis [28].

It has been established that the "switching" of macrophages to an alternative phenotype is necessary for the transition from inflammation to proliferation in the process of wound healing. Numerous clinical and experimental studies have confirmed the key role of inflammation in further wound-healing mechanisms in adult mammals [26, 29]. It is believed that in mammals, wound repair is evolutionarily optimized for rapid healing under conditions of contamination, where an overcompensatory and rapid inflammatory response allows the wound to heal quickly without developing infection [23].

The purpose of the proliferative stage is to reduce the area and close the lesion by contraction and fibroplasia, creating a viable epithelial barrier. The processes of re-epithelialization, angiogenesis, and fibroplasia begin in the microenvironment of the acute wound during the first day and can unfold up to 14 days after the onset of the lesion [21, 22].

The process of re-epithelialization is provided by local keratinocytes at the wound edges and epithelial stem cells from hair follicles or sweat glands [30]. The proliferation and migration of keratinocytes are activated by the signaling pathways of epithelial and non-epithelial cells at the wound edges, which release cytokines and growth factors [31]. Approximately ten hours after the onset of the lesion, the development and stretching of pseudo-obstructions of keratinocytes, loss of cell-to-cell contacts, retraction of tonofilaments, and formation of actin filaments at the edges of the cytoplasm are observed [22]. Activated keratinocytes migrate along the pre-formed fibrin clot in the higher layers of granulation tissue due to enzymatic loosening of intercellular desmosomes. This process is called the "stirring" of keratinocytes and occurs from the wound edges to the center until the migrating cells touch each other. The fusion of opposite epithelial layers is carried out by the degradation of actin fibers in the filopodia, which are replaced by intercellular adhesion contacts. After that, the keratinocytes reconnect with the substrate and restore the basement membrane. The process of re-epithelialization is completed by the differentiation of epithelial cells with the formation of a multilayered epidermis [32].

The repair of the skin vasculature is a complex cascade of cellular, humoral, and molecular events in the wound bed to restore nutritional perfusion. Activated by growth factors, the endothelial cells of the preserved vessels secrete proteolytic enzymes, dissolving the basal lamina, and acquire the ability to proliferate and migrate into the wound. This process is also known as "sprouting". The endothelial cells release matrix metalloproteinases at the beginning of proliferation, lysing the surrounding tissue for continuous endothelial proliferation. The newly formed sprouts form small tubular channels that connect with others to form a vascular loop. After that, the new vessels differentiate into arteries and venules and

mature by further stabilizing their vessel walls through the recruitment of pericytes and smooth muscle cells [21]. The initial blood flow completes the angiogenic process, and the restored microcirculation allows for the transport of fluid, oxygen, nutrients, and immunocompetent cells to the stroma [33].

The last stage of the proliferation phase is the development of acute granulation tissue. This transitional tissue begins to form on the fourth day, gradually replaces the temporary wound matrix based on fibrin/fibronectin, and can form a scar when it matures [34]. The granulation tissue is characterized by a high density of fibroblasts, granulocytes, macrophages, capillaries, and collagen fiber bundles (mainly type III). The dominant cells in this phase are fibroblasts, whose main functions are the production of collagen and extracellular matrix substances (fibronectin, glycosaminoglycans, proteoglycans, and hyaluronic acid), as well as growth factors and chemokines [21].

The formation of the extracellular matrix is an important step, as it provides a framework for cell adhesion and critically regulates and organizes the growth, movement, and differentiation of cells within it [35]. Subsequently, collagen synthesis increases throughout the wound, while fibroblast proliferation gradually decreases, regulating the balance between synthesis and degradation in the newly formed stroma. At the end of this phase, the number of maturing fibroblasts decreases by differentiating into fibrocytes and myofibroblasts and is terminated by sequential apoptosis [36].

Remodeling is the final phase of wound healing and lasts from 2-3 weeks to 1 year or more after injury. The main goal of the remodeling stage is for the tissue to achieve maximum tensile strength through reorganization, degradation, and resynthesis of the extracellular matrix. After the wound is closed by a layer of keratinocytes, an attempt is made to restore the normal structure of the dermis, and the granulation tissue is gradually rebuilt to form scar tissue, which is less cellular and vascular. During the maturation of the newly formed connective tissue, the components of the extracellular matrix undergo certain changes. Type III collagen, which was produced in the proliferation phase, is gradually replaced by stronger type I collagen, oriented in the form of small parallel bundles of sufficient thickness [34]. At the same time, myofibroblasts cause wound contraction due to their attachment of cytoplasmic actin filaments to collagen fibers, contributing to a reduction in the scar surface. In addition, angiogenic processes are reduced, blood flow in the wound decreases, and the metabolic activity of the acute wound slows down and finally stops [37].

Muscle tissue in mild injuries can fully regenerate and restore its functional capabilities. However, in the case of serious injuries, the damaged muscle cannot recover to a functional level due to the formation of fibrous scar tissue [38]. The most common cause of muscle damage is mechanical trauma. This destroys the integrity of the plasma membrane of the myofiber and the basal lamina, causing an influx of extracellular calcium, which ultimately leads to muscle protein degradation and necrosis [39]. Muscle degeneration is also facilitated by the formation of edema and hematoma due to the activation of acute inflammation. After the initial degeneration, muscle regeneration mediated by muscle stem cells (satellite cells) is activated. However, the longer and more intense the inflammatory process, accompanied by increased production of proinflammatory mediators and nitric oxide, the more likely muscle fibrosis is to develop [40].

The role of interleukins and growth factors in the regulation of wound healing. The dynamics, quantitative, and qualitative characteristics of reparative processes are strictly coordinated and regulated by many factors. Among them, interleukins and growth factors are of great importance.

Interleukins are known to play an important role in the regulation of wound healing. After an injury, IL-1β is one of the first to be synthesized; it induces the synthesis of other pro-inflammatory cytokines, such as TNF-α and IL-6, low-molecular-weight inflammatory mediators (nitric oxide and prostaglandins), and chemokines that attract neutrophils to the inflammatory zone. IL-1β also activates T- and B-lymphocytes, stimulates hematopoiesis, and phagocytosis, and increases vascular wall permeability [41].

IL-6 is produced in traumatic or infectious injury and stimulates the synthesis of a wide range of acute phase proteins by hepatocytes, hematopoiesis, and the differentiation of T- and B-lymphocytes. An important feature of IL-6 is its effect on the transition of the early inflammation phase to a later one, the so-called "leukocyte switch". This occurs by reducing the recruitment of neutrophils, attracting monocytes and their differentiation into macrophages [42, 43].

After cessation of the damaging factor and clearing the wound from necrotic masses, the production of pro-inflammatory interleukins decreases, and the secretion of anti-inflammatory interleukins is activated. IL-10 and IL-4 inhibit the synthesis of proinflammatory cytokines, the cytotoxic activity of T cells, and macrophages, and regulate the proliferation and apoptosis of B lymphocytes, fibroblasts, epithelial and endothelial cells [44].

Along with interleukins, growth factors play a crucial role in skin wound healing. Filling of the wound

defect and restoration of the anatomical and functional integrity of damaged soft tissues is achieved by granulation tissue. Fibroblast activation and angiogenesis are of great importance. Regulation of the process of granulation tissue development and transformation is ensured by the body's local cellular, tissue, and general factors.

One of the main regulators of granulation tissue formation and growth is bFGF and VEGF. Of all the known growth factors, bFGF has the widest range of target cells. bFGF is a mitogen, a factor of differentiation and phenotypic transformation of various cell types. It stimulates the migration and proliferation of fibroblasts, endothelial cells, and keratinocytes, and increases the rate of formation and growth of granulation tissue, new blood vessels, and epidermal regeneration. bFGF activates angiogenesis and stimulates fibroblast chemotaxis and their synthetic function for the synthesis of extracellular matrix proteins, such as collagen and fibronectin. Due to these properties, bFGF significantly accelerates the regeneration of skin wounds [45, 46].

VEGF is one of the most important and potent growth factors that stimulate angiogenesis. It acts as an endothelial cell mitogen, a chemotactic agent, and an inducer of vascular permeability [47].

During normal acute wound healing, the synthesis of proinflammatory and anti-inflammatory cytokines and growth factors is strictly coordinated and ensures the sequence and duration of the repair stages, as well as leads to complete healing in the optimal time frame. An imbalance in these interactions can lead to errors in the repair mechanisms and result in impaired wound healing [4, 23].

Main types of disorders in the process of chronic wound healing. Chronic skin lesions that do not heal for a long time are often the result of local factors or systemic diseases. The most common cause of delayed wound healing is chronic inflammation [48]. It can occur in the presence of microorganisms or foreign bodies in the wound, due to an imbalance of pro- and anti-inflammatory mediators and is characterized by increased involvement of neutrophils and macrophages and overexpression of inflammatory cytokines [49]. Leukocytes recruited to the damaged area release reactive oxygen species, which, in the case of excessive and prolonged production, damages cells, interfering with the proliferation/differentiation of keratinocytes and fibroblasts and leading to cell apoptosis. In addition, oxidative stress causes the degradation of growth factors, reducing the amount and bioavailability of these molecules [50]. Increased levels of proinflammatory cytokines affect further wound healing mechanisms by increasing the production of matrix metalloproteases and other proteases, which impairs cell proliferation/migration and reduces the accumulation of extracellular matrix components [49].

Disruption of the remodeling of the newly formed granulation tissue is another important defect in wound healing, leading to the formation of hypertrophic and keloid scars [51]. Such disorders most often occur as a result of excessive local or systemic inflammation or mechanical impact on the wound; risk factors may also include hypertension, increased levels of sex hormones (pregnancy, adolescence), and genetic predisposition [52]. A common feature of chronic fibrotic disorders is a persistent stimulus that supports the production of growth factors, proteolytic enzymes, angiogenic factors, and fibrogenic cytokines that stimulate the deposition of extracellular matrix components, destroying the normal histoarchitecture of regenerating tissues [53]. Elevated levels of circulating IL-4, TGF-β, and IL-6 stimulate the proliferation of fibroblasts and myofibroblasts and their deposition of collagen and proteoglycans in scar tissue. Studies have shown that collagen synthesis is increased 7-fold in hypertrophic scars and 20-fold in keloid scars compared to normal scars. Due to the high degree of cross-linking, the deposited fibers become excessively stiff and thick or are thinner and create "nodules" [54].

An imbalance of proangiogenic VEGF and antiangiogenic endostatin leads to pathological angiogenesis. It has been established that newly formed vessels have a high density of location on the inflamed periphery of the pathological scar, but are mostly absent in the inactive center [55].

Delayed re-epithelialization may be another disorder in the wound repair process. Studies have shown that due to chronic inflammation and reduced vascularization, keratinocytes from the edges of the pathological wound acquire a hyperproliferative state, and no signs of their migration (epithelial "tongue") are observed. The newly formed thickened epidermis had signs of hyper- and parakeratosis, indicating inappropriate cell differentiation [56]. It is believed that the molecular mechanism of the decrease in the migratory potential of keratinocytes during abnormal healing is associated with the proteolytic degradation of growth factors and extracellular matrix proteins [57].

Previous studies have identified the main factors that harm wound healing. First and foremost, these are bacterial infections, which are highly likely to occur in skin injuries. In response to an infection, the body triggers an inflammatory mechanism with the migration of leukocytes and the release of cytokines. However, the phagocytic activity of leukocytes leads to the release of endotoxins by bacteria, which can cause local necrosis and increased inflammation by increasing proinflammatory mediators, increasing the activity of

metalloproteinases, and decreasing the release of growth factors [58].

Hypoxia of the tissues at the site of injury can also lead to delayed healing. The hypoxic wound microenvironment is important because when blood supply is disrupted due to injury, it stimulates the release of mediators by cells that coordinate the mechanisms of angiogenesis, re-epithelialization, and the synthesis of growth factors and cytokines. However, excessive hypoxia leads to the synthesis of reactive oxygen species and pro-inflammatory cytokines, which can impair the healing process. In addition, an optimal balance of oxygenation is necessary to prevent wound infection, improve the angiogenic response, and increase the differentiation, proliferation, and migration of fibroblasts and keratinocytes [59].

Impairs healing and malnutrition, prolonging inflammation and remodeling of the extracellular matrix. For example, the following nutrients are important for wound healing: omega-3 fatty acids (promote the synthesis of cell membranes), vitamin A (improves keratinocyte proliferation), and vitamin C (involved in collagen synthesis) [60]. Proteins and amino acids, such as arginine, cysteine, methionine, and glutamine, modulate the activity of immune cells and control collagen synthesis [61]. Zinc is a cofactor for RNA and DNA biosynthesis; iron acts as a cofactor in collagen synthesis and plays an important role in oxygen transport as part of the hemoglobin molecule [60].

Stress can also adversely affect wound healing by increasing the production of adrenaline, norepinephrine, cortisol, and glucocorticoid hormones. Stress hormones reduce the release of cytokines and the immune response of leukocytes, which reduces the activity of inflammatory processes and can delay the healing process [62]. Levels of sex hormones can also affect repair processes. Estrogen has anti-inflammatory activity by reducing leukocyte infiltration, increasing the rate of re-epithelialization and angiogenesis in wounds [63]. On the contrary, androgen hormones (testosterone and 5α-dihydrotestosterone) increase the level of proinflammatory cytokines and leukocyte migration, creating a chronic inflammatory effect on skin wounds [64].

Many diseases affect the cardiovascular, respiratory, or immune systems and impair wound healing by interfering with the mechanisms of inflammation, angiogenesis, re-epithelialization, and matrix remodeling. At the same time, chronic wounds can contribute to the aggravation of metabolic disorders in the patient's body [65].

Diabetic foot ulcers are a common and serious complication of diabetes mellitus. The inability of patients' bodies to secrete insulin normally and/or their insensitivity to it leads to the accumulation of advanced glycation end-products in tissues, which induces oxidative stress, promotes leukocyte migration and activation, and increases the release of pro-inflammatory cytokines, provoking chronic inflammation, often with purulent and necrotic complications [60, 66]. Hyperglycemia also negatively affects skin microcirculation, leading to a hypoxic environment and reduced angiogenesis, proliferation, and differentiation of keratinocytes and fibroblasts, delaying re-epithelialization and extracellular matrix remodeling [67]. Studies confirm the important role of insulin as a growth factor that promotes endothelial cell proliferation, the transition of macrophages from the M1 to the M2 phenotype, and the reduction of pro-inflammatory cytokines and matrix metalloproteinases [68, 69].

Chronic wounds are often caused by venous hypertension, blood stasis due to venous thrombosis, or valve insufficiency in the lower extremities. Back pressure increases the permeability of blood vessels, which leads to the leakage of macromolecules and erythrocytes into the perivascular space, where they can act as chemoattractants for leukocyte infiltration. Subsequent edema and fibrosis impede the diffusion of oxygen, growth factors, and nutrients into the wound tissue [70].

In renal diseases, hemodynamic disorders in the soft tissues are often observed in the form of capillary network thinning, and endothelial necrosis, resulting in poor perfusion [71]. Negative metabolic changes lead to the accumulation of uremic toxins and the development of oxidative stress. Frequent skin complications of chronic renal failure include neuropathy, calciphylaxis, nephrogenic systemic fibrosis, and amyloidosis [72]. Most patients with kidney disease are characterized by a chronic inflammatory status, which can lead to impaired repair of damaged tissues and the formation of wounds that do not heal for a long time [60].

Pressure ulcers are common in paralyzed or unconscious patients who can neither feel nor respond to the periodic need for repositioning. Soft tissues over bony prominences such as the sacrum, hips, and ankles are particularly vulnerable to pressure ulcers, often occurring even after two hours of immobility. Prolonged compression or displacement of the skin, when tissue compression exceeds capillary pressure, leads to ischemia; necrosis occurs as a result of tissue hypoxia and ischemia-reperfusion injury [73].

One of the factors that negatively affect wound healing is the presence of foreign bodies in the wound cavity, which contribute to additional trauma and infection of soft tissues, and when present in the body for a long time, create a focus of chronic inflammation of varying intensity [74, 75].

Thus, the etiology of chronic wounds is diverse, the repair cellular and molecular mechanisms are complex, and their disorders are poorly understood. The diverse range of comorbidities creates additional obstacles in the design of experimental and clinical trials. This is compounded by the lack of appropriate animal models of wound healing [49]. It is known that animal models cannot fully reflect the processes of damage repair in humans due to many anatomical and physiological differences. For example, the skin of rats is highly elastic and demonstrates a high degree of wound "tightening" during healing [76]. Also, the peculiarities of the immune system and collagen synthesis can accelerate wound closure. However, understanding the mechanisms of the healing process and the impact of certain factors can identify biomarkers of key stages of repair that could serve as prognostic indicators [77].

CONCLUSIONS

The possibility of rapid and high-quality restoration of skin and muscle functions after injuries is ensured mainly by the proliferation and subsequent differentiation of cells of the basal layer of the epidermis, dermal fibroblasts, mesenchymal stem cells, and muscle satellite cells. Healing of acute wounds occurs through a series of successive stages with a strictly coordinated interaction of many pools of cells and numerous bioactive molecules. The influence of adverse factors (infections, mechanical irritants, diseases, nutritional disorders, etc.) leads to a violation of the sequence and duration of healing stages, intercellular and cell-matrix interactions, and dynamics of the content of regulatory cytokines in the patient. Chronic wounds can be characterized by a long-term inflammatory state, insufficiency of trophic and oxygenation, delayed formation of the extracellular matrix and epithelization of the defect, and formation of scars. A wide range of problems arising in the healing of soft tissue injuries necessitates further fundamental and clinical research.

PROSPECTS FOR FUTURE RESEARCH / ПЕРСПЕКТИВИ ПОДАЛЬШИХ ДОСЛІДЖЕНЬ

The following basic research can provide a solid basis for the development of new drugs and technologies for the treatment of skin and soft tissue wounds.

AUTHOR CONTRIBUTIONS / ВКЛАД АВТОРІВ

All authors substantively contributed to the drafting of the initial and revised versions of this paper. They take full responsibility for the integrity of all aspects of the work.

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CONFLICT OF INTEREST / КОНФЛІКТ ІНТЕРЕСІВ

The authors declare no conflict of interest.

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