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AN OVERVIEW OF WOUND HEALING WITH A BRIEF SUMMARY OF BIOMATERIALS APPLIED IN CHRONIC WOUND HEALING

Z. Lehečková, A. Stunová, L. Vištejnová

Biomedical Center, Faculty of Medicine in Pilsen, Charles University, alej Svobody 1655/76, Pilsen, Czech Republic

1. WOUND HEALING

Wound healing is an essential physiological process that involves a complex organization of cells, chemical signals and other components to repair a tissue. The aim of the process is to obtain functional and esthetically satisfactory substitution of tissue, a scar (1, 2).

Normal wound healing processes follow specific time sequences and can be generally categorized into four phases that are hemostasis, inflammation, proliferation and tissue remodeling. The particular phases of wound healing, however, are not completely separated but mutually overlapping in time (4). Many inner and outer factors can interfere with these processes, resulting in delayed wound healing such as chronic wounds or hypertrophic

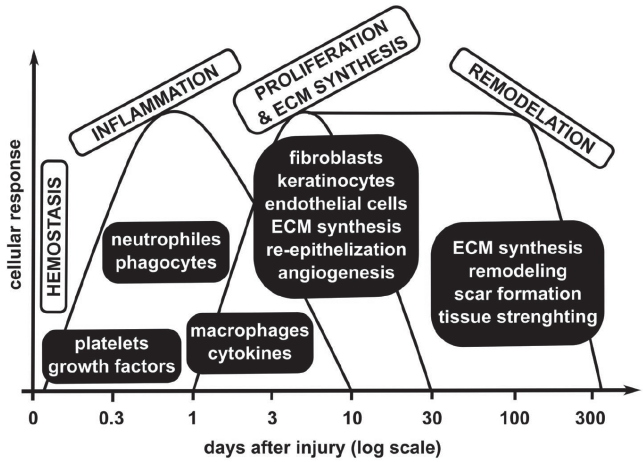

Fig. 1 Phases of acute wound healing, participating cells and overlapped ongoing processes. Immediately after skin injury, a temporary repair is achieved by clot formation. The clot plugs a defect and subsequent steps to regeneration of the wound bed are initiated. Immune cells, fibroblasts and new blood vessels overrun the clot and form a contractile granulation tissue. Wound maturation and scar formation comprises of remodelation of collagenous structures, fibroblasts differentiation into myofibroblasts, wound contraction and reduction of neovascularization (8, 43).

scarring (3). For each phase are predominant different cell types and signaling molecules (e.g. cytokines and chemokines) (Fig. 1).

Immediately after an injury, the response of body is to prevent exsanguination and promote hemostasis (5). Vasoconstriction, platelet plug and activation of clotting cascade result in fibrin clot formation (4). Since the mechanical barrier is no longer intact, the inflammatory phase is important to prevent infection, clearing the wound bed from invading microorganisms and necrotic tissue (6). Proper wound healing is achieved by adequate activation of neutrophils and macrophages, which release pro-inflammatory cytokines, such as tumor necrosis factor α (TNF-α), platelet derived growth factor (PDGF) or interleukins 1, 6, 8 (IL1, IL6, IL8) and anti-inflammatory factors including transforming growth factor β (TGF-β), fibroblast growth factors (FGFs) or epidermal growth factor (EGF) (7). The proliferative phase occurs about third day of wound healing and lasts up to 2–4 weeks after an injury, widely overlapping with the preceding inflammatory phase (8). It is characterized by actions such as fibroplasia, re-epithelialization, angiogenesis and wound contraction (1, 9). With progression of the proliferative phase, a provisional fibrin matrix is replaced by a newly formed granulation tissue (8). The remodeling phase is the last and the longest phase of the wound healing. The process begins 2–3 weeks after the injury and continues in order of months to years (10). The wound maturation process is balancing between ECM production and tissue breakdown. Collagen, which is extensively produced in the proliferative phase, becomes more organized, increasingly cross-linked strengthened, and ultimately forms the mass of a mature scar (11). However, a damaged tissue never regains the properties of uninjured skin. A scar usually achieves its maximum approximately 70–80% of the original strength (12, 13).

2. ACUTE AND CHRONIC WOUNDS

Under normal physiological conditions, the acute wound healing is highly efficient and restoration of the functional tissue occurs in a time frame of days or weeks depending on the severity of injury. While a small cut is healed in a few days, large wounds may take several weeks to repair and result in a usually noticeable scar (14, 15).

When the physiological repair process does not work properly, the healing response is altered and leads to progress of an ulcerative skin defect, the chronic wound (14). There are several definitions of chronic wound, not clearly established. One of the commonly accepted is a wound, which is not healed in four weeks, originally used as a standard definition of a venous leg ulcer. Another defines chronic wounds as those failing to heal with standard therapy in an ordered and well-timed manner (16). Anyway, there is a correlation of wound etiologies and the timeline of healing process (16, 17).

Chronic wound is caused by two main external insults – systematic chronic diseases and microorganism invasion that interrupts the wound healing process. Underlying pathologies include among others venous insufficiency, diabetes mellitus, arterial occlusion or high external pressure, leading by different mechanisms to failure of healing process. It is characterized by dysfunctional cellular events, aberrant cytokine and growth factor

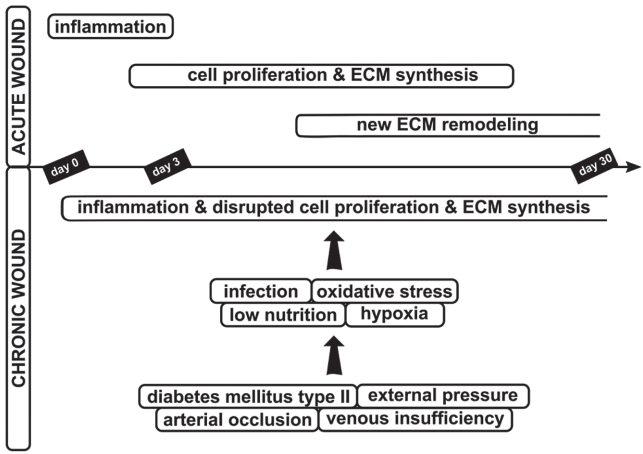

Fig. 2 Acute and chronic wound. Pathologies such as diabetes mellitus type II, external pressure, venous insufficiency or arterial occlusion negatively affect healing process which results in disrupted cellular response (14, 15).

activity (Fig. 2). These abnormalities result in hyper-proliferative epidermal edge creating ulcers covered with exudate and necrotic debris. Instead of a proper granulation tissue there are vessels surrounded by fibrin cuffs, very little vessel sprouting and few or none myofibroblasts. A heavy inflammatory invasion occurs including presence of neutrophils and pro-inflammatory macrophages, whose activities differ from those in physiological healing process (14, 15).

The majority of chronic wounds can be classified into three main categories: venous leg ulcers with prevalence of 2% in developed countries; pressure ulcers as a consequence of compromised mobility and sensory perception with an incidence of about 38% in acute care settings and about 24% in long-term and home care settings; and diabetic foot ulcers based on neuropathy, ischemia, and trauma, which affect 25% patients with diabetes mellitus (18, 19).

3. CLINICAL FACTORS AFFECTING WOUND HEALING

Hypoxia, infections, age, gender, sex hormones, stress, ischemia, chronic diseases (e.g. diabetes), medications, obesity, alcohol, smoking, immunodeficiency, or nutrition are the main factors affecting wound healing (20, 21). Increased age and psychological stress are major risk factors for delayed wound healing (21). Emotional stressors both directly (hormone and cytokine secretion) and indirectly (social behavior) influence physiological processes and impact the healing (22). Some of the medicaments also affect wound healing process, among others glucocorticoid steroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and chemotherapeutic drugs (21). Moreover, an appropriate nutrition

(sufficiency of carbohydrates, proteins, fat, vitamins, micronutrients and trace elements) is one of the main aspects of successful wound healing (21, 23).

4. BIOMATERIALS IN CHRONIC WOUND HEALING

There are many factors responsible for the chronic wound persistence (21).The failure of wound healing is related to infection, alterations in inflammatory response, delayed re-epithelialization, improper collagen synthesis, ECM formation and remodeling, deficient angiogenesis, or inadequate apoptosis (24).

Both traditional and modern wound healing therapies can be targeted to all troubleshooting aspects of healing. The healing success of every advanced medical device depends primarily on an efficient debridement of wound bed when bacteria and necrotic tissue has to be removed and a vascularized tissue has to be exposed to get in touch with medical device (25). The milestone of healing process is the clearance of infected wound bed from bacteria and the skip from chronic inflammation to the effective immune cell response followed by functional re-epithelization, new ECM formation and angiogenesis, i.e. granulation tissue formation. The final remodeling of tissue represents non-disrupting phase of healing process without the need of hospital care.

Many wound dressings have been developed to both to treat the wound infection and to promote healing process itself (Tab. 1). Current wound dressings include traditional gauze and advanced types of wound dressings combining natural and synthetic polymers and/or nanoparticles which can be further enriched by growth factors and bioactive molecules including antibiotics. Structurally, the wound dressings are developed in the form of microfibers (26), nanofibers (41), hydrogels (27, 28), hydrocolloids (29), films or foams (25). The construction and function of wound dressing meets not only the biological criteria but also the clinicians' and patients' requirements for comfortable practical usage (e.g. minimal pain upon removal, prolonged exchange times).

Tab. 1 Types of current wound dressings (25, 40).

Form of material	**Commercial product**	**Function**
Hydrogel	Carrasyn, Curagel, Nu-Gel, Purilon, Restore, SAF-gel, Xcell	autolytic debridement, moisturing
Hydrocolloid	Aquacel, Comfeel, DuoDERM, Granuflex Tegasorb	granulation tissue formation
Alginate	Algisite, Kaltostat, Sorbsan, Tegagen	hemostatic
Film	Bioclusive, Blisterfilm, Cutifilm, Flexigrid, OpSite, Tegaderm	moisturing, bacteria barrier
Foam	3M Adhesive Foam, Allevyn, Lyofoam, Tielle	moisturing, bacteria barrier
Skin substitue	Alloderm, Apligraf, Hyalograft, Integra Omnigraft	full thickness skin replacement

Natural polymers applied in wound dressing development are derived from silk fibroin [30], alginate (31), collagen (32), cellulose (33), chitosan (34) or hyaluronic acid (42). Their purpose is wound bed moisturizing or providing provisional matrix for resident cells' actions (e.g. migration, new ECM production). Synthetic polymers in wound dressings are poly(lactic acid) (PLA) (35), poly(glycolic acid) (PGA) (36), poly(lactic-co-glycolic acid) (PLGA) (37), polycaprolactone (PCL) (38) or polyethyleneglycol (PEG) (39). They serve as carriers of antibiotics, antimicrobial peptides, growth factors and other bioactive compounds or as structural and mechanical support for new tissue formation by the means of tissue engineering.

The special issue of wound healing therapy is skin substitutes, the most frequently used in third degree burns or venous and pressure ulcers. They are designed to restore the full thickness skin by combination of synthetic porous, microfiber or nanofiber mesh made of PLA, PCL or PGA and collagen layer of porcine or bovine origin. Growth factors or even fibroblasts and keratinocytes are incorporated in advanced versions of skin substitutes (40).

5. CONCLUDING REMARKS

Nowadays progress in wound healing dressings goes hand in hand with new material development, but the traditional wound debridement still remains the gold standard in wound therapy. A wide range of medical devices is in clinical use. However, there is no straightforward procedure how to heal chronic wound, which is probably arising from the patient and wound heterogeneity. Successful healing depends on the combination of more approaches – defense against infection, immune system stimulation and support of fibroblasts', keratinocytes' and endothelial cells' functions. The current advanced medical devices for wound healing are designed to facilitate one or more of these obstacles in one device. The future devices are being developed not only to heal the wound but also to monitor the healing process at a physical and molecular level.

SUMMARY

Wound healing is a highly organized and complex process leading to tissue restoration after injury. It is a dynamic interaction between immune, mesenchymal and epithelial cells, soluble mediators and extracellular matrix components. Acute wound occurs in four overlapping phases – hemostasis, inflammation, cell proliferation and tissue remodeling, and is resolved within a few days or weeks depending on wounded area without any medication. In chronic wound the balance among particular healing phases is altered due to prolonged infection connected with associated diseases such as diabetes mellitus or venous insufficiency. This review summarizes basic principles of acute and chronic wound healing and provides a brief outline of biomaterials applied in current approaches for wound therapy.

Hojení ran a stručný přehled biomateriálů používaných v léčbě chronických ran

SOUHRN

Hojení ran je komplexní proces sloužící k obnově poškozené tkáně a udržení homeostázy organismu. Proces hojení lze rozdělit na čtyři na sebe navazující fáze – hemostázu, zánět, proliferaci a remodelaci tkáně. Zatímco se akutní rány hojí bez nutnosti terapeutického zásahu v řádech několika dní až týdnů, chronické rány setrvávají ve fázi zánětu. Přechod do chronicity je způsoben dlouhodobou infekcí související s narušenou imunitní odpovědí, která bývá často asociována se systémovými onemocněními, jako je např. diabetes mellitus nebo žilní nedostatečnost. Tato práce popisuje základní principy hojení akutní a chronické rány a shrnuje přírodní a syntetické materiály pro vývoj moderních kožních krytů.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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Author's address: Z. L.: alej Svobody 1655/76, 323 00 Pilsen, Czech Republic