Innovative Therapies for Wound Healing

Subjects: Pathology

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Wound healing is divided into four overlapping phases: hemostasis, inflammation, proliferation, and remodeling/maturation. During hemostasis, endothelial cells secrete the von Willebrand factor, favoring the adhesion of platelets, which release mediators. During the inflammatory phase mast cells promote vasodilation by the secretion of histamine or serotonin. During the proliferative phase, fibroblasts, in addition to being involved in the formation of granulation tissue, are involved both in the regulation of keratinocyte migration and proliferation other than in angiogenesis. The main processes that distinguish the maturation (or remodeling) phase are collagen restoration and wound contraction, the latter due to myofibroblasts originating from the fibroblasts.

Keywords: wound healing ; therapy ; MSCs ; drugs ; lasers ; light-emitting diodes

1. Introduction

The development of knowledge about wound healing (WH) throughout history has been remarkable. Historically, wounds were often related to infection, and patients consequently died from septicemia rather than from the wound itself. With the advent of light microscopy, a greater awareness of the fine cellular mechanisms of wounds has evolved, and this has aided our understanding of the treatment and care needed. Nevertheless, compromised WH is a major concern in public health. This is demonstrated by the fact that millions of people suffer from chronic wounds (CWs) [1][2].

Impaired WH appears to be a major concern in the public health sector, as expensive and complex treatments are necessary for its management. Millions of patients need care for chronic wounds and this costs thousands of millions in USD. This burden is increasing, mainly due to the growing incidence of aging, diabetes, and other risk factors in the population. A similar scenario is observed in Europe, where it is estimated that over 1.5 million people could be affected by CWs. As a result, WH is of great interest, and this is demonstrated by the number of fellowship programs offered for various medical professionals in this field, including vascular surgeons, nurses, dermatologists, and general practitioners. There is a demand for new technologies in WH to be introduced. Furthermore, additional problems exist because a comprehensive understanding of the biological mechanisms related to wound healing has not yet assumed popular relevance; rather, the focus is more directed toward niche problems, where, contrary to some disciplines, few scholars confront each other regarding the problems considered [1][2][3].

Guidelines undoubtedly represent an aid for wound care during clinical practice [4][5], in particular considering the fact that the biofilm, which maintains the CW in the inflammatory phase, is responsible for 80% of infections and must be removed [5]. Among the new techniques, it is particularly worth mentioning those concerning the effects of four basic compounds, i.e., octenidine (OCT), polyhexamethylene biguanide (PHMB), povidone–iodine (PVP-I), and sodium hypochlorite (NaOCl), as well as nanosilver, on cells and the inflammatory processes that act on the removal of the biofilm [5].

2. Impairment of Wound Healing and Recent Therapeutic Strategies

Wound care represents an important problem in medicine today. This section is dedicated to the most innovative therapies proposed for this issue.

The presence of epidermal stem cells (ESCs) within the skin appears to be an advantage for the adoption of therapies. Use of these cellular types influences the proliferation and migration of fibroblasts and keratinocytes, as well as angiogenesis [6].

In mesenchymal stem cell (**MSC**) therapy, the techniques are based on the use of scaffolds seeded from MSCs and biomaterials such as collagen or cellulose. MSCs stimulate granulation tissue formation, angiogenesis, and future vascularization. Endothelial cells are recruited due to the release of various factors such as FGF or ANG1. The action of MSCs is essentially the modification of the production of TNFalpha and the reduction of the function of natural killer (NK) cells in the inflammatory phase, varying the activity of IFNgamma. If MSCs are used during the last phase of healing, particularly during scar formation, there is a lowering of the TGFbeta1/TGFbeta3 ratio, an increase in IL10, as well as a reduction in IL6 and IL8 [7].

Recently Kua et al. [8] investigated the use of **human umbilical cord cells** for the treatment of skin wounds.

The literature includes various examples describing the action of **drugs** on wound healing. These include anticoagulants, antimicrobials (various classes of antibiotics), anti-angiogenesis agents (e.g., bevacizumab, aflibercept), antineoplastic drugs, antirheumatoid drugs), nicotine, steroids, and vasoconstrictors. Among the various drugs used, steroids and non-steroidal anti-inflammatory drugs (NSAIDs) also deserve attention [9]. Among the new drugs, Exendin 4 (Exe4) is considered an important candidate. Exe4 is a naturally occurring peptide that has 53% similarity with Glucagon-Like Peptide-1 (GLP1), an intestinal insulinotropic peptide that is a member of the incretin hormone family. GLP1 exerts an important postprandial insulinotropic effect, being responsible for about 60% of postprandial insulin secretion. Experimental evidence suggests a possible role for Exe4 in promoting tissue regeneration [10][11].

Extending the use of phototherapy to wound healing is now becoming increasingly important. Lasers are very important in the treatment of assisted healing, most of which use fractional ablative lasers such as CO_2 or erbium, but non-ablative fractional lasers or vascular lasers are also commonly used [12].

The combination of harmless light in the protoporphyrin absorption spectrum with non-toxic photosensitizing dyes is used in photodynamic therapy (PDT) [13][14].

The role of PDT in CWs has been explored; the main advantage of the technique being the possibility of reducing all types of microorganisms by inducing ROS and without inducing resistance to conventional antibiotics. Furthermore, PDT-induced tissue regeneration and the decrease in metalloproteinase activity and the regeneration of collagen need to be considered [15][16]. However, the use of PDT for assisted WH is not yet habitual in clinical practice as there are few studies published, and multiple repeated sessions are needed with the actual available lights and photosensitizers [14].

Low-level laser light therapy (LLLT) induces cellular modification (photobiomodulation) leading to beneficial clinical effects. LLLT can be applied with low fluences or laser light, but currently, to simplify the use of the technique, light-emitting diodes (LEDs) have been promoted. The action of LLLT is linked to the action of cytochrome c which, by absorbing photons, induces an increase in ATP production and an increase in ROS and transcription factors [17]. However, the role of LLLT remains controversial.

Light-emitting diodes (LEDs) are revolutionizing the entire lighting industry due to their ease of use. However various technical differences distinguish LEDs from LLLTs [18][19][20][21]. The effects of the use of LEDs tend to decrease the inflammatory state of the lesion in progress [18][19][20] and allow for a targeted modulation of the biofilm [11].

Electrical stimulation is one of the more promising possible adjuvant therapies, regarding which deeper studies have been published. Some clinical trials have demonstrated the utility of electric field stimulation in CWs such as pressure ulcers and leg ulcers. This technique promotes the proliferation phase and regeneration mainly through the TGFbeta regulation [22]. Ultrasound, delivered in different ways to the target tissue, has also been used as a promising treatment [23][24].

Among the new recent techniques, Bianchi et al. [25] have proposed the use of **nano-fibrous scaffolds**, which have anti-inflammatory properties. The nanofibers come from industrial procedures (electrospinning), using substances such as polybutyl cyanoacrylate (PBCA) combined with copper oxide nanoparticles and casein phosphopeptides (CPP).

Since the use of conventional antibiotics induces antibiotic resistance, Lin et al. [26] developed metal–organic frameworks (**MOFs**), which are complex chemical structures in which copper coordinates with organic ligands.

In contrast, novel isoxazole derivatives or graphene oxide compounds activated by light-emitting diodes were proposed by Bachor et al. [27] and Di Lodovico et al. [28]. These compounds shown anti-microbial activity toward *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

As the use of exosomes as a therapy for wound healing is now clear, Sousa et al. [29], aware of the fact that this therapy has not yet been added to the common treatments, analyzed the substantial efforts that remain necessary before proposing applicable therapeutic approaches using these extracellular vesicles that are produced in the endosomal compartment of most eukaryotic cells.

Finally, considering that in vivo drug studies are limited for many reasons, including ethical ones, Cialdai et al. [30] have developed a new culture system based on enriched culture media and a mechanical support capable of modeling the physiological mechanical tension of the tissue and possibly monitoring its changes during the wound-healing process.

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