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A Review of Genes Involved in Wound Healing

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Abstract

Background: Gene therapy holds immense potential in the field of wound healing. However, we still do not recognize this procedure well enough to give oversight effectively to improve healing processes. A wide range of information has been achieved from the database for gene expression profiling by clinical trials, So we performed this study to gain a better understanding of the mechanisms behind wound healing and how it could be utilized to develop new therapies and treatments.

Methods: In this study, we have been focusing on wound-healing genes, conducting a thorough review to explore the various genes and pathways involved in this process. For this purpose, a total of 320 articles were collected. All experimental studies, systematic or narrative reviews, studies and clinical trials included in this paper were searched on PubMed, Medline, Embase, Science Direct, and Scopus databases in English using the following terms: Wound Healing, wound regeneration, Gene Transfer, and Gene Therapy were used to search the mentioned databases. Unfortunately, we didn't find a large sample cohort study on this topic. A total amount of 330 articles were collected based on the guidelines of the PRISMA method. Both inclusion and exclusion criteria were settled.

Results: During the last decade, different models of gene delivery have been introduced, which include viral transfection and Non-viral techniques. In this regard, TIMP-2 protein and VEGF mutants such as VEGF165, CARP, and HIF-1 are the genes that accelerate the rate of tissue repair.

Conclusion: The process of wound healing is mainly related to the change of expression of genes that have a role in the parts of inflammation and repair. In our study, some of the most suitable genes involved in the wound-healing process are mentioned.

Keywords: Wound healing, Gene therapy, Growth factor, inflammation, regeneration

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Introduction

The largest organ, the most exposed one, is the skin. Owing to the increased number of traumas and their difficult pathophysiological conditions, clinicians face severe medical conditions (1). In the process of wound healing, various types of cells set and do their particular actions at specified stages. The process of wound healing is a complex one that consists of multi-stages of inflammation, Epidermal keratinocyte migration, and remodeling of the extracellular matrix (ECM), which happen in temporally overlapping sequences (2).

Over the past three decades, many clinical trials have been conducted to cover the gap available in the knowledge of wound healing mechanisms. Due to the shortage of knowledge on the overall mechanism of tissue repair, the therapies available in this process are limited. Partial-thickness skin grafts are capable of creating an

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↑What is "already known" in this topic:
Several key function genes have been identified to play a role in skin wound healing. These genes have been categorized according to the pathophysiological stages that best correlate with their temporal expression profile during wound healing.

→What this article adds:
Among the many genes involved in wound healing, this study aims to review those having the most critical action during this process. These genes, or their products, could be potential targets of intervention in patients with hard-to-cure wounds. For example, the TIMP-2, VEGF mutants such as VEGF165, CARP, and HIF-1 are the genes that have been addressed in this review.

exterior wound at the donor site, which is specified through its injuries' depth. The possibility of extending this injury to the epidermis and papillary dermis is high which are well known for their extended healing period and often cause scars (3, 4). Thus, clinicians are following these types of wounds to compare the formation of scars and superficial wound healing processes in clinical trials (5).

Microarray technologies of DNA are capable of providing the knowledge of providing genome-wide profiling of gene expression, which makes it possible for clinicians and researchers to examine the healing process of the wound in both in-vitro and in-vivo models. Moreover, it provides a wide range of gene sets and their data on various stages of normal wound healing (6). These types of time-course clinical trials make the opportunity for researchers to examine the dynamic behavior of gene expression and the differences that may be available in molecular and cellular status over time (7). Some recent studies have studied the role of DNA microarrays in physiological and pathophysiological transcriptional responses during the wound-healing process (8). Anyway, the biological data achieved from these clinical trials have not been fully explored yet. Due to the rapid advances in bioinformatics technologies, a wide range of information has been achieved from the database for gene expression profiling by clinical trials (9). Developing new and more cost-effective therapies is not only of great interest but also necessary for the better constancy of national health systems. This review covers current knowledge of the genes recently implicated in wound healing and a better understanding of the mechanisms behind wound healing and how they can be utilized to develop new therapies and treatments.

Methods

Aiming to provide adequate knowledge of genes involved in wound healing, a variety of studies on the matter of genes involved in wound healing from 2010 to 2021 were collected. All experimental studies, systematic or narrative reviews, studies, and clinical trials included in this paper were searched on PubMed, Medline, Embase, Science Direct, and Scopus databases in English using the following terms: Wound Healing, wound regeneration, Gene Transfer, and Gene Therapy were used to search the mentioned databases. To accredit the collected data all related review articles, reports, and clinical trials were used. On this subject, a total amount of 330 articles were collected based on the guidelines of the PRISMA method. Both inclusion and exclusion criteria were settled (10). Our inclusion criteria were human studies and original articles. In all articles, the titles and in some of the randomly selected ones, the abstracts were reviewed independently to be selected as the important ones in the inclusion criteria. Likewise, the papers with more related content were chosen to be reviewed exactly and those with less appropriate content were excluded.

Wound healing biology

Wound healing is a multifaceted process; it occurs through a series of cellular and molecular procedures. As shown in Figure 1, it consists of several stages: Hemostasis, inflammation, Proliferation, and remodeling (11).

A few minutes after the injury, there will be an infiltration of neutrophils, monocytes, and lymphocytes to the wound site which is identified as the first phase. They protect protease and then respondent oxygen species that are critical for scrubbing cell remains through the phagocytosis process. However, this assault is a common mechanism of the body to protect the wound site from any invading noxious microorganisms (12). Moreover, this phase is the utmost essential one for the construction of appropriate growth factors and macrophages within the cytokine network which is set by monocytes. This phase acts by way of the start point of the wound healing process with the expression of tumor necrosis factor-alpha (TNF alpha), platelet-derived growth factors (PDGFs), and colony-stimulating factor-1 (CSF-1). two days after injury, those have an important role in moderating the adaptation among the early stage of inflammation and the beginnings of the wound healing process are the cytokines (13). About 2-7 days after the outset of injury, the second phase begins which is incepts of the wound healing process. The main sign of the start of this phase is the epidermal

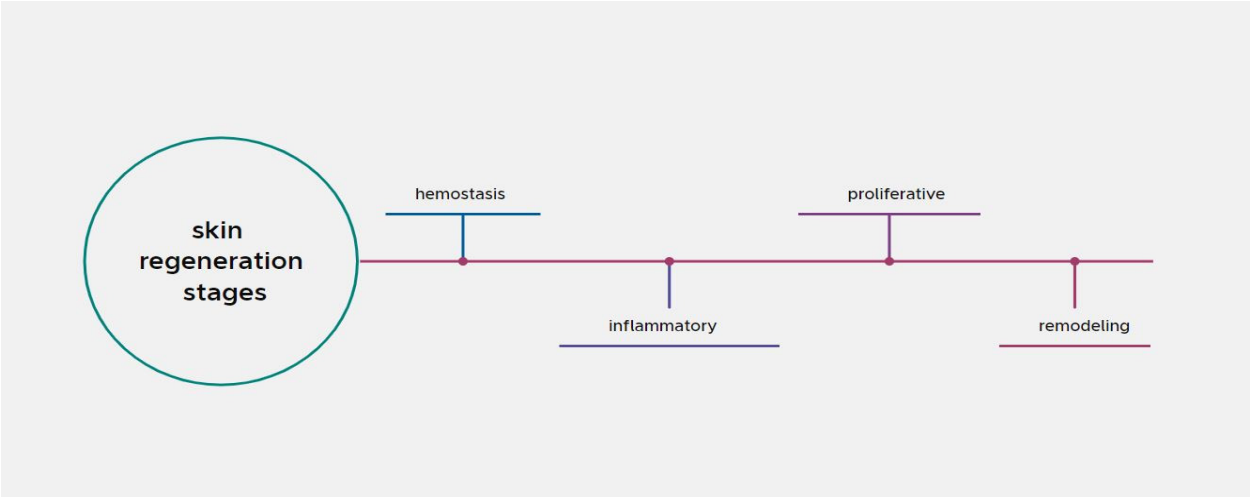

Figure 1. Sequential illustration of the wound healing stages

keratinocyte migration at the wound side. In this phase, the migration of fibroblasts and endothelial cells will come off to the clot. Then the extracellular matrix will place and after that state granulation (14). After this phase, the wound will be remodeled and fibroblasts will be converted into myofibroblasts which help to bond the wound. Within this phase, the deposition of collagen will occur plenty. Closing the external surface of the wound with a new epidermis is the main function of keratinocytes. In the third phase of wound healing, originally, granulation tissue will be transferred to the scar tissue, then the evidence of the successive layers of collagen will be seen, and the scar will be remodeled, typically going on a few months (15, 16).

The process of wound healing is complicated and mainly moderated by molecules that perform as mutual mediators and receptors. In this regard, the interactions play a key role in networking the wound healing steps. The stated proteins, which were revealed many years ago, are known as growth factors and have a substantial role in controlling the regular process of wound healing. Different types of cells that have a role in tissue regeneration could synthesize and secrete growth factors which include fibroblasts, platelets, epithelial and inflammatory cells, and vascular endothelial cells (17, 18). The deficiency of growth factors can disrupt the process of wound healing. Various factors could affect a deficiency of growth factors, for example, in patients with diabetic ulcers, the deficiency of production and secretion results in impaired wound healing (19). Additionally, in patients who burn or someone with venous stasis ulcers, the lack of growth factors could be observed as a result of macromolecular secretion of fibrinogen, a-macroglobulin, and albumin (20). Gushiken et al. (21) studied the growth factors involved in various phases of wound healing. According to their findings, during the healing progression growth factors and cytokines perform as regulators. It might cause impaired wound healing or abnormal scarring such as keloids.

Mechanisms of physiological and pathological wound healing

As mentioned in advance, through the process of wound healing, an interactive reaction will be sent to the injured tissue. This process is an intricate interaction that contains different types of cytokines, soluble mediators, and extracellular matrix molecules (22). By the way, one of the most fundamental knowledge of tissue regeneration is knowledge about the signal, temporal set and the controlling methods in the process of wound healing. Additionally, we should be acquainted with the principal phases of the normal wound healing process which include homeostasis, inflammation, granulation tissue formation, and remodeling. It should be noted that all procedure of biological actions in the wound healing process in all varieties of tissues is the same (23).

Straightly after the wound, the clotting cascade will be made active by limited proteolysis that causes hemostasis which mainly consists of platelet degranulation and polymerization of fibrinogen. Next, extra serum and cell-derived extracellular matrices (CD-ECMs) are stored at the wound site which mostly consists of vitronectin, thrombospondin, and fibronectin. This complex process simplifies forming a temporary matrix through which cells can migrate (24). This matrix works by way of a growth factor and reservoir of cytokines released from activated platelets. Owing to the adhesion of cells to the extracellular matrix molecules, the connection of cell-matrix could be mediated by different classes of cell membrane receptors containing the integrin family (25). Altogether, cytokines and molecules of the extracellular matrix generate chemotactic signals for activating and engaging apparent tissue-resident and non-resident inflammatory cells that may enter the wound site. The dissemination or reposition of lymphocyte cells, neutrophils, and macrophages are essentially committed in the defense functions and beginning process of granulation tissue forming which all happen through reactive oxygen species, cytokines, and the synthesis of strong protease enzymes such as Cathepsin G (CathG) protein, elastase enzyme, and proteinase 3 (PR3) enzyme (26). During the formation of granulation tissue, the cellularity of the site will rise, and solvable mediators will be discharged from invading mesenchymal cells. Whatever motivates the migration of keratinocytes and the process of cell proliferation are releasing soluble mediators for achieving the reepithelization step (27). Farther, soluble mediators could be released as activated keratinocytes which are very important for both angiogenesis and fibroplasia steps as the principal specification of granulation tissue construction. After refreshing the entirety of the tissue lack, inflammation will be solved, and at that time, granulation tissue recedes. Next, the scar tissue will be created, and finally, the wound comes in the remodeling phase. Several months after the last phase, a stable situation will be proceeding between the creation of the new components of the scar matrix and their degradation by proteases (28).

The classical model of wound healing

In the typical model of wound healing, three phases overlay each other. Cutaneous wounds motivate a collection of cellular responses, including coagulation, activation of platelets, infiltration of inflammatory cells, Re-epithelialization process, and lastly, granulation tissue formation which is constructed by fibroblasts and blood vessels (29). The wound repair, in all tissue, is a usual biological procedure and it involves four multifaceted steps: homeostasis/coagulation; inflammation, migration and proliferation; re-epithelialization and restoration. The process of wound healing in the skin onsets with hemostasis is specified through the appearance of platelets (30). At the beginning of the healing process, a platelet mass will be formed at the wound site and after that, initiated platelets release cytokines which have an important role in the healing of the wound including platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF-β). Following that platelet aggregates detected in the wound site, coagulation system enzymes will be activated there and the conversion of fibrinogen to fibrin will occur. A temporary matrix to simplify the healing

process of tissue could result from the arranged network (31). Several hours after the formation of clots, the migration of keratinocytes to the site from the edges of the injury will be behold which is identified to be the inception of the closing of the wound (32). During the inflammatory step neutrophils, macrophages, and mast cells will emerge. In the wound site, first of all, neutrophil cells penetrate. In the next 24 hours, neutrophil cells in the wound site become the major leukocyte which supports the process of eliminating bacteria, injured matrix, and foreign materials (33). After 48 hours' tissue macrophages will enter and create both growth factors and cytokines. Furthermore, they have an important role in debridement and perform as phagocyte cells for eradicating matrix debris. Activated macrophages appeared simultaneously with the lymphocytes' appearance. It is also a sign of the inflammatory phase's end at the beginning of the proliferative phase in the wound healing process (34).

Collagen, fibronectin, and proteoglycans are produced in the proliferative phase, which is essential in forming angiogenesis, continued epithelization, and extracellular matrix. Fibroblasts are predominant cells in the proliferative phase which produce matrix and collagen. Platelet cells, macrophages, and T cells produce TGF-β which is a strong stimulus for fibroblasts and has a significant role in the proliferative phase (35). The process of angiogenesis is started following the endothelial cell's migration to the fibrin matrix. Moreover, aimed to form new capillaries, the interstitial matrix should be degraded through endothelial cells. The angiogenesis process will be stimulated by basic fibroblast growth factor (bFGF), and vascular endothelial growth factor (VEGF) along with TGF-β (36). Remodeling is the final stage of the wound healing process, which includes the degradation of collagen by proteolytic enzymes which are produced by macrophages, neutrophils, and fibroblasts. The mentioned phase could be specified through the penetration of mastocytes which manage the repair process of the wound by increased inflammatory signaling (35, 36).

Growth factors involved in tissue repair

Nowadays, numerous progress has been made in the knowledge of the wound healing process. Following the progress of related literature, various types of cells and the order in which they appear in the wound site have been established well. In this regard, different growth factors and their functions have been elucidated (2). Despite the progress achieved in the comprehension of wound healing-related science, many steps have not been known and discovered appropriately, yet The border of this field of study consists of visual remnants of the wound and prevention of keloid scar formation and hypertrophic.

Of the most common threads in the medical specialty are tissue injuries. In this regard, knowing wound healing is mandatory to achieve a predictable sequence of events. We are having a comprehensive knowledge of the total process of wound healing, the cells that have a role in it, and molecular signaling improves the optimization of this crucial process. The advances in the molecular science of wound healing provided the possibility of gaining a clear comprehension of the complex interaction between the cells involved in the process of wound healing. In this regard, one of the most important factors involved in improving the wound healing process is having a great comprehension of the growth factors. These factors mainly include scarless wound healing and the transplant of tissues engineered from progenitor cells (37).

The overall process of wound healing consists of a complex cellular interaction between fibroblast cells, myofibroblast cells, endothelial cells, keratinocyte cells, immune cells, and smooth muscle cells. The mentioned interactions are moderated by different factors including growth factors, blood components, hormones, and second messenger molecules. Some growth factors have a crucial role in wound healing which include epidermal growth factor (EGF), fibroblast growth factor (FGF), insulin-like growth factor (IGF), keratinocyte growth factor (KGF), platelet-derived growth factor (PDGF), transforming growth factor (TGF), and vascular endothelial growth factor (VEGF). Moreover, these factors have been used in the clinical setting to improve the process of wound healing (38).

Gene therapy in tissue repair

Various technologies of delivery that are effective in gene transfer are employed successfully nowadays in vivo and ex vivo gene therapy settings (39). Using in vitro approaches, the cells that are involved will be separated from the wound site and then manipulated in culture to alter their gene expression profile. After that, the cultured cells will be transplanted back into the donor (40). Recently numerous clinical trials have been done to examine the properties of parenchymal cells derived from diverse tissue target cells for genetic engineering manipulation. Anyway, any novel development in the culture conditions for non-differentiated progenitor cells, a more exciting target for genetic manipulation, will be observed. Moreover, the overall function of genetically modified cells is improved in an in vitro approach using the combination of biomaterials supporting cells with modified cells before transplantation (41). Due to the direct delivery of the genes to target tissue in vivo gene therapy, the requirement of cell transplantation and culture will be eliminated. To put it simply, the DNA vector harboring the encoding sequence in this method is required to be inserted into host cells in vivo. This approach is a straightforward one that is mainly associated with the tissues in which cells could not be cultured or transplanted, like the nervous system (42). Even though in vivo approaches have some clear advantages, targeting genes to particular cells of a specific tissue will not always be easy. Based on the studies carried out recently, injected plasmid-DNA could be transferred to distant organs by CD11b+ cells beyond regional lymph nodes. Additionally, the transgene transport and cellular uptake could be amplified using inflammation in this model (43).

The most suitable genes for tissue repair

In the process of management of the genes that have a role in the healing process of a wound, we should investi-

Table 1. The role of genes in wound healing

Gene symbol	Description of the role	First author, Year, Ref.
TIMP-2	As a metalloproteinase (MMP) inhibitor in rat model	Fan D, 2020 (45)
VEGF165	Enhancing the durability within the protease-rich microenvironment of the wound.	Tocco I, 2012 (46)
iNOS	iNOS genes could be regulated by HIF1-α overexpression of HIF1-α which is capable of activating multiple members of the VEGF family, improving revascularization and the rate of wound healing	D'Aguanno S, 2021 (48)
CARP (Ankrd1)	In terms of the evaluation of potent effects on wound neovascularization and endothelial migration in several animal models	Shinjo SK, 2017 (49)
SMAD	regulating inflammation in chondrocyte differentiation and cutaneous tissue repair.	Liarte S , 2020 (50)
FGF-2	In gene transfer	Benington L, 2020 (52)

gate the growth factors that are specified to be suitable candidates for the healing of tissue. According to previous studies, it has been proved that effective pathogenic factors of a non-healing wound environment are high levels of protease enzymes in the wound (44). Similarly, Fan et al. (45) reported that using recombinant TIMP-2 as a metalloproteinase (MMP) inhibitor improved the rate of wound healing in the rat model. In a study by Tocco et al. (46), a new protease-resistant VEGF165 molecule was introduced which was capable of enhancing the durability within the protease-rich microenvironment of the wound. The mentioned VEGF mutant is capable of exerting superior angiogenic properties at the site of chronic wounds. Additionally, Schrumpf et al. (47) proved that gene transfer of pro-inflammatory cytokines has a significant role in regulating the innate immune response. On the other hand, in the process of wound healing transcription factors might be measured as the main target of gene therapy which has the possibility of activating multiple targets and pathways. Hypoxia-inducible genes have the possibility of being transcribed by attaching to a hypoxic response element in the gene promoter. This possibility is achieved from the hypoxia-inducible factor 1-alpha (HIF 1-α) gene. VEGF and iNOS genes could be regulated by HIF1-α which is capable of activating multiple members of the VEGF family, improving revascularization and the rate of wound healing (48). Recently, the effects of transcriptional cofactors and cardiac adriamycin-responsive protein (CARP) have been studied in terms of the evaluation of potent effects on wound neovascularization and endothelial migration in several animal models (49). Additionally, cell signaling processes such as SMAD proteins have been proven to have a significant role in regulating inflammation in chondrocyte differentiation and cutaneous tissue repair. Therefore, improving the activity of SMAD enhances the healing response in repairing cartilage and cutaneous (50). The techniques of gene transfer are the most suitable choices which could be applied in medical applications directly. Additionally, the genes used as growth factors have been modified to be more appropriate for gene transfer. For instance, the application of FGF-2 as a pleiotropic mitogen-activated protein in various organ systems and gene transfer approaches has been restricted due to the lack of FGF-2 as a classical secretion signal peptide (51). A study by Bennington et al. (52) introduced a modified form of FGF-2 in gene transfer applications, which provides an appropriate molecule (Table 1). The lack of a significantly large matched cohort study is one of the limitations of this paper. So we suggested a large-scale study on this subject.

Conclusion

In the process of cutaneous wound healing, the expression of genes increases significantly, which implicates both inflammation and healing aspects. During the process of wound healing, the genes expressed profile will change from inflammation to repair and angiogenesis. This conversion in the profile of the gene may explain the participation of M2 phenotype macrophages.

In our review, we assessed multiple microarray gene expression profiles. Identification of essential hub genes in various stages of wound healing is associated with the prognosis, onset, and development of the wound healing process. Anyway, further clinical trials should be carried out to assess the biological process and action of the introduced genes in the overall process of wound healing.

Ethical approval

This study was approved by the ethics committee at Iran University of Medical Sciences with the ethics code "IR.IUMS.REC.1398.03".

Authors Contribution

Farhangniya: conception, design, material preparation, data collection, writing, and revision; Samadikuchaksaraei: conception and design; all authors confirmed the final version of the manuscript.

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Conflict of Interests

Ali Samadikuchaksaraei is a shareholder and CEO of Baztarmim Company, which is mainly focused on the production of tissue engineering products. The other author has no conflicts of interest to declare.

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