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Genes involved in wound healing: a narrative review

Reza Akhavan-Sigari[1&2]

[1] Department of Neurosurgery, University Medical Center Tuebingen, Tübingen, Germany
[2] Department of Health Care Management and Clinical Research, Collegium Humanum Warsaw Management University Warsaw, Poland

ABSTRACT

Objective: The repair process of wounds consists of a consecutive interaction of different types of cells, soluble mediators, and Extracellular Matrix (ECM). This study aims to provide a review of genes involved in wound healing.

Design: This is a narrative review.

Material and Method: Aiming to provide a comprehensive database of genes involved in wound healing a wide range of studies were studied. The most well-known databases such as PubMed, Medline, Embase, Science Direct, and Scopus were reviewed up. In this regard, a total of 320 articles were collected.

Results: Having an appropriate knowledge of the pathophysiology of wound healing provided a more advanced technology to authorize optimization of microenvironments within wounds. 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, VEGF mutants like VEGF165, HIF-1, and CARP are among the most suitable genes that accelerate the rate of tissue repair.

Discussion: The process of wound healing is mainly associated with the increment of expression of genes that has a role in the aspects of inflammation and repair.

Conclusion: In our study, most suitable genes involved in the wound healing process are introduced. The repair process of wounds consists of a consecutive interaction of different types of cells, soluble mediators, and Extracellular Matrix (ECM). This study aims to provide a review of genes involved in wound healing.

Key words: wound healing, gene therapy, gene transfer, growth factor

Address for correspondence:

Reza Akhavan-Sigari,
Department of Neurosurgery,
University Medical Center Tuebingen,
Tübingen, Germany,
Email: rasigari@yahoo.de

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INTRODUCTION

The largest organ, the most exposed one, and the most sensitive tissue of the human body is the skin. Because of 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 consisted of multi-stages of inflammation, Epidermal keratinocytes 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 with the aim of covering 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 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 the possibility for clinicians and researchers to examine the healing process of wound in both in-vitro and ex-vitro models. Moreover, it provides a wide range of gene sets and their data about various stages of normal wound healing [6]. These types of time course clinical trial makes 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 of bioinformatics technologies, a wide range of information has been achieving from the database for gene expression profiling by clinical trials. In this regard, the present study is aimed to review all available studies to investigate the most suitable genes involved in wound healing [9].

METHODS AND MATERIALS

Aiming to provide adequate knowledge of genes involved in wound healing a variety of studies on the matter of genes involved

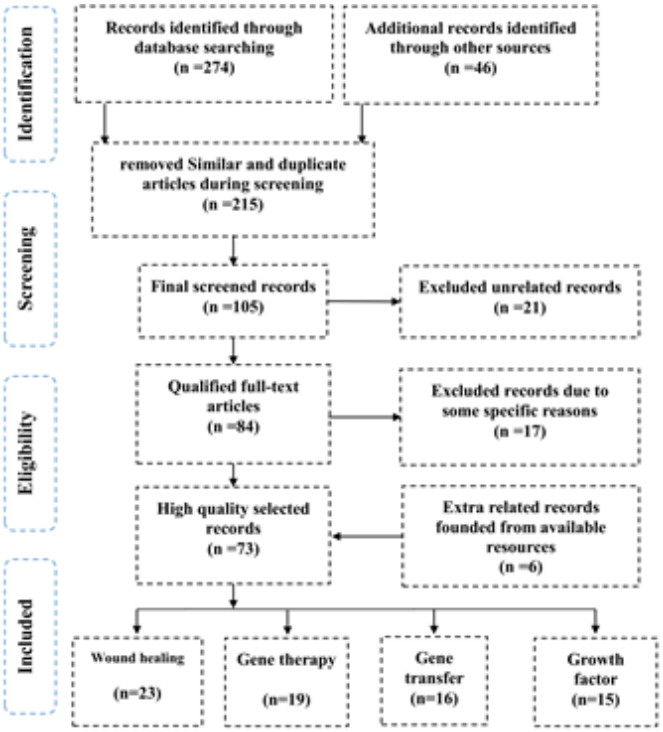

Fig. 1. Schematics diagram of selection of article based on PRISMA method

in wound healing from 2010 were reviewed. The most well-known databases such as PubMed, Medline, Embase, Science Direct, and Scopus were reviewed up in English up to October 2021. Phrases such as Wound Healing, Gene Transfer, and Gene Therapy were used to search the mentioned databases. To empower the collected data all related review articles, reports, and clinical trials were used. In this regard, a total amount of 320 articles were collected which based on the guidelines of the PRISMA method both inclusion and exclusion criteria were determined. Nearly 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 inclusion criteria. Similarly, the papers with more relevant content were chosen to be reviewed more precisely and those with less relevant content were removed from the inclusion criteria. All the processes of selection and deletion of articles are shown in detail in figure 1.

LITERATURE REVIEW

Wound healing biology

Following an injury, an inevitable chain of events will happen which include three main phases of inflammation, tissue formation, and tissue remodeling [10]. A few minutes following the injury, there will be an invasion of neutrophils, monocytes, and lymphocytes to the wound site which is known as the first phase. They protect protease and then reactive oxygen species that is essential for cleaning up cell debris through phagocytosis process. However, this invasion is a natural mechanism of the body to protect the wound site from any invading harmful microorganisms [11]. Moreover, this phase is the most important one for the production of appropriate growth factors and macrophages, within the cytokine network which is activated from monocytes. This phase acts as 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). The cytokines have a significant role in moderating the conversion between the primary phase of inflammation and the start of the tissue healing process two days following the injury [12]. About 2 days-7 days after the start of injury, the second phase starts which is the starting of wound healing process. The epidermal keratinocytes migration at the wound edge is the main sign for the start of this phase. Within this phase, the migration of fibroblasts and endothelial cells will happen to the clot, then the extracellular matrix will deposit and after that so-called granulation [13]. After phase two, the wound will be remodeled and fibroblasts will be converted into myofibroblasts which help to contract the wound. Within this phase, the Sedimentation of collagen will happen in abundance. The role of keratinocytes is to close the surface of the wound by a new epidermis. Within the third phase of wound healing, at first, granulation tissue will be transmitted to scar tissue, then the deposition of the consecutive layers of collagen will be seen, the scar will be remodeled that normally lasts a few months [14, 15].

The process of wound healing has many complicated interactions which mainly are moderated by molecules that act as both mediators and receptors. In this regard, these interactions play a crucial role in linking the wound healing steps. The mentioned proteins which were discovered in the seventh decade of 1900 are known as growth factors, and have a significant role in controlling natural process of wound healing. Various types of cells that have a role in tissue repair could synthesize and secrete growth factors which include fibroblasts, platelets, epithelial and inflammatory cells, and vascular endothelial cells [16, 17]. The shortage of growth factors disrupts the process of wound healing. Many factors could result in a deficiency of growth factors. For instance, in patients with diabetic ulcers, the shortage of production and secretion result in impairs wound healing [18]. Additionally, in patients with venous stasis ulcers, and burns the shortage of growth

factors could be observed as a result of macromolecular leakage of fibrinogen, a-macroglobulin, and albumin [19]. Gushiken et al investigated the growth factors involved in different phases of wound healing [20]. Based on their reports, during the healing process growth factors and cytokines act as regulator. It's while might cause abnormal scarring or/and impaired wound healing.

Mechanism of phisiological and pathological wound healing

As mentioned before, during the process of wound healing an interactive response will be sent to injured tissue. This process is a complex interaction that consisted of different types of cytokines, soluble mediators, and extracellular matrix molecules [21]. In this regard, one of the most fundamental understandings about the tissue repair process is being informed about signal, and temporal triggers and the way that wound healing process is controlled. Moreover, we should know about the main phases of the normal healing process of the wound which include; homeostasis, inflammation, granulation tissue formation, and remodeling. It should be noted that in all types of tissues the sequence of biological events in the wound healing process is the same [22]. Directly after the injury, the clotting cascade will be activated by limited proteolysis which could result in hemostasis which mainly includes platelet degranulation and polymerization of fibrinogen. Following that, extra serum and Cell-Derived Extracellular Matrices (CD-ECMs) accumulate at the wound site which mainly include vitronectin, thrombospondin, and fibronectin. This complex process simplifies forming a temporary matrix through which cells could migrate [23]. This matrix acts as a growth factor and reservoir of cytokines released from activated platelets. Due to the adherence of cells to the molecules of the extracellular matrix, the communication of cell-matrix could be mediated through various classes of cell membrane receptors which include the integrin's family [24]. Simultaneously, cytokines and molecules of the extracellular matrix create chemotactic cues for activating and recruiting certain tissue-resident and non-resident inflammatory cells which may enter to the wound site. The diffusion or accumulation of neutrophils, lymphocyte cells, and macrophages are mainly involved in the defense functions and starting process of granulation tissue formation which all happen through reactive oxygen species, cytokines, and the synthesis of strong protease enzymes such as elastase enzyme, Cathepsin G (CathG) protein, and proteinase 3 (PR3) enzyme [25]. During the formation of granulation tissue, the cellularity of the site will increase, and soluble mediators will be released from invading mesenchymal cells. Releasing soluble mediators motivate the migration of keratinocyte and the process of cell proliferation for achieving the reepithelization step [26]. On the other side, soluble mediators could be released from activated keratinocytes which are very important for both angiogenesis and fibroplasia steps as their main specification of granulation tissue formation. After restoring the total integrity of the tissue deficiency, inflammation will be resolved, then granulation tissue regresses, after that the scar tissue will form and finally the wound enters to the phase of remodeling. Several months following the last phase, a balanced situation will be created between the synthesis of the novel components of the scar matrix and their degradation by proteases [27].

The classical modelof wound healing

In the classical model of wound healing three phases overlapping each other. Cutaneous wounds cause a collection of cellular responses including coagulation, activation of platelet, infiltration of inflammatory cells, Re-epithelialization process, and finally granulation tissue formation which is created by fibroblasts and blood vessels [28] (Figure 2).

The process of wound healing in the skin starts with hemostasis specified through the appearance of platelets [30]. At the beginning of the healing process a platelet aggregation will be formed at the wound site and after that activated platelets release cytokines which has significant role in the healing of wound which include Platelet-Derived Growth Factor (PDGF) and Transforming Growth Factor-Beta (TGF-β). Following that platelet clots observed in the wound site, coagulation system enzymes will be activated there and the conversion of fibrinogen to fibrin will happen. A provisional matrix to simplify the healing process of tissue could be resulted from the prepared network [31]. Several hours following the formation of clots, the departure of keratinocytes to the site from the edges of the injury will be observed which is known to be the start of closing of

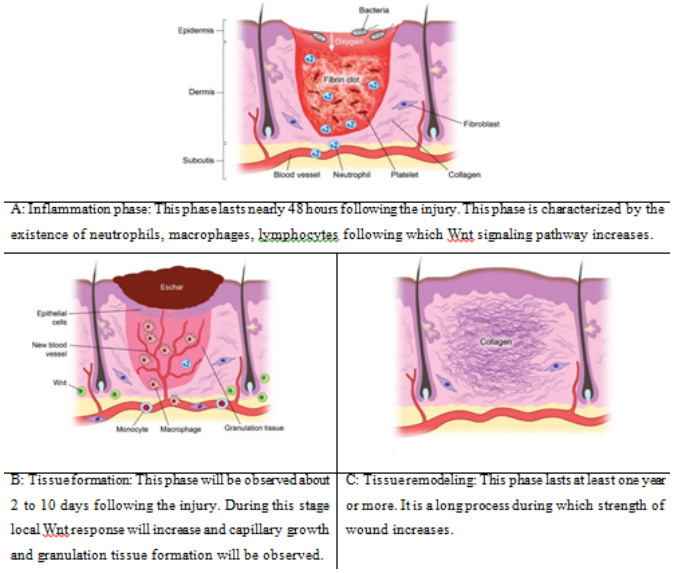

Fig. 2. Classical stages/phases of wound healing. Derived in accordance with [29]

the wound [32]. During the inflammatory phase of neutrophils, macrophages, and mast cells will appear. Neutrophil cells are the first which penetrate the wound site. After 24 hours, in the wound site neutrophil cells become the predominant leukocyte which helps in removing bacteria, damaged matrix, and foreign materials [33]. Following 48 hours' tissue macrophages will arrive and produce both growth factors and cytokines. Moreover, they have a significant role in deébridement and acts as phagocyte cells for removing matrix deébris. Activated macrophages were appeared simultaneously with the lymphocytes appearance. It is also a sign of inflammatory phase's end the beginning of proliferative phase in wound healing process [34].

Collagen, fibronectin, and proteoglycans are produced in proliferative phase which are essential in forming angiogenesis, continue epithelization, and extracellular matrix. Fibroblasts are predominant cells in proliferative phase which produce matrix and collagen. Platelet cells, macrophages, and T cells produce TGB-β which is strong stimulus of fibroblasts and has a significant role in the proliferative phase. Following the endothelial cells migrated to the fibrin matrix, the process of angiogenesis starts. Moreover, aimed to form new capillaries, the interstitial matrix should be degraded through endothelial cells. Angiogenesis process will be stimualted by basic Fibroblast gRowth Factor (bFGF), and Vascular Endothelial Growth Factor (VEGF) along with TGF-β. 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 mastocyte which manage the repair process of host wound by increased inflammatory signaling [35, 36].

Growth factors involved in tissue repair

Nowadays, numerous progress has been made in the knowledge of wound healing process. Following the progress of related literature various types of cells and their 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 [37]. In spite of the progression achieved in the comprehension of wound healing related science, there are many steps that 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. The healing process of incision created by a scalpel, tissue death caused by myocardial infarction, and trauma resulting from a bullet are all similar predictable reparative processes. Having the knowledge of the healing process of the damaged tissue and the effective factors in this process make it easy for surgeons to be ensured about achieving a suitable outcome from surgery [38].

Of the most common threads in the medical specialty are issue injuries. In this regard, having the knowledge of wound healing is mandatory to achieve a predictable sequence of events. Having a comprehensive knowledge about the total process of wound healing, the cells which has role in, and molecular signaling improves the optimization of this crucial process. Due to the advances happen in 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 wound healing process is having a great comprehension of the growth factors. These factors mainly include scarless wound healing and transplant of tissues engineered from progenitor cells [39].

The overall process of wound healing consisted of a complex cellular interaction between fibroblast cells, myofibroblasts 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 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 clinical setting for stimulate the process of wound healing [40].

Therapeutically application of growth factors

When wounds are chronic, due to the deficiency of growth factors the usage of growth factors will be developed widely. Therefore, improving the concentration of growth factors in the wound site at precise times intervals causes hopeful therapeutic approach. However, although this approach provides the possibility of improvement of wound healing rate with application of topical growth factors, the achievement of clinical trials has been limited [41]. Novel studies have introduced just one drug-using recombinant growth factor (recombinant human platelet-derived growth factor-BB (becaplermin) which is also confirmed by the US Food and Drug Administration. In a similar study by Matoori et al it was reported that recombinant human platelet-derived growth factor-BB could be used diabetic foot ulcers with a high confidence. They also described the way in which different growth factors affect various wound healing process which is composed of a complex and variable interaction between cells, soluble cytokine receptors, extracellular matrix, and blood elements such as plasma, red blood cells, white blood cells, and platelets [4 2 , 43].

The usage of single growth factors may just have a transient influence on the improvement of the process of wound healing. The proteins which regulates cell growth have been tested as a toll for increment of local concentrations of growth factors [44]. Anyway, producing such growth factors are labor-intensive and very expensive compared to vectors or plasmids applied for gene transfer. Proteolytic enzymes in the fluid and leukocytes of the wound may cause infection in the site of applied growth factors. Additionally, some active proteins would remain in the wound site following these interactions which causes diffusion into the wound tissue. Additionally, due to the fundamental role of growth factors in the controlling of wound healing process, multiple molecular genetic approaches will develop with a focus on the enhancement and stimulation of this protein group. In this regard, the novel studies are focusing on the current status of gene transfer using growth factor genes [45]. As mentioned in Table 1.

Gene transfer in wound healing

As a very precise and targeted tool, gene therapy is used to deliver tiny proteins to cells and tissues. Gene transfer has remarkable focus on skin and wound because they are easily accessible to be manipulated and inspected and the epidermis has capable of

Tab. 1. Growth factors which has a significant role in different phases of wound healing. Derived in accordance with [46]

Growth factors			Target	Effect	Source
Transforming Growth Factor (TGF) family	TGF-α		Mesenchyme and Epidermis tissues	Proliferation and Pleiotropic motility of Cells	Epidermal and Macrophage Cells
	TGF-β	TGF-β1-β2	Fibroblast and Keratinocyte Cells	Tensile Strength and Fibrosis	Macrophages and Platelets
		TGF-β3	Epidermis tissue	Anti-scarring effects	Macrophage
Fibroblast Growth Factor (FGF) family	b-FGF		Fibroblast cells	Wound vascularization	Epidermal and Macrophage Cells
	KGF (FGF-7)		Epidermis tissue	Proliferation and Pleiotropic motility of Cells	Fibroblast cells
Epidermal Growth Factor (EGF) family	EGF		Mesenchyme and Epidermis tissues	Proliferation and Pleiotropic motility of Cells	Platelets
	HB-EGF		Mesenchyme and Epidermis tissues	Proliferation and Pleiotropic motility of Cells	Macrophage cells

renewing itself. Long-term expression is achieved by a limited number of current gene transfer methods, which might be enough and satisfactory while treating wounds. Gene therapy of wounds involves two main challenges. First, the proper gene needs to be specified and, second, the specified gene needs to have an expression which produces proteins in the target area at therapeutic levels in a reliable and predictable manner [47, 48].

Both ex vivo or in vivo techniques can be used to perform gene therapy. Although these approaches are more expensive and burdensome, they are more precise, and in case of using selection methods, their transfection ratios might approach 100%. A number of the same vectors are utilized by in vivo techniques, to which a chemical or mechanical method is sometimes added to make the process easier [49].

Viral technigues

Elimination of particular structural genes such as those which are important for viral replication and replacing them with viral genome sequences result in the production of viral vectors. In spite of the efficiency of the methods, there is concern that the replication capacity of the virus might return as a result of homologous recombination [50]. During gene deletion, the size of the gene in the virus can also be a concern. Finally, in the clinical situation, the feasibility of repeated delivery of the gene might be restricted or eliminated by the immune reactions [51]. The most popular vector is the retroviral type which is utilized in more than one third of the trials. This vector has particular capability which result in a successful stable transfection. Anyway, retrovirus has a deficiency due to their sole usability which only could be used in vitro techniques for skin and wound cells' transplantation [52].

Regarding delivering genes to different systems of wound and skin in both in vitro and ex vitro settings, adenoviral vectors are abler. Its weakness is the high toxicity of the first generation of vectors and the induction of a strong immune reaction. Producing Helper-Dependent Adenovirus (HDAd) with deleted viral coding sequences eliminate some of these disadvantages. The adenoviral vectors are less able to provide stable transfection because they are not integrated into the host genome. Herpes simplex vectors and Adeno-associated virus vectors are employed in a more limited number of clinical protocols [53].

Non-viral techniques

With the purpose of introducing genes into target cells the technique of non-viral gene therapy (more physiological) have advanced rapidly. Non-viral vectors are reported to less inefficient; however, recent studies have demonstrated that functional alterations are exerted at low level of transgene expression by effective gene transfer approaches. Among the advantages of non-viral gene transfer systems are delivering genes to target cells without probable cellular damage as a result of persistence or repeated exposure to the viral vectors and their potential for being combined with wild type viruses [54]. Moreover, because such synthetic systems utilize plasmid constructs which can be grown with present fermentation technology, it is easier to manufacture them on a large scale. Among the most promising non-viral delivery systems are the following receptor-mediated delivery vectors, lipofection, and plasmid DNA (pDNA). There are some clinically inefficient non-viral transfection techniques, such as electroporation, laborious microinjection of DNA. In a recent study by Sarkar et al, a new and elegant non-viral approach was introduced for stabling transfect epidermal progenitor cells. A developed system based on streptomyces phage PhiC31-integrase was applied for putting the large human COL7A1 gene to keratinocyte cells in patients who are suffering from recessive dystrophic epidermolysis bullosa severe generalized (RDEB-sev gen). This approach, as a non-viral one may be very beneficial for delivering large genes [55].

Chemical and phisical transfer technigues

A large number of gene transfer techniques utilize naked or uncoated DNA. A 30-G needle, solid microneedles or gold DNA-coated particles accelerated into the tissue can be used to deliver it to the skin or wound. Despite their simplicity, these methods generally lead to lower yield than in vitro methods [56]. However, a higher rate of yields from in vivo transfection can be obtained if viral vector such as adenovirus is combined with physical techniques such as microseeding method which utilizes multiple oscillating solid needles. For certain applications like vaccination, adequate yields and great practicability have been reported as a result of in vivo particle-mediated gene transfer (gene gun). In chemical methods, cationic liposomes are used to create complex negatively charged DNA molecules [57]. In earlier studies, Diethylaminoethyl (DEAE)-dextran and calcium phosphate were

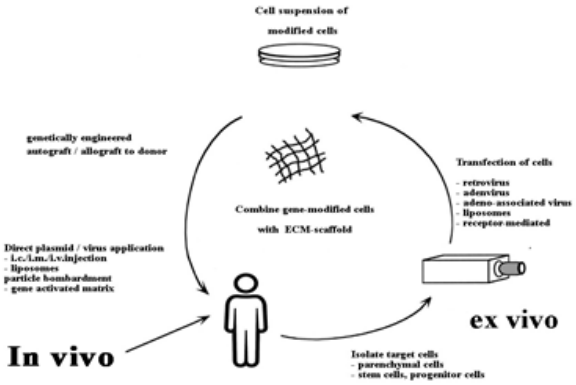

Fig. 3. The technologies of gene transfer that are used in the process of wound healing. In the cases of in vitro gene transfer, at first, the target cells are isolated from a small biopsy and then cultured. After obtaining an adequate number of cells, they will be incubated accompanied by viral and/or non-viral vectors which contain an interesting therapeutic gene. After that for ensuring an adequate number of transfected cells, cells could be selected. Then transgenic cells could be combined to the biodegradable natural matrix so that genetically engineered grafts could be transplanted to the donor. Derived in accordance with [64]

also used [58].

Gene therapy in tissue repair

Various technologies of delivery which are effective in gene transfer have been used in tissue repair which are studied and employed successfully nowadays in vivo and ex vivo gene therapy settings (Figure 3) [59]. Using ex-vivo approaches, the cells which are involved will be separated from the wound site, then manipulated in culture genetically. After that the cultured cells are will be transplanted back into the donor, which created a novel introduction of genetic material into a specific type of cell [60]. Recently numerous clinical trials have been done to examine the properties of parenchymal cells derivated from diverse tissues target cells for gene transfer. Anyway, any novel development in the culture conditions for non-differentiated progenitor cells, a more exciting target for gene transfer will be observed. Moreover, the overall function of gene-modified cells is improved in an ex vivo approach using the combination of biomaterials supporting cells with modified cells before transplantation [61]. 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 mainly is associated with the tissues in which cells could not be cultured or transplanted, like the nervous system [62]. In spite of the fact that in vivo approaches have some clear advantages, targeting genes to particular cells of a specific tissue will not be always easy. Based on the studies carried out recently, intradermally utilized 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 [63].

The most suitable genes for tissue repair

The process of management of the genes which have role in the healing process of wound, we should investigate the growth factors which specified to be suitable candidate's in the healing of tissue. According to the previous studies, it has been proved that effective pathogenic factors of non-healing wound environment are high level of protease enzymes of the wound [65]. Similary, a study by Fan et al it was reported that using recombinant TIMP-2 as an metalloproteinase (MMP) inhibitor improved the rate of wound healing the rat model [66]. In a study by Tocco et al, 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.

CONCLUSION

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

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