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Role of growth factors and biomaterials in wound healing

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ABSTRACT

Wound healing is a biological complex process that involves several cell types under the control and regulation of several growth factors and cytokines. There have been efforts to study the therapeutic effects of granulocyte-macrophage colony-stimulating factor, platelet-derived growth factor, transforming growth factor-β, vascular endothelial growth factor and basic fibroblast growth factor on chronic wounds. In addition, the effects of biomaterials such as nano-fibrous chitin and chitosan have been proven to be effective on wound healing. Furthermore, stem cell therapy using adipose-derived stem cells (ASCs) has been developed as a new therapeutic method for wound repair and healing. In this review, we will summarize the role of stem cells; growth factors and biomaterials in wound healing and repair.

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KEYWORDS

Wound healing; stem cells; biomaterials; growth factors; wound repair

Introduction

Wound healing is a normal biological process following a soft tissue injury and it’s a highly organized cascade of events that includes phases such as haemostasis, inflammation, proliferation and remodelling [1]. Therefore, interference with any of the four stages during the wound healing can result into an impaired healing process [2]. During chronic wounds, regeneration of tissue is arrested in the inflammatory stage that can result to pathologic inflammation and failure of initiation of advanced stages of wound healing [3]. Mulder et al. stated that there is an abnormal production of inflammatory cytokines when there is a prolonged inflammatory phase [4]. Hence, the increased presence of neutrophils can act as a marker for chronic wounds [5,6]. According to Guo et al. the extracellular matrix (ECM) has been degraded as a result of an increase in inflammatory cells and which ultimately leads to increase in secretion of matrix metalloproteinases (MMPs) and loss of vital growth factors necessary for proper wound healing [7,8]. Table 1 shows the important factors involved in chronic wounds.

Stem cells application in wound healing

Stem cells are cells that can retain prolonged self-renewal ability and can differentiate into numerous tissue types [9]. There are different sources of stem cells such as embryonic stem cells, induced pluripotent stem cells, bone marrow stem cells (BMSCs) and adipose-derived stem cells (ASCs) [10]. Various researchers have reported the use of stem cells as a potential wound healing agent in both preclinical and clinical cases, mainly in critical limb ischemia and diabetic wounds [11–13]. Aranguren et al. reported the administration of BMSCs and peripheral-derived mononuclear cells to patients with chronic wounds [13]. Topical delivery of bone marrow-derived mesenchymal stem cells (MSCs) on a collagen sponge scaffold has been reported by Yoshikawa et al. to show positive significant improvement in wound healing [14] in 18 of 20 patients. In other similar and separate clinical studies, autologous biograft and MSCs was demonstrated to improve a diabetic wound healing [15].

Adipose-derived stem cells role in wound healing

Park et al. [16] reported the examination of the secretion profile of ASCs in their study. They found out that the cells secreted by ASCs were transforming growth factor (TGF-β), vascular endothelial growth factor (VEGF), keratinocyte growth factor (KGF), fibroblast growth factor 2 (FGF2) [17], fibronectin and collagen 1 [18], and these factors have been said to speed up the process of wound healing in normal and chronic wounds [19]. In another preclinical study of chronic wound, a mouse model is used to evaluate the efficiency of ASCs [20] full-thickness skin wound. Histological examination was done and it showed a prolonged healing time, increased epithelialization rate, increased rate of granulation tissue formulation and higher capillary formation rate when compared with control groups [21]. Altman et al. [22] reported that seeded ASCs on silk suture could be efficient in closing full-thickness skin wounds in mice (Table 2). ASCs can enhance tissue regeneration by either differentiating into skin type cells or by secreting paracrine factors, which results into initiation of healing process or inhibiting inflammatory response (Figure 1).
Adipose-derived stem cells and growth factors

ASCs have been reported to secrete several growth factors such as insulin-like growth factor (IGF), hepatocyte growth factor (HGF), transforming growth factor-beta 1 (TGF-β1) and vascular endothelial growth factor (VEGF) [23]. ASCs also secrete factors in vitro that can stimulate proliferation of fibroblasts and keratinocytes. Wu et al. [24] demonstrated that injection of BMSCs markedly improved the closure of wound and strength in diabetic mouse model for wound healing. In another similar study, conditioned medium (CM) derived from BMSCs have been reported to enhance wound-healing response by Kim et al. They concluded in their study that CM derived from BMSCs increased collagen synthesis thereby leading to enhanced wound healing [18].

Table 1. Factors affecting chronic wounds.

<table>
<thead>
<tr>
<th>Specific factors</th>
<th>Physiological factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure of wound to bacteria, viral or parasitic infections</td>
<td>Aging process can lead to development chronic wound</td>
</tr>
<tr>
<td>Reduced blood and oxygen flow to a wound</td>
<td>Chronic diseases such as cancer and genetic disorder diseases.</td>
</tr>
<tr>
<td>Presence of cancerous cells</td>
<td>Presence of alcohol and cannabis</td>
</tr>
<tr>
<td>Exposure of wound to radiation</td>
<td>Taking harmful drugs can lead to chronic wound</td>
</tr>
<tr>
<td>Trauma</td>
<td>Nutritional deficiencies</td>
</tr>
<tr>
<td>Secretion of local toxins</td>
<td>Presence of urea in the blood</td>
</tr>
<tr>
<td>Arterial/venous insufficiency</td>
<td>Impairment in the functions of the peripheral nerve</td>
</tr>
</tbody>
</table>

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Table 2. Showing applications of ASCs in wound healing.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>[11]</td>
<td>Shows the application of ASCs in the formulation of collagen gel</td>
</tr>
<tr>
<td>[24]</td>
<td>Demonstrated the use of ASCs in the design of an atelocollagen scaffold</td>
</tr>
<tr>
<td>[47]</td>
<td>Demonstrated the use of ASCs in the design of a silk fibroin scaffold</td>
</tr>
<tr>
<td>[23]</td>
<td>Reported the injection of ASCs</td>
</tr>
<tr>
<td>[18]</td>
<td>Reported the direct injection of ASCs</td>
</tr>
<tr>
<td>[29]</td>
<td>Reported the injection of ASCs</td>
</tr>
<tr>
<td>[21]</td>
<td>Reported the application of noncultured ASCs in the formulation of an atelocollagen matrix</td>
</tr>
<tr>
<td>[30]</td>
<td>Reported the use of ASCs in platelet-rich plasma</td>
</tr>
<tr>
<td>[32]</td>
<td>Demonstrated the direct injection of ASCs into chronic wounds</td>
</tr>
<tr>
<td>[33]</td>
<td>Demonstrated the direct injection of ASCs into chronic wounds</td>
</tr>
<tr>
<td>[34]</td>
<td>Demonstrated the injection of ASCs into flap</td>
</tr>
<tr>
<td>[38]</td>
<td>Demonstrated the direct injection of ASCs around the wound site</td>
</tr>
<tr>
<td>[40]</td>
<td>Reported the use of ASCs in the formulation of collagen gels</td>
</tr>
<tr>
<td>[42]</td>
<td>Showed the application of ASCs on acellular dermal matrix</td>
</tr>
<tr>
<td>[43]</td>
<td>Formulated a conditioned medium of genetically modified ASCs</td>
</tr>
</tbody>
</table>

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Figure 1. Showing potential mechanism of skin repair by ASCs. This figure was adapted from [46] with copyright permission.
Galiano et al. [25] also in their study demonstrated that VEGF can possibly enhance wound healing in a genetically diabetic mice model. The healing process was confirmed by the angiogenesis in the wound bed and recruitment of BMSCs [26].

**Clinical application of adipose-derived stem cells**

Clinical application of ASCs as a therapeutic alternative is widely adopted because it's easy to harvest fat tissue, abundant and ethical concerns does not in fact exist [27]. Recently, ASCs have been reported to be efficient in preclinical studies of chronic wounds and as such ASCs studies have progressed from translational phase into clinical trials [28]. Table 3 shows the use of ASCs in various available clinical trials [29]. Lendeckel et al. [30] were among the first researchers to report the clinical use of ASCs usingstromal vascular fraction (SVF) in a case report to treat calvaria defect after head injury. In their report, they used fibrin glue combined with SVF [31]. They concluded that there was newly formed cranial bone after three months post-surgical treatment and there were also clear evidences of near total healing of calvaria defect. Mesić et al. in their study, reported that ASCs combined with bone morphogenetic protein (BMP-2) and tricalcium phosphate scaffold resulted in effective healing of osteogenic defect [32]. The management and treatment of Crohn’s disease has been reported to be achieved via the administration of ASCs [33].

**Growth factors and the process of wound healing**

**Platelet-derived growth factor (PDGF)**

PDGF plays a vital role in each phase of wound healing process. As reported by Trengove et al., PDGF is released from de-granulating platelets following an injury into the wound fluid [34]. PDGF initiates inflammatory response by stimulating mitogenicity and chemotaxis abilities of cells such as neutrophils, macrophages, fibroblasts and smooth muscle cells to the site of the wound [35]. The role of PDGF has been identified during the epithelialization stage of wound healing to up-regulate the production of growth factors such as insulin growth factor (IGF)-1 and thrombospondin-1 and inturn IGF-1 increases the motility of keratinocyte cells and

<table>
<thead>
<tr>
<th>Biomaterials</th>
<th>Cells/Animals</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chitin</td>
<td>Fibroblast</td>
<td>Chitin demonstrated no positive effects on proliferation</td>
<td>[50]</td>
</tr>
<tr>
<td>Chitin</td>
<td>3T6</td>
<td>Migratory process is inhibited by chitin, chitosan.</td>
<td>[51]</td>
</tr>
<tr>
<td>Chitin</td>
<td>HUVECs</td>
<td>Migratory actions were improved by chitin and chitosan.</td>
<td>[51]</td>
</tr>
<tr>
<td>Chitin</td>
<td>Bovine PMNs</td>
<td>The biomaterials activated bovine poly morphonuclear cells</td>
<td>[51]</td>
</tr>
<tr>
<td>Chitin</td>
<td>Canine PMNs</td>
<td>The biomaterials activated canine poly morphonuclear cells</td>
<td>[52]</td>
</tr>
<tr>
<td>Chitin</td>
<td>Canine PMNs</td>
<td>They are induced complement-mediated chemotactic actions</td>
<td>[53]</td>
</tr>
<tr>
<td>Chitin</td>
<td>Macrophage</td>
<td>Chitin is a size-dependent stimulator of macrophage IL-17A production and its receptor expression</td>
<td>[55]</td>
</tr>
<tr>
<td>Chitin</td>
<td>Dog</td>
<td>Numbers of MN and poly-morphonuclear neutrophil cells were bigger in the chitin group than in the control group.</td>
<td>[56]</td>
</tr>
<tr>
<td>Chitin-sponge</td>
<td>Dog, cow, cats</td>
<td>Chitin-sponges were used in 30 study cases as filling agents for surgical tissue defects.</td>
<td>[57]</td>
</tr>
<tr>
<td>Chitin-cotton</td>
<td>Dog, cow, cats</td>
<td>Chitin-cotton was used in 8 cases of trauma and 12 cases of abscess as a wound dressing</td>
<td>[57]</td>
</tr>
<tr>
<td>Chitin-flake</td>
<td>Dog, cow, cats</td>
<td>Chitin-flake was used in 9 cases of trauma as a wound dressing</td>
<td>[57]</td>
</tr>
<tr>
<td>Chitin/NWF</td>
<td>Dog</td>
<td>The quantity of PGE2 in the exudate induced by chitin was about five times as high as that in the exudate induced by chitin.</td>
<td>[56]</td>
</tr>
<tr>
<td>Chitin</td>
<td>Dog</td>
<td>Chitin activated the complement components C3 and C5, but not C4</td>
<td>[58]</td>
</tr>
</tbody>
</table>

Adapted from [49] with copyright permission.

<table>
<thead>
<tr>
<th>Growth factor</th>
<th>Brand name</th>
<th>Administration</th>
<th>Wound type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recombinant human granulocyte-macrophage colony-stimulating factor</td>
<td>Leukine</td>
<td>Subcutaneous injection</td>
<td>Chronic venous ulcers</td>
</tr>
<tr>
<td>Recombinant human granulocyte colony-stimulating factor</td>
<td>Leucomax</td>
<td></td>
<td>Second-degree burns</td>
</tr>
<tr>
<td>Recombinant human platelet-derived growth factor</td>
<td>Telbermin</td>
<td>Topical</td>
<td>Diabetic foot ulcers</td>
</tr>
<tr>
<td>Recombinant human vascular endothelial growth factor.</td>
<td>Regranex</td>
<td>Topical</td>
<td>Pressure ulcers</td>
</tr>
<tr>
<td>Recombinant human basic fibroblast growth factor.</td>
<td>N/A</td>
<td>Topical</td>
<td>Pressure ulcers</td>
</tr>
</tbody>
</table>

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thrombospondin-1 inhibits proteolytic and enzymatic degradation of PDGF [36]. Becaplermin is an FDA rh-PDGF approved drug for the treatment of DFUs and has shown to fast-track the process of wound closure in DFUs in randomized clinical trials (Table 3).

**Fibroblast growth factor (FGF)**

Several members of the fibroblast growth factor family (FGF) have been reported to play important roles in the process of wound healing [37]. The sources of FGFs are keratinocytes, fibroblasts, endothelial cells, smooth muscle cells, chondrocytes and mast cells [38]. Di Vita et al. stated that during acute wound, there is a rise in the production of FGF-2 and are said to be responsible in granulation tissue formation, re-epithelialization and tissue remodelling [39]. Furthermore, synthesis and deposition of several extracellular matrix constituents and increased keratinocyte motility in vitro studies are regulated by FGF-2 [40]. Table 3 shows the use of FGF in available clinical trials [41].

**Vascular endothelial growth factor (VEGF)**

VEGF family consist of several members, and one of its member such as VEGF-A initiates the process of wound healing by promoting biological processes and events such as early angiogenesis and especially migration of endothelial cell [42]. Administration of VEGF-A has been reported to restore impaired angiogenesis process in diabetic ischemic limbs in an animal model as well as improving re-epithelialization process of diabetic wounds [43]. Table 4 shows randomized controlled trials using several VEGF-based therapies for wound healing.

### Biomaterials and wound healing process

Various reports on the useful effects of biomaterials such as chitin and chitosan for wound healing have surfaced recently [44]. Chitin and chitosan are the most applied biomaterials for wound healing, and recently isolation and production of nanofibrillar chitin and chitosan have been formulated and as such the use of chitin and chitosan has been exhibited in wound healing [45]. Table 5 and 6 represent the summary of the various uses of chitin and chitosan for wound healing, respectively.

**Conclusions**

Biomaterials such as chitosan and chitin have been established to be an efficient biomaterial to stimulate wound healing. Various studies have reported that these biomaterials are non-toxic, biodegrading slow rate and biocompatible material that make chitin and chitosan important biomaterials for wound healing. The use and administration of growth factors and cytokines have been described to be necessary for the initiation and regulation of the process of wound healing and can also serve as a potential therapeutic alternative for healing wounds. Growth factors such as GM-CSF, PDGF, bFGF and VEGF have been shown to be a potential therapeutic means for wound healing in various randomized controlled trials. However, there is still need for larger randomized controlled trials to be carried out to investigate side-effect profiles and long-term effects. Furthermore, pre-clinical studies have shown that ASCs are effective for wound healing in animal models of chronic wounds. However, ASCs are said to secrete growth factors, cytokines and chemo-attractants that can promote the process of angiogenesis and increase blood supply thus supporting the tumour growth as such; more research work and clinical studies are still needed to extensively investigate this side-effects.

**Disclosure statement**

There is no conflict of interest in this paper.

**References**


