An insight into the role of growth factor in wound healing

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ABSTRACT

Wound healing is a well-orchestrated and firmly restricted process in which numerous cell types, cytokines and growth factor have effect in a systematic manner. Any split in this process would cause hindrance in healing process which would enhance hospitalization time, expenditure, death and morbidity. The researchers especially Scientists and clinicians are demanding to discover efficient, safe and sound and economical process for the treatment as well as management of acute wound and non-healing chronic wound. Medicinal herbs have been extensively explored and achieved significant attention because of its essential curative compounds. In current day's significant improvement have been made in to explore the knowledge and perceptive of growth factors. By nature the growth factors are proteins which correspond to the activities to cells. The function of the growth factors reliant on the receptor site they attach to. Growth factors were primarily known for the various kind of reaction produced by them, but innovative research has revealed that numerous of these cells might achieve various kinds of reactions. In wound repair, the growth factor is a significant factor of the thriving healing of the wound. The growth factors may facilitate the regulation of several activities and pathways which is implicated in healing. The role of growth factor is a developing quarter of science which recommends the prospective for wound management substitutes.

Keywords: Wound; wound healing; growth factor; acute wound; chronic wound

Introduction

The wound is defined as the interruption of regular anatomy of structure and function of the body. As per the wound healing society the healing process may be defined as a multifaceted energetic process that consequence in the re-establishment of anatomic stability and function [1]. Wound healing is an enthralling biologic episode which is necessary for endurance of human being. A systematic understanding of the physiology of wound healing is an important prerequisite to provide the efficient treatment and care which may lead to optimize wound healing followed by its complications. This wound is mostly classified in to acute and chronic depending upon the nature of healing process. Acute wounds are characterized as tissue damage or injury caused by any types of physical or surgical cuts and the healing process may take a definite time period. Chronic wounds are characterized as the tissues damage which may heal lethargically due to repeated invective to the tissue as well as other pathophysiological conditions. Tissue repair of the wound comprises of a series of overlapping proceedings which may start straight away following wound formation. The first process after wounding is hemostasis, inflammation and migration of cell. Second phase is characterized as tissue rebuilding followed by matrix deposition and angiogenesis. And the final phase is known as the remodeling of tissue which involves the matrix contraction and cell maturation and its death [2].

Growth factors play a vital role for the better wound healing due to its exclusive ability for the stimulation of cell division especially mitosis of quiescent cells. Form the literature survey, it was found that the growth factors are categorized into five different groups such as; (i) platelet derived growth factor, (ii) epidermal growth factor, (iii) fibroblast growth factor, (iv) transforming growth factor-$^{\beta}$, (v) vascular endothelial growth factor. The platelet derived growth factors are found in the fibroblast, endothelial cell, macrophages and platelet which are mitogenic for vascular smooth muscle as well as fibroblast. The epidermal growth factors are available in almost all body fluids as well as platelet which are mitogenic for most epithelial tissue, fibroblast and epithelial cell. Another important one is fibroblast growth factor which is found in fibroblasts, bone cells, astrocytes, smooth muscle, and endothelial cell which targets for

mesenchymal and neural cell. The transforming growth factor-β is an important growth factor which is located in the platelets, lymphocytes, macrophages, fibroblasts, keratinocytes and bone cells. This growth factor inhibits in-vitro replication of most cells including endothelial cells; keratinocytes and this may stimulate and inhibit fibroblast secretion. The vascular endothelial growth factor is found in pituitary cells, which only target the mitogenic endothelial cell [3].

Platelet-derived growth factors (PDGF) stimulate DNA synthesis and chemotaxis of fibroblasts and smooth muscle cells along with collagen, glycosaminoglycan, collagenase production by fibroblasts. These in-vitro properties recommend that PDGF, which is delivered by platelets to the wound site, may take part in an imperative role in the beginning of the healing process of wound [4].

Epidermal growth factor (EGF) is a polypeptide consists of 53 amino acids that was initially isolated from the sub-maxillary gland of mouse by Stanley Cohen in 1962 and got the Nobel Prize winning. The EGF family consists of four proteins: EGF, TGF-alpha, heparin-binding EGF, and amphiregulin. EGF exhibited great promise for enhanced wound healing but may be harmful due to the restricted effect in chronic wound healing in association with invasive neoplasm [5].

The fibroblast growth factor (FGF) group contributes to the regulation of practically every characteristic of improvement and organogenesis, and subsequent to birth to tissue maintenance, in addition to meticulous feature of the physiology of the organism. From in-vivo study it was evaluated that FGF 2 may be responsible for significant decrease in healing time, improvement of scar quality [6].

The TGF-β family comprises of TGF-β -1, TGF-β - 2, TGF-β -3, bone morphogenic proteins i.e., activin A, activin B, and activin C, growth differential factors, and anti-Mullerian hormone. Macrophages, fibroblasts, keratinocytes, and platelets are the principal resource of production of these factors. The release of TGF-β1 at before time period of the wound healing process timely conscript inflammatory cells into the wound site which are later implicated in a negative feedback through release of superoxide from macrophages. Additionally, TGF-β1 advances the angiogenic properties of the endothelial progenitor cells to assist blood supply to the wounded area and stimulates tightening of fibroblasts to facilitate wound closure. The

migration of keratinocytes is also upheld by TGF- β 1 through the regulation of cell migration. TGF-β 1 is one of the major collagen-stimulating factors, particularly for type I in fibroblasts. Both TGF-β1, TGF-β2is implicated in the conscription of both fibroblasts and immune cells from circulation and the wound boundaries into the injury site. These proceedings direct towards production of granular tissue, angiogenesis, and collagen synthesis [7].

VEGF (vascular endothelial growth factor) mainly regulates the angiogenesis process in wound healing. It is secreted by tissues in response to ischemic and inflammatory stimuli and consequences in endothelial migration, proliferation, and improved vascular permeability. The VEGF expression is regulated throughout wound healing which is most vital while angiogenesis show to be troubled in the healing process of abnormal wounds [8].

The role of growth factors in various phases of wound healing process

The process of wound healing starts at the instant of injury and involves both populations of resident as well as migratory cell, extracellular matrix and the action of soluble mediators. The mechanisms behind the healing process is explained, which consists of (1) inflammatory mediators and growth factors; (2) cell–cell and cell–extracellular matrix interactions that manage cell proliferation, migration and differentiation; (3) proceedings involved with epithelialization, fibroplasia and angiogenesis; (4) wound contraction; and (5) remodelling. These mechanisms are began at the instance of physical injury and continue constantly during the repair process of wound [9].

The healing process of wound mainly comprises of four interrelated and overlapped phases such as; homeostasis, inflammation, proliferation and remodeling, and any kind of faults in the respective phases may unconstructively manipulate this process. Usually wound care products put impact to this process by enhancing one or more of these phases. An ultimate wound healing promoting agent should have an effect on all phases and also have antimicrobial property for the prevention of promising contamination at the injured region. In this context, few wound care products restrain assorted growth factors as well as antibiotics in the marketplace. In particular, various cicatrizing drugs having antimicrobial activity such as Dexpantenol® and Hametan® are being preferred to use in the dermatology clinics. Apart from these clinically

preferred and patented drugs, different plant extract and their formulations has been anticipated as an alternative therapy for acute and non-healing wounds [10].

The Growth factors are concerned with cell division, migration, differentiation, protein expression as well as production of enzyme. The healing properties of growth factors are intervened during the stimulation of angiogenesis process and cellular proliferation. That influences both synthesis and deprivation of the extracellular matrix. It is also plays a part in cell inflammation and fibroblast activity. Consequently growth factors may influence the inflammation, proliferation and migration phases of healing. A mixture of growth factors have been informed which take part in the wound healing including epidermal growth factor (EGF), platelet derived growth factor (PDGF), fibroblast growth factor (FGF), transforming growth factor (TGF-$^{\beta}$1), insulin-like growth factor (IGF-1), human growth hormone and granulocyte-macro- phage colony-stimulating factor (GM-CSF) [11].

The permeation of cells at the site of injury happens subsequent to the invasion of monocytes into the wound tissue and their differentiation into macrophages. Macrophages can also supply numerous growth factors and pro-inflammatory cytokines such as IL-1α and IL-1β, TNF-α, platelet derived growth factor (PDGF), TGF-α, keratinocyte growth factor, and vascular endothelial growth factor (VEGF). It is significant to note that inflammation can cause either beneficial or critical effects throughout management of several diseases, and therefore, manage over inflammation is extremely essential. Based on the a range of growth factors and cytokines concerned in ordinary and acute wound healing process, the mechanism of modulation of inflammatory processes in wound repair should be cleared for many types of prescribed drug [12].

The molecular mechanism of damaged cell in healing process

In response to macrophage-synthesized growth factors such as PDGF, FGF, VEGF, TGF-a, TGF-b, KGF, etc., the fibroblasts, a serious constituent of granulation tissue, start to transfer, proliferate and produce the components of extra cellular matrix, such as glycosaminoglycans and proteoglycans, and collagen, a critical incident in the proliferation phase of healing. Collagen is released to the extracellular space in the form of pro-collagen and then chopped in to terminal segments, which is known as tropo-collagen. Tropo-collagen can combine with new tropo-

collagen molecules to form collagen filaments that are rich in hydroxylysine and hydroxyproline moieties and allow it to shape strong cross-links. The immovability of the collagen fiber depends on the intermolecular cross-links that create collagen fiber resistant to destruction. The more cross-links in intra-molecular and inter-molecular of collagen, the more improved full potency in wound healing. As a result, collagen produces tight cross-links to other collagen and with protein molecules by escalating the tensile strength of the healing wound. In additional we recognize the hydroxylation of proline and lysine residues depends on the presence of oxygen, vitamin C, ferrous iron, and a-ketoglutaric acid. Collagen fibers are deposited in a structure of fibronectin which serves as an anchor for the myofibroblast that migrates in some wound healing.

Cell differentiation is a method, which is distinguished by the loss of intrinsic and particular phenotype of a cell and the alteration of a novel phenotype into another, which is distinguished by vary in phenotype, morphology and function. The growth factors are essential messengers for cell transition such as mesenchymal-to- mesenchymal transition and endothelial-mesenchymal transition that could occur by TGF-$^{\beta}$ signal pathway or by Notch signal pathway which restrains the regulation of endothelial cell adhesion molecule VE-cadherin. The epithelial-mesenchymal transition (EMT) is the communication for the establishment of the promising basement membrane and consequent re-epithelialization. It plays an vital role in wound healing. Sensible EMT can hasten wound healing and the irregular regulation of EMT is intimately associated with hypertrophic scar and tissue fibrosis. The outcomes showed that the epithelial cells put on mesenchymal phenotypic characteristic and stronger ability in movement and relocation, where b2-AR is a vital molecule which mediates EMT process.

Enormous manipulation in molecular biology in non-healing wounds has been identified in the past years. The effects comprise hyperglycemia, reduce or impaired production of cytokines, growth factors and their receptors that hinder the function of cells such as macrophage, angiogenic response, collagen accumulation, quantity of granulation tissue, keratinocytes and fibroblast migration and proliferation, number of epidermal nerves. [13]

Growth factors in complicated and challenged wound healing

Growth factors are categorized in to different types of cytokines which are proteinaceous in nature and act as internal cellular signals to allow cells to communication. Generally, the

growth factors are the subclass of cytokines which is meant for proliferation, stimulation and migration of cells and new tissue production. The variety of cytokines is from 6kD to 70 kD and they express cellular behavior when they are available in little quantity. Cytokines may control cellular activities and function via endocrine, paracrine, autocrine, and intracrine mechanisms. Consecutively for a meticulous cytokine to alter a cellular activity, the target cell must have a receptor. Once receptor binding takes place, then a cascade of intracellular signals are activated and ultimately consequences in a precise response. Inside a healing wound, a mixture of proteins has been recognized that reveal special properties significant for wound repair. One group of proteins has been known as growth factors although their actions are not limited to prompt the growth. Actually, the term is preferred to tag the growth factors is frequently ambiguous as the names were consequential from tissues in which the factors were originally recognized. A frequently mentioned case of the outdated method in which growth factors are tagged is PDGF. PDGF was initially recognized as the granules of platelets, but in view of the fact that has also been found in macrophages, endothelial cells, and smooth muscle cells. Several proteins are accomplished of both chemotactic and mitogenic functions. For that reason, they are imperative in determining both the progression of cells in the "healing module" and their respective functional activities. A number of growth factors for epithelial refurbish are indistinguishable to those liable for hard tissue regeneration [14].

The curative objective of growth factors for the advancement wound healing process

Different medical approaches and curative intrusions can impinge on the several processes implicated in the wound healing. Next to wound healing, the healing period might be diminutive or reduced when there is less injured tissue. New practices of topical growth factor function and incision priming with PDGF or IL-1 can optimize the cellular and molecular environment equally by reducing healing time. Electrical Field stimulation might optimize the remodelling phase by upholding extra competent fibroblast recruitment and collagen deposition, prosthetic materials can help in tissue repairing, and gene therapy, which is presently in pre-clinical improvement, may be able to afford a method for discriminating healing. Every wounding compensates the tissue and changes the local surroundings. The reaction of host to wound consists of numerous processes of tissue healing which are triggered by tissue injury, and includes four uninterrupted phases including coagulation and haemostasis, inflammation,

proliferation and wound remodelling with scar tissue deposition. Accurate clinical management could absolutely persuade the wound healing process and diminish probable impediments [9].

Advances in the ground of materials science in combination with the most favorable treatment of growth factors and cytokines is necessary in order to improve chronic wound healing, mainly in the case of burn wound management. In particular, the hindrance of scarring, keloid formation or contractures, and cosmetically satisfactory healing is still a dispute [15].

Conclusions

A number of clinical studies have been performed and concluded that, the growth factors have a greater impact on the each phases of healing process of wound by coordinating the interaction of cells present within the wound. Even though potential early on studies treating chronic wounds with growth factors, consequences with conventional bolus dosing of a single growth factor have yielded insignificant results due to short half-life, a intimidating microenvironment loaded in protease activity, and deprived delivery mechanisms failing to transport valuable dosages in an appropriate temporal manner. This recommends that, inhibitions or up- regulation of growth factors in the phases of healing process is considered which may be a possible therapeutic approach for better advancement of wound healing. Progress in tissue engineering and regenerative medicine has provided technologies proficient of delivering various growth factors in a spatially oriented approach. These technologies comprise of polymer systems, scaffolds, and hydrogel that have confirmed enhanced response by target tissues when growth factors are delivered in this biomimetic manner. Treatment of chronic wounds with growth factors has the potential to accelerate healing with improved delivery systems in a manner as compared with traditional delivery systems.

ACKNOWLEDGEMENT

The authors are thankful to Centurion University of Technology and Management, and Siksha ‘O’ Anusandhan Deemed to be University Bhubaneswar, Odisha, India for providing support and encouragement to carry out the scientific work.

CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest in this study. The authors are responsible for the content and writing of the manuscript.

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