Xournals

Academic Journal of Biotechnological Research

ISSN UA | Volume 01 | Issue 01 | May-2018

Growth Factors of Platelet-rich Plasma in Wound Healing

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Available online at: www.xournals.com

Received 12th December 2017 | Revised 19th February 2018 | Accepted 21st April 2018

Abstract:

Autologous platelet rich plasma is an advanced wound therapy to treatment for chronic wounds diseases. These increase of chronic degenerative diseases associated with ageing makes wound care a tremendous socio-economic burden. There is need to develop wound healing therapies to improve cutaneous wound healing. Due to low-invasive procedures, use of regenerative therapies which is becoming increasingly popular and needed to apply them. Platelet-rich plasma (PRP) is gaining interest due to its potential to stimulate and accelerate the wound healing process. In healing process, growth factors forming PRP play a crucial role. In this paper, discuss about the growth factors in the context of overall repair process on cutaneous wound which concluded with the summary of preliminary results from human clinical trials evaluating the effects of growth factors in healing of chronic wound disease.

Keywords: *Wound healing, platelet-rich plasma, growth factors, therapies*

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Introduction

Vertebrates have the largest organ that is skin, including 10% of the total body mass and covers the entire surface area. Skin play an important role in defense and survival which has self-repairing and self-renewing capacity, acting as an important barrier from outer environment to the inner environment. If skin occur disturbance of normal anatomic structure and functional integrity can be described as a wound. Wound healing is a complex and dynamic process mediated by interacting molecular signals involving mediators and cellular events. When wounds start healing, normally process are resolve with complete wound closure and these healing of acute and chronic wounds can become impaired by patient factors and wound factors. Restarting a wound with impaired healing is difficult because good standard wound care cannot always provide an improved healing outcome and advanced therapies.

Platelet-rich plasma is defined as a portion of plasma fraction of autologous blood having a platelet concentration above baseline. It is also referred to as platelet-enriched plasma, platelet-rich concentrate, and autologous platelet gel and platelet releasate. Platelet rich plasma (PRP) gel is advanced endogenous therapy for chronic and acute wounds. PRP gel has been used to stimulate wound healing for more than 20 years. Cytokines, growth factors, chemokines, and a fibrin scaffold derived from a patient's blood that is consist into autologous PRP gel. There are several growth factors which are involved in wound healing process such as platelet-derived growth factor (PDGF), epidermal growth factor (EGF), fibroblast growth factor (FGF), insulin-like growth factor (IGF1, IGF2), vascular endothelial growth factor (VEGF), transforming growth factor (TGF-β), and keratinocyte growth factor (KGF).

Growth Factors

Polypeptide growth factor may be defined as agents that promote cell proliferation and metabolism through interaction with specific cell membrane-bound receptors. Migration of cells into wound space by induce of protein, serving as chemoattractants to recruit important cells such as leukocytes and fibroblasts into the wounded area. Growth factors have biological activity that can vary widely.

All growth factors are discuss here which is continues to expand.

Platelet-Derived Growth Factor (PDGF)

Structure and Source

It is store into the alpha-granules of circulating platelets and released at wound sites during blood clotting and it may synthesized at cutaneous wound sites by infiltrating macrophages and epithelial cells and fibroblasts. In serum, PDGF is the major mitogen for fibroblasts and it is a strongly cationic polypeptide of molecular weight and composed of two non-identical polypeptide chains that is linked by disulfide bonds. Mitogen activity is destroy by reduction of disulfide bonds and it generates two individual protein species. Two distinct reveals by sequence analysis but related sequences of these species, suggesting that PDGF from human platelets is a heterodimer of two chains.

PDGF exists in three isoforms: PDGF-AA, PDGF-BB, and PDGF-AB. PDGF-AA and PDGF-BB chains consist of two disulfide-linked homologous polypeptide chains. A and B chain share 60% homology to each other. PDGF-B chain is encoded by the c/sis oncogene localized on chromosome 22, whereas the PDGF-A chain is encoded by a gene on chromosome 7.

Biological Function of PDGF in vitro and vivo

In vitro, PDGF applies effective and diverse effects on target cells expressing the specific PDGF receptors. PDGF major vitro function is to induce mitogenesis in quiescent target cells of mesenchymal origin, such as diploid fibroblasts, osteoblasts, fibroblasts periodontal ligaments (PDL), arterial smooth muscle cells and brain glial cells.

In vivo, researchers have reported that acute skin injury in swine induces the controlled co-expression of PDGF and PDGF receptor mRNAs and their respective protein products in skin epithelial cells and connective tissue fibroblasts. It molecules are secreted by monocytes, macrophages and injured endothelial cells which is responsible for continuation of the repair process. Use of PDGF on wound healing in vivo were contradictory and the studies of use of PDGF in Syrian hamster model indicated that there were no significant influence on the rate of wound contradiction or on the time to complete healing to full-thickness wound.

Transforming Growth Factor (TGF-β)

Structure and Source

TGF-β belongs to a large family of biologically active polypeptide factors which is share certain structural and functional characteristics. It includes the TGF-β supergene family members that is activins and inhibins, Mullerian-inhibiting substances in mammals, decapentaplegic gene product (DPP-C) which found in Drosophila, and many of the bone morphogenetic proteins. These protein share 25 to 35% sequence homology with TGF-β. It contain the three different gene products of TGF-β that is TGF-β_1, TGF-β_2 and

TGF-β_3 which has been only identified recently and share 80% homology with TGF-β_1 and TGF-β_2.

Biological function of TGF-β in vitro and vivo

In vitro, TGF-β has been shown in mitogen for osteoblasts and Schwann cells of the peripheral nervous system. It is inhibit the proliferation of epithelial cells and endothelial cells that is along with the growth of T and B lymphocytes. On cell proliferation, effects of TGF-β dependent to a large degree on which other growth factors are operating in that cell environment. But in vivo, TGF-β plays a key role in wound repair that is localization at site of acute injury with its chemotactic properties for inflammatory and connective tissue cells and its stimulatory effect on deposition of connective tissue matrix.

Fibroblast Growth Factors (FGF)

Structure and Source

FGFs are a class of heparin-binding proteins that include mitogenic, chemotactic, or angiogenic activity in a variety of cells, including epithelial, mesenchymal, and neuronal cells. Basically two principals are identified in two forms that is basic FGF and acidic FGF. bFGF is a protein with a molecular weight of 14 to 16 kDa and a pI of 9.6. aFGF has a molecular weight of 15kDa and a pI of 5.6 to 6.0. bFGF and aFGF are single-chain polypeptides which share 55% homology. bFGF can be found into the different tissues that is mesodermal and neuroectodermal origin but in aFGF can be found in brain and bone. In human, bFGF is found on chromosome 4 but in case of aFGF found on chromosome 5 and both FGF show a slight homology to IL-I.

Biological function of FGF in vitro and vivo

In wound healing, FGF is multifunctional and influences many cellular events. It is shown to be mitogenic for a variety of cell types such as fibroblasts, smooth muscle cells, endothelial cells, chondrocytes, and osteoblasts. These mitogenic effects on various cell types that is FGF stimulates other critical cellular events and these events such as angiogenesis, tumorigenesis, chemotaxis, protease induction, neutrite outgrowth, and the production of lymphokines and collagenase. Both acidic and basic FGFs are tightly bound to heparin and heparin sulfate that serve as carrier proteins for FGF. It contain two heparin binding sites and remains biologically active when bound to heparin and it protects FGF from inactivation. But in vivo, FGF has been shown to enhance angiogenesis and granulation tissue formation. According to Davidson and coworkers demonstrated that FGF injected into polyvinyl sponge, improve blood vessel formation and accumulation of collagen. In case of rat, when FGF injected into incisional wounds that increased the wound-breaking strength and cellular organization of these wound. In further report, showed that polyclonal antibody to basic FGF injected into wounds decreased the accumulation of cells and collagen within wound.

Insulin-like Growth Factor I and II (IGF-I and IGF-II)

Structure and Source

Somatomedins are referred to as IGF-I and IGF-II. Molecular weight is 7.6kDa with basic peptide (pI) 8.4 of IGF-I or somatomedin–C but in IGF-II also known as multiplication stimulating activity that is natural peptide with molecular weight of 7.5kDa. Both IGFs are single-chain polypeptides and share 47% sequence homology with insulin and 62% homology with each other. At higher concentration, IGF can be found in plasma that is in active state bound to larger molecular weight carrier proteins. Other sources of IGF are include liver, kidneys and fibroblasts. It is considered to be mediated growth-promoting effects of growth hormone as well as playing an important role in fetal growth.

Biologic Functions of IGF in Vitro and Vivo

Somatomedins are anabolic proteins with a variety of effects that include cell replication, synthesis of glycogen, protein and transport of glucose and amino acids across the cell membrane. IFG-II synthesis is highest in fetal fibroblasts and declines as animals get older in vitro. IGF-I levels increase with age and IGF-II levels found in many tissues of adult rats. IGF-I synthesis in fetal and adult tissues is partially regulated by growth hormone but in case of IGF-II concentrations in serum are not regulated by growth hormone. With decreasing binding affinities, IGF-I receptors bind with IGF-I, IGF-II and insulin but IGF-II receptors bind with IGF-II with less affinity and IGF-I but not bind with insulin. In vitro results, wound repair by occupied with IGF-I and IGF-II that is important mediators. Wound fluid from human, rate and rabbit acute wounds that contains a significant amount of IGF-I. IGF-I from the wound fluid is more loosely complexed than it is in normal plasma than that the IGF-I from wound is more biologically active. In DNA synthesis in human fibroblasts, IGF-II is three times less effective than IGF-I that has been shown to enhance wound healing following topical applications to full-thickness dermal wounds on the backs of normal-healing rats.

Epidermal Growth Factor (EGF)

Structure and Source

EGF is a relatively small single-chain polypeptide that is consist of 53 amino acids with a molecular mass of approximately 6 kDa. EGF and TGF-α are also share functional and structural similarities and TGF-α bind with EGF receptor. This receptor contain molecular weight is 170kDa single-chain protein with specific tyrosine kinase activity. Both receptors are detected in proliferating and differentiating epidermal cells.

Biologic Effects of EGF in Vitro and vivo

EGF has been stimulate mitogenesis with its associated increase in DNA, RNA and protein synthesis. It is also stimulate with epithelial cell migration. In vitro, it is helps the growth and differentiation of keratinocytes. But in vivo, EGF on corneal wound healing and it is enhance the proliferation of corneal epithelium. According to Mathers et al. stated that "the effects of various doses of exogenously applied EGF on full-thickness comeal wounds and found that EGF increased wound tensile strength in these wounds in a dose-dependent manner". These wounds shown an increase fibroblasts response at concentrations of 0.1 and 0.01 mg/ml of EGF.

Review of Literature

Crovetti 2004, concluded that wound healing is a complex process and first damage blood vessels, triggers coagulation and provokes an acute local inflammatory response because of circulating platelet aggregation and degranulation in which released the several cytokines that is TGB-β which is induces chemotaxis of neutrophils and monocytes in wound site and PDGF leads to fibroblasts recruitment and proliferation and matrix remodeling. Restoration of tissue integrity involves a cascade of overlapping events including inflammation, epithelialzation, angiogenesis and matrix deposition. Platelet gel is a tool for bringing to wound area growth factors by platelet lysate and matrix proteins by cryoprecipitate and help the functional recovery of physiological tissue reparation.

Gurgen 2008, stated that treating of wound healing by using of platelet-rich plasma of different aetiologies. In case of no show any progress in treatment of wound aetiology after 6 months then standard wound care should be done. Further research should be done in this field for the treatment of disease in which needed sufficient sample sizes that prove the efficacy of platelet-rich plasma. Some studies are focus on outcomes as well as for variations in platelet counts, growth factor concentrations and applicability and cost-effectiveness.

Cornick et.al 2014, concluded that better understanding of wound healing and growth factors in normal tissue without injury in which new therapeutic modalities are being investigated for treatment of wound healing. It is realize that a number of growth factors and cytokines and inflammatory cells govern the inflammation and wound healing. Effective therapy is reduce the bacterial load, establish control of sever inflammation and concomitantly increase the tensile strength of the wound. Some growth factors have been proven in preclinical research and its clinical efficacy has yet to be confirmed in humans.

Lee et.al 2014, stated that burn wound dressing materials are woven silk membranes that possess good biocompatibility. In all experimental groups, wound healing with silk dressing material was better but no silk dressing produced a typical inflammation and only minimal foreign body reactions. For burn wound dressing material, woven silk membrane could be used.

Zhao et.al 2017, dictated that three factors are affected on average fiber diameter from high to low were voltage, flow speed and solidification distance and three factors are also affected on fiber uniformity from high to low were flow speed, solidification distance and voltage. Even though the water absorption ratio of electrospun membranes was inferior to commercial wound dressings, it may be applicable for wound healing since RGD-pNSR16 may be not covalently bonded with Polyvinyl alcohol (PVA), and it could be released and induce adherence, proliferation, and migration of cells.

Eswaramoorthy and McKenzie 2017, concluded that wound healing is a major challenges in medical industry. Moisture, chemical and biological environment are controlling the dressings accelerate wound healing. By controlling the wettability, water and air permeability and antimicrobial action of wound-dressing materials, done the treatment of plasma surface. Effective tool is done the treatment of plasma that is not only modifying the surfaces of the dressings but also for including molecules and cells to give specific assistance to the healing process. In healing of wound, provision of suitable proteins on surfaces of dressing has been shown to assist.

Conclusion

Platelet-rich plasma is play an important role in wound healing that is a well-orchestrated, complex series of actions normally resulting in the restoration of structural integrity and partial or complete function of

damaged tissue. Under investigation, factors that stimulate and regulate this cascade of events. One factors of this events stimulating that seen in wound healing which is polypeptide growth factors. This paper represent the interaction, function and mechanism of growth factors in the context of overall soft-tissue repair process. By the combination of growth factors, wound healing (soft tissue) should be repair. Growth factor describe on soft tissue that is further define in therapeutic value of using polypeptide growth factors for treatment of chronic ulcer and sever acute injuries.

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