A Review of Platelet Derived Growth Factor Playing Pivotal Role in Bone Regeneration

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This article is focused on the literature review and study of recent advances in the field of bone grafting, which involves platelet-derived growth factor (PDGF) as one of the facilitating factors in bone regeneration. This article includes a description of the mechanism of PDGF for use in surgeries where bone grafting is required, which promotes future application of PDGF for faster bone regeneration or inhibition of bone growth if required as in osteosarcoma. The important specific activities of PDGF include mitogenesis (increase in the cell populations of healing cells), angiogenesis (endothelial mitoses into functioning capillaries), and macrophage activation (debridement of the wound site and a second phase source of growth factors for continued repair and bone regeneration). Thus PDGF can be utilized in wound with bone defect to conceal the wound with repair of bony defect.

Key Words: PDGF, PDGF receptors, bone grafting, bone regeneration

INTRODUCTION

Platelet-derived growth factor (PDGF) is a two-chain polypeptide, which belongs to the growth factor family. The original source of PDGF was platelets, but PDGF or PDGF-like peptides have been isolated from a variety of normal and neoplastic tissues, including bone matrix and osteosarcoma cells.[1–3] Platelets do not bind to intact endothelium. PDGF is contained in alpha granules of platelets and is released only during blood clotting or when platelets adhere at sites of blood vessel injury. Secretion of platelets can be initiated by exposure of platelets to the foreign surfaces such as subendothelial basement membrane or collagen.[4,5] PDGF may serve to promote wound healing since it is the most potent mitogen in serum for cells of mesenchymal origin including fibroblasts, glial cells, and smooth muscle cells, [6–8]

PDGF stimulates bone DNA and protein synthesis, and may be a systemic or local regulator of skeletal growth. As a systemic growth factor, it could be released during platelet aggregation and have important effects in the early stages of fracture healing. As a local factor, it may interact with other hormones and growth factors (eg, it promotes bone cells to respond to other factors present in the skeletal tissue).[1] In addition to its effects on bone formation, PDGF has been shown to stimulate bone resorption so that it appears to have complex effects on bone remodeling. In this review paper we have focused on the effects of PDGF on bone regeneration.

STRUCTURE OF PDGF

PDGF was originally identified as an essential component for the culture of serum-dependent cells. Four different chains (A, B, C, and D) are identified in the structure of PDGF. PDGF is now considered as a family of five heterodimeric and homodimeric proteins (PDGF-AB, PDGF-AA, PDGF-BB, PDGF-CC, and PDGF-DD).[9] The mature parts of the A- and B-chains of PDGF are ~100 amino acid

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DOI: 10.1563/AAID-JOI-D-11-00173

residues long and show ~60% amino acid sequence identity. Each chain has 8 cysteine residues, which are perfectly conserved between the 2 chains; 2 of the cysteine residues are involved in cysteine bonds between the 2 subunits in the PDGF dimer, and the other 6 are engaged in intrachain disulfide bonds.[10,11] Mutation of the interchain disulfide bonds is compatible with retained biological activity of PDGF.[12,13] because the molecule still occurs as a dimer.

The A, B, C, and D chain genes of PDGF are localized to the chromosomes 7p22, 22q13, 4q31, and 11q22 respectively. Their expression is independently regulated by PDGF receptors (PDGFRs).[6] PDGF isoforms exert their cellular effects by activating two structurally related cell surface receptor tyrosine kinases (α-PDGFR and β-PDGFR). The α-PDGFR and β-PDGFR genes are localized on chromosomes 4q12 and 5q33, respectively.[6]

Physical and Chemical Characterizations of PDGF

PDGF is difficult to purify as it is in very small quantities in platelets possessing contaminating proteolytic activity. PDGF is a highly basic glycoprotein with pH 10.2.[14,15] PDGF-A is 31 kD and contains 7% carbohydrate, whereas PDGF-B is 28 kD and contains 4% carbohydrate. PDGF A and B have essentially equal mitogenic activity and amino acid composition and immunological reactivity.[14,16]

The response to PDGF depends on the isoforms of PDGF delivered, the type of target cell, and the specific cell-surface receptor expressed on the target cell.[17] At a wound site, PDGF attracts neutrophils and macrophages and stimulates macrophages to release additional growth factors that are important for wound healing.[18] PDGF receptors have been found on all of the connective-tissue cells associated with bone healing, including fibroblasts, vascular smooth-muscle cells, osteoblasts and chondrocytes. Preclinical animal studies have demonstrated that PDGF- BB has a stimulatory influence on bone formation.[20,21]

PDGF Receptors (PDGFRs)

Both PDGFRs contain 5 extracellular immunoglobulin-like domains: a transmembrane domain, a juxtamembrane domain, split kinase domains, a kinase insert domain and a cytoplasmic tail.[6] These 2 receptors share 31% identity in the ligand binding domain, 27% identity in the kinase insert, and 28% identity in the C-terminus, whereas they are 85% and 75% identical in the 2 halves of the kinase insert domain.[6]

PDGF isoforms exert their effects on target cells by activating two structurally related protein tyrosine kinase receptors. The α- and β-receptors have molecular sizes of ~170 and 180 kD respectively, after maturation of their carbohydrates.[22] The structures of PDGF receptors are similar to those of the colony stimulating factor-1 receptor and the stem cell factor receptor.[23]

Cellular Effects and Expression of PDGF Receptors

The α-receptor binds both the A- and B-chains of PDGF with high affinity, whereas the β-receptor binds only the B-chain with high affinity. Both α- and β-receptor homodimers transduce mitogenic signals. Activation of the β-receptor stimulates chemotaxis; in contrast, activation of the α-receptors inhibits chemotaxis of certain cell types including fibroblasts and smooth muscle cells. Both the α-receptor and the β-receptor mediate an increase in intracellular Ca^{2+} concentration, albeit the β-receptor more efficiently than the α-receptor. PDGF also inhibits gap junctional communication between cells and exerts an antiapoptotic effect.[24,25]

Because there are differences between α- and β-receptors in their binding specificity of PDGF isoforms and in the signals they transduce, the response of a cell to PDGF stimulation will be determined by which of the two receptor types the cell expresses. The classical target cells for PDGF express both α- and β-receptors, but generally higher levels of β-receptors.[24] Activity through the receptor is shown in Figure 1.

Activation of PDGF Receptors Through Dimerization

A common theme for activation of tyrosine kinase receptors is ligand-induced receptor dimerization, which juxtaposes the intracellular parts of the receptors and allows autophosphorylation of tyrosine. Because PDGF is a dimeric molecule, it can bind 2 receptors simultaneously and thus form a bridge between the receptors. The ligand binding epitopes in PDGF α- and β-receptors are located in

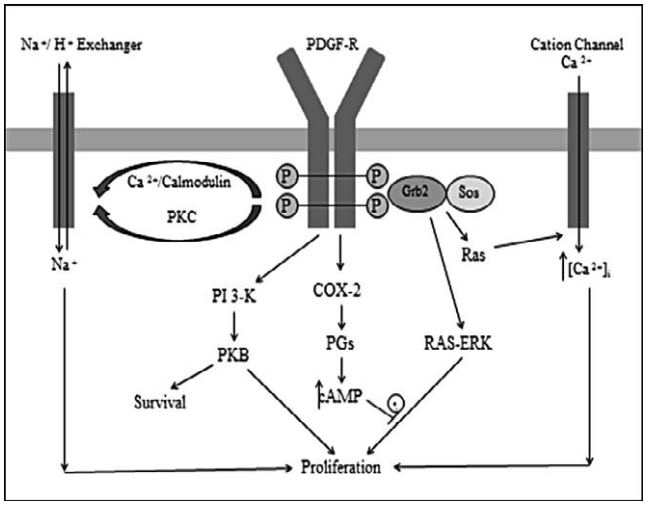

Figure 1. Activity through the receptor and expression.

the three outermost Ig domains.[26] Ig domain 2 appears to be most important for ligand binding.[27] In addition to the bridging effect of PDGF, the dimeric receptor complex is further stabilized by direct receptor-receptor interactions mediated by Ig domain 4.[27–29]

PDGF Binding Proteins

PDGF interacts with matrix molecules and also with soluble proteins. Like many other cytokines, PDGF binds to α_2-macroglobulin.[30] This interaction regulates the amount of PDGF available for interaction with receptors. Another PDGF binding protein was isolated from a rat neural retina cell line and named as PDGF-associated protein (PAP).[31] PAP binds PDGF with low affinity and was found to enhance the activity of PDGF-AA but depress the activity of PDGF-BB. Moreover, the extracellular part of PDGF α-receptor has been detected in normal human plasma; it is possible that such circulating soluble receptors can compete with cell-associated PDGF receptors for ligand binding.[32]

Receptor Binding Epitopes in PDGF

With the use of site-directed mutagenesis, the receptor binding epitopes in PDGF have been localized. Each PDGF molecule contains 2 symmetric receptor binding epitopes, each one built up by structures from both chains in PDGF.[33–35] PDGF-BB interacts with α- and β-receptors with similar affinity. The interaction appears to involve overlapping but not identical regions in the ligand, since residues in loop 2 are more important for binding to the β-receptor than to the α-receptor.[33]

Intracellular Signal Transduction

Autophosphorylation of PDGF receptors

The cascade of intracellular signal transduction begins with dimerization of PDGF receptors, which thereafter induces autophosphorylation to serve two important functions. On one hand, phosphorylation of a conserved tyrosine residue inside the kinase domains leads to an increase in the catalytic efficiencies of the kinases. On the other hand, autophosphorylation of tyrosine residues located outside the kinase domain creates docking sites for signal transduction molecules containing SH2 domains.[24]

Binding of SH2 domain proteins to PDGF receptors

The SH2 domain is a conserved motif of ~100 amino acid residues that can bind a phosphorylated tyrosine in a specific environment. The signal transduction molecules contain several different types of motifs that mediate interactions between different components in signaling pathways. Moreover, SH3 domains recognize proline-rich sequences, PH domains recognize membrane phospholipids and PDZ domains recognize COOH-terminal valine residues in specific sequence contexts.[36]

A large number of SH2 domain proteins bind to PDGF α- and β-receptors. Some of these SH2 domain protein are themselves enzymes such as phosphatidylinositol 3′-kinase (PI 3-kinase), phospholipase C (PLC)-γ, the Src family of tyrosine kinases, the tyrosine phosphatase SHP-2, and a GTPase activating protein (GAP) for Ras. Other molecules such as Grb2, Grb7, Nck, Shc, and Crk are devoid of enzymatic activity and have adaptor functions linking the receptor with downstream catalytic molecules.[37] They are transcription factors that, after phosphorylation on tyrosine, dimerize and translocate into the nucleus where they affect the transcription of specific genes. Each SH2 domain molecule that binds to the PDGF receptors initiates a signal transduction pathway.[24] Pathways are illustrated in Figure 2.

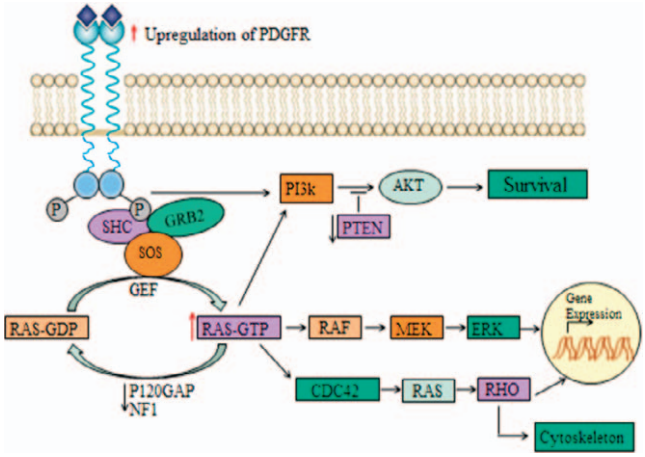

Figure 2. Intracellular signal pathways of PDGF.

PI 3-Kinase

Members of the PI 3-kinase family that bind to and are activated by tyrosine kinase receptors consist of a regulatory subunit, p85 and a catalytic subunit, p110.[38,39] Phosphatidylinositol 3′-kinase has a number of downstream effecter molecules and it mediates many different cellular responses, including actin reorganization, chemotaxis, cell growth, and antiapoptosis.[40]

PLC-γ (phospholipase C-γ)

Phospholipase C-γ acts on the same molecule as PI 3-kinase to produce inositol 1,4,5-trisphosphate and diacylglycerol, mobilize intracellular Ca^{2+} from internal stores and activate certain members of the Protein Kinase C family.[41] The binding of PLC-γ to the PDGF receptor leads to its phosphorylation on specific tyrosine residues, whereby its catalytic activity increases.[42] Phospholipase C-γ appears not to be of primary importance for the stimulation of cell growth and motility in most cell types.[43]

Src

Members of the Src family of tyrosine kinases are characterized by the presence of 1 SH3 domain and 1 SH2 domain in addition to the catalytic domain.[44] The binding of the SH2 domain to autophosphorylated PDGF receptors, in conjunction with dephosphorylation of the COOH-terminal of phosphorylated tyrosine kinase and phosphorylation of other tyrosine in the molecule, activates Src. Src appears to be important for the mitogenic response of PDGF, however, direct binding of Src to the PDGF α-receptor is not necessary for mitogenic signaling.[45]

Grb2/SOS

Grb2 is an adaptor molecule with one SH2 domain and two SH3 domains; the latter domains mediate binding of SOS, a nucleotide exchange factor for Ras which converts inactive Ras·GDP to active Ras·GTP.[46] Activated Ras binds to the serine/threonine kinase Raf-1 that initiates activation of the mitogen-activated protein (MAP) kinase cascade, a pathway which is implicated in stimulation of cell growth, migration, and differentiation.[47,48]

SHP-2

SHP-2 is a ubiquitously expressed tyrosine phosphatase with two SH2 domains, both of which need to bind to phosphorylated tyrosine residues for full activation of the catalytic activity.[49] However, SHP-2 may also be involved in positive signaling through its ability to act as an adaptor that binds Grb2/SOS to activate Ras[50] and through its ability to dephosphorylate the COOH-terminal tyrosine residue of Src to activate Src.[24]

GAP (GTPase activating protein)

GTPase activating protein binds to only PDGF β-receptors.[51] It converts Ras-GTP to Ras-GDP and thus has a modulatory role in Ras activation by PDGF receptors.[52] The magnitude of Ras activation in PDGF-stimulated cells will thus be dependent on stimulatory as well as inhibitory signals.

Stat

The family of Stat molecules has 7 members of which Stat1, Stat3, Stat5, and Stat6 have been shown to bind to the activated PDGF β-receptor and to be phosphorylated after PDGF stimulation; binding also occurs to the α-receptor, albeit only weakly.[53,54] After phosphorylation on tyrosine, Stats dimerize and translocate to the nucleus, where they act as transcription factors.[24]

Adaptors

Adaptors are molecules that are devoid of intrinsic catalytic activity; after binding to the PDGF receptors through their SH2 domains, they connect the receptor with downstream effecter molecules. The regulatory subunits of PI 3-kinase and Grb2[55] are

examples of adaptor molecules. Other adaptor molecules that bind to PDGF receptors are Shc, Grb7, Nck, and Crk.[24,56]

Control of PDGF signaling

Several mechanisms for modulation of signaling via PDGF receptors have been elucidated. For instance, MAP kinase, which is activated by Ras, phosphorylates and inactivates SOS, which thereby leads to a decreased Ras activation.[57] Another negative-feedback mechanism involves cAMP-dependent protein kinase, which is activated by PDGF through induction of prostaglandin synthesis and activation of adenylyl cyclase.[58] Moreover, angiotensin II has been shown to delay PDGF-BB-induced DNA synthesis in vascular smooth muscle cells; the mechanism behind its effect remains is unknown.[59]

A striking feature of PDGF signaling is that the strength of signals is modulated by the simultaneous activation of stimulatory and inhibitory signals. Thus the tyrosine phosphorylation induced by the PDGF receptors is balanced by activation of tyrosine phosphatase by PDGF.[60,61] Another example is the binding of GAP to the receptor, which will counteract the Ras activation induced by Grb2/SOS binding to the receptor.[61]

Cooperation with integrin signaling

Most of the cell types that are responsive to PDGF are anchorage dependent (ie, they are dependent for their growth on contacts with matrix molecules surrounding the cell). Such contacts are mediated by integrins, which are transmembrane receptors for matrix molecules. Binding of integrins to their extracellular matrix molecules leads to the formation of focal adhesions with the assembly of a large complex of signaling molecules around its cytoplasmic tails, including Src, PI 3-kinase and Ras. Integrin signaling enhances growth factor-mediated cell proliferation and cell migration and is necessary to prevent apoptosis.[62] On the other hand, fibrillar collagen suppresses PDGF-induced DNA synthesis in arterial smooth muscle cells.[63] This effect is likely to be mediated by an integrin-dependent suppression of cyclin E-Cdk2 activity.

Engagement of β_1-integrins by pleating of fibroblasts on collagen or fibronectin caused a transient tyrosine phosphorylation of PDGF receptors in the absence of PDGF.[64] On the other hand, PDGF simulates the synthesis of the collagen binding integrin $\alpha_2\beta_1$.[65,66]

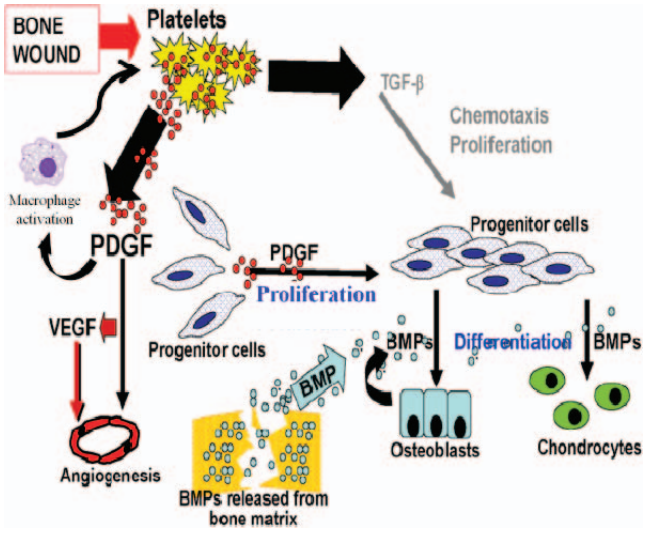

Figure 3. Role of PDGF and mechanism of bone regeneration.

PDGF in Bone Regeneration and Bone Grafting

PDGF, stored in platelets and produced by macrophages, has the characteristics of a wound hormone whose role is to increase the numbers of mesenchymal cells in the wound.[67] This is accomplished by two activities: (1) as platelets aggregate in the wound, they release PDGF which diffuses into the surrounding tissue and acts as a chemo attractant, recruiting cells into the wound;[68] (2) At the higher levels found in the wound, PDGF increases the proliferation of the cells.[69] In this way, PDGF regulates the number of cells in the wound and the deposition of matrix.[70]

PDGF activates cell membrane receptors on target cells, which in turn are thought to develop high-energy phosphate bonds on internal cytoplasmic signal proteins; the bonds then activate the signal proteins to initiate specific activities within the target cell.[71] The most important specific activities of PDGF include mitogenesis (increase in the cell populations of healing cells), angiogenesis (endothelial mitoses into functioning capillaries), and macrophage activation (debridement of the wound site and a second phase source of growth factors for continued repair and bone regeneration).[72,73] The role of PDGF and mechanism in bone regeneration is illustrated in Figure: 3.

The life span of a platelet in a wound and the period of the direct influence of its growth factors are less than 5 days.[74] The extension of healing and bone regeneration activity is accomplished by sequence of 2 mechanisms. First, it increases the population of marrow stem cells and then activates them to turn into osteoblasts, which secrete TGF-β themselves. A dominant and more important mechanism is chemotaxis and activation of macrophages that replaces the platelets as the primary source of growth factors after the third day.[75,76] follows. The macrophage is attracted to the graft by the actions of PDGF and by an oxygen gradient between the graft dead space and the adjacent normal tissue.[72]

The recombinant B chain homodimer of human PDGF was studied for its effects on bone formation in cultured rat calvarias. PDGF at 10–100 ng/mL stimulated [^{3}H] thymidine incorporation into DNA by up to six-fold and increased the DNA content and the number of colcemid-induced metaphase arrested cells.[77] The effect was confirmed in the fibroblast and precursor cell-rich periosteum. As a result of its mitogenic actions, PDGF enhanced [^{3}H] proline incorporation into collagen, an effect that was observed primarily in the osteoblast-rich central bone. The effect of PDGF was not specific for collagen since it also increased noncollagen protein synthesis.[77]

In addition, PDGF increased bone collagen degradation. The mechanism for its effect on bone collagen degradation is not known, but it could be related to an increase in collagenase production. Because PDGF causes a relatively moderate effect on collagen synthesis and it increases collagen degradation the net result of its chronic administration could be a decrease in bone mass. On the other hand, short term exposure to the factor could produce the benefits of its mitogenic and as a consequence anabolic actions.[77]

By scatchard analysis Gilardetti and colleagues have estimated that there are approximately 43 000 PDGF-AA binding sites per cell and 55 000 PDGF-BB binding sites per cell.[78] IL-1 β significantly reduces the capacity of normal human osteoblastic cells to bind PDGF-AA and significantly decreased both PDGF-AA induced cell migration and thymidine incorporation.[78]

All platelets degranulate within 3–5 days and that their initial growth factor activity may expire by 7–10 days. This initial boost that platelet rich plasma (PRP) appears to give the process may be useful because it "jump-starts" the beginning of a cascade of regenerative events that continue to form a mature graft.[79] The bone regeneration begins by the initiation of mitosis in stem cells and endothelial cells, as well as the activation of osteoblasts and vascular growth directed by PDGF and TGFs. It is evident radiographically that adding PRP to graft material significantly reduced the time for graft consolidation and maturation and improved trabecular bone density.[79]

Functions of PDGF In Vivo

Embryonic development

The recent inactivation of the genes for PDGF[80,81] in mice has provided insight into the in vivo function of PDGFs. The notion that PDGF and PDGF receptors have important roles during embryonic development is evident by the findings that in each case the mice died during embryogenesis or perinatally.

The abnormalities that were accounted because of lack of PDGF were fatal and were with involvement of many systems. Kidney development was severely affected with a total absence of mesangial cell development.[82] There was also defective development of blood vessels with dilated aorta and characteristic bleeding at the time of birth.[83] Heart defects were noticed with an increased size and trabeculation of the myocardium. Absence of PDGF-A chain gene led to defective development of the alveoli of lung, giving emphysema-like phenotype and leading to death.[80] Inactivation of α- receptor led to cranial malformations and deficiency of myotome formation.[24]

CNS

Analysis of the temporal-spatial expression of PDGF ligands and receptors provides evidence for a role of PDGF in the development of the CNS through paracrine and autocrine stimulation. B-chain protein is found in neurons in several CNS regions of the embryo and in the adult.[84] The PDGF B-chain content stays at a high level in the adult olfactory system.[82] As the primary sensory neurons of the olfactory system retain their capacity to regenerate

in an adult suggests role of PDGF as a neurotrophic factor.[82]

Expression of the PDGF α-receptor is found in glial precursors in various regions of the developing CNS.[81] PDGF α-receptor is a critical determinant for the development of the oligodendrocyte compartment of the brain. The distribution of PDGF receptors and the cognate ligands in the CNS suggests a role in the development of functional properties of the brain and spinal cord.[24]

Vascular system

An important role of PDGF is found in cardiac angiogenesis.[85] Administration of PDGF-BB has been shown to induce functional anastomoses in vivo.[86] Moreover, PDGF B-chain produced by capillaries may have a generally important role to recruit pericytes that is likely to be required to promote the structural integrity of the vessels.[87] PDGF has also been implicated in the regulation of the tonus of blood vessels.

Another effect of PDGF that is of importance in the vascular system is its feedback control effect on platelet aggregation. Platelet-derived growth factor stimulation leads to decreased platelet aggregation.[88] Human platelets that are a rich source of PDGF have PDGF α-receptors but not β-receptors.[89] After thrombin-induced platelet aggregation, the content of the α-granule, including PDGF is released. The fact that thrombin-induced platelet aggregation is accompanied by activation of platelet PDGF α-receptors and that this effect can be inhibited by PDGF antibodies indicates that the PDGF released from platelets serves an autocrine feedback role in control of platelet aggregation.[90]

Wound healing

The healing of soft tissues involves re-epithelialization, angiogenesis, and extracellular matrix deposition. Three lines of studies support a role for PDGF in wound healing (ie, investigations of the effects of PDGF in vitro on cell types important for wound healing, analyses of the expression of PDGF and PDGF receptors during the wound-healing process, and studies of the effect of topical application of PDGF to healing wounds).

It stimulates mitogenicity and chemotaxis of fibroblasts and smooth muscle cells and chemotaxis of neutrophils and macrophages. It also stimulates macrophages to produce and secrete other growth factors of importance for various phases in the healing process. Moreover, PDGF has been shown to stimulate production of several matrix molecules like fibronectin, collagen, proteoglycan, and hyaluronic acid. PDGF may also be of importance at later stages of wound healing as it stimulates contraction of collagen matrices in vitro[91] implicating a role in wound contraction in vivo. Moreover, PDGF stimulates the production and secretion of collagenase by fibroblasts, suggesting a role in the remodeling phase of wound healing.

For PDGF to affect wound healing in vivo it has to be present at the site of the wound. Studies show that PDGF is released by platelets and secreted by activated macrophages[92] thrombin-stimulated endothelial cells, smooth muscle cells of damaged arteries, activated fibroblasts, as well as by epidermal keratinocytes.[93] Interestingly, with the use of isoforms-specific monoclonal antibodies, a markedly up regulated level of PDGF-AA was observed in capillaries and fibroblasts of acute wounds and in chronic wounds treated with PDGF-BB; in contrast, normal skin and nonhealing dermal ulcers did not contain PDGF.[94]

A single application of PDGF-BB to incisional wounds increased the wound-breaking strength to 150%–170% of control wounds and decreased the time of healing.[95] Wounds treated with PDGF showed an increase of granulation tissue rich in fibroblasts and glycosaminoglycans and an increased rate of re-epitheliazation and of neovascularization.[96] Thus PDGF does not alter the normal sequence of repair but increases its rate. PDGF-BB was found to increase healing also in patients with decreased healing capacity such as diabetics.[97]

In humans, regenerative surgery using recombinant human platelet derived growth factor-BB (rhPDGF-BB) on a beta-tricalcium phosphate (β-TCP) vehicle or combined with demineralized freeze-dried bone allograft (DFDBA) resulted in robust regeneration of cementum, periodontal ligament, and bone. Studies have indicated significantly higher improvements in terms of probing depth (PD) reduction and Clinical attachment level (CAL).[78]

Future of PDGF

The discovery of PDGF has opened up new doors for finding out the better and novel ways to treat

the wounds and also opened up new possibilities to regenerate bone in fracture areas or augmentation of bone grafts for better and fast consolidation at desired places. As the use of PDGF is growing, there remains an endless possibility to find out the new uses of PDGF.

From current knowledge of PDGF we can find out some novel uses for PDGF. Like as we know PDGF prolongs the survival of dopaminergic neurons in the brain so it can be used in the future for treatment of Parkinson's disease. PDGF and PDGF receptors are upregulated in infarcted human brain tissue, suggesting a role in neuroprotection and regeneration. Different studies have been published mentioning the use of PDGF in venous ulcers, in treatment of clear renal cell carcinomas, Achilles tendinopathy, and in vascularized organ transplants.

There is good evidence that PDGF overactivity is involved in the development of several serious disorders, including certain malignancies, atherosclerosis, and various fibrotic conditions like keloids. The development of clinically useful PDGF antagonists is therefore highly warranted. One promising type of antagonist is inhibitors of the PDGF receptor kinases. Several such inhibitors have been described; future studies will aim to identify potent inhibitors that are specific for PDGF receptors and that do not inhibit other kinases. And also inhibition of RAS proteins by directing antibodies against nucleotide exchange factors like SOS or antibodies specific for RAS can prevent further activation of MAPK cascade and can halt the mitogenic activity. These mechanisms can be exploited for treating malignancies.

PDGF-α specific antibody may promise bright future for wound healing treatment as it can boost chemotaxis and enrich the immune response resulting in faster wound healing. PDGF-C appears to contribute to wound healing in adults since PDGF-C stimulated fibroblast proliferation, epithelial migration, extensive vascularization and neutrophil infiltration. There is direct and indirect evidence that PDGF-C contributes to angiogenesis. In the future much of the focus will be on new class of PDGF, PDGF-C, and PDGF-D to find out their properties and uses in different fields.

So, with all these future impacts of PDGF, its potential uses in different fields of medicine will prove to be the subject of future discoveries.

Abbreviations

CNS: central nervous system
GAP: GTPase activating protein
MAP: mitogen-activated protein
PAP: PDGF-associated protein
PDGF: platelet-derived growth factor
PDGFR: platelet-derived growth factor receptor
PLC: phospholipase C-γ
PRP: platelet-rich plasma

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