International Journal of Genetics and Molecular Biology Vol. 3(5), pp. 72-80, June 2011
Available online at http://www.academicjournals.org/ijgmb
ISSN2006-9863 ©2011 Academic Journals

Review

Platelet-derived growth factor (PDGF) signaling: Detailed mechanistic insights

Ammad Ahmad Farooqi*#, Syed Shoaib#, Ali Nawaz, Asma M Riaz, Rashad Hussain, Shahzeray Mukhtar, Sehrish Minhaj and Shahzad Bhatti#

Institute of Molecular Biology and Biotechnology (IMBB), the University of Lahore, Pakistan.

Accepted 1 June, 2011

It is worth mentioning that large body of experimental evidence interconnects the deregulation of specific platelet-derived growth factor (PDGF) functions to cellular transformation, yet complete picture of determinants of molecular mechanisms through which PDGF contributes to tumorigenesis remain indefinable. In this review, we have summarized current comprehension concerning PDGF functions, and attempted to understand its multifaceted and contradictory activities in the perspective of both normal cellular homeostasis and molecular disorders. Furthermore, PDGF is tightly buffered at multiple levels by downstream components and effectors, which have turned this linear signaling pathway into an integrated one. In support of this notion, PDGF and its downstream components in turn cross-talk with a number of other pathways, consequently leading to an intricate network of signals that may have derailed activities when perturbed. Here, we evaluate the current status of the PDGF transduction cascade with particular emphasis on the most current data on targets and regulation of the PDGF axis. We also bring to limelight, molecular details of PDGF signal transduction cascade, endocytosis and membrane trafficking, as well as interactions with the actin cytoskeleton which may add to the recently appraised multifunctionality of PDGF. This provides novel therapeutic implications based on the targeted modulation of PDGF-cross-talking signals with minimal off target effects.

Key words: Platelet-derived growth factor, cancer, cellular transformation.

INTRODUCTION

Cancer is a life threatening disease that is insurmountable to date because of suppression of tumor suppressors and overexpression of oncogenes. Another interesting piece of evidence is that all the mechanisms underlying carcinogenesis, local invasion and the formation of metastases are clinically and significantly relevant, however they are the least well understood at the molecular level. Dismantling their mechanistic insights is one of the foremost challenges for investigative and applied cancer research. Recent experimental advancement has acknowledged a number of molecular pathways and cellular mechanisms that lie beneath the multistage progression of metastasis. These comprise tumour invasion, tumour-cell dissemination. The PDGF has emerged as a significant signaling molecule within eukaryotic cells. Major strides have been made in clarifying and identifying downstream mechanisms that modulate its effects in cells and are instrumental in signal dissemination. Here, we provide a summary of recent advances in the field concerning the role of PDGF in physiological and pathological cell function within a more comprehensive framework of PDGF signal transduction. Emphasis is placed on the implications of PDGF in human diseases ranging from cancer to cellular disorders.

The platelet-derived growth factor (PDGF) belongs to the family of mitogens (Carl et al., 2002), the growth factor superfamily (Sun and Davies, 1995), like the other members of this family PDGF has differentiating, proliferating, and migrating roles in developing and developed cell conditions. The PDGF has two isoforms, A and B

*Corresponding author. E-mail: ammadahmad638@yahoo.com, drshahzadbhatti@yahoo.com

#These authors contributed equally to this work

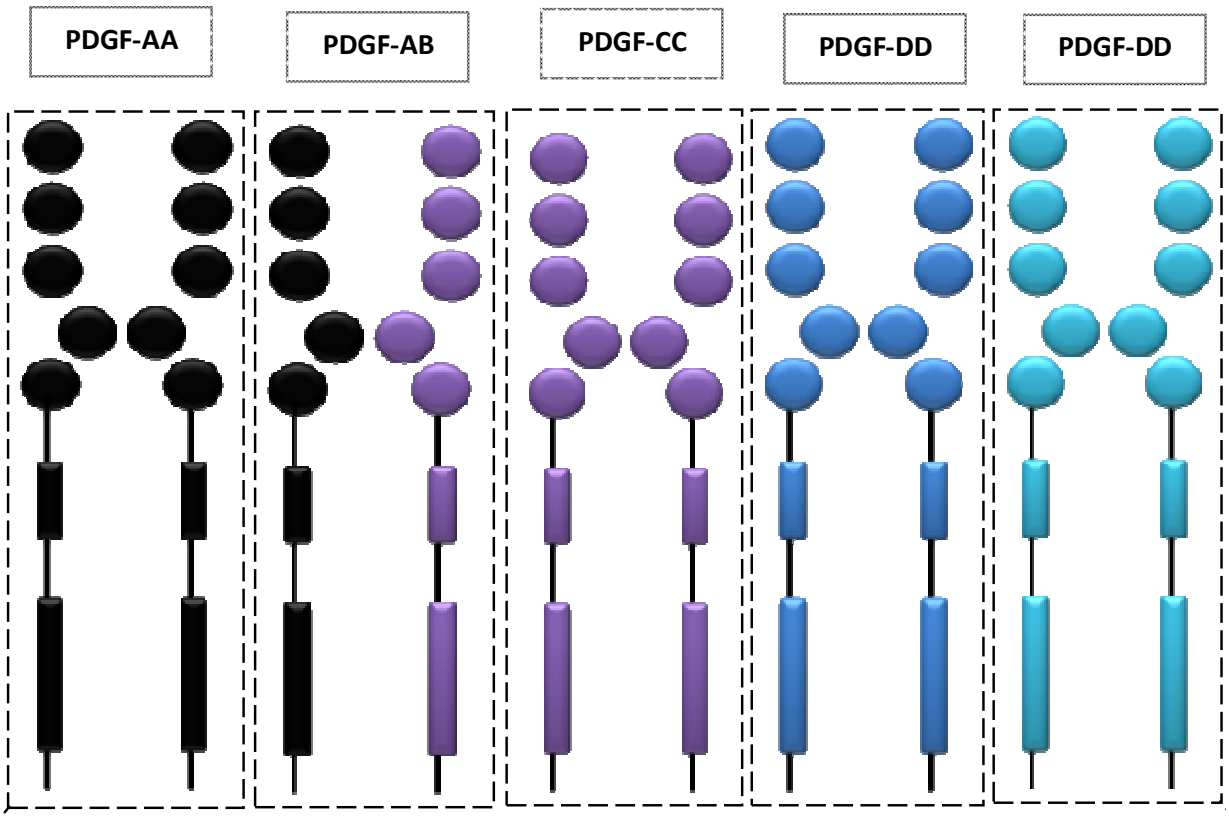

Figure 1. The dimeric forms of PDGF , usually combination of two polypeptide chains making homodimeric or hetrodimeric combinations. These are PDGF-AA, PDGF-BB, PDGF-AB, PDGF-CC and PDGF-DD. Both PDGF-A and PDGF-B are found in homo and hetrodimeric forms while the PDGF-C and PDGF-D only had homodimeric form.

while the novel studies depict that PDGF has two more isoformic mitogen members, PDGF-C and PDGF-D (Xuri and Eriksson, 2003). The PDGF is found as a dimeric form by the combination of two polypeptide chains, these could make different combinations, for example, PDGF-AA, PDGF-BB, PDGF-AB, PDGF-CC and PDGF-DD (Heldin and Westmark, 1990). This is so because all the homodimeric or hetrodimeric forms are inactive in monomeric forms, all these forms are having relative affinities with two receptors, PDGFR-α and PDGFR-β (Bowen et al., 1989; Gronwald et al., 1988).The PDGF-A and –B can be found in both homo and hetrodimeric forms (PDGF-AA, -AB, -BB), but the novel members PDFG-C and –D can exist in only homodimeric form (PDGF-CC and-DD) (Lix et al., 2000; Bergsten et al., 2001; Changsirikulchai et al., 2002).

The PDGF is said to induce many intracellular signals, once the receptor gets attached to the substrate. Various genes are being regulated by this growth factor and its isoforms (Cochran et al., 1983; Linzer and Nathans, 1983; Almendral et al., 1988). Round about 80 genes are being pinpointed to be stimulated under the response of PDGF these include a variety of protein encoding genes and also some growth and cell regulatory factors (Almendral et al., 1988).

ROLE OF PLATELET-DERIVED GROWTH FACTOR (PDGF) IN CONTEXT OF SMOOTH MUSCLE CELL'S REGULATION

The PDGF along with the basic fibroblast growth factor belonging to the super family of growth factors plays an important role in many cellular functions like proliferation, migration and survival, an interactive crosstalk prevails between these two growth factors in an overlapping way (Pintucci et al., 2005). The vascular smooth muscle cells have two distinct phenotypes the contractile and the proliferative one in both normal and pathological conditions, respectively. The synthetic phenotype among these two is said to be induced by the potent PDGF isoform, PDGF-BB, which acted synchronously with the Fibroblast Growth Factor-2 (FGF2), in cell proliferation and down regulation of adaptor protein smooth muscle α-actin (SMA). This underscores the fact that PDGF, PDGFR and FGF2 act collaboratively to downregulate the expression of SMA, as without inhibition of SMA the plasticity of vascular smooth muscle cell (VSMC) is not compromised (Chen et al., 2009). In VSMC the FGF-2 expression is being implicated by the PDGF-BB, talking specifically about the vascular aortic smooth muscle cells induction of high molecular weight (HMW) FGF-2 is seen

which accumulates in the nucleus or nucleolus while the low molecular weight FGF-2 does not do so (Pintucci et al., 2005). The platelet derived growth factor isoform BB is a tyrosine kinase receptor agonist and plays transactivating role in VSMCs proliferation it usually transactivates the EGF receptor (EGFR) or the FGF receptor (FGFR) to induce the VSMCs proliferation. It is an experimental fact that FGF concentration in the medium remains constant. What seems to justify the situation is that FGF is attached to the membrane via heparan sulfate proteoglycans (HSPGs). For the detachment of the FGF from the membrane there must be an activity of biological scissors (Proteases). However decreased concentration of FGF in the membrane is indicative of the fact that there is no scissoring activity (Rapraegeret al., 1991; Rhoadset al., 2000; Myler et al., 2002; Rauch et al., 2004). Other than the release of FGF in the external environment, FGF transcription is triggered by PDGF-BB (Bilato et al., 1995). Another body of evidence states that there is a translocation of exogenous FGF into the cell (Malecki et al., 2004) that increases the cellular contents of FGF (Figures 2a and b).

ROLE OF PLATELET-DERIVED GROWTH FACTOR (PDGF) IN DIFFERENT METASTATIC AND ANGIOGENIC CASCADES

Normally, various growth factors are explicited in neoplastic cells, some of which are frequently upregulated. The tumor vasculature depends on an interactive loop of these factors which leads to disorganized neovascularization and metastasis. The phenomenon is said to be looped, as the FGF's upregulation increases PDGFR-α and -β expression at transcription level, similarly PDGF-BB enhances the cell's response by upregulation of FGFR-1, so that's how both factors are regulating the neoplasticity angiogenesis and metastasis (Lars et al., 2007). PDGF-BB signaling pathways also regulate neovascularization which is a well studied aspect, quiescent endothelial cells which are usually unresponsive to PDGF-BB become sensitive to it after it is being transcriptionally activated by fibroblast growth factor (FGF)-2, the transcriptional activation switches the PDGF receptor expression in activated cells with a positive feedback looping by PDGF-BB that activates the FGF-2 signaling system (Yihai et al., 2008) (Figure 3).

PDGF-BB also had an involvement in tumor lymphangiogenesis among several other tumor-derived growth factors; PDGF-BB upholds the basic mitogen activating protein kinase (MAPK) pathway which leads to metastasis in lymph nodes (Renhai et al., 2004). An Autocrine pool of PDGF/PDGFR is needed for a neoplastic cell's metastatic activity through some distinct pathways, like the PDGF, is also pooled into the epithilial mesenchymal transition (EMT) induced by transforming growth factor beta (TGF-β). This correlated activity of PDGF is autocrine, in which the RAS molecule is first capacitated and this modulates PI3K pathway, so that a dampened PDGF signaling would constitute to defective EMT (Martin et al., 2006; Jie et al., 2010).

PDGF's involvement in EMT is accompanied by TGF-β in this crosstalk, PI3K and (ERK)/ RAS are predominantly activated. The PI3K basically enhances the RAS and this enhanced regulation is both the upstream and downstream of RAS (Chun-Chao et al., 2009). A TGF-β independent mechanism is also suggested by Lahsnig et al. (2009) which includes the involvement of a novel interleukin like EMT inducer (ILEI) protein, ILEI enhances the RAS expression. Here a link between transcriptional activity and anti apoptotic signaling of the transcription factor NFKB is seen, NFKB accomplishes its anti-apoptotic activity after being induced by PDGF transcriptionally, through RAS and PI3K pathways, so NFKB being the target, links the anti-apoptotic signaling with transcriptional machinery (Romashkova and Makarov 1999).

A novel signal transducer PDGF-DD is also involved in neovascularization. It is upregulated in pathological angiogenesis. Here a novel mechanism reports the involvement of glycogen synthase kinase-3β (GSK3β), which is antiangiogenic effector in PGDF-DD targeting. PDGF-DD mediates Ser- 9 phosphorylation and Tyr-216 dephosphorylation of GSK3β, which blunts its antiangiogenic activity, so that PGDF-DD can be a therapeutic target for neovascular diseases (Anil et al., 2010).

ROLE OF PLATELET-DERIVED GROWTH FACTOR (PDGF) IN BREAST CANCER PROGRESSION

PDGF-D is found to be upregulated in invasive breast cancer cell lines, it also correlates with Notch-1 expression and increases deoxyribonucleic acid (DNA) binding activity of NFKB, as impaired PDGF-D compromised NFKB activity (Wang et al., 2007; Ahmad et al., 2010). Furthermore, phospholipase D is also an important member of this molecular hierarchy including PDGF-D induced NFKB's activation. Two binding sites of NFKB are critically important for transcriptional activation of PLD-1 which is further involved in carcinogenesis (Kang et al., 2010).

Breast cancer cells migrate and metastasize over the surface and deregulation of mechanisms that limit cell migration may be predominantly important in the pathogenesis of the disease. Hence, PDGF has a significant and previously uncharacterized function in the regulation of breast cancer cell migration, and impacts distinct signaling pathways.

INTERPLAY OF PLATELET-DERIVED GROWTH FACTOR (PDGF) WITH MICRO-RNAs

It is a well acclaimed fact that interaction between cancer

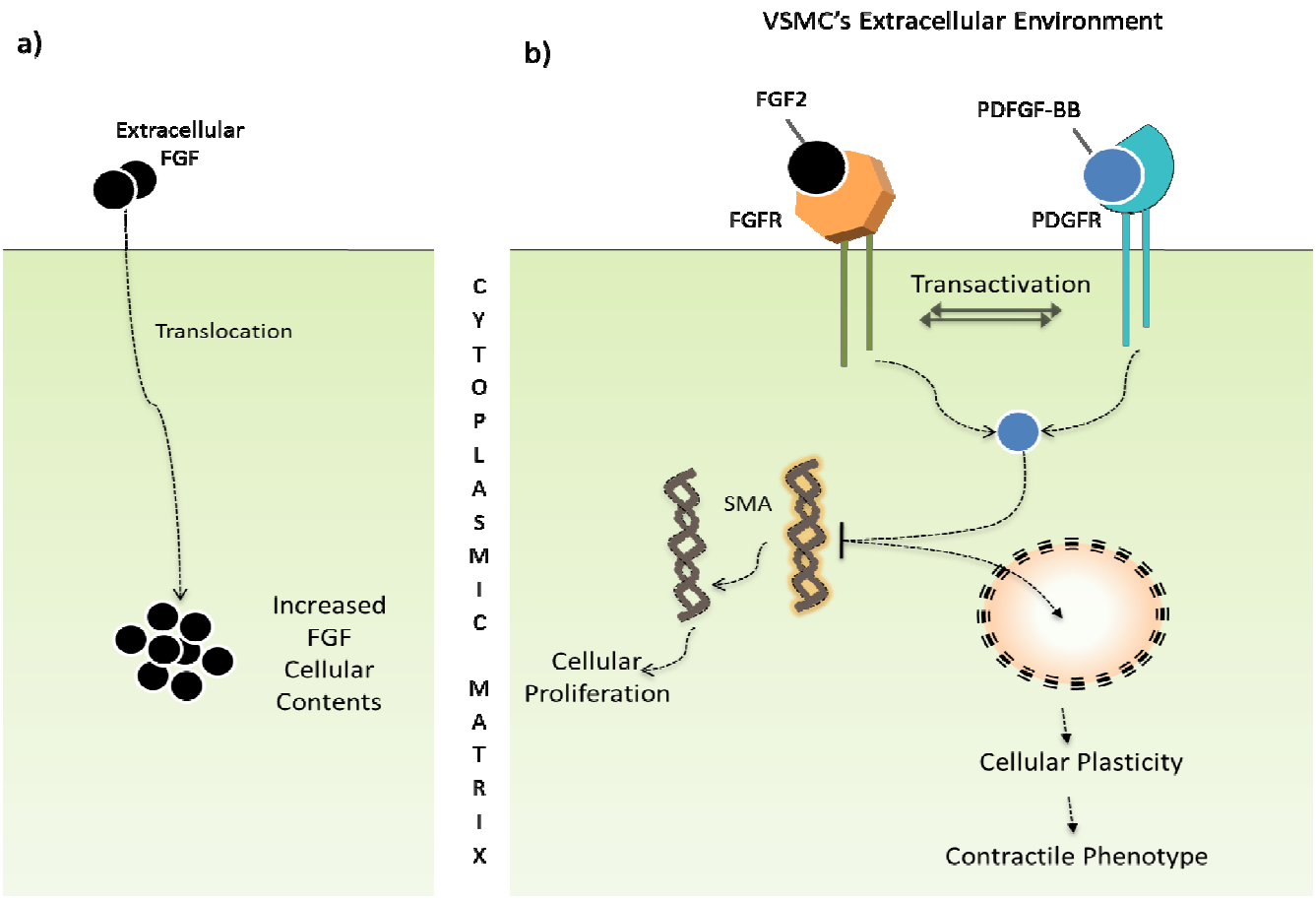

Figure 2. (a) The translocation of fibroblast growth factor which results in increased FGF cellular contents of the cell, at this stage the body of evidence states regulated PDGF/PDGFR signaling by FGF concentration, (b) Transactivation of both the receptors ,the FGFR and the PDGFR is the opening event in this mechanism, FGFR basically transactivates the PDGFR now the induced PDGF would contribute to the further signaling by deactivating the adaptor protein smooth muscle alpha actin (SMA), which normally enhances the cellular plasticity and the contractile phenotype is maintained, but in the inactive form SMA would be contributing to the cell proliferation.

cells and microenvironment has a decisive role in tumor development and progression. Even though microRNAs regulate all the key biological mechanisms, their influence on tumor microenvironment is orchestrated and co-ordinated in a spatio-temporal manner. In the upcoming section, we highlight the role of microRNAs in the tumor-supportive capacity of stromal cells.

Studies involving inhibition of PDGF implicates responsiveness of micro-ribonucleic acids (miRNAs) towards PDGF signaling. Specifically, in case of human multipotent mesenchymal stromal cells (MSC), Goff et al. (2008) suggests interplay of miRNAs with PDGF, in gene expression and differentiation (Goff et al., 2008). Recent studies about micro-RNA give us some novel approaches, like their involvement in EMT. miR-200 is down regulated by PDGF-D, further downstream signaling involves upregulation of ZEB1 (zinc-finger E-box binding homeobox 1) ZEB2 and Snail2 proteins. This phenomenon imparts invasiveness in prostate cancer cell lines (Kong et al., 2009). An antagonistic interaction prevails between PDGF and miR200. However a reasonable upregulation of ZEB is triggered by PDGF. PDGF induced miR-221 regulates signaling which is responsible for some specific gene expression in SMCs and cell proliferation. The impartment of a less contractile phenotype to the SMCs is transcriptionally induced by miR-221 when treated with PDGF, again some target genes are down-regulated like c-Kit and p27Kip1, among these the down regulation of c-Kit is very important as it further inhibits a nuclear coactivator called myocardin, so this gene expression along with the cell proliferation destines the less contractile phenotype for VSMCs (Davis et al., 2008). PDGF-BB controls the expression of miR-24 which imparts synthetic (proliferative) phenotype to the VSMC. PDGF-BB signaling prevails antagonistically with that of TGFbeta signaling, this induction leads to down-regulation of some downstream molecules like Tribbles-like protein-3 (Trb3), along with Trb3 Smad protein's expression is also compromised, and finally this anta-gonism works out with a change in synthetic phenotype

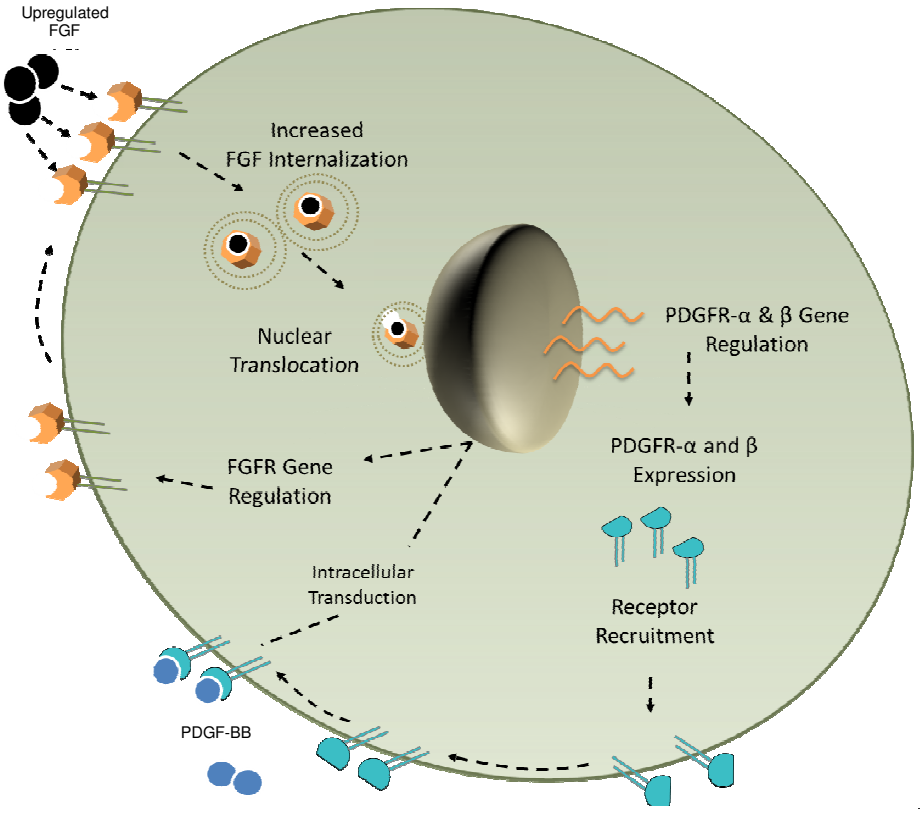

Figure 3. Autocrine pool between the PDGF-BB and FGF; the FGF transcriptionally activates the PDGF receptors which are then recruited to the membrane. FGF and PDGF trigger expression of FGFR and PDGFR respectively. There is a decrease in the number of the receptors residing in plasma membrane after consequent internalization .Therefore there is a crosstalk of the downstream proteins to switch on the expression of the receptors to sensitize the cell to the respective ligands. Ligands responsiveness depends on the population of receptors residing in the membrane.

from contractile (Chan et al., 2009). Accumulating evidence suggests a molecular circuitry in which miRNA and their correlated targets collaborate to regulate tumor expansion and invasiveness through the synchronized activity on stromal and cancer cells.

PLATELET-DERIVED GROWTH FACTOR'S (PDGF) DYNAMICS WITH LRP

LRP (LDL receptor-related protein) is involved in mediating internalization and degradation of PDGFR in collaboration with Cbl, knockdown of LRP masks PDGFR from degradation by Cbl; however, an intriguing observation was made by Takayama et al. (2005), that ablation of LRP did not affect the rate of recycling, rather, there was an increase in the degradation and endocytosis of PDGFR. Simultaneously kinase activity of PDGFR is remarkable. This aspect is puzzling because internalization of the receptor might not effect the kinase activity, however despite the degradation of receptor any kinase activity depicted, gave a clue that any other kinase enzyme is involved. PDGFR is actively engaged in communicating the signals from extracellular environment to the cytoplasm. Factor VII-activating protease (FSAP) is involved in cleaning PDGF protein however its activity is inhibited when it gets complexes with PN-I, this hetrodimer has an enhanced affiliation for LRP and it internalizes this protein complex, if an interactive crosstalk is established between hetrodimer and LRP's, it sequesters LRP from PDGFR as a result of which PDGFR is not internalized and stays embedded in the plasma membrane, offering a binding site to PDGF and signal transduction initiates, hence forth PDGF is protected from cleavage by FSAP; and LRP is detached from PDGFR that maintains required density of the receptors on the membrane (Muhl et al., 2007).

LRP works synchronously with PDGFR to initiate PI3K dependent signaling, which is essential for maintaining vascular integrity (Zhou et al., 2009). LRP is also necessary for ERK activation, so LRP works concomitantly with PDGFR; abrogated LRP blunts the activity of ERK. This aspect rules out the presumed role of ERK to be a potential candidate for kinase activity or kinase activity in LRP deficient cells (Muratoglu et al., 2010).

LRP also intervenes in PDGF ligand and receptor expression triggered by TGF mediated signaling, TGF induces expression of the target genes via SMAD proteins which moves into the nucleus and switches on PDGF and PDGFR. However, there is desensitization to TGF mediated signaling, if LRP or HHM (human homologue of Maid) quench or extinguishes the signals generated by TGF (Boucher et al., 2007) or in case the PDGFR is recycled back. The recycling mechanisms include different inducers and ablators like, there is a molecular sea-saw of PKC (protein kinase c) and TC-PTP (T-cell protein tyrosine phosphatase), the resulting ups and downs of these two proteins dictate endocytosis or recycling of PDGFR, PKC and TC-PTP work in an anti parallel manner. PTP attenuates recycling and enhances endocytosis. Conversely PKC is involved in the recycling of the receptor via Rab4a (Hellberg et al., 2009).

PLATELET-DERIVED GROWTH FACTOR (PDGF) AND DORSAL RUFFLE FORMATION

PDGF shows response in dorsal ruffle formation when actin cytoskeleton is activated by mitogens activity. mAbp1 (Mammalian actin-binding protein-1) has been accused of mediating clathrin mediated endocytosis and is necessary for PDGF-mediated dorsal ruffle formation and localization. mAbp1 hampers directly with actin regulatory protein WIP (WASp-interacting protein). This interaction is critical in the dorsal ruffle formation and the SH3 domain of WIP is responsible for this concurrence (Cortesio et al., 2010). In concordance with the assumption that PDGFR is involved in dorsal ruffle formation, another protein cdc-42 interacting protein 4 (CIP4) was observed to downregulate the PDGFR which blunted ruffle formation. However knockdown of CIP4 recapacitated dorsal ruffle formation and cellular migration. This evidence strengthens the potential role of PDGFR in dorsal ruffle formation. The exact mechanism of CIP4-like proteins was revealed by its experimental deregulation. These results suggest a role of CIP4-like proteins in membrane tubulation. CIP4-like proteins regulates internalization of PDGFβ receptor which in turn has an affect on PDGF-dependent activities like actin reorganization and cell migration (Toguchi et al., 2010).

PLATELET-DERIVED GROWTH FACTOR (PDGF) AND HETRO-NUCLEAR RIBONUCLEOPROTEIN

PDGF induced the ubiquitination and degradation of MRLC (mRNA-encoding myosin regulatory light-chain) by MIR (MRLC-interacting protein). The activity of MIR is dependent on its association with a binding partner hnRNP (heterogeneous nuclear ribonucleoprotein), protection of MRLC's degradation by MIR inhibits novel dynamics of the cell which includes wound healing, wound healing was compromised in the cell line deficient for MIR (Nagano et al., 2006). Similarly PDGF has a dominant role in inhibiting the shuttling of hnRNP's from nucleus to the cytoplasm, but if there is an impaired PDGF signaling it would facilitate the trafficking of hnRNP's from the nucleus to cytoplasm. This is indicative of the fact that PDGF is involved in dual activities, one is that, it strictly inhibits hnRNP's in the nuclear premises but conversely it is also involved in executing various cytoplasmic dynamics with the courtesy of hnRNPK (Van der et al., 2000).

PLATELET-DERIVED GROWTH FACTOR (PDGF) AND NON-INVASIVE EPITHELIAL MESENCHYMAL TRANSITION (EMT)

Another aspect of PDGF signaling is that it is involved in epithelial mesenchymal transition (EMT) but scrupulously involved in resisting cellular migration, which is an aspect of non invasive tumor in this condition this was observed that PDGF was independent without using TGFR mediated signal transduction which is a usual path. EMT was observed in both SMAD competent and deficient cells, which proves that PDGF mediated EMT is respective of TGF signaling (Ikushima et al., 2008). The novel findings also show that PDGF had a role in non-invasive EMT, in this mechanism there is again no correlation between TGFβ/Smad signaling with that of PDGF. The phenomenon was confirmed in mesothelial cells by an increased SNAIL and decreased E-Cadherin expression with presence of epithelial and mesenchymal markers (Pranali et al., 2010).

THERAPEUTIC DIMENSIONS OF PLATELET-DERIVED GROWTH FACTORS (PDGFS)

Despite considerable advancement in understanding the PDGF-signaling network, effective therapies remain inadequate due to unsatisfactory disruption of oncogenic pathways, drug resistance and drug-induced toxicity. This intricacy of cancer defines a vital goal for researchers and clinicians to develop novel therapeutic interventions.

PDGF dimers are documented to portray a cell survival landscape via phosphorylation of GSK. It executes the pro-survival effect by inducing serious modifications in GSK. In a recent experimental approach, Kumar et al. (2010) showed that PDGF-DD is specifically a regulator of angiogenic and apoptotic molecules like GSK3β, which is found to be upregulated in pathological angiogenic conditions. The PDGF's working mechanism is basically the phosphorylation of Ser at 9th and dephosphorylation of Tyr at 216th residues rendering the cell more viable for survival. Further more in antiangiogenic activity would critically require GSK3β, when experimented on PDGF-DD gene (Kumar et al., 2010). Likewise the role of PDGF-DD reported by Kumar et al. (2010), PDGF-CC is also a candidate of GSK3β's regulator and is said to have

a roleplay in neuroprotection. The PDGF-CC gene infection to the cells confirm, that it's having an anti apoptotic role, this observation was made in neuronal cells of both brain and retina. So, it could play its role in treatment of neurodegenerative diseases (Tang et al., 2010).

Leukemic cells display a dense PDGFR- β localization in the membrane. It was involved in the downstream activation of PKB. However, treatment of leukemic cells with neutralizing antibody of PDGFBB attenuated the signal transduction. On a similar note, hepatic stellate cells have a robust expression of PDGFR-β and IGFR. Both receptors work in collaboration to induce molecular connivance. Treatment of liver cells with EGCG down-regulates the expression of both receptors (Yasuda et al., 2009; Yang et al., 2009).Same PDGFR-β was abrogated in liver cells using a dominant negative PDGFR-β that blunted the proliferation aspect of hepatic cells. Therefore RNA interference of this receptor might play an imperative role in producing an antineoplastic effect. Multiple receptor kinase inhibitors have more pronounced effect in terms of therapy as tumorigenesis or any other molecular discrepancy is addressed in amore broader manner (Erawan et al., 2004; Chen et al., 2008; Yuqing et al., 2009). PDGF has a considerable role in cardiac therapy. In accordance with the approach, intramyocardial administration of PDGF could be good therapeutic agent for patients having myocardiac infarction (Patrick et al., 2006; Hiranmoy et al., 2009). A number of experimental approaches to remuscularize the injured heart by means of adult stem cells and pluripotent stem cells, cellular reprogramming and tissue engineering are underway. Even though many challenges remain, these interventions may ultimately lead to improved approaches to treat or prevent heart failure. However detailed study in animal models is unavoidable to get a step closer to translational medicine. Interstitial fluid pressure is one of the hindrances faced while treating neoplastic cells. This pressure could be reduced by intervening some normal signaling mechanisms, specifically PDGF and vascular endothelial growth factor (VEGF) signaling when blocked would increase vascular remodeling and decrease vascular leakiness.Specific inhibitors can be used in combinations to make this happen by targeting the kinase activity of receptors involved (Agnieszka et al., 2009). PDGF is also having a therapeutic role in osteoporosis and bone repair, bone formation and fracture healing are some aspects of PDGF. PDGF-BB and up to some extent PGF- AA could be thus vast therapeutic entities for the treatment of osteoporosis and bone malfunctions. In case of bone malfunctioning α-receptor targeting is a probable anabolic enhancer of bone metabolism in humans (Simon et al., 2009). Further more PDGF-BB has a role in wound healing, adenovirus based gene delivery system brings about a remarkable change in the bone repair mechanism, and the phenomenon was dose dependent. This depicts the potential of PDGF-BB as a regenerative agent as well as its involvement in tissue and osseointegration (Chang et al., 2010). Undeniably, after the completion of target validation for several candidates, the development of therapeutic PDGF is now moving to a new stage that encompasses pharmacological drug delivery, preclinical toxicology and regulatory guidelines.

CONCLUSIONS

It is noteworthy that emergence of tumour-specific, molecularly targeted agents underscores a paradigm shift in cancer therapeutics, with lesser reliance on therapeutic interventions that non-discriminately kill tumour and host cells. Even though the multiplicity of targets giving rise to this new-fangled generation of anticancer drugs has expanded, many challenges persist in the design of individualized medicine. The multipart interplay of signal-transduction cascades is an additional roadblock that complicates the customization of cancer treatments to target single mechanisms.

It is intriguing to note that MicroRNAs (miRNAs) offer new therapeutic targets for many cellular disorders, as their multidimensional roles in development and cellular processes make them interesting to explore. We still do not fully comprehend the molecular mechanisms by which miRNAs mediate transcriptome nor do we know the entire repertoire of mRNAs each miRNA regulates. Nonetheless, recent advancement in the development of effective rational drug design to block miRNAs suggests that anti-miRNA drugs may be a new frontier in translational oncology.

REFERENCES

Agnieszka KW, Yoko H, Mikhail B, Aive Å, Linda S, Ingrid M, Rolf KR, Kristofer R, Carina H, Carl-Henrik H (2009). Combined Anti-Angiogenic Therapy Targeting PDGF and VEGF Receptors Lowers the Interstitial FluidPressure in a Murine Experimental Carcinoma. PLoS One, 4(12): e8149.

Ahmad A, Wang Z, Kong D, Ali R, Ali S, Banerjee S, Sarkar FH (2010). Platelet-derived growth factor-D contributes to aggressiveness of breast cancer cells by up-regulating Notch and NF-kappaB signaling pathways. Breast Cancer Res. Treat., April 9.

Almendral JM, Sommer D, MacDonald-Bravo H, Bruckhardt J, Perera J, Bravo R (1988). Complexity of the early genetic response to growth factors in mouse fibroblasts. Mol. Cell. Biol., 8: 2140-2148.

Anil K, Xu H, Chunsik L, Yang L, Arvydas M, Zhongshu T, Fan Z, Harald FL, Pachiappan A, Lijin D, Zhijian W, Linda YZ, Lianchun W, Wang M, Peter C, Triantafyllos C, Xuri L (2010). Platelet-derived Growth Factor-DD Targeting Arrests Pathological Angiogenesis by Modulating Glycogen Synthase Kinase-3β Phosphorylation. J. Biol. Chem., 285: 15500-15510.

Bergsten E, Uutela M, Li X, Pietras K, Ostman A, Heldin CH, Alitalo K, Eriksson U (2001). PDGF-D is a specific protease-activated ligand for the PDGF beta-receptor. Nat. Cell Biol., 3: 512-516.

Bilato C, Pauly RR, Melillo G, Monticone R, Gorelick-Feldman D, Gluzband YA, Sollott SJ, Ziman B, Lakatta EG, Crow MT (1995). Intracellular signaling pathways required for rat vascular smooth muscle cell migration: interactions between basic fibroblast growth factor and platelet-derived growth factor. J. Clin. Invest., 96: 1905-1915

Boucher P, Li WP, Matz RL, Takayama Y, Auwerx J, Anderson RG, Herz J (2007). LRP1 functions as an atheroprotective integrator of TGFbeta and PDFG signals in the vascular wall: implications for Marfan syndrome. PLoS One, 2(5): e448.

Bowen-Pope DF, Hart CE, Seifert RA (1989). Sera and conditioned media contain different isoforms of platelet-derived growth factor (PDGF) which bind to different classes of PDGF receptor. J. Biol. Chem., 264: 2502-2508.
Carl HH, Eriksson U, Ostman A (2002). New members of the platelet-derived growth factor family of mitogens. Arch, Biochem, Biophys., 398(2): 284-90.
Chan MC, Hilyard AC, Wu C, Davis BN, Hill NS, Lal A, Lieberman J, Lagna G, Hata A (2009). Molecular basis for antagonism between PDGF and the TGFbeta family of signalling pathways by control of miR-24 expression. EMBO J., 29(3): 559-573.
Chang PC, Seol YJ, Cirelli JA, Pellegrini G, Jin Q, Franco LM, Goldstein SA, Chandler LA, Sosnowski B, Giannobile WV (2010). PDGF-B gene therapy accelerates bone engineering and oral implant osseointegration. Gene. Ther., 17(1): 95-104.
Changsirikulchai S, Hudkins KL, Goodpaster TA, Volpone J, Topouzis S, Gilbertson DG, Alpers CE (2002). Platelet-derived growth factor-D expression in developing and mature human kidneys. Kidney Int. 62: 2043-2054.
Chen PY, Simons M, Friesel R (2009). FRS2 via fibroblast growth factor receptor 1 is required for platelet-derived growth factor receptor beta-mediated regulation of vascular smooth muscle marker gene expression. J. Biol. Chem., 284(23): 15980-15992.
Chen SW, Chen YX, Zhang XR, Qian H, Chen WZ, Xie WF (2008). Targeted inhibition of platelet-derived growth factor receptor-β subunit in hepatic stellate cells ameliorates hepatic fibrosis in rats. Gene. Ther. 15: 1424-1435.
Chun-Chao W, Murat C, Jason MH (2009). PI3K-dependent cross-talk interactions converge with Ras as quantifiable inputs integrated by Erk. Mol. Syst. Biol., 5: 246.
Cochran BH, Reffel AC, Stiles CD (1983). Molecular cloning of gene sequences regulated by platelet-derived growth factor. Cell, 33: 939-947.
Cortesio CL, Perrin BJ, Bennin DA, Huttenlocher A (2010). Actin-binding protein-1 interacts with WASp-interacting protein to regulate growth factor-induced dorsal ruffle formation. Mol. Biol. Cell., 21(1): 186-197.
Davis BN, Hilyard AC, Nguyen PH, Lagna G, Hata A (2009). Induction of microRNA-221 by platelet-derived growth factor signaling is critical for modulation of vascular smooth muscle phenotype. J. Biol. Chem., 284(6): 3728-38.
Erawan BK, Jens H, Doris S, Jens T, Axel MG, Ralf W (2004). Dominant-negative soluble PDGF-β receptor inhibits hepatic stellate cell activation and attenuates liverfibrosis. Lab. Invest. 84: 766-777.
Goff LA, Boucher S, Ricupero CL, Fenstermacher S, Swerdel M, Chase LG, Adams CC, Chesnut J, Lakshmipathy U, Hart RP (2008). Differentiating human multipotent mesenchymal stromal cells regulate microRNAs: prediction of microRNA regulation by PDGF during osteogenesis. Exp. Hematol., 36(10): 1354-1369.
Gronwald RG, Grant FJ, Haldeman BA, Hart CE, O'Hara PJ, Hagen FS, Ross R, Bowen-Pope DF, Murray MJ (1988). Cloning and expression of a cDNA coding for the human platelet-derived growth factor receptor: evidence for more than one receptor class PNAS, 85(10): 3435-3439.
Heldin CH, Westermark B (1990). Signal transduction by the receptors for platelet-derived growth factor. J. Cell Sci. 96: 193-196.
Hellberg C, Schmees C, Karlsson S, Ahgren A, Heldin CH (2009). Activation of protein kinase C alpha is necessary for sorting the PDGF beta-receptor to Rab4a-dependent recycling. Mol. Biol. Cell, 20(12): 2856-2863.
Hiranmoy D, Jon CG, Matthew J, Manjusri D, Nasreen A, Anna B, Mahmood K, Ramasamy S, Hai-Quan M, Brian DH, Periannan K, Vincent JP (2009). Stem Cell Therapy with Overexpressed VEGF and PDGF Genes Improves Cardiac Function in a Rat InfarctModel. PLoS One, 4(10): e7325.
Ikushima H, Komuro A, Isogaya K, Shinozaki M, Hellman U, Miyazawa K, Miyazono K (2008). An Id-like molecule, HHM, is a synexpression group-restricted regulator of TGF-beta signalling. EMBO J., 27(22): 2955-2965.
Jie L, Yuquan W, Kang L, Chuang Y, Yajuan T, Qingali Q, Ping C, Wei W, Huozhen H, Li Y (2010). Synergistic effects of FGF-2 and PDGF-BB on angiogenesis and muscle regeneration in rabbit hind limb ischemia model. Microvasc Res., 80(1): 10-7.
Kang DW, Min DS (2010). Platelet derived growth factor increases phospholipase D1 but not phospholipase D2 expression via NFkappaB signaling pathway and enhances invasion of breast cancer cells. Cancer Lett., 294(1): 125-133.
Kong D, Li Y, Wang Z, Banerjee S, Ahmad A, Kim HR, Sarkar FH (2009). miR-200 regulates PDGF-D mediated epithelial-mesenchymal transition, adhesion, and invasion of prostate cancer cells. Stem. Cells, 27(8): 1712-21.
Kumar A, Hou X, Lee C, Li Y, Maminishkis A, Tang Z, Zhang F, Langer HF, Arjunan P, Dong L, Wu Z, Zhu LY, Wang L, Min W, Colosi P, Chavakis T, Li X (2010). Platelet-derived growth factor-DD targeting arrests pathological angiogenesis by modulating glycogensynthase kinase-3beta phosphorylation. J. Biol. Chem., 285(20): 15500-10.
Lahsnig C, Mikula M, Petz M, Zulehner G, Schneller D, van Zijl F, Huber H, Csiszar A, Beug H, Mikulits W (2009). ILEI requires oncogenic Ras for the epithelial to mesenchymal transition of hepatocytes and liver carcinoma progression. Oncogene, 28(5): 638-650.
Laila JR, Jan EV, Johan RL (2005). Structural and functional specificities of PDGF-C and PDGF-D, the novel members of the platelet-derived growth factors family. FEBS J., 272(22): 5723-41.
Lars JN, Renhai C, Eva-Maria H, Zongwei W, Xing Z, Daniel W, Keiko F, Ebba B, Yihai C (2007). Angiogenic factors FGF2 and PDGF-BB synergistically promote murine tumor neovascularization and Metastasis. J. Clin. Invest., 117(10): 2766-2777.
Linzer DIH, Nathans D (1983). Growth-related changes in specific mRNAs of cultured mouse cells. PNAC USA 80, 4271-4275.
Li X, Ponten A, Aase K , Karlsson L, Abramsson A, Uutela M, Backstrom G, Hellstrom M, Bostrom H, Li H, Soriano P, Betsholtz C, Heldin CH, Alitalo K, Ostman A, Eriksson U (2000). PDGF-C is a new protease-activated ligand for the PDGF alpha-receptor. Nat. Cell Biol., 2: 302-309.
Malecki J, Wesche J, Skjerpen CS, Wiedlocha A, Olsnes S (2004). Translocation of FGF-1 and FGF-2 across vesicular membranes occurs during G1-phase by a common mechanism. Mol. Biol. Cell, 15: 801-814.
Martin J, Andreas S, Richard M, Peter S, Norbert K, Paola C, Michael D, Carlos CC, Hartmut B, Stefan G (2006). Autocrine PDGFR signaling promotes mammary cancer metastasis. J. Clin. Invest., 116(6): 1561-1570.
Muhl L, Nykjaer A, Wygrecka M, Monard D, Preissner KT, Kanse SM (2007). Inhibition of PDGF-BB by Factor VII-activating protease (FSAP) is neutralized by protease nexin-1, and the FSAP-inhibitor complexes are internalized via LRP. Biochem. J., 404(2): 191-196.
Muratoglu SC, Mikhailenko I, Newton C, Migliorini M, Strickland DK (2010). Low density lipoprotein receptor-related protein 1 (LRP1) forms a signaling complex with platelet-derived growth factor receptor-beta in endosomes and regulates activation of the MAPK pathway. J. Biol. Chem., 285(19): 14308-14317.
Myler HA, West JL (2000). Heparanase and platelet factor-4 induce smooth muscle cell proliferation and migration via bFGF release from the ECM. J. Biochem., 131: 913-922.
Nagano K, Bornhauser BC, Warnasuriya G, Entwistle A, Cramer R, Lindholm D, Naaby-Hansen S (2006). PDGF regulates the actin cytoskeleton through hnRNP-K-mediated activation of the ubiquitin E3-ligase MIR. EMBO J., 25(9): 1871-82.
Patrick CH, Hsieh MD, Catherine MAD, Joseph G, Francisco UCMS, Richard TL (2006). Local Controlled Intramyocardial Delivery of Platelet-Derived Growth Factor Improves Post infarctionVentricular Function without Pulmonary Toxicity. Circulation. 114: 637-644.
Pintucci G, Yu PJ, Saponara F, Kadian-Dodov DL, Galloway AC, Mignatti P (2005). PDGF-BB induces vascular smooth muscle cell expression of high molecular weight FGF-2, which accumulates in the nucleus. J. Cell Biochem., 95(6): 1292-300.
Pranali P, Judy WM, Martin K, Juan-Carlos R, Catherine MH, Peter JM (2010). Platelet derived growth factor B and epithelial mesenchymal transition of peritoneal mesothelial cells. Matrix Biol. 29(2): 97-106.
Rapraeger AC, Krufka A, Olwin BB (1991). Requirement of heparan sulfate for bFGF-mediated fibroblast growth and myoblast differentiation. Science, 252: 1705-1708.
Rauch BH, Millette E, Kenagy RD, Daum G, Clowes AW (2004).

Thrombin- and factor Xa-induced DNA synthesis is mediated by transactivation of fibroblast growth factor receptor-1 in human vascular smooth muscle cells. Circ. Res., 94: 340-345.
Renhai C, Meit AB, Piotr R, Steve C, Stina G, Dagmar G, Björn M, Fumitaka I, Katerina T, Steen D, Toshio O, David GJ, Yihai C (2004). PDGF-BB induces intratumoral lymphangiogenesis and promotes lymphatic metastasis. Cancer Cell. 6(4): 333-45.
Rhoads DN, Eskin SG, McIntire LV (2000). Fluid flow releases fibroblast growth factor-2 from human aortic smooth muscle cells. Arterioscler Thromb Vasc. Biol., 20: 416.
Romashkova JA, Makarov SS (1999). NF-kappaB is a target of AKT in anti-apoptotic PDGF signalling Nature. 401(6748): 86-90.
Simon G, Andreas L, Marie L, Manolis H, Athanasios M, Eleftherios T (2009). Investigating the role of PDGF as a potential drug therapy in bone formation and fracture healing. Expert Opin. Investig. Drugs. 18(11): 1633-1654.
Sun PD, Davies DR (1995). The cystine-knot growth-factor superfamily. Ann. Rev. Biophys. Biomole. Struct. 24: 269-91.
Takayama Y, May P, Anderson RG, Herz J (2005). Low density lipoprotein receptor-related protein 1 (LRP1) controls endocytosis and c-CBL-mediated ubiquitination of the platelet-derived growth factor receptor beta (PDGFR beta). J. Biol. Chem., 280(18): 18504-18510.
Tang Z, Arjunan P, Lee C, Li Y, Kumar A, Hou X, Wang B, Wardega P, Zhang F, Dong L, Zhang Y, Zhang SZ, Ding H, Fariss RN, Becker KG, Lennartsson J, Nagai N, Cao Y, Li X (2010). Survival effect of PDGF-CC rescues neurons from apoptosis in both brain and retina by regulatingGSK3beta phosphorylation. J. Exp. Med., 207(4): 867-880.
Toguchi M, Richnaua N, Ruusala A, Aspenström P (2010). Members of the CIP4 family of proteins participate in the regulation of platelet-derived growth factor receptor-beta-dependent actin reorganization and migration. Biol. Cell, 102(4): 215-230.
Van der H, Van Oordt W, Diaz-Meco MT, Lozano J, Krainer AR, MoscatJ, Cáceres JF (2000). The MKK (3/6)-p38-signaling cascade alters the subcellular distribution of hnRNP A1 and modulates alternative splicing regulation. J. Cell Biol., 149(2): 307-316.
Wang Z, Kong D, Banerjee S, Li Y, Adsay NV, Abbruzzese J, Sarkar FH (2007). Down-regulation of platelet-derived growth factor-D inhibits cell growth and angiogenesis through inactivation of Notch-1 and nuclear factor-kappaB signaling. Cancer Res., 67(23): 11377-11385.
Xuri Li, Ulf E (2003). Novel PDGF family members: PDGF-C and PDGF-D. Cytokine & growth factor reviews 14(2): 91-98.
Yang J, Liu X, Nyland SB, Zhang R, Ryland LK, Broeg K, Baab KT, Jarbadan NR, Irby R, Loughran TP (2010). Platelet-derived growth factor mediates survival of leukemic large granular lymphocytes via anautocrine regulatory pathway. Blood, 115(1): 51-60.
Yasuda Y, Shimizu M, Sakai H, Iwasa J, Kubota M, Adachi S, Osawa Y, Tsurumi H, Hara Y, Moriwaki H (2009). (-)-Epigallocatechin gallate prevents carbon tetrachloride-induced rat hepatic fibrosis by inhibiting theexpression of the PDGFRbeta and IGF-1R. Chem. Biol. Interact., 182(2-3): 159-64.
Yihai C, Renhai C, Eva-Maria H (2008). Regulation of tumor angiogenesis and metastasis by FGF and PDGF signaling pathways. J. Mole. Med., 86(7): 785-789.
Yuqing L, Xiao MW, Eric LHL, Scott LF, Wei C, Nancy PSH, Lei L, Tao Y, Sheung TF, Hui Z (2009). Therapeutic targeting of the PDGF and TGF-β-signaling pathways in hepatic stellate cells byPTK787/ZK22258. Lab. Investig., 89: 1152-1160.
Zhou L, Takayama Y, Boucher P, Tallquist MD, Herz J (2009). LRP1 regulates architecture of the vascular wall by controlling PDGFRbeta-dependent phosphatidylinositol 3-kinase activation. PLoS One, 4(9): e6922.