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Review

Investigating the potential role of platelet derived growth factor (PDGF)

Syed Shoaib Ahmed[1], Atif Adnan[1], Anam Batool[1], Ziaur Rahman[1], Muhammad Ilyas[1] and Syyada Samra Jafri[1]*

[1]University of Lahore, Pakistan.
[2]National Centre of Excellence in Molecular Biology, University of the Punjab, Lahore, Pakistan.

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PDGF is a growth factor and is extensively involved in multi-dimensional cellular dynamics. It switches on a plethora of molecules other than its classical pathway. It is engaged in various transitions of development however if the unleashed potentials lead astray it brings forth tumorigenesis. Conventionally, it has been assumed that the components of this signaling pathway show fidelity and act with a high degree of autonomy. However, as illustrated by the PDGF signal transduction, reinterpretation of recent data suggests that machinery is often shared between multiple pathways and other components crosstalk to each other through multiple mechanisms. There is a very indiscriminate line that demarcates between normal division and neoplasia. A number of unidentified proteins might be instrumental to this transition. The signal perpetuation is a remarkable portfolio of tumor progression.

Key words: Neoplasia, platelet derived growth factor, fibroblast growth factor-2, mitogen activating protein kinase, epithilial mesenchymal transition.

INTRODUCTION

PDGFs are the growth factors which have a broad spectrum of implications. These factors are involved in multifaceted mechanistic details. Various activities of the cell are triggered ranging from organogenesis to the repair. The amplitude of the signals determines the fate of the cell. In case of derailed or deregulated transduction, error prone activities are instigated.

The platelet derived growth factor belongs to the family of mitogens (Carl et al., 2002), the growth factor super-family (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 while the novel studies depict that PDGF has two more isoformic mitogen members PDGF-C and PDGF-D (Xuri and Eriksson, 2003; Figure 1). The PDGF is found as dimeric form by the combination of two polypeptide chains, these could make different combinations e.g. 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).(Xuri 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).

THE ROLE OF PLATELET DERIVED GROWTH FACTOR IN CONTEXT OF SMOOTH MUSCLE CELL'S REGULATION

The platelet derived growth factor along with the basic

*Corresponding author. E-mail: samra_syeda02pk@yahoo.com.

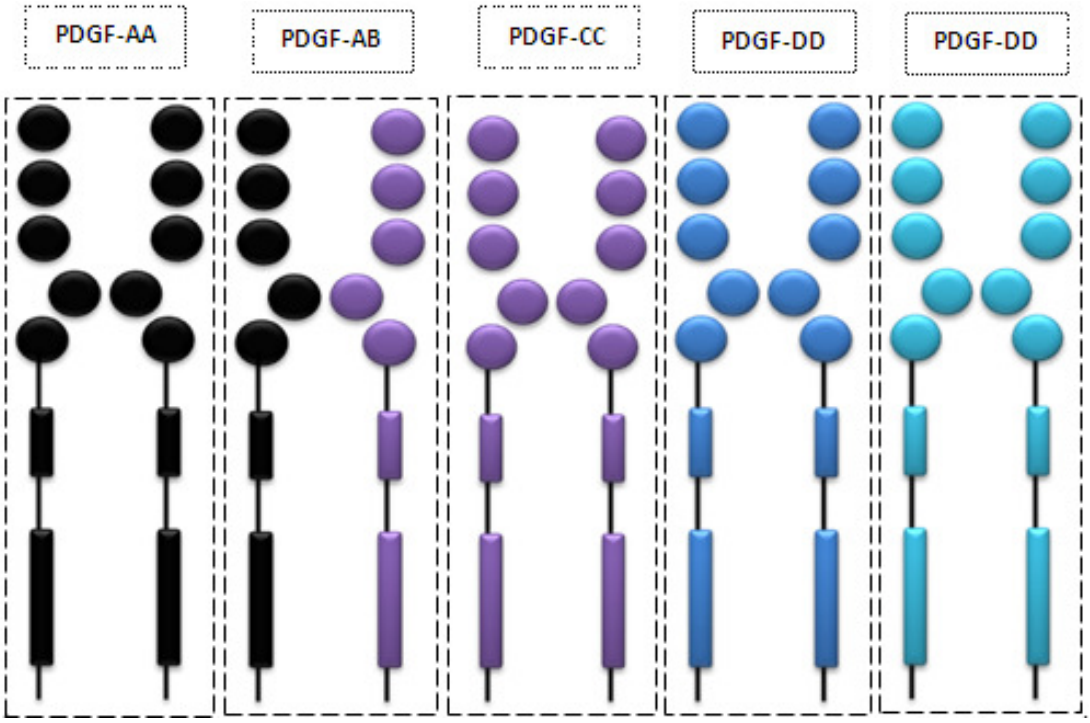

Figure 1. PDGF'S isoforms. The dimeric forms of PDGF, these are usually the combination of two polypeptide chains making homodimeric or hetrodimeric combinations. They are PDGF-AA, PDGF-BB,PDGF-CC AND PDGF-DD. Both PDGF-A and PDGF-B are found in hom and heterodimeric forms while the PDGF-C AND PDGF-Dpnly had homodimeric form.

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 the PDGF, PDGFR and FGF2 act collaboratively to downregulate the expression of SMA, as without inhibition of SMA the plasticity of VSMC is not compromised (Chen et al., 2009). In vascular smooth muscle cells 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 (Rapraeger et al., 1991; Rhoads et 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 2b).

ROLE OF 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

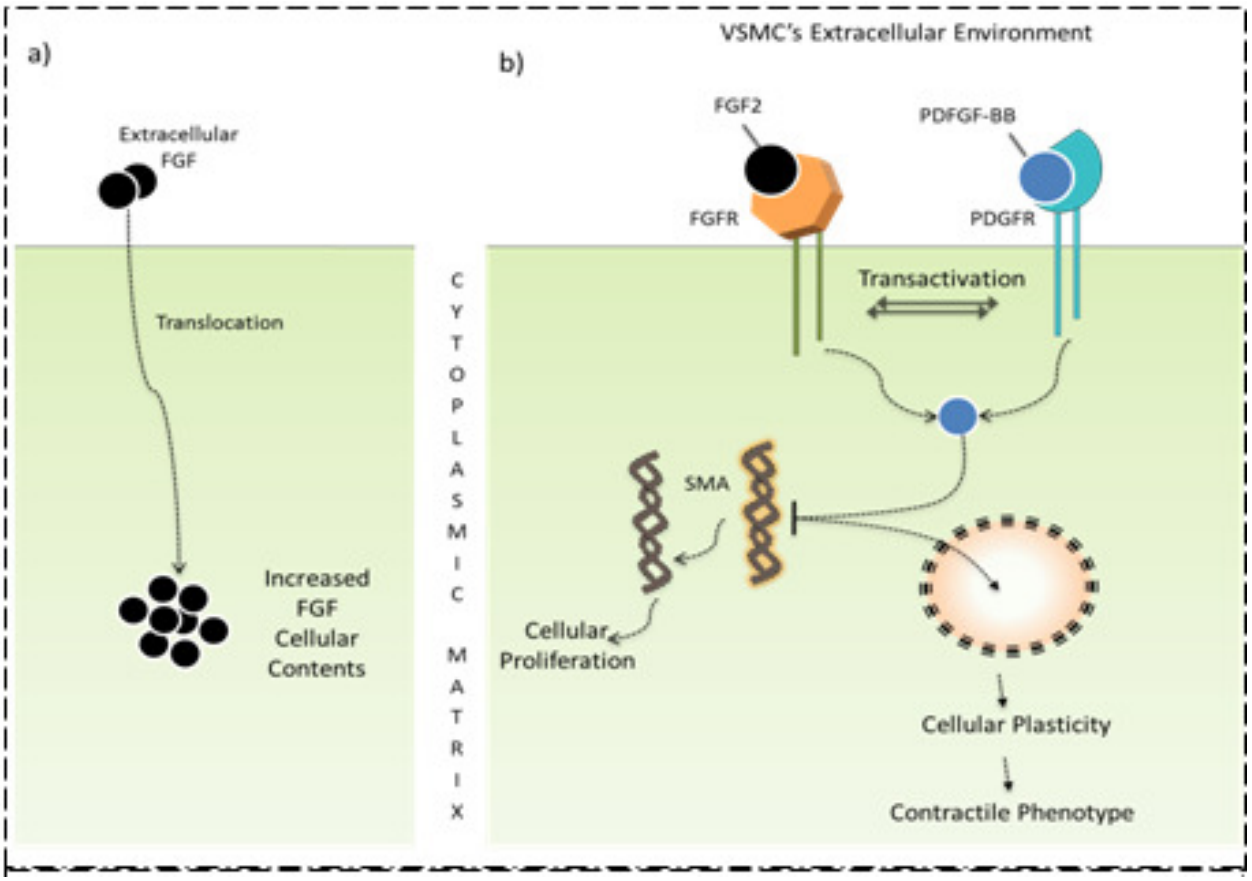

Figure 2. (a) FGF Translocation, The translocation of fibroblast growth factor which results in increased FGF cellular contents of the cell, at this stage the body of evidence states regulated PDGF/PDGFR signaling by FGF concentration; (2b) Transactivating activity of FGF2 and PDGF-BB, Transactivation 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.

and -β expression at transcription level, similarly PDGF-BB enhances the cell's response by upregulation of FGFR-1, so that's how both these 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 TGF-β, this correlated activity of PDGF is autocrine in which first the RAS molecule is capacitated which modulates PI3K pathway, so 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, this enhanced regulation is both 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

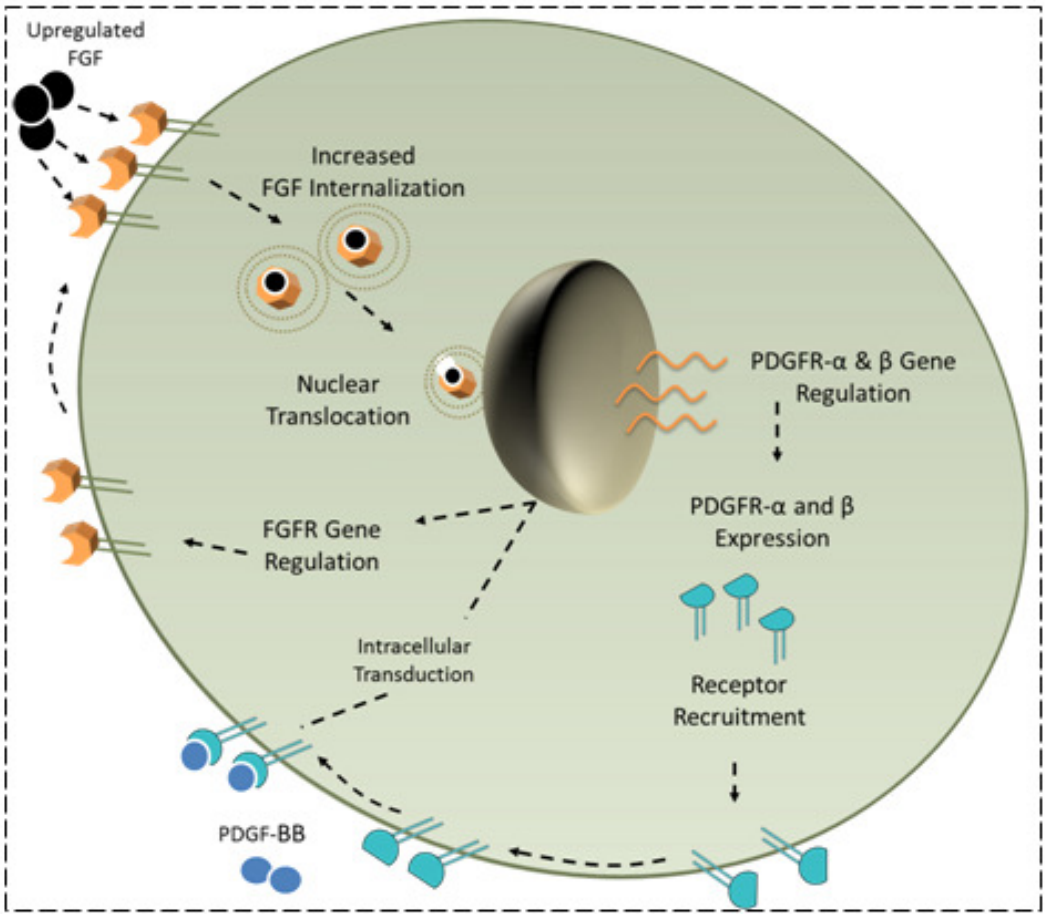

Figure 3. Autocrine Pool between the PDGF-BB and FGF: The FGF transcriptionally activates the PDGF receptors which are then recruited to the membrane. FGF and PDGF trigger expression of FGFR and PDGFR respectively. There is a decrease in the number of the receptors residing in plasma membrane after consequent 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.

activity after being induced by PDGF transcriptionally, through RAS and PI3K pathways, so NFKB being the target, links the anti-apoptotic signaling with transcript-tional 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 anti-angiogenic activity, so PGDF-DD can be a therapeutic target for neovascular diseases (Kumar et al., 2010).

ROLE OF 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 DNA binding activity of NFKB, as impaired PDGF-D compromised NFKB activity (Ahmad et al., 2010; Wang et al., 2007). 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 isfurther involved in carcinogenesis (Kang et al., 2010).

INTERPLAY OF PDGF WITH MICRO RNAS

Studies involving inhibition of PDGF implicates responsiveness of 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 downregulated 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 downregulated like c-Kit and p27Kip1, among these the downregulation 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., 2009). 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 downregulation of some downstream molecules like Tribbles-like protein-3 (Trb3), along with Trb3 Smad protein's expression is also compromised, and finally this antagonism works out wit a change in synthetic phenotype from contractile (Chan et al., 2009).

PDGF'S 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 (Takayama et al., 2005). PDGFR is actively engaged in communicating the signals from extracellular environment to the cytoplasm. 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 internalizes an stays embedded in the plasma membrane, offering a binding site to PDGF and signal transduction initiates, henceforth 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 a 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).

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 the 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, 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).

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, this 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).

PDGF AND NON INVASIVE 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 PDGFS

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 confirms, that it exhibits an anti apoptotic role, this observation was made in neuronal cells of both brain and retina.sos 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 the receptors work in collaboration to induce molecular connivance. Treatment of liver cells with EGCG downregulates the expression of both receptors (Yasuda et al., 2009, Yang et al., 2010). 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, organs when usually treated locally do not toxify other organs, so PDGF was intramyocardially administered to throw some lime light on the PDGF's involvement in cardiac therapy, the results clearly prescribes PDGF as a cardiac performance enhancer and could be good therapeutic agent for patients having Myocardiac infarction (Patrick et al., 2006, Hiranmoy et al., 2009). 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 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 enha-ncer 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).

CONCLUSIONS

There is an immense repercussion of PDGF on the plasticity of the cell. The PDGF transduction cascade is

instrumental to the cellular remodeling. The basic framework of the cell is reoriented and restructured to dedicate the transition. The PDGF ligand triggers the expression of PDGFR and FGFR. This captivating feature of PDGF enhances the FGF signaling as thee is an enhanced migration of the newly synthesized receptor to the membrane.

There is an integration of two linear cascades in case of PDGF and TGF signaling. The Ras proteins which are hallmark features of growth factor signaling are also contributory in TGF signaling. This collaboration generates an overlapping pathway which leads to oncogenesis. Moreover a different trend is observed in TGF signaling which is TGF independent signal cascade. ILEI is the protein that converts the signal generation from ligand dependent to independent mode. This phenomenon executes the abolition of the gate keeping proteins of the membrane. The juxta positioning of the two individual proteins of two adjacent cells is compromised. These proteins are shuttled to the cytoplasm, this abrogates cell-cell junction and results in metastatic dissemination of the cells.

PDGF is engaged in the repression of miRNA 200. This transcript is anti-neoplastic however PDGF shuts down the transcription of miRNA 200. This opens new horizons as demolition of the miRNA 200 can be mediated at transcriptional level. Taking into consideration the post transcriptional silencing, the mRNA decay is the frontline mechanism that degrades mRNA transcript. Hence those roadmaps must be sketched to address each and every key mediator actively engaged in degrading miRNA 200 and enhancing oncogenesis.

Future directions

In the quest to recognize PDGF signaling, great strides have been made to comprehend how these proteins control their downstream targets. However, scores of mechanisms by which these proteins generate linear or integrated cascades remain obscure. Recent structural data supports the idea that PDGFR is a sophisticated machine with multiple signaling outputs. Misrepresentation of growth factor signaling is the most imperative prerequisite in tumor progression. PDGF signaling regulates tumor progression by a tumor cell-autonomous mechanism or through tumor–stroma interaction and has either a tumour-suppressing or tumour-promoting function depending on cellular context. Numerous cellular context-dependent factors tightly maintain the balance of PDGF signaling and contribute to the regulation of PDGF-induced cell responses.

With an addition of substantial fraction of elucidations to the pre-existing understandings of PDGF, it is now evident that an integrated network of proteins triggers the dynamics of the cell. A positive feedback regulation exists between PDFG and FGF. Both the proteins switch on the expressions of their native receptors. This intriguing interactive display unmasks an imperative perpetuation of the cascade. In order to outnumber the displaced receptors endocytosis, there is a continuous supply of the receptors to the plasma membrane to maintain the threshold value of the population of the receptors. Henceforth the responsiveness of the cell towards FGF and PDGF is ensured. This collaboration is indicative of the fact that blunting of refractoriness is essential to induce oncogenesis. Another thing that cannot be overlooked is the crosstalks of two linear transduction cascades. This integrated framework works with striking synergy during tumor development. It is necessary to revisit the existing web of proteins with reference to PDGF signaling to tailor some effective clinical outcomes.

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