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Review article

Diverse effects of platelet-derived growth factor-BB on cell signaling pathways

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ABSTRACT

Platelet-derived growth factor-BB (PDGF-BB) is involved in the tissue repair and tumor progression effects, and act as a rapid and early effector cytokines which are released in response to pathogen-induced changes in the microenvironment. Recent researches have implicated PDGF-BB as a potential contributing factor to the spectrum of the cell signaling pathway of interrelated diseases, particularly mesangial cells, mesenchymal stem cells, human dermal fibroblasts, tumor pericytes and smooth muscle cells. In this review, we generalize the present literatures on the roles of PDGF-BB in the various interrelated diseases, providing insights or strategies into the underlying cellular and signaling mechanisms that will help guide future studies further into promising interventional targets with therapeutic potential.

1. Introduction

Platelet-derived growth factor(PDGF)-BB possesses mitogenic, differentiating, chemotactic and angiogenic properties and is involved in wound healing; yet, like the other members of the PDGF family of cytokines, PDGF-BB has been associated with a number of pathologies [1,2]. In particular, PDGF-BB has been implicated in various common benign tumors and malignancies [3–10], (i.e. meningioma, glioblastoma, breast cancer, pancreatic cancer, prostate cancer, esophageal squamous cell carcinoma, ovarian cancer and liver cancer) and several nonneoplastic diseases [11–17] (i.e. chronic hepatitis B, inflammatory bowel disease, Graves' disease, chronic pancreatitis, asthma, microangiopathy, Parkinson's disease). The roles played by PDGF-BB in tumor cell conditions are dynamic, wherein it can exert both protective and pathogenic functions, as has been shown for the bone metastasis in the breast cancer [5].

Recently, the research of the pathogenic roles of PDGF-BB has expanded its impact on the cell signaling pathway of interrelated diseases. Up to now, dedications of PDGF-BB have been reported in mesangial cells, mesenchymal stem cells, human dermal fibroblasts, tumor pericytes and smooth muscle cells [18–23]. In this regard, we generalize and discuss the present literatures on the effects and underlying molecule mechanisms of PDGF-BB related to the cell signaling pathway with the aim of supplying new therapeutic insights or strategies for improved management of the related diseases.

2. Biology of PDGF-BB

PDGF-BB, a member of the PDGF family that comprises PDGF-AA, PDGF-AB, PDGF-BB, PDGF-CC, and PDGF-DD [24], has become the focal point of growing importance owing to the potential of its tissue repair [25] and tumor progression effects [21,22]. The PDGF A and B chain forerunners in human are individually encoded by two homologous genes located on chromosomes 7 [26] and 22 [27,28]. In addition, there is the c-sis proto-oncogene similar to the B chain gene [29–31]. Human PDGF B is comprised of 7 exons [32], among which a big portion of exon 1 and the whole exon 7 are untranslated regions (UTRs). Surprisingly, the close homology between PDGF B and the v-sis oncogene [30,33] of simian sarcoma virus (SSV) is existed. And the 60% amino acid homology between the PDGF A, B chains and eight conserved cysteine residues are reported [26,31]; six of them are related to intra-chain disulfide bonds, and the rest of two are related to inter-chain disulfide bridges. The latter were displayed to be not indispensable for dimerization [34].

PDGF, a heat-steady, positively charged protein, is engendered by osteoblasts, platelets and monocytes/macrophages [35].which embodying the B chain are an ingredient of the activity initially depicted as macrophage-derived growth factor [36]. PDGF-BB is a distinctive ligand which could easily interact with all three PDGF receptors [37]. PDGF-BB has been accepted as a chief mediator in wound healing and tissue repair [38]. Furthermore, PDGF-BB is well known for its mediate angiogenic function via its furtherance of vascular endothelial growth

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factor (VEGF) secretion [39], and it also plays a significant part in keeping the stability of newly shaped blood vessels [40,41]. PDGF-BB can facilitate the osteogenous differentiation of bone marrow stem cells (BMSCs) and has been diffusely applied in bone regeneration [42]. More significantly, PDGF-BB is also a crucial chemo-attractive agent for mesenchymal stem cells (MSCs) [43–45].

Platelet-derived growth factor exerts its functions through combining with one of the two structurally relevant PDGF receptors, and the genes of encoding PDGF receptors have been located at the long arm of human chromosome 5 [46,47]. Both PDGF α receptor (PDGFαR; Mw = 123 kDa) and β receptor (PDGFβR; Mw = 124 kDa) are part of the class III receptor tyrosine kinases. Resembling the growth factor itself, the receptor is also displayed in homo (αα and ββ) and hetero (αβ) dimeric forms [37]. The α-receptor subunit combines all isoforms of PDGF with equivalent affinity; nevertheless, the β subunit combines just the B-chain with pretty high affinity [48–51].All receptors are mainly expressed on the cell membrane with minor expression in the lysosomes [1,52].

3. PDGF-BB and cell signaling pathways

It is well known that PDGF-BB is concerned with various cell behaviors involving the pathogenic processes resulting in tissue injury and tumor metastasis through a variety of stresses, such as mesangial cells, mesenchymal stem cells, human dermal fibroblasts, tumor pericytes and smooth muscle cells. In the following sections, we will discuss the effects and the underlying mechanisms of PDGF-BB/PDGF-BB R signing in multifarious cell signaling pathways.

4. PDGF-BB and mesangial cells

Mesangial cell proliferation may play some unique roles in most kidney diseases. Among them, IgA nephropathy (IgAN) is the most common glomerulopathy all over the world, and approximately 20–30% of those having IgAN will be confronted with final kidney failure, and will require hemodialysis and/or a renal transplant [53]. The pathologic characteristics of IgAN contain high levels of circulatory IgA and mesangial cell proliferation.

Considering that PDGF-BB is a well-documented stimulative factor for glomerulonephritis, and mesangial cells express high levels of the PDGF-BB receptor [54,55], it has been speculated that PDGF-BB may also express a similar effect on mesangial cell in IgAN. Recently, Katsuma et al. demonstrated that PDGF-BB could play a potentially important role in the proliferation of kidney mesangial cells by HIGA mice related to IgAN [18].

The stimulative mechanisms of PDGF-BB in IgAN might include endothelial differentiation gene-5 (EDG5), a receptor for sphingosine 1-phosphate (SPP). EDG5 has been lately reported to be concerned with multiple signaling pathways [56]and mediating SPP-induced cell proliferation in rat hepatoma cells [57]. When stimulated with PDGF-BB at the early stage of IgAN, mesangial cells engender and release PDGF-BB, and the expression of PDGF-BB receptor on the cell membrane is concomitantly raised in both an autocrine and a paracrine way [58,59]. Moreover, it's formerly reported that PDGF-BB can activate sphingomyelinase and ceramidase in mesangial cells, leading to a raised synthesis of SPP [60]. Apart from the raised release of SPP from mesangial cells, it could also be released from the activated or aggregated platelets [61–64]. The strengthened expression of EDG5 by PDGF-BB displayed in the recent research [18], and the enhanced output of its ligand SPP by PDGF [60] could synergistically facilitate the mesangial cell proliferation. To sum up, the PDGF-SPP-EDG pathway might behave in a positive feedback loop to augment the cascade of events connecting growth factor signaling with cellular proliferative activity (Fig. 1). In addition, mesangial cells are regulated by reactive oxygen species (ROS) induced by PDGF-BB [65].

5. PDGF-BB and mesenchymal stem cells

Mesenchymal stem cells (MSCs) protect infarcted hearts partly via paracrine release of various growth factors and cytokines that promote cardiac repair [66]. However, a lot of clinical tests have displayed that the cardio-protective effects of MSC therapy are moderate and of finite duration, partly owing to low rates of engraftment, trans-differentiation and cell fusion [67–70]. Correspondingly, many countermeasures have been intended to ameliorate the therapeutic efficacy of MSCs, including ameliorating their survival ratio in vivo, capability to facilitate angiogenesis, and amplification of MSC paracrine signaling.

In consideration that PDGF-BB is a puissant chemo-attractive agent for mesenchymal stem cells (MSCs) [43–45], it has been speculated that PDGF-BB may also facilitate the MSC-mediated cardioprotection. Lately, it's researched that PDGF-BB can play a beneficial role in MSC-mediated cardioprotection by a mouse model of cardiac ischemia-reperfusion injury [19].

when stimulated with PDGF-BB, the PDGF receptors touch with a quantity of signaling molecules including JNK and gene-regulating transcription factors such as c-Jun and STAT family members [71,72], which may occur a series of changes. Interestingly, it was the preconditioning with a JNK inhibitor but not inhibitors of p38 MAPK or ERK1/2 that impeded PDGF-induced proliferation [73]. Over-expression of a dominant-negative form of c-Jun activated by JNK also prevents PDGF-induced proliferation [74]. In the above mouse model of cardiac ischemia-reperfusion injury, pretreatment of MSCs with PDGF-BB for 48 h obviously ameliorated MSC-mediated cardioprotection [19]. Besides raising the release of protein factors, PDGF-BB may also activate the release of microvesicles and exosomes that convey mRNAs and miRNAs to cells in the ischemic region through horizontal transfer [75]. Such transfer of intracellular genetic agent would control the proliferation, differentiation, and cell-cycle reentry of resident cardiac progenitor cells, hence inhibiting tissue injury and resulting in tissue self-repair [76]; restrain ischemic cardiomyocyte injury and death; and reorganize epithelial cells and fibroblasts to weaken ventricular remolding after ischemic injury [19] (Fig. 2).

6. PDGF-BB and human dermal fibroblasts

Human dermal fibroblasts(HDFs) play significant parts in dermatic wound repair and remolding owing to proliferating to transfer into the wound bed, synthesizing new extracellular matrixs(ECMs), and expressing thick actin bundles of myofibroblasts [77]. A quantity of growth factors have been revealed to influence HDF movement directly or indirectly. They comprise transforming growth factor-β1 andβ2, vascular endothelial growth factor and platelet-derived growth factor (PDGF) [77,78]. In the midst of them, the effect of PDGF-BB was best described [1,79]. Researches in ex-vivo indicated that PDGF-BB is a crucial mitogen and a powerful motogen for HDF chemotaxis [80].PDGF-BB activates HDF production of matrix proteins, containing fibronectin [81], collagen [82], and hyaluronic acid [83]. PDGF-BB also activates synthesis of collagenases in HDFs [84].

Transfer of HDFs is pivotal for dermatic wound repair. But the concrete mechanism remains unclear. Studies reveal that PDGF-BB is the primary pro-motility factor in human serum for HDF motility via the Gene Cassette approach [20]. PDGF-BB and collagen use diverse and interlaced signaling pathways to regulate HDF transfer [84]. It's reported that just ERK1/2 and FAK pathways are concerned with the initial stage of HDF transfer via collagen. Other kinases such as Akt,-Pak,p38 and JNK, however, are demanded distinguishingly for PDGF-BB signaling, which primarily results in polarization, strengthens motility, and supplies directionality [85] (Fig. 3). Among them, Akt plays an important role in processing both migratory and proliferative signals from PDGF receptor [86]. Nevertheless, it transmits just the migratory, but not the proliferative signal to downstream effector, p38; because p38 is only demanded for HDF transfer but not DNA synthesis [87].

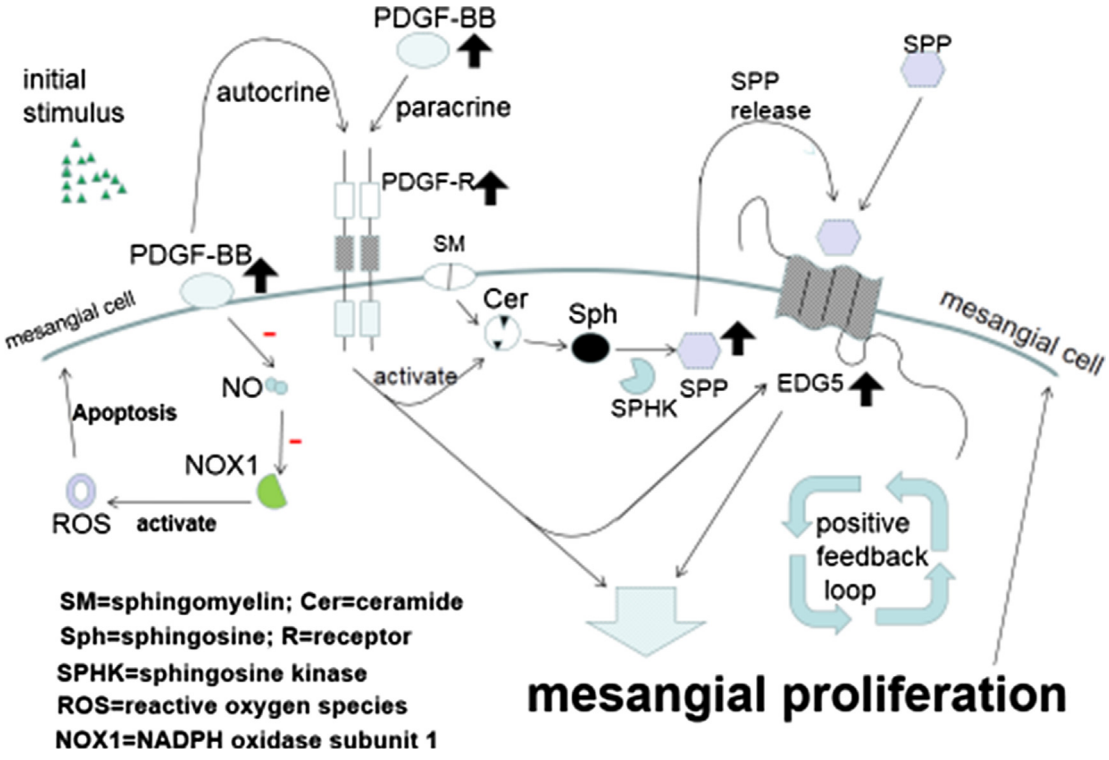

Fig. 1. Simplified model of PDGF-BB signal transduction in mesangial proliferation. Upon stimulated, mesangial cells produce and release PDGF-BB, and concomitantly induce the expression of PDGF-BB receptor. PDGF-BB can also activate sphingomyelinase and ceramidase in mesangial cells, which leads to a raised synthesis of SPP. The recent research reveals that the intensive expression of EDG5 by PDGF, and the augmented production of SPP can synergistically facilitate cell proliferation. In addition, mesangial cells are regulated by ROS induced by PDGF-BB.

Accordingly, Akt must relay the proliferative signal to some other effector(s) in the same cells [86]. Although ERK1/2 and JNK pathways are utilized via both migration and DNA synthesis signals, these kinases seem to be capable of explicating the differentia from diverse upstream activators. For instance, ERK1/2 are capable of distinguishing activating signals coming via Pak or coming through Ras and Raf [88,89]. The former is for motility and the latter for mitogenesis [20].

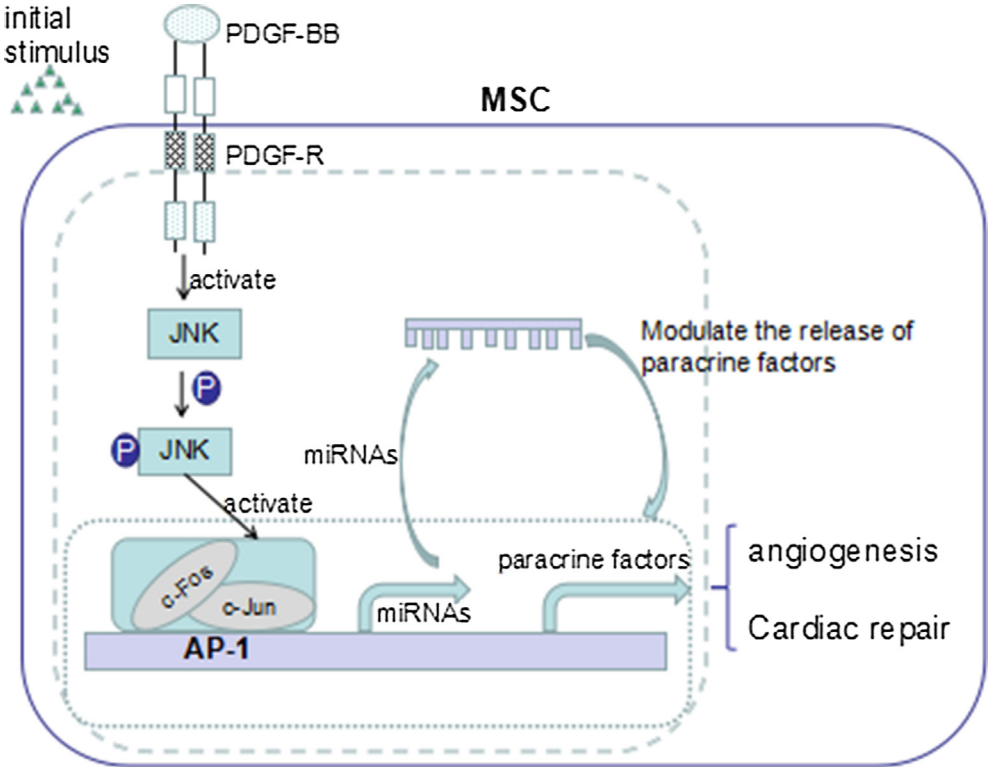

Fig. 2. Simplified model of PDGF-BB signal transduction in ameliorating MSC therapeutic efficacy. PDGF-BB binding to its receptor (PDGFR) activates JNK to p-JNK, which then phosphorylates and activates c-Jun. c-Jun then binds to its partner c-Fos to form the activator protein-1 (AP-1) heterodimer that activates specific miRNAs and paracrine factors that induce angiogenesis and cardiac repair.

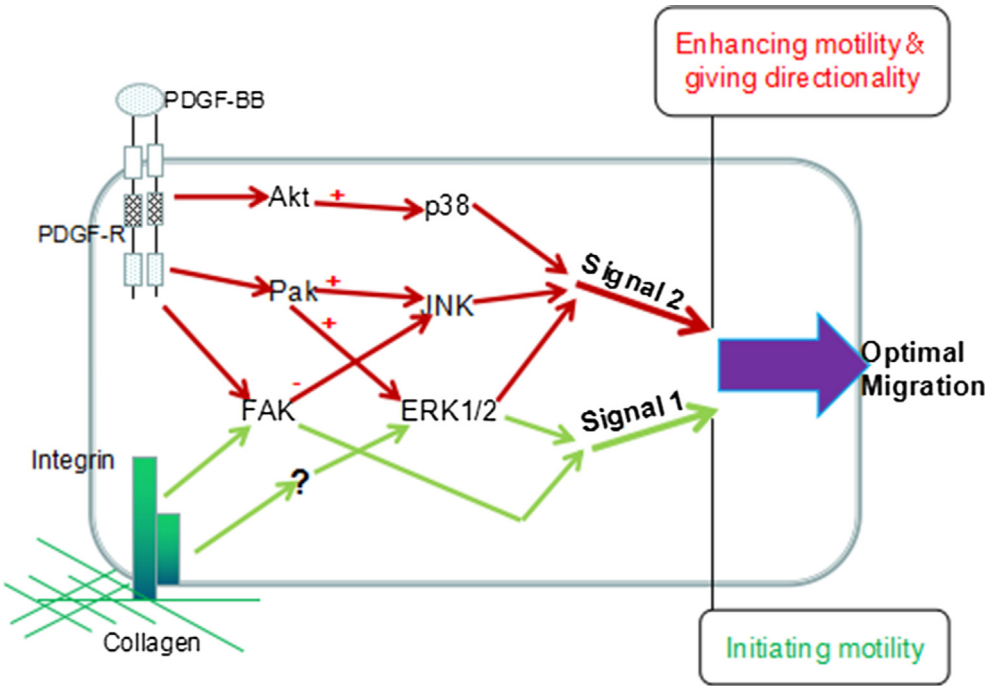

Fig. 3. Simplified signaling model of collagen and PDGF-BB in the control of HDF migration. Collagen matrix promotes HDF migration (signal 1, green). PDGF-BB strengthens and supplies directionality for the collagen-driven migration (signal 2, red). Researches reveal that collagen and PDGF-BB together determine the optimal HDF motility. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

7. PDGF-BB and tumor pericytes

With regard to a tumor to develop and to metastasize, it is considered that tumors must go through two pivotal procedures: Firstly, to gain an ample supply of oxygen and nutrition from effective blood delivery, original tumors produce functional vascular networks via a procedure known as angiogenesis [90]. Secondly, tumor cells go through an epithelial-mesenchymal transition(EMT) to obtain invasive and migratory abilities, to spread throughout the body and distant metastases of seed cells [91–93]. Tumor angiogenesis under most circumstances forms deviant and leaky blood vessels, which impedes tumor perfusion in reality [94]. Therefore, vascular maturation is a much important procedure to insure optimal tumor perfusion, ordinarily performed through the recruitment of pericytes to newly produced vessels [95]. The significant role of the PDGF-BB/PDGFRβ signaling played in vascular maturation has been well described via genetic approaches [96,97]. During the vascular growth, endothelial cells (EC) secrete PDGF-BB, which not only strengthens the motility of pericytes but also produces a chemotaxis-like gradient to promote the pericyte recruitment [98,99]. Recently, a number of researches have been reported to associate PDGF-BB signaling with vascular remolding in tumors and display that transgenic PDGF-BB expression in tumors could raise pericyte density [100–102]. Because tumor derived PDGF-BB cannot facilitate the formation of the chemotaxis-like gradient in the surrounding region of endothelium [100], the potential mechanism about tumor-derived PDGF-BB facilitating pericyte recruitment remains unclear.

Because CXCR4 expression has been detected in the pericyte progenitor cells [103] and primary pericytes [104], it's reported that SDF-1α may serve as a compensating factor for the PDGF-BB induced pericytes recruitment in cancerous vascular remodeling [22]. Blockade of the SDF-1α/CXCR4 axis not only abolishes the PDGF-BB induced pericyte recruitment in vitro but also significantly decreases pericyte coverage of PDGF-BB–overexpressing tumors [105–108]. Moreover, there is evidence that PDGF-BB in a paracrine manner can increase the secretion of SDF-1α in ECs due to the up-regulation of the mRNA synthesis of SDF-1α [21,22].This up-regulation mechanism is mainly dependent on the activation of HIF-1αthrough the PI3K/Akt/mTOR signaling pathway [109–111] (Fig. 4).

8. PDGF-BB and smooth muscle cells

Smooth muscle cells (SMCs) play important roles in neointimal formation and airway remodeling. During the repair of vascular injury or stimulation of inflammation, various cytokines, such as platelet–derived growth factor (PDGF), that are able to stimulate the proliferation and migration of smooth muscle cells are released [112]. The neointimal formation has been implicated in abnormal proliferation and migration of vascular smooth muscle cells (VSMCs), which may result in arteriosclerosis and restenosis. The airway remodeling is related to unbalanced proliferation and migration of airway smooth muscle cells (ASMCs), leading to chronic airway diseases. Therefore, exploring the underlying molecular mechanism may be beneficial for the development of effective strategies for inhibiting these processes.

Under normal circumstances, PDGF-BB induces the activation of Ca2+/calmodulin-dependent kinase II (CaMKII), ERK1/2, Akt, cyclic adenosine monophosphate (cAMP) response element binding protein (CREB), β-catenin (βC), p38 mitogen-activated protein kinase (MAPK), JNK1/2 and Phospholipase C (PLC) -γ1, and ultimately stimulating smooth muscle cells proliferation and migration [23,113–116]. However, it's reported that Iptakalim opened K_{ATP} channels, increasing K^+ efflux and decreasing Ca^{2+} influx, then restraining the activation of CaMKII directly [113]. Further investigation confirmed that overexpression of microRNA (miR) –612 suppressed the PDGF–BB–induced Akt protein expression [114]. And other research revealed that propofol or midazolam attenuated PDGF-BB-induced phosphorylation of p38 MAPK [23]. Moreover, the study demonstrated that hinokitiol inhibited JNK1/2 and PLC-γ1 phosphorylation [116]. Taken together, the underlying mechanism of PDGF–BB and smooth muscle cells has made a big step towards clinical application (Fig. 5).

9. Conclusion

Although recent research on PDGF-BB has made significant progress in elucidating the cell signaling pathway of interrelated diseases, their specific molecular mechanism remain largely unknown. The roles that have been defined to date for PDGF-BB in the pathogeneses of interrelated diseases (in the animal models and agreeing with observations in human cases) suggest its therapeutic potential upon the complete

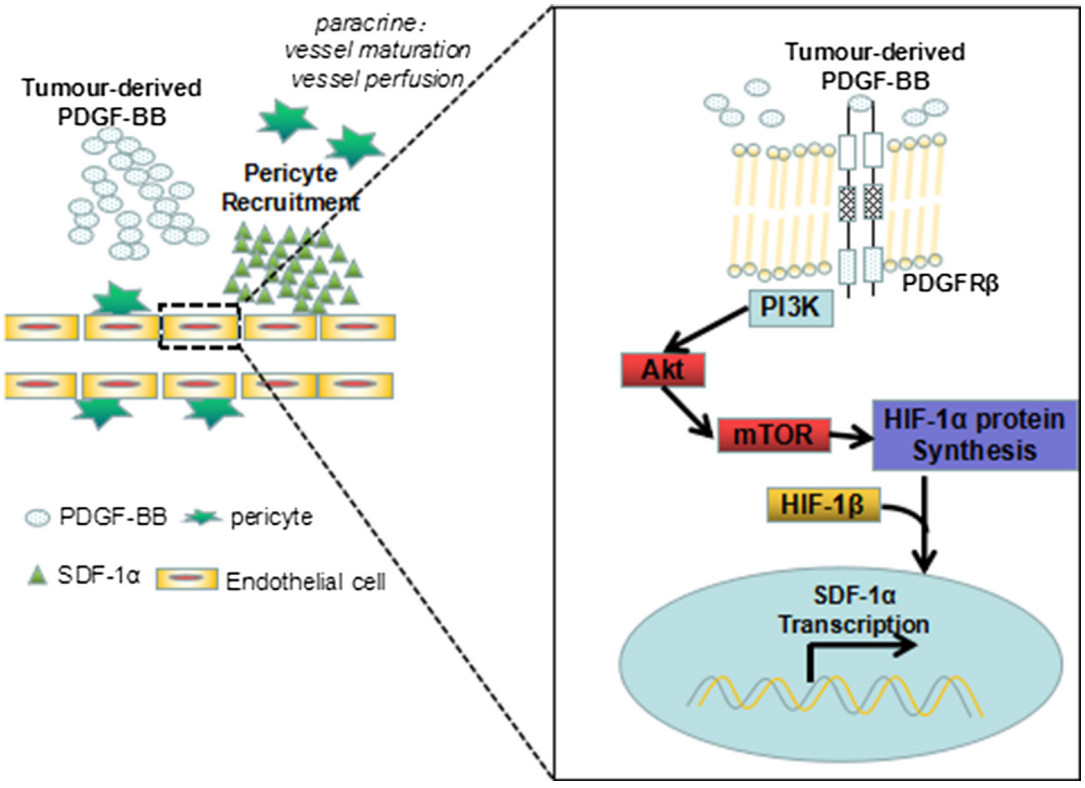

Fig. 4. Overexpression of PDGF-BB raises tumor pericyte content via SDF-1α/CXCR4 axis. Tumor-derived PDGF-BB stimulates SDF-1αtranscription and expression in ECs via the activation of HIF-1αthrough the PDGFRh/PI3K/Akt/mTOR pathway. EC-derived SDF-1αforms a chemotaxis gradient that coincides with the PDGF-BB–induced pericyte recruitment during cancerous vascular remodeling process.

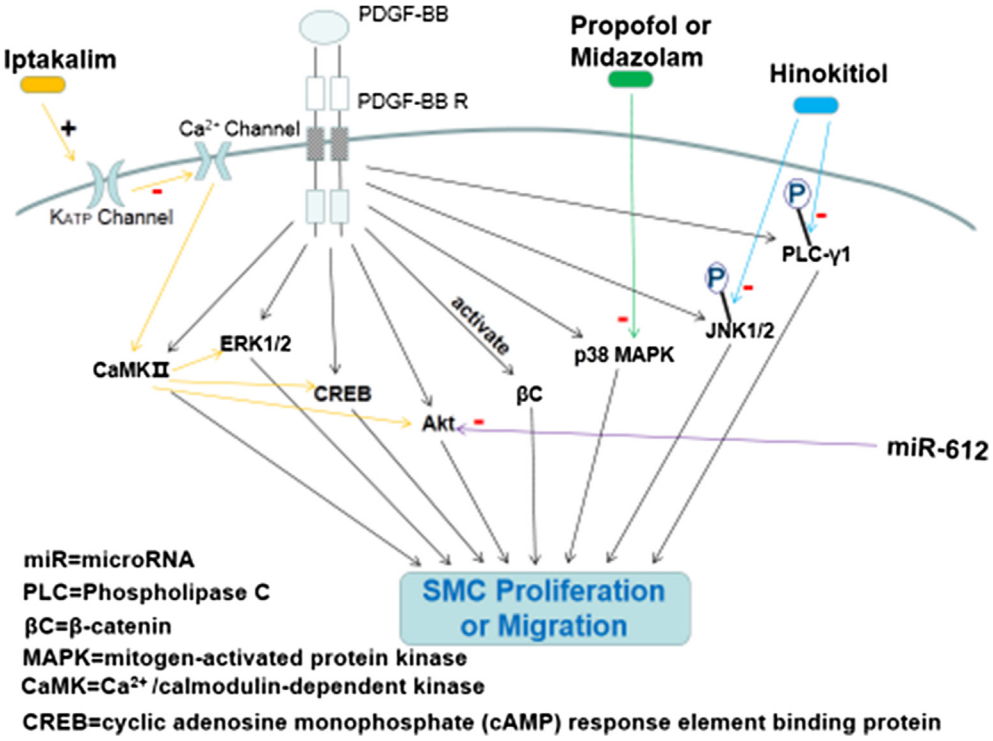

Fig. 5. Simplified signaling model of PDGF-BB in the control of SMC proliferation and migration. The inhibited effect of Iptakalim (signal, yellow); the restrained effect of miR–612 (signal, purple); the negative effect of Propofol or Midazolam (signal, green); the restraining phosphorylation of Hinokitiol (signal, blue). Researches reveal that microRNA, medicines and PDGF-BB together determine the optimal SMC proliferation and migration. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

elucidation of the distinct mechanisms of PDGF-BB in various interrelated diseases.

Conflicts of interest

The authors declare no conflict of interest or funding.

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