PDGF receptors as cancer drug targets

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Introduction

Ever since the discovery 20 years ago that the transforming retroviral *v-sis* oncogene is derived from the platelet-derived growth factor (PDGF) B chain gene, PDGF signaling has been an interesting target for cancer treatment. In addition to its role in autocrine growth stimulation of tumor cells, PDGF has also been suggested to regulate tumor stroma fibroblasts and tumor angiogenesis (Figure 1). The occurrence of clinically useful PDGF receptor antagonists, like Glivec (STI571/Gleevec), now allows for an evaluation of the importance of PDGF receptor signaling in malignancies (Buchdunger et al, 1996; Capdeville et al., 2002). This review summarizes the biology of PDGF and discusses the role of PDGF receptor expression in different tumor compartments. Two sets of recent findings are particularly emphasized: the first set demonstrates clinical responses to PDGF antagonists in autocrine settings, and the second set presents beneficial effects of targeting PDGF receptors in the tumor stroma in animal models.

Cell biological and physiological functions of PDGF

Four PDGF polypeptide chains have been identified, which make up five dimeric PDGF isoforms: PDGF-AA, -AB, -BB, -CC, and -DD (Heldin et al., 2002). The isoforms exert their cellular effects through tyrosine kinase α- and β-receptors (Figure 1). All PDGF isoforms, except PDGF-DD, induce PDGF α-receptor dimerization, whereas PDGF-BB and -DD activate PDGF β-receptor dimers. In addition, all isoforms except PDGF-AA activate both receptor types in cells coexpressing the α- and β-receptors. Ligand-induced receptor dimerization causes receptor autophosphorylation, whereafter intracellular signaling pathways are activated by recruitment of SH2 domain-containing signaling molecules (e.g., c-Src, phospholipase C-γ, phosphatidyl-inositol-3′-kinase and the Grb2/Sos complex) to specific phosphorylated tyrosine residues. Activation of these pathways ultimately induces various cellular responses, including cell proliferation, survival, and migration.

Targeting of the genes for PDGF-A and B chains, and for the two receptors, has provided a detailed understanding of the physiological functions of PDGF during development (Betsholtz et al., 2001). Processes driven by the PDGF β-receptor include pericyte recruitment to capillaries, development of smooth muscle cells in vessels, and development of mesangial cells in the kidney. Activation of PDGF α-receptors by PDGF-AA is required for formation of alveolar smooth muscle cells, hair follicle development, proper villus formation in the gut, and oligodendrocyte development. In the adult, PDGF receptor signaling contributes to wound healing through stimulation of, e.g., fibroblasts, smooth muscle cells, and different inflammatory cells. PDGF β-receptors also regulate the interstitial fluid pressure (IFP) and thus potentially control transport from the vasculature into the extracellular compartment of connective tissue (Heuchel et al., 1999; Rodt et al., 1996).

PDGF antagonists

Several types of PDGF antagonists have been described, including antibodies or DNA aptamers against ligands or the extracellular part of the receptors, as well as low molecular weight receptor kinase inhibitors (Östman and Heldin, 2001). Glivec represents a kinase inhibitor for which there is already some clinical experience (Capdeville et al., 2002); in addition to the PDGF α- and β-receptors, Glivec also inhibits Kit, Abl, and Arg tyrosine kinases. It is used in the treatment of chronic myelogenous leukemia and gastrointestinal stromal tumors (GIST), characterized by overactivity of Abl and Kit, respectively, and has shown rather mild side effects (Capdeville et al., 2002). Another PDGF receptor antagonist that, despite having a broad specificity, shows a tolerable toxicity profile and promising results from phase I clinical trials is SU11248 (Mendel et al., 2003).

Autocrine PDGF receptor signaling

In certain malignancies, characteristic genetic alterations have been identified which cause constitutive activation of PDGF

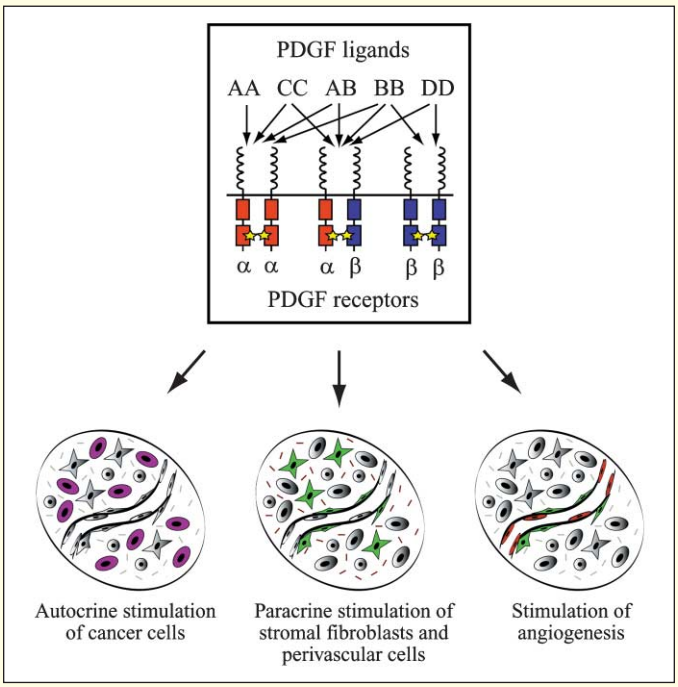

Figure 1. The PDGF system is involved in multiple tumor-associated processes

Upper: PDGF ligand binding specificity to PDGF receptors. Lower: PDGF receptors are expressed by many different cell types within tumors, and signaling from PDGF receptors can thus promote tumor progression in various ways. Tumor cells, purple; endothelial cells, red; fibroblasts, smooth muscle cells, and pericytes, green; extracellular matrix, brown.

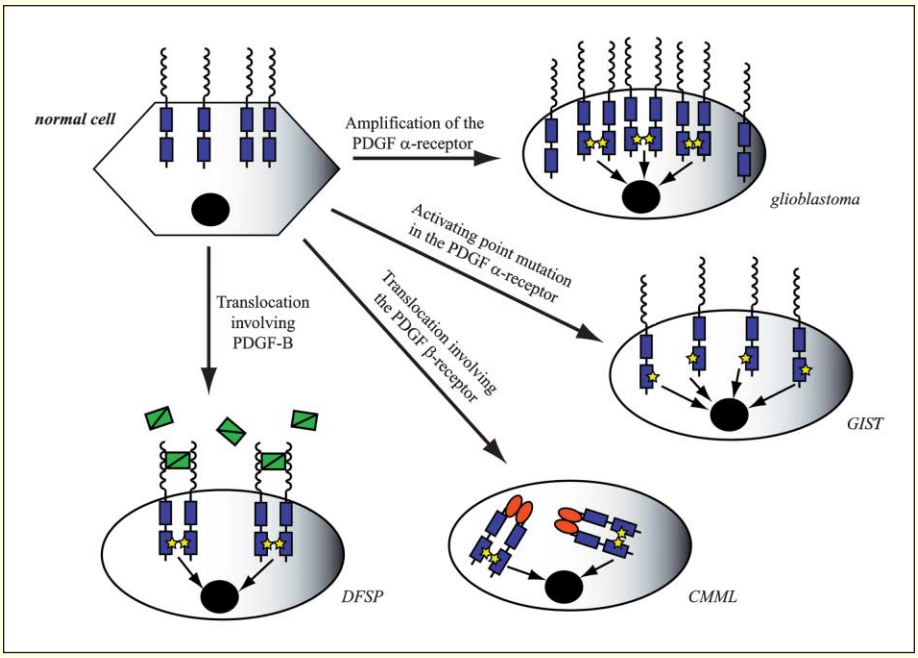

Figure 2. Examples of genetic alterations that give rise to dysregulated PDGF receptor signaling in different tumors

Examples of malignancies in each category are given in italics. It is not fully elucidated whether the activation of amplified or point-mutated PDGF receptors is dependent on PDGF ligand(s). Active PDGF receptor kinase, yellow star; PDGF ligand, green; dimerization domain not derived from the PDGF receptor, red.

receptors and autocrine growth stimulation (Figure 2). Amplification of the PDGF α-receptor gene occurs in a subset of high-grade gliomas (Fleming et al., 1992; Kumabe et al., 1992), and a ligand-independent deletion mutant of the PDGF α-receptor fusion has also been characterized (Clarke and Dirks, 2003). Fusions of the PDGF β-receptor with proteins (e.g., the transcription factor Tel or rabaptin-5, which causes dimerization and thereby constitutive activation of the receptor kinase) have been described in patients with chronic myelomonocytic leukemia (CMML) (Golub et al., 1994; Magnusson et al., 2001). Also, a constitutively active PDGF α-receptor fusion protein, FIPL1-PDGFRα, has been identified in patients with idiopathic hypereosinophilic syndrome (Cools et al., 2003a). Activating point mutations and small deletions in the PDGF α-receptor gene were also recently found in a subset of patients with GIST (Heinrich et al., 2003). Finally, dermatofibrosarcoma protuberans (DFSP) tumors are associated with translocations which fuse the collagen 1A1 gene with the PDGF B chain and lead to constitutive production of fusion proteins which are processed to PDGF-BB (O'Brien et al., 1998; Shimizu et al., 1999; Simon et al., 1997). In addition to these mutationally caused changes in PDGF ligand and/or receptor expression, upregulation is also well documented in, e.g., soft tissue sarcomas and gliomas (reviewed in Östman and Heldin, 2001).

A series of studies have indicated that autocrine PDGF receptor signaling contributes to the growth of glioma cells. Also, the more recently identified PDGF isoforms, PDGF-CC and -DD, have been implied in autocrine glioma signaling (LaRochelle et al., 2002, Lokker et al., 2002). Inhibition of growth of cultured glioma cells has been achieved with different PDGF antagonists, including dominant negative forms of PDGF or PDGF receptors (Shamah et al., 1993; Strawn et al., 1994). More recently, intracranial growth of gliomas in mice was also shown to be sensitive to treatment with STI571 (Kilic et al., 2000). A causative role for autocrine PDGF receptor signaling in gliomas is also indicated by the development of gliomas after in vivo PDGF B chain gene transfer to neuroglial progenitor cells (Dai et al., 2001; Uhrbom et al., 1998). Together, these studies have led to the initiation of different clinical trials from which results are still pending.

Clinical responses to PDGF antagonists in CMML and DFSP

In a pioneering study, Apperley et al. recently treated four CMML patients, all with PDGF β-receptor-activating translocations, with 400 mg per day of STI571 (Apperley et al., 2002). Normalized peripheral blood count was observed after one week of treatment in all four patients. In three of the patients, t(5;12) translocation-positive cells were undetectable after 12 weeks of treatment, whereas the fourth patient required 36 weeks of treatment before translocation-positive cells were no longer seen. The responses persisted after 9 to 12 months of treatment. In addition to this study, a case report has also been published which describes rapid response and molecular remission in another patient with CMML (Magnusson et al., 2002).

Recent case reports have described reduction in tumor volume in patients with DFSP (Maki et al., 2002; Rubin et al., 2002). Two weeks of treatment with 400 mg STI571 per day of a patient with an unresectable tumor reduced the hypermetabolic tumor uptake of ^{18}F-FDG to background levels. After two additional weeks of treatment, tumor volume was reduced by 75%, allowing tumor resection; no viable tumor cells were seen in the resected specimen. Similar observations of reduction in tumor mass have been observed in other DFSP patients (M.C. Heinrich, personal communication). However, not all DFSP patients respond to treatment, since rapid progression and subsequent death, after a transient response to STI571, have also been reported (Maki et al., 2002).

Inhibition of PDGF receptor signaling in tumor stroma enhances the therapeutic effects of chemotherapy in animal tumor models

Paracrine stimulation by PDGF can affect tumor stroma recruitment and growth, as evidenced by studies showing an increased rate or incidence of tumor formation upon transfection of PDGF into receptor-negative tumor cell lines (Forsberg et al., 1993; Skobe and Fusenig, 1998). Furthermore, the desmoplastic response of breast carcinoma cells, characterized by excessive production of extracellular matrix and proliferation of myofibroblast-like cells, has been shown to be dependent on PDGF (Shao et al., 2000). Although no studies so far have demonstrated antitumor effects after targeting of stromal PDGF antagonists, the effects of combining stroma-targeting PDGF antagonists with, for example, antiangiogenic drugs merits further investigations. The clinical potential of such approaches is

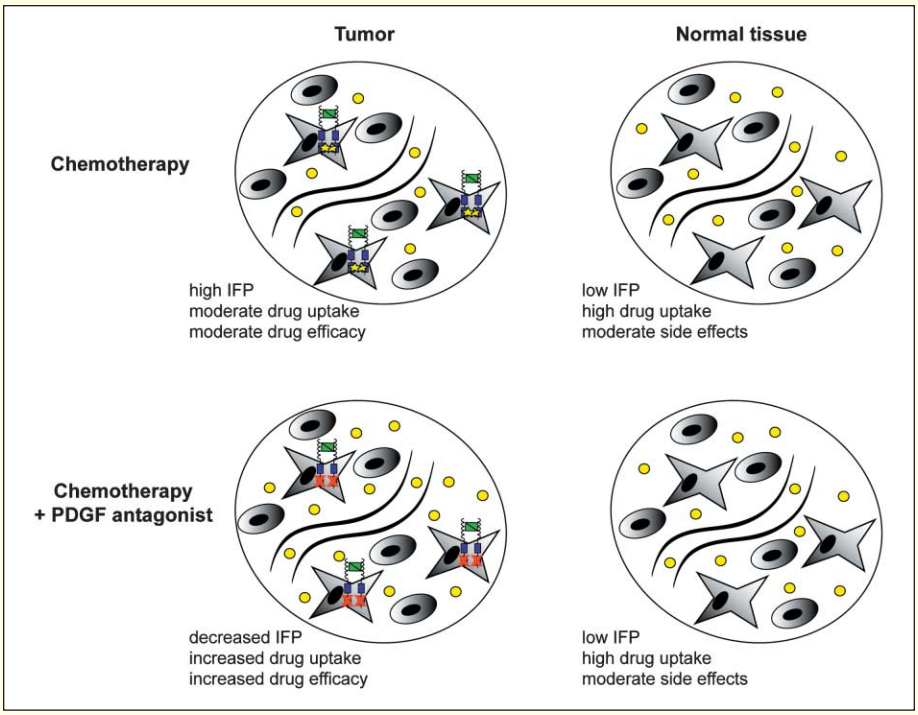

Figure 3. Schematic illustration of the transvascular transport in tumors and normal tissue with or without treatment with PDGF receptor inhibitors

Active PDGF receptor kinase, yellow star; inhibited PDGF receptor kinase, red cross; cytotoxic drug, yellow circle.

underscored by the recent observation that more than 50% of solid tumors on an NCI tumor tissue array express PDGF β-receptors in the tumor stroma (T.S., unpublished data).

The notion that PDGF receptors in tumor stroma are indeed candidate targets for cancer therapy has recently found support from studies where PDGF receptor inhibitors were used in animal tumor models displaying expression of PDGF receptors exclusively in stromal fibroblasts and perivascular cells. As expected, no effects on tumor growth rate were observed by monotherapy with PDGF receptor inhibitors. In contrast, striking results were obtained when PDGF antagonists were combined with chemotherapy (Pietras et al., 2002). The combined treatment resulted in an increased efficacy, corresponding roughly to a 3-fold increase in the dose of the cytotoxic drug, and transpired without any apparent escalation of toxicity. The enhanced therapeutic response occurred in parallel to a tumor-selective increase in drug uptake (Pietras et al., 2002, 2003). Following PDGF receptor inhibition, the tumor content of the cytotoxic drugs paclitaxel and epothilone B, as well as of the tracer compound ^{51}Cr-EDTA, increased by as much as 4-fold. In contrast, tumor angiogenesis and tumor cell sensitivity to chemotherapy were unchanged by administration of PDGF antagonists and could not account for the beneficial effects. The observed therapeutic synergy is thus best explained by the increased tumor uptake of cytotoxic drugs.

The increased interstitial fluid pressure (IFP) in solid tumors constitutes one of many hindrances for drug delivery (Jain, 2001). A possible reason for the enhanced transvascular transport occurring upon blocking of PDGF receptor signaling is thus offered by studies showing a reduction in tumor IFP after treatment with PDGF antagonists (Figure 3) (Pietras et al., 2001, 2002). Further support for this hypothesis is provided by the observations that the kinetics of the effects of PDGF antagonists on tumor IFP are identical to the time frame in which augmented drug transport is observed (K.P., unpublished data). Additional mechanistic studies are clearly warranted to further investigate the mechanism(s) underlying the PDGF antagonist-induced increased transvascular transport. Furthermore, only clinical studies will reveal if the drug uptake effects also occur in human tumors and, if that is the case, if these effects will be able to override other resistance mechanisms like expression of multidrug resistance genes and/or p53 mutations.

PDGF receptors as potential targets for antiangiogenic therapy

Most solid tumors display expression of PDGF receptors on endothelial or perivascular cells (Hermanson et al., 1988; Sundberg et al., 1993; Pietras et al., 2003). A possible role of PDGF receptor signaling in angiogenesis is implied by proangiogenic activity of PDGF-AB and -BB in the chick chorioallantoic membrane assay (Risau et al., 1992), and of PDGF-AB, -BB, and -CC in the mouse corneal pocket assay (Cao et al., 2002). Tumor angiogenic effects of PDGF-DD were also recently demonstrated (Li et al., 2003).

Concerning the mechanism of the proangiogenic effects of PDGF, there is strong evidence for an important role of PDGF in pericyte recruitment (Hellström et al., 1999). PDGF receptor signaling might therefore contribute to tumor angiogenesis by increasing pericyte recruitment and vessel maturation. Experimental support for this notion was recently obtained with the demonstration of PDGF-dependent recruitment of pericytes to tumor vessels in a mouse model of glioma (Guo et al. 2003). Upregulation of PDGF receptors on tumor endothelial cells under special circumstances has also been described. In a mouse model of prostate cancer bone metastasis, PDGF β-receptor expression was observed on endothelial cells of tumors growing in the bone, but not on endothelial cells of normal bone or of tumors growing in surrounding muscle (Uehara et al., 2003). Interestingly, antiangiogenic effects, including increased endothelial cell apoptosis and reduced microvessel density, were observed in bone lesions after treatment with STI571.

Perspectives

Encouraging effects of treatments with PDGF receptor inhibitors have been obtained in malignancies where PDGF autocrine stimulation or PDGF receptor activation is caused by specific mutational events. Whether patients carrying tumor types in which PDGF and/or PDGF receptors are overexpressed as a consequence of epigenetic mechanisms, e.g. as frequently occurs in glioblastoma, will also benefit from treatment with PDGF antagonists remains to be established. The continued search for mutations in PDGF ligands and receptors

is highly motivated and likely to reveal additional patient subsets that could benefit from treatment with PDGF antagonists. Continued identification of additional PDGF receptor inhibitors for Glivec-resistant PDGF receptor variants, as described in this issue of *Cancer Cell*, is also highly warranted (Cools et al., 2003b). Improved methods for detection of activated PDGF receptors would be most useful for screens of tumor arrays to identify tumor subsets, which should be selected for the more work-intensive genetic analyses. Development of activation-specific antibodies is thus an important goal. In this regard, the successful development of activation-specific EGF receptor antibodies, suitable for immunohistochemical applications, is encouraging (Albanell et al., 2002; Baselga et al., 2002).

The findings of enhanced therapeutic response after inhibition of PDGF receptors in tumor stroma dramatically broaden the spectrum of tumor types for which treatment with PDGF antagonists could be considered. However, the outcome of clinical studies exploring this concept will be highly dependent on the recruitment of the optimal patient subset. Also for this purpose, activation-specific receptor antibodies would be useful, as well as surrogate markers for identification of patients displaying changes in tumor uptake of drugs upon PDGF receptor inhibition.

The selective upregulation of PDGF receptors on endothelial cells in the mouse model of prostate cancer bone metastases should stimulate further study of expression of PDGF receptors on tumor endothelial cells. The frequent expression of PDGF receptors on perivascular cells also suggests as yet unexploited therapeutic opportunities. The well-documented effect of PDGF on pericyte recruitment points to the possibility of combining antiendothelial agents, like vascular endothelial growth factor receptor inhibitors, with pericyte-targeting PDGF antagonists. Finally, it has been shown that bone marrow-derived cells contribute to the angiogenic switch in tumors (Coussens et al., 2000). PDGF receptor inhibitors can possibly inhibit this process, since PDGF stimulates migration and proliferation of macrophages (Siegbahn et al., 1990).

In summary, there are several possible indications for use of PDGF antagonists in tumor treatment. Additional preclinical and clinical studies are highly warranted to explore these possibilities.

Acknowledgments

Ingegärd Schiller assisted with expert secretarial help.

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Note added in proof:

The benefits of combining PDGF antagonists and VEGF antagonists in a mouse model of pancreatic islet cancer are shown in a report by Bergers et al.: Bergers, G., Song, S., Meyer-Morse, N., Bergsland, E., and Hanahan, D. (2003). Benefits of targeting both pericytes and endothelial cells in the tumor vasculature with kinase inhibitors. J. Clin. Invest. *111*, 1287–1295.