COMMENTARY

Signal transduction by the receptors for platelet-derived growth factor

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Introduction

Platelet-derived growth factor (PDGF) is a connective tissue cell mitogen that originally was purified from human platelets, but recently has been found to be produced by many different cell types (reviewed by Ross *et al.* 1986; Heldin and Westermark, 1989). The *in vivo* function of PDGF remains speculative, but the fact that PDGF is released by platelets and by cells involved in the inflammatory reaction and that it stimulates proliferation, chemotaxis and matrix production, suggest a role in tissue repair processes. It is also possible that PDGF is involved in regulation of cell growth and differentiation during embryonal development, since it has been found to be expressed in mouse (Rappolee *et al.* 1988) and *Xenopus* (Mercola *et al.* 1988) embryos and in human placenta (Goustin *et al.* 1985). Such a function has been demonstrated in the developing rat optic nerve where PDGF secreted by type-1 astrocytes control the differentiation of O–2A progenitor cells into oligodendrocytes and type-2 astrocytes (Noble *et al.* 1988; Richardson *et al.* 1988; Raff *et al.* 1988). PDGF may also be involved in pathological processes. Thus, unscheduled production of PDGF may account for the excessive cell proliferation seen, e.g., in atherosclerosis and tissue fibrosis, as well as in malignancies. The potent transforming activity of PDGF is illustrated by the fact that the PDGF B chain gene is similar to v-*sis*, the transforming gene of simian sarcoma virus, and that cell transformation by this virus is exerted by autocrine action of a PDGF-like factor (reviewed by Westermark *et al.* 1987).

The object of this commentary is to discuss the recent advances in research on PDGF, which have revealed that PDGF is a family of closely related isoforms that activate, with different efficiencies, at least two different receptor types. Recently, some insight has also been gained into possible postreceptor events involved in the mitogenic signal pathway.

Three PDGF isoforms that bind to two different receptor types

PDGF is a dimeric molecule composed of disulphide-bonded, homologous polypeptide chains, denoted A and B. All three combinations, AA, AB and BB, of PDGF chains have been identified and purified from platelets and transformed cells (Stroobant and Waterfield, 1984; Heldin *et al.* 1986; Hammacher *et al.* 1988; Bowen-Pope *et al.* 1989). Both PDGF chains are synthesized as precursor molecules that undergo dimerization and proteolytic processing after synthesis. The isoforms differ in their functional activities (see further, below), as well as in their secretory behaviour; whereas PDGF-AA and PDGF-AB are rapidly secreted after synthesis, PDGF-BB remains to a large extent associated with the producer cell (Robbins *et al.* 1985; Östman *et al.* 1988), the significance of which remains to be elucidated.

Binding experiments with radiolabeled PDGF isoforms revealed that two different receptor types exist (Hart *et al.* 1988; Heldin *et al.* 1988), i.e. α- and β-receptors (the designations A-type and B-type receptors have also been used). The α-receptor binds all PDGF isoforms with high affinities, whereas the β-receptor binds PDGF-BB with high affinity, PDGF-AB with lower affinity, but appears not to bind PDGF-AA with any appreciable affinity. Human fibroblasts have both α- and β-receptors, but there are also examples of normal cells having only α-receptors, e.g. O–2A progenitor cells of the rat optic nerve (Hart *et al.* 1989), and only β-receptors, e.g. rat brain capillary endothelial cells (Smits *et al.* 1989). Both receptor types transduce potent mitogenic signals, but in human fibroblasts only the β-receptor mediates chemotaxis and actin reorganization (Nistér *et al.* 1988; Hammacher *et al.* 1989; Siegbahn *et al.* 1990). The signal transduction from the α-receptor may be cell type-specific, however, since a hematopoietic cell line transfected with α-receptor cDNA responds chemotactically to PDGF (Matsui *et al.* 1989*b*).

Analysis of cDNAs for the α-receptor (Matsui *et al.* 1989*a*; Claesson-Welsh *et al.* 1989) and the β-receptor (Yarden *et al.* 1986; Claesson-Welsh *et al.* 1988; Gronwald *et al.* 1988) for PDGF have revealed closely related molecules. The extracellular parts of the two receptors contain five immunoglobulin-like domains, each with an overall amino acid sequence similarity of 30 %. The intracellular parts of the receptors contain protein tyrosine kinase domains, which in each receptor contain inserted sequences of about 100 amino acids without homology to

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kinase domains. The amino acid similarities between the receptors are about 80% in the kinase domains and in the sequences between the transmembrane parts and the kinase domains, and about 30% in the kinase inserts and in the carboxy-terminal tails. The function of the characteristic inserts in the kinase domains remains to be elucidated; studies on transfected β-receptor mutants lacking the insert have suggested that it has a role in determining the substrate specificity or catalytic efficiency of the kinase (Escobedo and Williams, 1988; Severinsson *et al.* 1990). There are two other proteins that have a similar structural organization and thus form a subfamily with the PDGF receptors among the protein tyrosine kinase receptors, i.e. the receptor for colony stimulating factor-1 (Coussens *et al.* 1986) and the c-*kit* product, a receptor for an unknown ligand (Yarden *et al.* 1987).

Activation of PDGF receptors

An important observation in relation to the *in vivo* function of PDGF came through immunohistochemical stainings of tissue sections using monoclonal antibodies specific for the PDGF β-receptor; it was found that the receptor is not present on cells in most normal tissues, in spite of the fact that the same cell types possess receptors when grown in tissue culture (Terracio *et al.* 1988). Receptors were found to be induced, however, in conjunction with inflammation *in vivo* (Rubin *et al.* 1988). These findings suggest that the response to PDGF *in vivo* depends not only on the availability of ligand, but also on the expression of the corresponding receptors. Data on α-receptors *in vivo* are not yet available, but it was recently shown that this receptor is down-regulated *in vitro* after exposure of 3T3 cells to transforming growth factor-β (Gronwald *et al.* 1989).

Some insight into the mechanism whereby ligand binding induces the activation of the receptor kinase, has recently been provided by the demonstration that PDGF induces dimerization of the β-receptor (Bishayee *et al.* 1989; Heldin *et al.* 1989; Seifert *et al.* 1989) (Fig. 1). Data have also been provided that support the notion that receptor dimerization or oligomerization is involved in the activation of the receptor for epidermal growth factor (Schlessinger, 1988). Analysis of dimerization of purified PDGF β-receptor revealed that it was maximal at 0.5 $\mu g\,ml^{-1}$ of PDGF-BB and decreased at higher concentrations of ligand (Heldin *et al.* 1989). This suggests that each subunit of the dimeric PDGF molecule binds one receptor molecule. It is conceivable that the dimerization makes possible an interaction between the kinase domains of the two receptor molecules leading to their activation. This may involve cross-phosphorylation on tyrosine residues, since ligand binding has been observed to induce 'autophosphorylation' of the PDGF β-receptor (Ek *et al.* 1982). The two major autophosphorylation sites in the β-receptor were recently localized to tyrosine residues in the kinase insert sequence, and in the second part of the kinase domain, respectively (Kazlauskas and Cooper, 1989). The role of autophosphorylation in the regulation of the receptor kinase, however, remains to be elucidated.

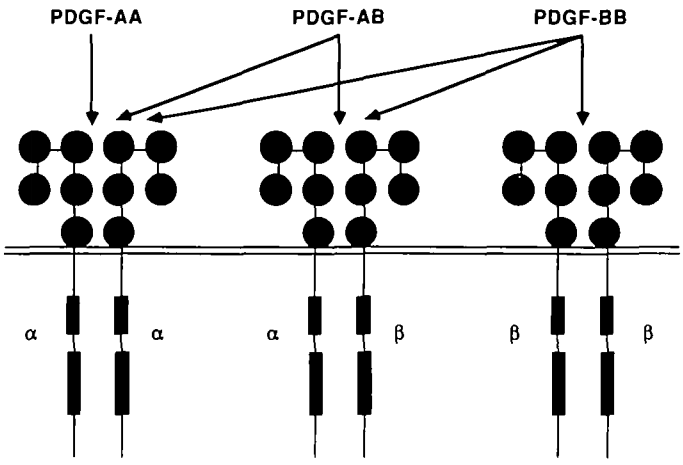

Fig. 1. Schematic illustration of the binding of the different isoforms of PDGF to homo- and heterodimeric complexes of PDGF receptors. The α- and β-receptors are drawn to indicate that they each contain 5 extracellular immunoglobulin-like domains and an intracellular split protein tyrosine kinase.

PDGF-AB binds with a 10-fold lower affinity than PDGF-BB to PDGF β-receptors (Severinsson *et al.* 1989), yet PDGF-AB is as potent a mitogen as PDGF-BB for human fibroblasts, in which activation of α-receptors only gives a limited mitogenic response. A possible explanation for this observation is that PDGF-AB binds to and activates the β-receptor more efficiently when α-receptors are present. PDGF-AB would thus bind simultaneously to one α-receptor and one β-receptor and by formation of a heterodimeric receptor complex simultaneously induce two signal pathways (Fig. 1). Indirect evidence in support of this possibility was recently obtained by studying the induction of actin reorganization and membrane ruffling in human fibroblasts, a response that is mediated by the β-receptor, but not by the α-receptor (Nistér *et al.* 1988; Hammacher *et al.* 1989). In the presence of α-receptors, PDGF-AB was found to induce actin reorganization, but in cells where the α-receptor was blocked by an excess of PDGF-AA, or where the α-receptor was down-regulated by prior exposure to PDGF-AA at 37 °C, the effect of PDGF-AB on actin reorganization was inhibited. In fact, in the absence of α-receptors, PDGF-AB acted as a β-receptor antagonist, presumably because it bound to β-receptors in a monovalent manner without activating them (Hammacher *et al.* 1989).

Substrates for the PDGF receptor kinases

The binding of PDGF to its receptors elicits a cascade of early cellular events, including protein phosphorylations on tyrosine as well as serine/threonine residues, phosphatidylinositol turnover, ion fluxes and gene expression. An intact tyrosine kinase activity has been shown to be essential for signal transduction by the β-receptor; this is most likely true also for the α-receptor but data are not yet available for this receptor. Thus, a PDGF receptor mutant in which the kinase activity has been extinguished by replacing the ATP binding lysine residue, is unable to mediate inositol lipid breakdown, calcium release, elevation of intracellular pH, gene expression, actin reorganization, chemotaxis or DNA synthesis (Escobedo *et al.* 1988; Westermark *et al.* 1990).

There has recently been some major progress in the attempts to link the tyrosine kinase activities of the PDGF receptors with the early signals in PDGF-stimulated cells, and several substrates have been identified, which may mediate some of the effects (Fig. 2). In many systems studied, however, it is not possible to conclude whether the

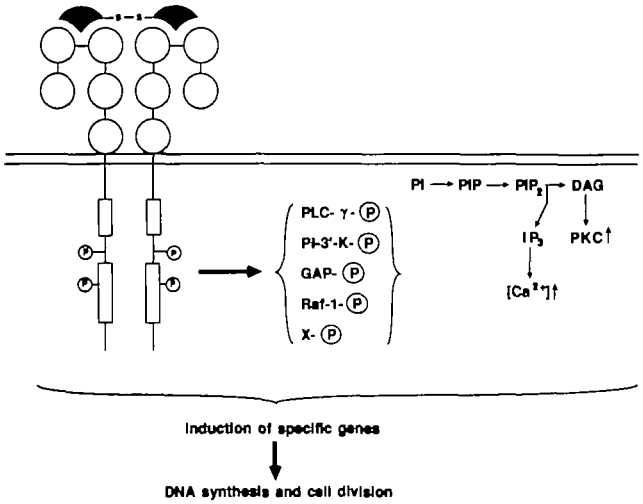

Fig. 2. Schematic illustration of intracellular signals arising from dimerized and activated PDGF receptors (α or β). Ⓟ symbolizes autophosphorylation of the receptor or phosphorylation of substrates on tyrosine residues. X denotes unknown substrates. For discussion see the text.

observed components are substrates for the kinases of the α- or the β-receptor, or both.

PDGF stimulates degradation of phosphatidylinositol bisphosphate, which leads to the generation of two second messengers, inositol trisphosphate, which releases intracellularly stored Ca^{2+} and diacylglycerol, which activates protein kinase C. A possible mechanism for this effect of PDGF was recently unravelled when it was shown that an enzyme that catalyzes the degradation of phosphatidylinositol bisphosphate, i.e. phospholipase C-γ (PLC-γ), is a substrate for the PDGF receptor kinase *in vivo* and *in vitro* (Meisenhelder *et al.* 1989; Wahl *et al.* 1989). The phosphorylation is most likely direct, i.e. no intermediate kinases are involved, and PLC-γ can be co-immunoprecipitated with the PDGF β-receptor. However, the important question of whether tyrosine phosphorylation of PLC-γ affects its enzymatic activity remains to be elucidated.

PDGF has also been found to regulate phosphatidylinositol metabolism in yet another way. Thus, a phosphatidylinositol-3′-kinase activity is activated by, and can be co-immunoprecipitated with, the PDGF β-receptor (Auger *et al.* 1989; Coughlin *et al.* 1989). This enzyme catalyses the phosphorylation of phosphatidylinositol or phosphatidylinositol phosphates at the 3′ position in the inositol ring, thus creating precursor molecules for novel inositol phosphates with still unknown effects on signal transduction.

A third potentially interesting substrate for the PDGF receptor kinase is a cellular GTPase-activating protein (GAP), which specifically interacts with Ras proteins that have been implicated in signal transduction pathways of several growth factors (Mulcahy *et al.* 1985). Both PDGF-AA and PDGF-BB were found to induce tyrosine phosphorylation of GAP and to induce a translocation of GAP from the cytoplasm to the cell membrane (Molloy *et al.* 1989). It is an interesting possibility that the tyrosine phosphorylation of GAP affects the interaction between GAP and Ras proteins and thus modulates the signals that arise from the GAP–Ras complex.

Finally, Raf-1, a serine/threonine kinase, has been found to be phosphorylated by, and to co-immunoprecipitate with, the PDGF β-receptor (Morrison *et al.* 1989). Tyrosine phosphorylation of Raf-1 was found to lead to a 4- to 6-fold increase of its serine/threonine kinase activity. Interestingly, protein kinase C, which is structurally related to Raf-1, is also activated in PDGF-stimulated cells, but by an indirect mechanism involving stimulation of phosphatidylinositol turnover (see above).

It is of considerable interest that the signal pathway of PDGF involves two protooncogene products. It is conceivable that constitutive activation of the products of *ras* and *raf*, e.g. in conjunction with retroviral transduction, lead to transformation of the cells by subverting the mitogenic pathway of PDGF.

Future perspectives

The recent understanding that PDGF is a family of isoforms that interact with two receptors in different dimeric configurations implies a growth regulatory system designed for fine tuning. The unravelling of the signal transduction pathways linked to each receptor type will guide our attempts to unravel the role of PDGF as a physiological growth regulator and possibly lead to a better understanding of its function in neoplastic transformation.

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