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PLATELET-DERIVED GROWTH FACTOR

Structure, function and implications in normal and malignant cell growth

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Platelet-derived growth factor (PDGF) is a potent mitogen for a variety of cell types. PDGF is made up as dimers of A and B polypeptide chains which are combined to generate the three isoforms of PDGF (AA, AB, BB). These bind with different specificities and affinities to two types of cell surface receptors (the α-receptor and the β-receptor), both being members of the protein tyrosine kinase family of growth factor receptors. A number of human tumor cell lines, particularly those established from glioma and sarcoma, have been shown to produce PDGF and express the cognate receptor type. In these instances, tumor cell growth may be enhanced by an autocrine receptor activation. In other tumor cell types, where PDGF is produced in the absence of receptor expression, the growth factor may act in a paracrine fashion. This view is supported by our recent finding that human melanoma cells that have been stably transfected with a PDGF B-chain cDNA, elicit a stroma response when transplanted to nude mice.

Except for the very first divisions of the fertilized oocyte, the completion of the vertebrate cell cycle is not an autonomous event, but is subject to positive and negative regulation by growth factors. Studies over the last decades have led to the identification of a number of polypeptide growth factors, most of which have been shown to exert key functions in fundamental biological processes such as cell growth, migration and differentiation. These growth factors can be grouped into various families according to their structural and functional characteristics (cf. (1)).

Growth factors exert their functions by binding to and activating specific cell surface receptors; the activated growth factor receptor transduces the signal and elicits a host of posttranslational, translational and transcriptional events that eventually lead to the initiation of the cell cycle, DNA synthesis and cell division. In several of the growth factor receptors, the extracellular ligand binding domain and the intracellular catalytic activity reside in the same polypeptide chain and are separated by a single membrane spanning segment (2). In most of these cases, the catalytic domain is a protein tyrosine kinase that upon activation phosphorylates tyrosine residues in the receptor molecule itself as well as several in other substrate proteins.

Recent evidence supports the notion that subversion of mitogenic pathways leads to uncontrolled growth and thereby contributes to malignant transformation and oncogenesis; in fact, the vast majority of oncogenes identified so far are perverted variants of normal cellular genes (protooncogenes) that encode key regulatory elements that control rate limiting events in growth stimulation, such as growth factors, receptors, transducing proteins, other intracellular signalling proteins, and transcription factors (3, 4). From a historical point of view, the first example was the discovery that the normal counterpart of the v-sis oncogene of simian sarcoma virus (SSV) is the cellular gene encoding the B-chain of platelet-derived growth factor (PDGF) (5–7).

Below we will highlight some of the most important aspects of PDGF and its receptors. For more extensive reviews on PDGF, see (8–10).

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Platelet-derived growth factor

Platelet-derived growth factor was originally discovered as a mitogenic activity present in serum but not in plasma (11) which was subsequently found to originate from platelets (12–14). More recent studies have shown that many different cell types produce PDGF; a much broader range of functions have therefore been attributed to PDGF than its mere presence in platelets would imply (8).

Structurally, PDGF is made up as a ~30 kDa dimer of structurally related polypeptide chains, A and B, which are covalently linked by disulfide bonds (reviewed in (9)). The A and B chains are encoded by separate genes, in the human genome located on chromosomes 7 and 22 respectively. All three possible dimers (PDGF-AA, PDGF-AB, PDGF-BB) have been shown to be natural cell products and can also be obtained as recombinant proteins. In the mature parts, the A and B chains are 60% similar in their amino acid sequences with a perfect match of the 8 cysteine residues.

Studies of wildtype or transfected cells have shown that PDGF-A is translated as a 23 kDa species that is dimerized and processed in the N-terminus to yield to a 30 kDa secreted PDGF-AA (15, 16). Alternative splicing of exon 6 encoded sequences in the PDGF-A transcript yields two separate C-termini of the product (17, 18). The most common transcript excludes exon 6 and gives rise to a C-terminus of 3 amino acids encoded by exon 7. Inclusion on exon 6 yields a C-terminus of 18 amino acids which include a high proportion of basic residues.

The primary translation product of the B-chain is a 28 kDa species that is dimerized and processed in both the N- and in the C-terminus; a 30 kDa form of PDGF-BB is the secreted product. In addition, an intracellular 24 kDA form of PDGF-BB is generated by further N-terminal processing (19). Immuno-electron microscopy (20) has shown that the 24 kDa species resides in endoplasmic reticulum and in the Golgi apparatus. According to our recent studies, cell association of the 24 kDa form of PDGF-BB is caused by the presence of a novel retention signal in the C-terminal propeptide of the B-chain precursor (19). A homologous stretch of amino acids is encoded by exon 6 in the long splice variant of the A-chain (PDGF-A_L) where it also causes cell retention. In addition, a similar sequence is also found in one of the splice variants of vascular endothelial growth factor/vascular permeability factor (VEGF/VPF) (21–23). Recent studies have suggested that the retention signal also confers binding to a heparan sulphate proteoglycan, associated with the cell surface or the extracellular, matrix (24, 25).

PDGF receptors: Structure, signal transduction and tissue distribution

Two distinct PDGF receptor types have been identified; the α-receptor binds all three isoforms of PDGF with high affinity whereas the β-receptor only binds PDGF-BB with high affinity, and PDGF-AB with a 10-fold lower affinity (8, 9). The two receptors are structurally and functionally related; their extracellular ligand-binding portions are made up by five immunoglobulin domains, both receptors have a single membrane-spanning segment, and both are endowed with intracellular protein tyrosine kinase domains (26–28). These features, in addition to the presence of an intervening sequence in the kinase domain, place the receptors in the same family as two protooncogene products, namely the CSF-1 receptor/c-fms product and the stem cell growth factor receptor/c-kit product (2).

Binding of PDGF to the proper receptor type leads to the activation of the intracellular kinase. Using the EGF receptor as a model, Joseph Schlessinger has championed the idea that receptor oligomerization is an initial and obligate event in the activation of the intracellular kinase (29); experimental data provide evidence for this concept with regard to the PDGF α- (30) and β-receptor (31–33). The current hypothesis for PDGF-induced receptor dimerization/activation is based upon the idea that the ligand is bivalent, such that one subunit chain in the dimer binds one receptor molecule. The two receptor molecules in the dimeric complex phosphorylate each other in trans (34). This model predicts that the cell surface expression of an inactive receptor molecule inhibits the ligand-induced activation of the wildtype receptor by a transdominant mechanism; experimental evidence in favor of this view has recently been obtained (35).

Several studies have shown that an intact protein tyrosine kinase activity is essential for PDGF receptor signal transduction. Several substrates have been described, e.g. phospholipase C-γ (PLC-γ), GTPase activating protein (GAP), phosphatidylinositol 3′-kinase (PI-3′-K), and members of the src family of protein tyrosine kinases (for references, see (9, 10)). All these substrates have a common structural motif, denoted src homology region 2 or SH2, which is designed for physical interactions with other proteins (36). It appears that the PDGF receptor interaction of the substrates mentioned above is mediated by the SH2 domains via binding to specific receptor autophosphorylation sites. There is a specificity in these interactions, such that three phosphorylated tyrosine residues in the kinase inert domain mediate the binding of PI-3′-K (Tyr-740 and Tyr-751) and GAP (Tyr-771) (37, 38), whereas PLC-γ interacts with phosphorylated Tyr-1009 and Tyr-1021 in the C-terminal tail of the receptor (39). The role of these substrates in the transmission of the mitogenic signal remains to be established.

The two types of PDGF receptor molecules are independently expressed on a number of cell types of various histogenetic origin (for references, see (8, 9)). Cells of fibroblastic origin are the most studied type; these have both α- and β-receptors as have vascular smooth muscle cells and placental trophoblasts. Cells with only α-receptors

include oligodendrocyte (O-2A) progenitor cells, mesothelial cells and liver capillary endothelial cells. Cells with only β-receptors are brain capillary endothelial cells, neurons, meningeal cells and Schwann cells. It thus appears that most of the cells that make up the central and peripheral nervous system are endowed with PDGF receptors of one type or another. The functional role of PDGF in neurobiological processes is therefore an important matter, especially since recent studies have shown that the ligand is also produced within the nervous system, e.g. by neurons (PDGF-B) (40), type 1 astrocytes (PDGF-A) (41, 42) and Schwann cells (PDGF-B) (43). In a recent study (44) we have for the first time been able to directly demonstrate a trophic effect of PDGF in brain tissue in vivo. The most dramatic effect was seen in glial cells and was mediated by the α-receptor, as judged from the equipotent activity of PDGF-AA and PDGF-BB.

The sis oncogene and its role in autocrine transformation

The c-sis/PDGF-B gene has been found as transduced onc sequences in two retroviral isolates, of which SSV is the best studied example (5–7, 45, 46). The transforming potential of c-sis/PDGF-B is identical to that of v-sis and studies of cells expressing v-sis (47) or recombinant c-sis/PDGF-B (16, 19) have shown that the respective translation products are similarly assembled and processed.

Whereas there is a consensus of opinion that sis-transformation is mediated by a PDGF-like growth factor that activates the cell's own receptor, the subcellular location of the autocrine receptor activation is a controversial issue. There seems to be no doubt that the endogenous receptor undergoes ligand-induced autophosphorylation in an intracellular compartment, probably already in the endoplasmic reticulum. Thus, autophosphorylated receptors of the high-mannose form have been demonstrated in the interior of v-sis-transformed cells (48, 49). Such receptors are not affected by suramin, in contrast to receptors activated at the plasma membrane by autocrine PDGF (50, 51). Additional evidence for an intracellular activation has been derived from studies in which the sis-product has a transforming activity even when retained in the endoplasmic reticulum by a KDEL retention signal hooked to the C-terminal end of the mature B-chain (52). One might also argue that our identification of a retention signal in PDGF-B actually favors the intracellular activation hypothesis. We have, however, found that the retention system is 'leaky'. This is especially apparent in transformation studies, which in all cases have employed genes with strong promoters/enhancers. There are also experimental data that are in conflict with the intracellular activation hypothesis. Thus, the intracellularly activated receptor fails to mediate an induction of c-fos mRNA expression (53). Moreover antibodies against PDGF in some instances revert the sis-transformed phenotype (54, 55). The finding that suramin reverts the phenotype completely (50) but has no effect on the intracellular autophosphorylation of the receptor (48, 51), is additional evidence against the model. We have therefore constructed a tentative model for the sis-induced autocrine transformation, according to which the ligand-receptor-complex is formed in the endoplasmic reticulum but has to be presented at the plasma membrane in order to elicit a mitogenic response, perhaps in order to associate with the relevant substrates.

PDGF and PDGF receptors in human tumor cells

The finding that PDGF mediates an autocrine transformation in responsive cells has prompted analyses of PDGF and PDGF receptor expression in tumor cells derived from spontaneous malignancies. Several examples have been found in which malignant cells produce one or several isoforms of PDGF concomitantly with the cognate receptor type (reviewed in (1, 10)) but it has been difficult to formally prove that the autocrine signal is of pathogenic importance. Interestingly, a recently finished survey of human glioma cell lines has shown that PDGF/PDGF receptor expression is not randomly distributed (56). In the vast majority of cell lines, the ligand expressed was found to match the receptor type, thus providing circumstantial evidence that the generation of an autocrine loop confers selective growth advantage. Since cell lines in long-term culture are not true representatives of the in vivo situation, we have recently extended our studies to glioma biopsies. Interestingly, we obtained evidence for two distinct autocrine loops, PDGF-B/β-receptor in endothelial proliferations (57) and PDGF-A/α-receptor in glioma cells proper (58). Whereas the α-receptor was present even in low grade gliomas, the expression of PDGF-B and β-receptor in endothelial cells and PDGF-A in glioma cells was clearly associated with progression to high grade gliomas.

Another interesting aspect of PDGF in malignancies has been derived from studies of carcinoma cells in culture. Anaplastic thyroid carcinoma cell lines were found to express β-receptors (59, 60) and α-receptors (60), in the latter case concomitantly with TSH receptors in contrast to normal thyrocytes which are completely devoid of PDGF recptors (61). A similar observation was recently made in lung carcinoma cells (K. Forsberg, J. Bergh, B. Westermark, submitted). These findings suggest that aberrantly expressed PDGF receptors in some cases are of pathogenic significance in carcinomas.

The finding that several PDGF receptor negative tumor cell types express high levels of PDGF (reviewed by (1, 10)) indicates that PDGF may have a paracrine function in tumorigenesis. There are several alternatives for such a function, e.g. in angiogenesis, connective tissue stroma development and suppression of natural killer cell activity (cf. (62)). Studies of human carcinoid tumors with an

abundant connective tissue stroma have shown a high expression of PDGF β-receptor on the stroma cells (63). Direct evidence for a role of PDGF in stroma formation has recently been obtained (K. Forsberg, I. Valyi-Nagy, C.-H. Heldin, M. Herlyn, B. Westermark, submitted). Human melanoma cells were stably transfected with a human PDGF B-chain cDNA and transplanted to athymic mice. The tumors that arose contained a connective tissue network with an abundance of blood vessels. There were no necroses in these tumors. In contrast, tumors derived from mock transfected control cells, were devoid of connective tissue stroma, had much fewer blood vessels, and contained large necrotic areas. These findings suggest that PDGF-BB mediates the generation of a connective tissue stroma. The stroma may constitute a solid support for the newly formed blood vessels and thereby facilitate the formation of a functional vascular system in the tumor.

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