CHAPTER 10

PDGF Pathways and Growth of Basal Cell and Squamous Cell Carcinomas

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Abstract

Ever since the discovery of the transforming retroviral v-sis oncogene, which encodes PDGF-B, PDGF signaling has been an interesting target for cancer treatment. In the last few years, compelling evidence supports the essential role of PDGF signaling for cancer cell proliferation and tumor angiogenesis in several types of human cancers, including nonmelanoma skin cancers. BCCs, the commonest human cancer, contain activation of the hedgehog pathway, frequently through inactivated mutations of tumor suppressor gene PTCH1. How does activation of the hedgehog pathway promote cell proliferation in the tumor? Our data indicate that PDGFRα activation is important for hedgehog signaling-mediated cell proliferation in BCCs. These findings not only detail the molecular basis of hedgehog-mediated tumorigenesis but also provide new designs for skin cancer therapeutics.

Signal Transduction by PDGFs and Their Receptors

Platelet-derived growth factor (PDGF) is one of the first growth factors to be characterized. PDGF functions as a potent mitogen in mesenchymal and glial cells. In addition, PDGF regulates cell morphology and cell movement, such as chemotaxis. PDGF signaling is involved in embryogenesis, carcinogenesis, atherosclerosis and wound healing. During carcinogenesis, PDGF receptor is frequently activated through over-expression of the ligand and its receptor.

PDGF belongs to PDGF/VEGF family with several conserved cysteine residues. Four PDGF family members have been identified: the classical PDGF-A and PDGF-B, and the novel PDGF-C and PDGF-D. PDGF expression is observed in a variety of cell types, including fibroblasts, keratinocytes, neurons, endothelial and epithelial cells, which can be regulated by external factors such as cytokines and thrombin. PDGF subunits are synthesized as precursor molecules, which undergo proteolytic processing. A variety of PDGF dimers can be formed from these subunits (Fig. 1), which then activate the PDGF receptor tyrosine kinases.

PDGF receptors contain an extracellular loop for association of the ligand, a transmembrane domain and an intracellular tail with a tyrosine kinase domain. PDGFs activate their receptors by promoting formation of receptor dimers: PDGFRαα, PDGFRαβ and PDGFRββ (Fig. 1). PDGF-dependent receptor dimerization triggers receptor autophosphorylation and subsequent signal transduction. The specific cellular functions of each PDGF subunit will partly depend on the availability of the receptor dimers (Fig. 1). PDGF receptors function in the cell through activating downstream effectors, such as PLC-γ, Grb2/ SOS, PI3K, GAP and Stat (Fig. 1).

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In Vivo Functions of PDGFs and Their Receptors

Studies of knockout mice have shed light on the in vivo roles of PDGFs and their receptors. All PDGF-A, PDGF-B, PDGFRα or PDGFRβ knockout are embryonic lethal whereas heterozygous mice are viable. PDGFRα null mice show the most severe phenotype. PDGFRα−/− mice display cleft face, spinal bifida, skeletal and cardiac defects, resulting embryonic lethality between E8 and E16. In comparison, PDGF-A deletion causes defect in alveoli development of lung, and the mutant mice die perinatally. These studies indicate that PDGFRα might mediate functions of other PDGF isoforms in addition to PDGF-A. Analyses of PDGF-A and PDGFRα null mice reveal that PDGF-A is often expressed in epithelium, muscle or neural tissues whereas PDGFRα expresses in the mesenchymal compartment, suggesting a paracrine mechanism of signaling (Table 1). The expression pattern of PDGF-C is similar to that of PDGF-A, suggesting an overlapping function of the two. It is therefore reasonable to believe that PDGF-C may be accountable for the phenotypic differences between PDGF-A null mice and PDGFRα null mice. PDGF-A, PDGF-C and PDGFRα are reported to be involved in intestinal, lung, skin, hair, testis and oligodendrocyte development.