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Gene Section
Review

PDGFB (platelet-derived growth factor beta polypeptide (simian sarcoma viral (v-sis) oncogene homolog))

Marie-Pierre Simon, Georges Maire, Florence Pedeutour

Institute of Signalling, Developmental Biology and Cancer Research, CNRS UMR 6543, Centre Antoine-Lacassagne, 06189 Nice cedex 2, France (MPS); UF Recherche Clinique 952, Laboratoire de Génétique, Université de Nice-Sophia Antipolis, CHU de Nice, 06202 Nice, France (GM, FP)

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Identity

Other names: V-sis platelet-derived growth factor beta (simian sarcoma viral oncogene homolog)

HGNC (Hugo): PDGFB

Location: 22q12.3-q13.1

Local order: Telomeric to TXN2 (thioredoxin, mitochondrial), centromeric to DMC1 (dosage suppressor of mck1, yeast homologue meiosis-specific homologous recombination).

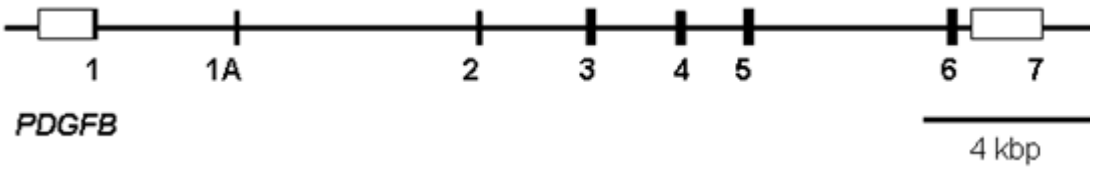
DNA/RNA

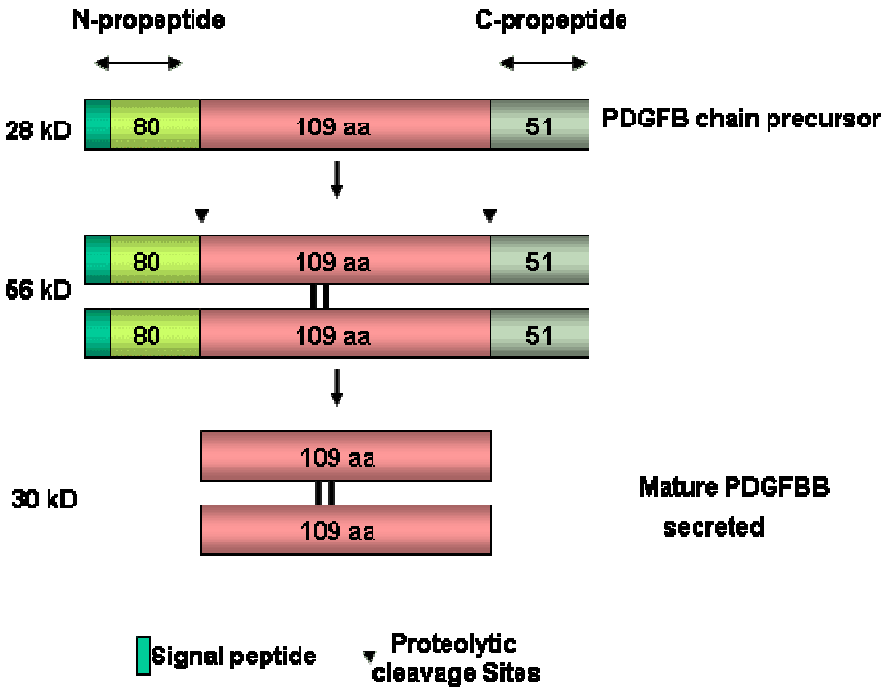
Description

The PDGFB gene encodes the human platelet-derived growth factor (PDGF) B chain precursor and is the cellular homologue of the v-sis oncogene. PDGFB gene is 22 kb in size and is composed of 7 exons. The exon 7 and most part of the exon 1 are non coding sequences (white boxes).

Transcription

The PDGFB chain precursor is usually translated from a 3.5 kb transcript. The first exon contains the sequence for the signal peptide preceeded by a 1 kb-long untranslated sequence with potent translation inhibitory activity. A 2.6 kb mRNA which initiates at an alternative exon 1, exon 1A, was described in the human choriocarcinoma cell line JEG-3. It initiates an open reading frame that is continuous with the code for the PDGF B chain precursor but lacks the code for the signal peptide.





Protein

Description

The PDGFB chains are synthesised as 240 amino acids precursors molecules containing amino and carboxy-terminal propeptides, which are removed by site-specific endopeptidases. Two PDGFB precursor chains associate in dimers to form the mature PDGFBB after proteolysis.

Expression

First isolated from human platelets, the PDGFBB is synthesized by a variety of different cell lineages.

Localisation

Secreted in the extra-cellular medium.

Function

The homodimer PDGFBB is a potent growth factor that acts as a mitogen and chemo-attractant for a variety of cells from mesenchymal origin. It has various roles in embryonic development, tissue regeneration, osteogenesis, fibrosis, atherosclerosis, and neoplasia.

Homology

Member of the PDGF/VEGF family.

Implicated in

Dermatofibrosarcoma Protuberans (DP)

Also called:
- Darier Ferrand tumour or Darier-Hoffmann tumour.
- Giant cell fibrosarcoma (GCF) (juvenile form of DP).
-Bednar tumour (pigmented variant of DP).

Disease

Infiltrative skin tumours of intermediate malignancy.

Prognosis

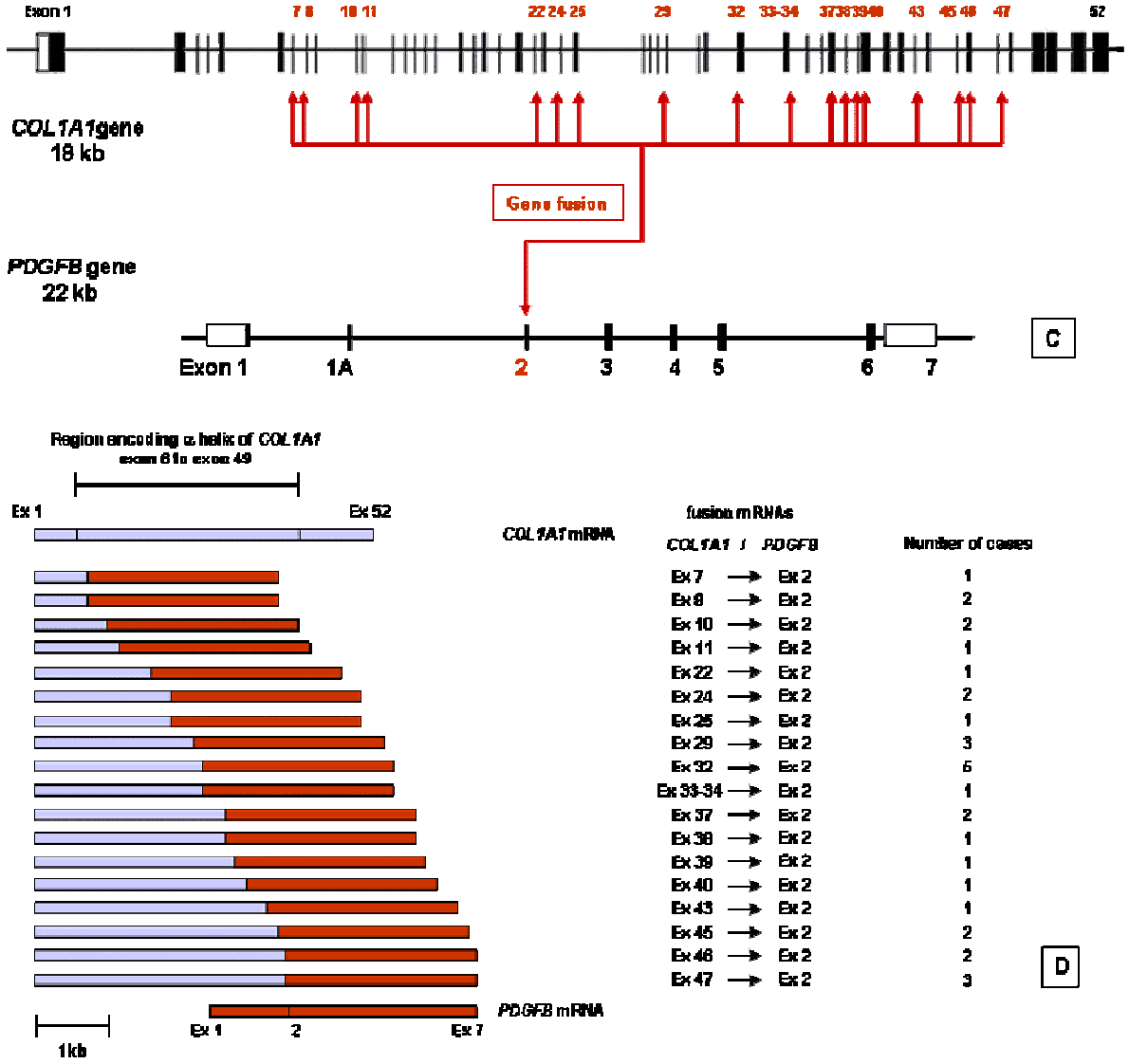
The prognosis is usually favourable. These tumours are locally aggressive and highly recurrent, but metastases or tumour-related deaths are extremely rare.

Cytogenetics

Dermatofibrosarcoma Protuberans, Giant Cell fibrosarcoma and Bednar tumours present specific cytogenetic features such as reciprocal translocations t(17;22)(q22;q13.1) (Fig A) or, more often, supernumerary ring chromosomes derived from t(17;22) (B). As shown by FISH analysis, the ring chromosomes contain chromosome 22 centromere and low-level amplification of 22cen-q13.1 and 17q22-qter sequences. To note, in most cases, the derivative chromosome 17 is not present. In contrast, several copies of the derivative chromosome 22 are generally observed.in addition to two apparently normal chromosomes 17.

Hybrid/Mutated gene

Both rings and der(22) translocated chromosomes present a same molecular rearrangement that fuses the collagen type I alpha 1(COL1A1) and the platelet-derived growth factor B chain (PDGFB) genes (C).
In all DP and GCF cases studied, the t(17;22)translocation results in chimerical COL1A1/PDGFB mRNA production, in which the PDGFB exon 1 is deleted and replaced by a variable segment of COL1A1 mRNA sequence. In the 32 cases tested the fusion mRNA was an in-frame fusion of one of the COL1A1 exons (varying from exon 7 to exon 47) to PDGFB exon 2 (D).



Abnormal protein

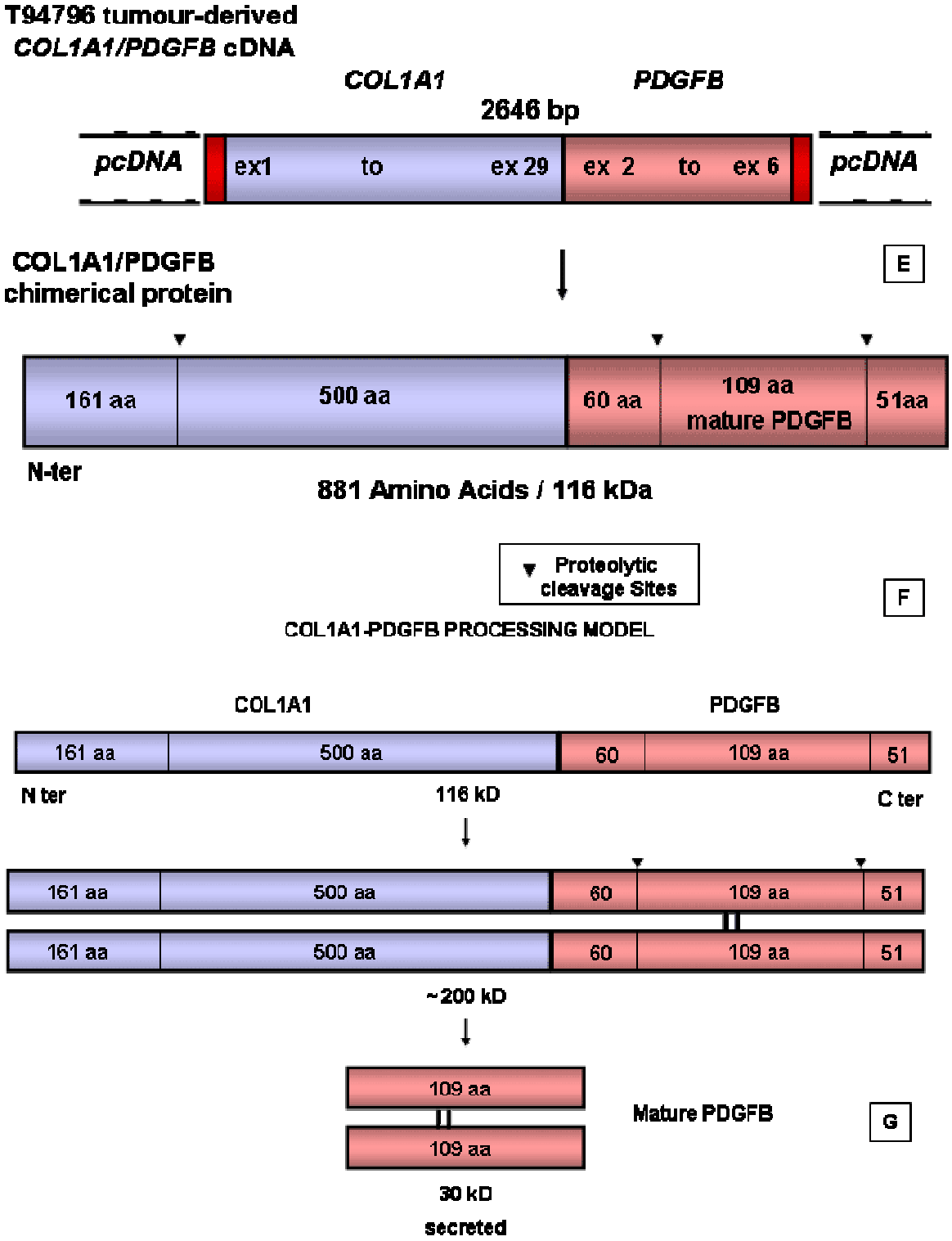
COL1A1 and PDGFB are both encoded as pro-peptides, which are processed by proteolytic cleavage at N and C-terminus, to give mature proteins. Sequences analyses of the chimerical COL1A1/PDGFB fusion transcripts showed that the COL1A1/PDGFB putative proteins displayed a pro-peptide structure, which preserved the N-terminus COL1A1 pro-peptide containing the signal peptide and the N and C-terminus PDGFB maturation cleavage sites.

The functional and structural properties of the COL1A1/PDGFB fusion protein were characterized by generating stable fibroblastic cell lines that expressed tumour-derived COL1A1/PDGFB chimerical genes. The diagram herein given presents the COL1A1/PDGFB chimerical protein encoded by the T94796 tumour-derived chimerical COL1A1/PDGFB cDNA sequence.

Oncogenesis

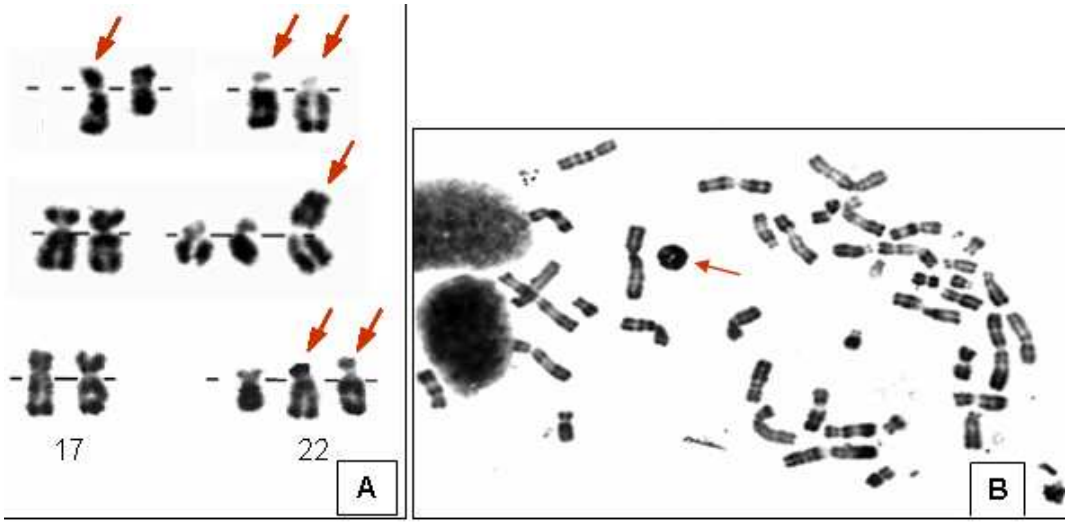
Transfected cells lines expressing the chimerical T94796-COL1A1/PDGFB proteins became independent upon growth factors, including PDGFB, and induced tumours formation in nude mice. In addition, it was shown that the COL1A1/PDGFB stable clones cells contained activated PDGF b-receptors and that the conditioned media from COL1A1/PDGFB transfected cells were able to stimulate fibroblastic cells growth. Anti-PDGFBB antibodies neutralized this effect.

These results strongly suggest that the COL1A1/PDGFB chimerical gene expression associated with DP, contributes to tumour formation through ectopic production of mature PDGFB and the formation of an autocrine loop.



A chimerical COL1A1/PDGFB cDNA sequence fusing COL1A1 exon 29 to PDGFB exon 2 was isolated from the DP T94796 tumour and stably transfected in the Chinese hamster lung fibroblastic cell line PS200 (E). The T94796 COL1A1/PDGFB chimerical protein sequence retained the COL1A1 N-terminus processing site encoded by the COL1A1 exon 6 and the N and C-terminus PDGFB processing sites encoded by the PDGFB exons 3 and 6 respectively (F). Mutagenesis experiments and immunodetection with anti-PDGFBB and specific anti-COL1A1/PDGFB antibodies showed that COL1A1/PDGFB expressing cells produced 116 kD chimerical COL1A1/PDGFB precursors chains, which formed dimers and were processed to give active 30 kD PDGFB-like dimers (G).

Breakpoints



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