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Gene Section
Mini Review

SMAD4 (mothers against decapentaplegic homolog 4 (Drosophila))

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Identity

Other names: MADH4; DPC4; JIP

HGNC (Hugo): SMAD4

Location: 18q21.1

Probe(s) - Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics.

DNA/RNA

Description

The gene encompasses 49.5 kb of DNA; 13 exons.

Transcription

3220 nucleotides mRNA.

Protein

Description

552 amino acids; 60.4 kDa protein. Smad4 belongs to the Darfwin family of proteins which harbours two conserved amino - and carboxyl-terminal domains known as MH1 and MH2, respectively. Smad4 in the basal state is found mostly as a homo-oligomer, most likely a trimer.

Expression

Ubiquitous.

Function

Smad4 is an intracellular mediator of TGF-beta family and activin type 1 receptor. Smad4 mediate TGF-beta signaling to regulate cell growth and differentiation. TGF-beta stimulation leads to phosphorylation and activation of Smad2 and Smad3, which form complexes with Smad4 that accumulate in the nucleus and regulate transcription of target genes. By interacting with DNA-binding proteins, Smad complexes then positively or negatively regulate the transcription of target genes.

Homology

With the other members of the Darfwin/Smad family.

Implicated in

Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome

Disease

Juvenile polyposis and hereditary hemorrhagic telangiectasia syndrome is an autosomal dominant disorder with distinct clinical features. One form corresponding to a predisposition to gastrointestinal polyps and cancer may be associated with mutations in Smad4 gene.

Oncogenesis

Polyps are formed by inactivation of the Smad4 gene through germline mutations and loss of the unaffected wild-type allele.

Pancreatic carcinoma

Disease

90% of pancreatic carcinomas show allelic loss at 18q.

A consensus region of homozygous deletion at 18q21.1 was found in one third of pancreatic carcinomas and intragenic mutations were found in another 20% of this tumor type.

Prognosis

Smad4 expression may be a molecular prognostic marker for pancreatic carcinoma. A lower patient survival may be associated with loss of Smad4 expression.

Oncogenesis

Smad4 was proposed to be a tumor suppressor gene that may function to disrupt TGF-beta signaling. Mutant Smad4 proteins, identified in human carcinomas, were found to be impaired in their ability to regulate gene transcription. Most of Smad4 gene mutations in human cancer are missense, nonsense, and frameshift mutations at the mad homology 2 region (MH2) which interfere with the homo-oligomer formation of Smad4 protein and hetero-oligomer formation between Smad4 and Smad2 proteins, resulting in disruption of TGF-beta signaling.

To be noted

Note

Mutation of Smad4 is seen also in approximately 15% of colorectal carcinomas and occasionally (less than 10%) in the rest of human cancers such as breast, ovarian, hepatocellular or head and neck squamous cell carcinomas.

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