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Gene Section
Review

SHH (Sonic hedgehog)

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Identity

HGNC (Hugo): SHH

Location: 7q36

Local order: Markers: RH69762, StSG39143

Note

Sonic hedgehog (SHH) is the vertebrate orthologue of Hedeghog (Hh) a morphogen signalling molecule discovered in a mutant drosophila (fruit fly). In addition to SHH, two other distinct Hh homologues have been cloned in vertebrates, Indian Hedgehog (Ihh) and (Dhh).

DNA/RNA

Description

3 exons, all 3 coding, cDNA to mRNA is 1576 bp.

Transcription

Coding sequence: nucleotides 152 to 1540. Two transcription start sites have been described.

Protein

Description

SHH is a secreted protein synthesised as a precursor molecule of 462 amino acids (45kDa); it harbors a signal sequence of 23 amino acids. Following removal of the signal sequence, a cholestreol-mediated autocatalystic cleavage results in a NH2 and a COOH subportions (N-SHH and C-SHH, respectively 19kDa and 25 kDa). N-SHH emcompasses amino acids 24-196. C-SHH encompasses amino acids 197-463. The C-SHH moeity bears the cholesterol transferase activity. Upon processing, the cholestreol molecule is covalently transfered to the C terminus of N-SHH through a nucleophilic substitution. Post-translational processing of N-SHH is thought to be necessary to its correct spatial distribution and effects during embryonic patterning. Except its role in the autocatalytic cleavage of precursor SHH, no biological activity of C-SHH has been evidenced.

Expression

SHH is the most broadly expressed member the hedgehog family. It is involved in the development of axial skeleton, notochord, spinal cord, floor plate, gut endoderm, and posterior limb (see also: Skeletal development in human: a model for the study of developmental genes .Ihh and Dhh play distinctive roles in the development of cartilage, and male germ cells respectively. In the adult, SHH plays roles in the hair follicle growth and cycle.

Localisation

SHH is secreted from producing cells to reach the surface of target cells were it interacts with its receptor, the multipass transmembrane protein PATCHED.

Function

SHH is implicated in segment polarisation. SHH biochemical function is the binding of PATCHED. This interaction modulates the activity of a third transmembrane protein called Smothened (SMO) apparented with G proteins-coupled receptors. SHH binding results in activation of the SHH/PATCHED pathway which eventually results in the modulation of the balance between cell proliferation and differentiation. In the absence of SHH, PATCHED acts as a constitutive repressor of the activity of SMO by posttranscriptionnal modifications. In contrast, the presence of SHH releaves PATCHED-mediated SMO inhibition and results in cell proliferation and transriptional activation of SHH target genes (PATCHED, Wingless, DPP, in Drosophila; PATCHED, Wnt, BMPs, in vertebrates) involving Ci

(Drosophila) or Gli (Gli-1, 2, 3, vertebrates) transcriptional factors. Most notably, SHH-induced SMO activation proceeds with transcription of PATCHED itself, suggesting a retroregulation loop, and hence a narrow maintenance of both free SHH and PATCHED/SMO complex concentration at the cell surface.
The important role of the SHH/PATCHED pathway in development and tissue homeostasis is attested by genetic disorders linked to specific dysregulation of this pathway. Familial mutations of PATCHED are linked to the Gorlin's or Nevoid Basal cell carcinoma syndrome. SHH mutations may result in sporadic or familial Holoproencepaly HPE (see below).

Homology

Alignement of full length human SHH and human IHH cDNAs reveals 71.608 % identities (GCG, Bestfit).

Mutations

Germinal

To the contrary of PATCHED, which mutation may result in familial predisposition to basal cell carcinoma and meduloblastoma, SHH mutations only result in developmental abnormalities. To date, there is actually no clear evidence that SHH mutation may be “naturally” associated with cancer. However, transgenic mice overexpressing SHH in the epidermal layer of skin develop basal cell carcinoma-like tumors.
Most SHH mutations that have been identified are associated with sporadic or familial cases of holoproencephaly (HPE, 1/133000 to 1/16000 viable birth) and Solitary Median Maxillary Central Incisor (SMMCI). Mutations are sparse over the SHH coding region. All types of mutation have been described. No evident correlation between mutation types and location, and patient phenotypes can be drawn

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