# Hedgehog signaling pathway

The Hedgehog signaling pathway is a signaling pathway that transmits information to embryonic cells required for proper cell differentiation. Different parts of the embryo have different concentrations of hedgehog signaling proteins. The pathway also has roles in the adult. Diseases associated with the malfunction of this pathway include basal cell carcinoma.

The Hedgehog signaling pathway is one of the key regulators of animal development and is present in all bilaterians.

The pathway takes its name from its polypeptide ligand, an intercellular signaling molecule called Hedgehog (Hh) found in fruit flies of the genus Drosophila. Hh is one of Drosophila's segment polarity gene products, involved in establishing the basis of the fly body plan. The molecule remains important during later stages of embryogenesis and metamorphosis.

Mammals have three Hedgehog homologues, Desert (DHH), Indian (IHH), and Sonic (SHH), of which Sonic is the best studied. The pathway is equally important during vertebrate embryonic development and is therefore of interest in evolutionary developmental biology. In knockout mice lacking components of the pathway, the brain, skeleton, musculature, gastrointestinal tract and lungs fail to develop correctly. Recent studies point to the role of Hedgehog signaling in regulating adult stem cells involved in maintenance and regeneration of adult tissues. The pathway has also been implicated in the development of some cancers. Drugs that specifically target Hedgehog signaling to fight this disease are being actively developed by a number of pharmaceutical companies.

Sterol synthesis is required for Sonic hedgehog signaling pathway.

Errors in Shh signal transduction play important roles in the formation of human tumors, including medulloblastoma (MB). It is not clear which products of sterol synthesis are necessary for Shh signal transduction or how they act.

Corcoran et al. showed that cholesterol or specific oxysterols are the critical products of sterol synthesis required for Shh pathway signal transduction in MB cells. In MB cells, sterol synthesis inhibitors reduce Shh target gene transcription and block Shh pathway-dependent proliferation. These effects of sterol synthesis inhibitors can be reversed by exogenous cholesterol or specific oxysterols.

They also showed that certain oxysterols can maximally activate Shh target gene transcription through the Smoothened (Smo) protein as effectively as the known Smo full agonist, SAG. Thus, sterols are required and sufficient for Shh pathway activation. These results suggest that oxysterols may be critical regulators of Smo, and thereby Shh signal transduction. Inhibition of Shh signaling by sterol synthesis inhibitors may offer a novel approach to the treatment of MB and other Shh pathway-dependent human tumors [1)].

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The sonic hedgehog (SHH) signaling pathway directs the embryonic development of diverse organisms and is disrupted in a variety of malignancies. Pathway activation is triggered by binding of hedgehog proteins to the multipass Patched-1 (PTCH) receptor, which in the absence of hedgehog suppresses the activity of the seven-pass membrane protein Smoothened (SMOH). De-repression of SMOH culminates in the activation of one or more of the GLI transcription factors that regulate the transcription of downstream targets. Individuals with germline mutations of the SHH receptor gene

PTCH are at high risk of developmental anomalies and of basal-cell carcinomas, medulloblastomas and other cancers (a pattern consistent with nevoid basal-cell carcinoma syndrome, NBCCS). In keeping with the role of PTCH as a tumor-suppressor gene, somatic mutations of this gene occur in sporadic basal-cell carcinomas and medulloblastomas.

A subset of children with medulloblastoma carry germline and somatic mutations in SUFU (encoding the human suppressor of fused) of the SHH pathway, accompanied by loss of heterozygosity of the wildtype allele. Several of these mutations encode truncated proteins that are unable to export the GLI transcription factor from nucleus to cytoplasm, resulting in the activation of SHH signaling. SUFU is a newly identified tumor-suppressor gene that predisposes individuals to medulloblastoma by modulating the SHH signaling pathway through a newly identified mechanism [2].

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2)
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