Sonic Hedgehog gene

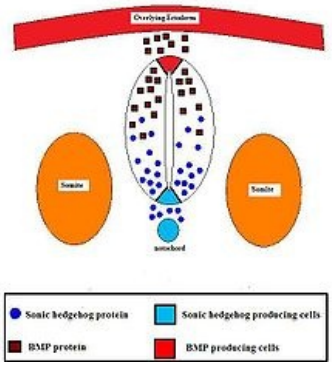
Sonic Hedgehog gene is probably the best-known member of the hedgehog (hh) family, i.e. a family of genes whose products are signal molecules that are very effective especially in embryonic development. The name hedgehog itself is derived from the shape of the larvae of the fruit fly with the mutation in the hh gene – these larvae have spiny bellies and resemble hedgehogs. Sonic hedgehog was named after the hero of the computer game Sonic the Hedgehog (https://en.wikipedia.org/wiki/Sonic_the_Hedgehog_(character)).

The Sonic Hedgehog gene has an irreplaceable function in:

- the development of the dorsoventral arrangement of the neural tube;
- the development of the anteroposterior arrangement of the limbs;
- development of central structures of the CNS.

Sonic Hedgehog (Shh) protein

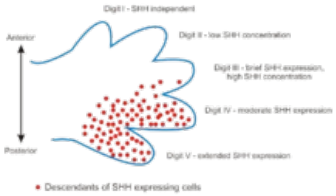
The Sonic Hedgehog Protein (Shh) is a signaling protein **with a highly conserved N-terminal region and a more variable C-terminal region**. To activate Shh, the signaling protein must first be cleaved from the propeptide, the remaining protein chain is subsequently glycosylated.



Gradient Shh při vývoji nervové trubice.

Steps of Shh signaling

1. In the cytosol, the C-terminal region is cleaved by autoprotease activity into an active N-terminal and an inactive C-terminal (the latter is not involved in signaling).
2. **The N-terminal part is covalently bound to cholesterol during cleavage**, subsequently the N-terminal peptide (19 kDa) leaves the cell, but remains bound on its surface.
3. Under the catalysis of the product of another gene (in Drosophila gene *disp*), the N-terminal peptide is released from the mother cell (i.e. from the cell where it was created).
4. Binding to the Patched receptor (Ptc) on the surface of the target cell (cholesterol bound to the N-terminal peptide facilitates this binding).
    1. **Ptc inhibits the transmembrane protein smoothed (smo)**, i.e. under normal conditions the signaling activity of the smo protein is inactivated by Ptc.
    2. Ptc associated with G-proteins and **binding to Shh is inactivated**.
5. Binding of Shh to Ptc inhibits its effect on smo, which is thereby activated for intracellular signaling.
6. Smo initiates a signaling cascade, culminating in the transcription factor Gli with a zinc finger motif.
7. Gli enters the nucleus, binds to specific DNA sequences and affects the transcriptional activity of a certain gene of the target cell.



Role gradientu Shh při vývoji anteroposteriorního uspořádání končetin.

Mutations in the Shh gene

The Shh gene is expressed in the notochord, prechordal plate and also the base of the neural tube and affects the development of the forebrain in particular.

- SHH induces NKX2.1 expression for the telencephalon.
- SHH induces the expression of PAX2 inhibiting the effect of PAX6 in the midline, thus initiating the division of the eye primordia and the adjacent region into paired ones.

Mutations in its sequence can therefore lead to, among other things holosencephaly, i.e. a developmental defect involving the absence of intermediate craniofacial structures. Manifestations of the disease show significant variability from defects involving only the formation of a single upper incisor or a single nasal cavity to cyclopsism or fusion of the cerebral hemispheres.

Links

References

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- NOVOTNÁ, – MAREŠ,. *Vývojová biologie pro mediky.* 1. edition. Karolinum, 2005. 99 pp. ISBN 80-246-1023-X.