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Commentary

Role of Hedgehog Signaling in the Development of Tissues and Organs

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DESCRIPTION

The signaling pathway that the Hedgehog (HH) family of secreted proteins activates and the proliferation, differentiation, and migration of cells play crucial roles not just in normal development but also in many types of cancer. Numerous levels of regulation have been identified by studies conducted over a forty-year period, including those involving the production, modification, release, and degradation of ligands as well as the functions of various receptors, coreceptors, downstream kinases, phosphatases, and effector transcription factors. Surprisingly, HH signaling has been linked to the primary cilium in vertebrates, a special cell surface organelle whose crucial roles in development and diseases were only been recognized in the last two decades.

The molecular interaction network has grown more complex because to the ongoing discovery of new HH signaling regulators and effectors. HH signaling is strictly regulated due to its importance for healthy embryonic development and its role in the patterning of different tissues and organs. Different lipid compositions that specify certain membrane regions, like those seen in the primary cilium of vertebrates, impose one such layer of regulation. Studies give a general review of the history of ciliary lipid compositions and how they have affected HH signaling.

This signaling route is stunningly dependent on numerous other lipids and sterols, functionally impacting HH ligand transport as well as intracellular signal transduction—a truly unique aspect of the HH pathway. These lipids and sterols include ciliary membrane-specific phosphoinositides. The SMO protein, which can interact with sterols in both covalent and non-covalent ways, is one illustration of the complex interaction between lipids and signaling.

However, ubiquitination and SUMOylation, two evolutionarily conserved regulatory mechanisms of HH signaling in Drosophila and mammals, are also applied to SMO. Researchers describe how these post-translational alterations control SMO traffickingand compare the mechanisms that emerged in flies and humans. The GLI family of transcription factors are the HH pathway's effectors, translating the HH signal into transcriptional reactions that result in cellular outputs.

Phosphorylation's role in regulating GLI

They present our current knowledge of how GLI proteins are processed and activated in both vertebrates and invertebrates using cAMP-dependent Protein Kinase (PKA), Casein Kinase 1 (CK1), and Glycogen Synthase Kinase 3 (GSK3)-mediated phosphorylation. They also go over the most recent findings, some of which are still up for discussion, such as the functions and controls of ciliary cAMP in HH signaling. They also talk about the identification of novel GLI regulators, including the Polo-Like Kinase 1 (PLK1), CK2, and members of the Fused family of kinases, which catalyze the phosphorylation of GLI proteins and support the functional control of these proteins.

Over the past ten years, there has been a lot of research on how micro RNAs (miRNAs) regulate HH signaling. However, the preferred genetic loss of function approach frequently produces a pitiful amount of useful data, possibly because this class of regulators as a whole or each miRNA individually exhibit functional redundancy and contextual dependence.

HH signaling plays crucial functions in the development of several organs. Researchers discuss the functions of HH signaling in cancer and cerebellar development. They examine earlier genetic research that showed how Purkinje Cells (PC) and Granule Cell Progenitors (GCP), the two main neuronal cell types of the cerebellum, interact through the SHH gene.

They concentrate on Cyclin D (CycD), Cyclin-dependent kinase 4 (Cdk4), and MYCN as GLI targets that directly control cell proliferation and their roles in the etiology of Medulloblastoma (MB), a pediatric cerebellar tumor. Finally, they go over the use of downstream CDKs, SMO, and GLI inhibitors as treatment options for MBs. Understanding the functions of HH signaling in cerebellar development and MB etiology is clinically important, as evidenced by the fact that some of the inhibitors are already approved or in clinical trials for MB treatment.

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