Hedgehog Signaling Pathway [1]


The hedgehog signaling pathway is a mechanism that directs the development of embryonic cells in animals, from invertebrates to vertebrates. The hedgehog signaling pathway is a system of genes [5] and gene products, mostly proteins, that convert one kind of signal into another, called transduction. In 1980, Christiane Nüsslein-Volhard [8] and Eric F. Wieschaus, at the European Molecular Biology Laboratory [10] in Heidelberg, Germany, identified several fruit fly (Drosophila melanogaster [9]) genes [9]. They found that when those genes [5] were changed or mutated, the mutated genes [5] disrupted the normal development of fruit fly larvae. The researchers called one of the genes [5] hedgehog (abbreviated hh). Nüsslein-Volhard, Wieschaus, and Edward B. Lewis [9], at the California Institute of Technology [10] in Pasadena, California, shared the 1995 Nobel Prize for Physiology or Medicine for their research on how genes [9] control early embryonic development in fruit flies. The hedgehog signaling pathway is conserved across many animal taxa, or phyla, from Drosophila [11] to humans [12]. The hedgehog signaling pathway controls several key components of embryonic development, stem-cell maintenance, and it influences the development of some cancers.

In the 1970s, Nüsslein-Volhard and Wieschaus studied mutations in genes [5] that altered the head to tail (anterior-posterior) body plan of Drosophila [11] larvae. The larval body plan of normal Drosophila [11] is composed of segments. Nüsslein-Volhard and Wieschaus in their 1980 article identified several genetic mutations that disrupted the Drosophila [11] larval body plan, including segment number, the pattern of the segments, and their orientations. The anterior portion of the bottom, or ventral, side of each segment is marked with a row of pointed cuticle projections, called denticles. The posterior portion is devoid of denticles, and is described as naked. Nüsslein-Volhard and Wieschaus found that several gene mutations caused the denticles on a larva to duplicate in number, resulting in loss of all or some of the naked portions of the larva's segments.

In one gene mutation, the denticles sticking out of the segment in all directions formed a pattern that resembled that of a hedgehog's spines, prompting Nüsslein-Volhard and Wieschaus to name the mutated gene hedgehog. They designated the hh gene as a segment polarity [13] gene because the duplicated denticles were oriented in the reverse direction from the normal denticles, a phenomena described by researchers as having reverse polarity [13] in each segment.


Unlike flies, which have only one hh gene, researchers found that there are several hh genes [5] in vertebrates, including upwards of five hh genes [5] in zebrafish, and three hh genes [5] in mammals. Ingham's group at the Molecular Embryology Laboratory in Oxford, UK, identified the hh gene family in zebrafish (Danio rerio [16]). Clifford Tabin's group at Harvard Medical School [17] in Boston, Massachusetts, isolated the vertebrate gene Sonic hedgehog (Shh), which is related to the Drosophila [11] hh gene. The scientists isolated the gene from the area that genetically instructs the developing limb, or limb bud, called the zone of polarizing activity (ZPA) in chicks (Gallus gallus [18]). Andrew P. McMahon's group at Harvard University [19] in Cambridge, Massachusetts, identified three members of the hh gene family in mice (Mus musculus [20]). They labeled those three genes [5] as Shh, Desert hedgehog (Dhh), and Indian hedgehog (Ihh). By 2015, researchers had concluded that the protein sequence of the Dhh protein is the most closely related of the three gene products to the Drosophila [11] hh protein. Ihh and Shh DNA sequences indicate that those genes [5] are more closely related to each other than to the Dhh gene, and scientists said that those two genes [5] resulted from a more recent evolutionary duplication. Drosophila [11] hh gene and vertebrate homologs function to provide cells with positional information [21] in developing organisms.
**Drosophila** ([1]) embryos lacking hh genes ([5]) die, revealing changes in their cuticle pattern, which suggests that **Drosophila** ([11]) require the gene for survival. In **Drosophila** ([17]), in addition to its role in patterning embryonic segments, the hh gene expression is in parts of the insect larvae that become the adult legs and wings, called the imaginal discs. The imaginal discs are similar in developmental function to the limb buds in vertebrates.

The hedgehog signaling pathway participates in the development of many tissue and organs. M. Michael Cohen, Jr., at Dalhousie University ([22]) in Halifax, Nova Scotia, titled his 2003 article “The Hedgehog Signaling Network,” due to the complexity of the interactions between the many genes ([5]) and secreted hh proteins. The hedgehog signaling network incorporates many genes ([6]) and proteins to function correctly. The hedgehog signaling network influences the transcription of many different target genes ([6]) that vary between tissues, cell types, and phylas.

By the second decade of the twenty-first century, the description of the hedgehog signaling pathway consisted of at least two parts, which were the cells that produce hh protein, and the cells that respond to the hh proteins. From hh genes ([6]) in the DNA of the nucleus ([23]), a cell that produces the protein first transcribes the hh protein as a string of amino acids, called a precursor protein, and processes the protein in the cell's cytoplasm, a process that yields an active protein with two lipid molecules. The two lipid molecules are a cholesterol on the C-terminal end of the active protein, and the lipid palmitate on the N-terminal end of the active protein. The two lipid molecules are necessary for the hh protein to be transported and attached to the cell surface membrane, and to establish a gradient of the protein in the extra cellular space. The processed hh protein is transported to the cell surface where it attaches with the lipid molecules to the outside of the cell membrane. Another protein embedded in the membrane, called a trans-membrane protein, named Dispatched, releases the active hh protein, called the hh ligand, into the space between cells, called an extra cellular space, where multiple hh ligands form a concentration gradient.

Other cells respond to the hh proteins. Each one of those cells has a protein, called Patched (Ptc), that spans through the cell's membrane and functions as a receptor for the hh ligand by physically attaching to it. Without the hh ligand attached to it, Ptc normally inhibits another trans-membrane protein called Smoothened (Smo), which itself prevents specific genes ([5]) from transcribing RNA. When the hh ligand binds to the Ptc protein, it activates the Smo protein. The Smo proteins interact with other molecules, which interact with others, in a process described as the hh signal cascading or transducing through the cell's cytoplasm and into the nucleus ([23]). Finally, molecules, connected in a chain or pathway of molecular interactions that was spurred by the hh ligand, attach to parts of the DNA in the nucleus ([23]), and they initiate specific genes ([5]) to produce RNA and proteins, or they inhibit specific genes ([5]) from doing so. Molecules that activate or inhibit other genes ([5]) from producing RNA and proteins are called transcription factors. In **Drosophila** ([11]), many of those transcription factors are called Cubitus interrupts (Ci), while in vertebrates many are classed in the GLI family of proteins.

The hh gene was the focus of much research by developmental biologists in the three decades after its first description. Researchers identified molecules that underpin mechanisms and processes that the hedgehog pathway controls. In the first decades of the twenty-first century, researchers studied the mechanism of how hh proteins function in short-range and long-range signaling between cells. They found that hh proteins distribute in tissues in a steep gradient, with high concentrations near the producing cells and lower amounts farther away from the producing cells. The ligands at either end of the hh ligand have some affinity for hh protein receptors, but their main function is to move the hh ligand through the tissue and establish the gradient.

There are similarities between the patterning of the neural tube ([25]) in vertebrate embryos and wing patterning of **Drosophila** ([11]). Mutations and improper development of this pathway lead to various embryonic defects and birth defects ([27]), especially those affecting the brain, head, and limbs. Too little hh protein signaling in **Drosophila** ([11]) can kill embryos or lead to embryos with abnormal wings. In humans ([12]), malfunctions, mutations, and incorrect regulation ([26]) of the hh signaling pathway are commonly associated with birth defects ([27]) and cancers. Cancers such as basal cell carcinoma, which is a skin cancer, or medulloblastoma, which is a brain cancer in children, are potential consequences of mutations to the hh pathway.

If Shh activity is lost in mammals, it can lessen the number of cells in the forebrain ([26]) and cause the forebrain ([29]) to fail to develop into two hemispheres. Scientists call the disorder holoprosencephaly: in fetuses, severe cases holoprosencephaly causes brain and facial defects, and the death of the fetus ([39]). In mild cases, brain development is closer to normal and facial defects are restricted to specific areas, such as cyclopism or having only one eye. Other examples of birth defects ([27]) that result from a mutation in hh signaling are Greig cephalopolysyndactyly syndrome, which affects head, face, and limb development. People with this disorder can have more digits than normal, webbed
embryonic development, stem-cell maintenance, and it influences the development of some cancers. Many animal taxa or phyla, from Drosophila to humans. The hedgehog signaling pathway controls several key components of research on how genes control early embryonic development in fruit flies. The hedgehog signaling pathway is conserved across California Institute of Technology in Pasadena, California, shared the 1995 Nobel Prize for Physiology or Medicine for their researchers called one of the genes hedgehog (abbreviated hh). Nüsslein-Volhard, Wieschaus, and Edward B. Lewis, at the Molecular Biology Laboratory in Heidelberg, Germany, identified several fruit fly (Drosophila melanogaster) genes. They found that when those genes were changed or mutated, the mutated genes disrupted the normal development of fruit fly larvae. The molecular organization and embryonic expression of the Segment Polarity Gene hh Is Expressed in Tissues with Polarizing Activity in Zebrafish Embryos. Cell 75 (1993): 1431–44.


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