The Hedgehog Signaling Pathway in Vertebrates ? [1]

By: Haskett, Dorothy Regan Keywords: signaling pathways [2]

The hedgehog signaling pathway is a mechanism that regulates cell growth and differentiation [4] during embryonic development, called embryogenesis [5], in animals. The hedgehog signaling pathway works both between cells and within individual cells. The hedgehog gene (*hh*) was observed in fruit flies (*Drosophila melanogaster* [6]) in 1980, and later in vertebrates in 1993. Unlike flies, which have one *hh* gene, vertebrates have several *hh* genes [7]. The hedgehog signaling pathway controls a wide range of developmental processes in the vertebrate embryo, and researchers found that dysfunction in the hedgehog signaling pathway leads to birth defects [8] including extra digits, cyclopia [9] with one eye and no forebrain [10], and cancers in adults and juveniles.

In 1980, Christiane Nüsslein-Volhard [11] and Eric F. Wieschaus in Germany researched how genes [7] control fruit fly development, and they named the *hedgehog* gene. They named the gene *hedgehog* because mutant fruit fly larva demonstrated an abnormal pattern of spiky projections, called denticles, on their exoskeletons that resembled the spines of a hedgehog. Until the early 1990s, researchers studied the *hh* gene (the abbreviation for the *hedgehog* gene) in the *Drosophila* [12] hedgehog pathway. They determined that the *hh* gene encodes a family of hh proteins, which mediate both cell-to-cell interactions and has long-range effects in developing *Drosophila* [12] embryos.

In 1992, three research teams published the sequence of the *hh* gene from *Drosophila* [12]: Jym Mohler and Kodela Vani at Barnard College in New York, New York; Phillip A. Beachy's group at Johns Hopkins University School of Medicine [13] in Baltimore, Maryland; and Thomas B. Kornberg's group at the University of California San Francisco in San Francisco, California. Analyses of the *hh* DNA sequence data led researchers to discover gene homologs, or genetic sequences similar to those in fruit flies but in vertebrates, a result that revealed a high degree of genetic conservation between species.

In 1993, Clifford Tabin and Andrew P. McMahon in the US and Philip W. Ingham in England published the DNA sequences of related genes [7], or homologs, to the *Drosophila* [12] *hh* gene in several vertebrate families. Unlike the fly, in which there is only one *hh* gene, the researchers identified different *hh* genes [7] in vertebrates. There are three classes of vertebrate *hh* genes [7]: Sonic hedgehog, Indian hedgehog, and Desert hedgehog, with most vertebrate species possessing one member from each gene family. Mammals, including humans [14], and birds [15] have one gene from each family: *Sonic hh* (*Shh*), *Indian hh* (*Ihh*), and *Desert hh* (*Dhh*). Zebrafish have at least five *hh* genes [7]: two Sonic class genes [7], *Shh* and *Tiggy-Winkle hh* (*Twhh*); two Indian class genes [7], *qiqihar hedgehog* (*Qhh*) and *echidna hedgehog* (*Ehh*); and one Desert class gene, *Dhh*.

In their 1993 experiment, Tabin's group at the Harvard Medical School in Boston, Massachusetts, isolated a vertebrate *Sonic hh* gene related to the *Drosophila* [12] *hh* gene in the developing limbs, or limb buds, of chicks (*Gallus gallus* [16]). The group demonstrated that *Shh*

gene expression occurs in the area of the margin of the developing limb bud, called the zone of polarizing activity (ZPA), and in other regions of the chick [17] embryo. Their research demonstrated that the *Shh* gene controls front to back or anterior to posterior pattering in the chick [17] limb, and prompts limbs to develop. When researchers removed the ZPAs from limb buds and attached them to other areas of the chicks, new limb buds develop in the presence of *Shh*.

McMahon's group at the Harvard Medical School [18] in Boston, Massachusetts, identified three members of mammalian *hh* gene family in mice (*Mus musculus* [19]) related to the *Drosophila* [12] *hh* gene: *Shh*, *Dhh*, and *Ihh*. They then compared, across species, the sequences of the genes [7] and the proteins made from the genes [7] to determine the evolutionary relatedness of each hedgehog gene. The protein sequence of the Dhh protein in mice is the most closely related to the hh protein in *Drosophila* [12], indicating that it is the oldest and most conserved between species. *Ihh* and *Shh* DNA sequences indicated that those genes [7] more closely related to each other than to the *Dhh* gene, and therefore resulted from a more recent evolutionary duplication event.

Ingham's group at the Molecular Embryology Laboratory in Oxford, England, identified three members of the *hh* gene family in five *hh* genes [7] found in zebrafish (*Brachydanio rerio* [20]). In the zebrafish embryos, Ingham's group identified a *Dhh* gene and the *Shh* gene as active in the notochord [21], a structure in chordate embryos, in the floor plate, a structure that in vertebrate embryos develops into the nervous system. They also found that the genes [7] functioned in the posterior fin mesoderm [22], the tissues associated with polarizing activities. *Shh* and *Twhh* genes [7] are expressed in fin bud development, but only *Shh* is required for proper development in zebrafish. The pattern of *Shh* expression in zebrafish mutants affects axial structures consistent with the role for the *Shh* gene in floor plate induction [23].

Ihh proteins function in developing bones, and they regulate the proliferation and differentiation [4] of cartilage cells, called chondrocytes. Dhh proteins also function in the development of sperm [24] cells during a process called spermatogenesis. Dhh proteins are necessary for the development of the glia [25] cells that insulate the peripheral nerves, called Schwann cells after Theodor Schwann who obseved them in nineteenth century Germany. Shh proteins function in the development of the central nervous system, and they establish lateral asymmetry, and function to establish the front-to-back (anterior-posterior) limb axis.

The *Shh* gene became one of the most studied of the *hh* genes [7]. Researchers experimented with vertebrate sonic hedgehog [26] proteins (N-Shh), and their results indicated that those proteins traveled outside of cells. Once in the extracellular environment, and with help from other molecules, N-Shh proteins can move at least twelve cell diameters to form a distribution gradient to target cells. For all hh signaling between cells, small differences in the concentration of the proteins can alter cellular functions and processes.

A flexible rod-shaped structure found in vertebrate embryos, called the notochord [21], defines the primary axis of the embryo. The notochord [21], located under the neural tube [27] of the developing vertebrate's central nervous system [28], secretes the N-Shh protein to form a gradient. The gradient of N-Shh protein specifies five distinct types of neuron [29] cells, called V0, V1, V2, and V3 interneurons, or motor neurons. In addition, the cells of the floor plate, which develop into the nervous system, respond to the highest concentration of N-Shh secreted by the notochord [21] and become non-neuron [29] supporting cells of the nervous system, called glial cells. The floor plate glia [25] cells begin to secrete N-Shh protein

themselves. The remaining neural tube [27] cells develop into various types of neural cells, specified by different concentrations of N-Shh proteins. Notochord cells develop into V3 cells in response to the second highest concentration of N-Shh protein after the floor plate. The third and fourth highest concentrations yield the motor neurons, V2, V1, and V0 neurons respond to the lowest concentration of N-Shh protein.

The hh family of proteins regulates multiple developmental processes in the vertebrate embryo, and can cause cancer or birth defects. Hedgehog family proteins are involved in cancers, for example, a human skin cancer called basal cell carcinoma, and a childhood brain cancer called medulloblastoma. Mutations and improper expression of Shh proteins lead to various embryonic defects and birth defects [8], especially those affecting the brain, head, and limbs. Shh protein functions for multiple events during embryogenesis [5], including craniofacial development. Mice lacking the *Shh* gene (*Shh* null) are born without their forebrains or mid-faces, a disorder called holoprosencephaly, and they have only one eye, a phenomenon called cyclopia [9]. If the *Shh* gene fails to produce Shh proteins in vertebrates, birth defects [8] result, especially in heads and faces.

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Subject

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