

Distinguished lecture explores contradictory role of Hedgehog signaling

By Jordan St Charles

In his Sept. 26 distinguished lecture, “Hedgehog signaling in organ homeostasis and malignancy,” Philip Beachy, Ph.D., described a role of Hedgehog signaling in preventing epithelial cancer in the bladder and pancreas, which contradicts the pro-cancer role that Hedgehog signaling has in the development of medulloblastomas and basal cell carcinomas. Hedgehog is the name of a particular signaling molecule that binds with a target protein in a biochemical process known as the Hedgehog pathway.

Beachy was hosted by Traci Hall, Ph.D., head of the NIEHS Macromolecular Structure Group, and Humphrey Hung-Chang Yao, Ph.D., head of the Reproductive Developmental Biology group. “His work is a must read for everyone who studies developmental biology,” said Yao in his introduction.

A professor of biochemistry and developmental biology in the Stanford School of Medicine, [Beachy](#)

(<http://stemcell.stanford.edu/about/Laboratories/beachy/index.html>)

has been a member of the National Academy of Sciences since 2002. His lab focuses on the function of Hedgehog proteins in morphogenesis and injury repair. Describing the diverse roles of Hedgehog signaling, Beachy’s topics ranged from its importance in embryonic development to a newly understood role in restraining proliferation of invasive carcinomas.

Linked Video

[**"Watch Beachy in this Stanford video, discussing the role of Hedgehog signaling in cancer, through minute 59:12" \(1:54:06\)**](#)

Hedgehog in development

Traditional studies of the Hedgehog pathway have focused on its role in embryo development. Disruption of the pathway during development can cause problems such as a rare birth defect called cyclopia, in which embryos lack midline structures of the face and brain and consequently develop only one eye and nostril.

In the Hedgehog pathway, the Hedgehog protein binds to a receptor known as Patched, activating an important downstream protein known as Smoothened and allowing important downstream events to take place. In the absence of Hedgehog, Patched inhibits the activity of Smoothened, preventing activation.

Hedgehog and bladder infections

In addition to its role in development, Hedgehog signaling is important for the recovery of organs following damage. Beachy described his work examining the Hedgehog role in bladder recovery from urinary tract infections.

When bacteria are introduced into the bladder, apoptosis, or cell death, occurs, followed by exfoliation of the top layer of cells. Basal cells, located below the top layer of cells, produce the Hedgehog signal in response to the bacterial damage. The Hedgehog signal then causes factors to be expressed that lead to cell differentiation, restoring function within the bladder tissue.



Beachy discussed new areas of research, including the role of Hedgehog signaling in processes in which the stroma actually restrains tumor growth. (Photo courtesy of Steve McCaw)



*“Beachy made the groundbreaking discovery of the Hedgehog signaling pathway and molecular regulation in *Drosophila*,” said Yao, when introducing Beachy. “I have known his work for a long time and it’s a great honor to have him here in person.” (Photo courtesy of Steve McCaw)*

Beachy reported that this feedback system functions in many tissue systems and ruminated on possible reasons that the system evolved in this manner. “The epithelia in all of our organs are the tissue layer that takes the hit,” he said. “If we breathe or eat something bad, it’s the lung or intestinal epithelium that is affected and the underlying stromal cells are not injured.”

Hedgehog signaling and epithelial cancer

Beachy’s lab has also studied the role of Hedgehog signaling in urothelial cancer development. Studying the origin of the cancer and whether cancer cells are derived from stem cells, the scientists were able to show that the basal cells that express Hedgehog can give rise to cancer cells. They further showed that if these cells are destroyed, cancer does not form, indicating that in this model, invasive carcinoma arises from basal cells.

However, when the researchers examined the cancer cells after they had become invasive, they found that these cells no longer expressed the Hedgehog protein. Further experiments indicated that Hedgehog signaling to the stroma causes release of pro-differentiation factors from stromal cells that can restrain tumor growth and progression.

This is very different from other cancers, such as medulloblastoma, in which Hedgehog activation within the primary cells of the tumor has been shown to promote cancer growth. Beachy suggested that these differences should be considered during treatment. “This suggests that the Hedgehog pathway and its antagonists have to be handled with care and patients should be monitored very closely,” he said.

(Jordan St Charles, Ph.D., is an Intramural Research and Training Award fellow in the NIEHS DNA Replication Fidelity Group.)



Beachy drew a diverse crowd including from left, Benjamin Scruggs, Ph.D., of the Chromatin and Gene Expression Group, Natacha Steinckwich-Besancon, of the Calcium Regulation Group, Doug Bell, Ph.D., head of the Environmental Genomics Group, and Steve Kleeberger, Ph.D., head of the Environmental Genetics Group. (Photo courtesy of Steve McCaw)



Birnbaum listened closely as Beachy outlined new studies into drugs that may block carcinoma development. (Photo courtesy of Steve McCaw)



The Reproductive Medicine Group was well represented, including from left, group lead Carmen Williams, Ph.D., Wendy Jefferson, Ph.D., biologist, and Alisa Suen, visiting predoctoral fellow. (Photo courtesy of Steve McCaw)

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