Keynote Lecture VII

A Tale of Tumor Suppressors in Hedgehog Signaling

Chi-chung Hui

Program in Developmental Biology, The Hospital for Sick Children, and Department of Molecular and Medical Genetics, University of Toronto, Canada

Dr Chi-chung Hui obtained his bachelor and Master degrees at the University of Hong Kong, and did his doctoral work in Nagoya University, Japan. He did postdoctoral training in Prof Yoshiaki Suzuki's laboratory at the National Institute for Basic Biology in Okazaki, Japan and in Dr Alexandra Joyner's laboratory at the Samuel Lunenfeld Research Institute in Toronto, Canada. In 1994, he joined the Research Institute of the Hospital for Sick Children in Toronto. His research program focuses on the biochemical and genetic dissection of the mammalian Hedgehog signaling pathway. Dr Hui is currently Head of the Program in Developmental Biology at the Hospital for Sick Children Research Institute and Professor of Medical Genetics and Microbiology at the University of Toronto.

The Hedgehog (Hh) family of secreted signaling molecules plays critical roles in embryonic patterning and organ development in both invertebrates and vertebrates. In humans, defects in Hh signaling result in a variety of congenital malformations found in many genetic disorders, including holoprosencephaly, Gorlin's syndrome, and Greig cephalopolysyndactyly. Abnormal activation of the Hh pathway is also a major aberration in common cancers, such as basal cell carcinoma of the skin (BCC), medulloblastoma (MB), upper gastrointestinal cancer, and prostate cancer.

My laboratory has been using the mouse as a model system to dissect the molecular mechanism of mammalian Hh-Gli signal transduction. In this lecture, I will present our recent work on the *Patched (Ptch)* genes, which encode the Hh receptor, and *Suppressor of fused (Su(fu))*, which encodes an inhibitor of Gli-dependent transcription. Both *Ptch* and *Su(fu)* are implicated as tumor suppressor genes as their mutations have been found in Gorlin's syndrome patients, which are associated with a high incidence of BCC and MB, as well as in sporadic MB. We have previously identified a second *Patched* gene *Ptch2*, which shows overlapping expression with *Sonic hedgehog* in the developing epidermis. Genetic studies in mice showed that *Ptch2* plays a specific role in adult skin homeostasis, and that *Ptch1* and *Ptch2* plays overlapping functions during epidermal development. While Su(fu) was generally thought to act negatively in Hh signaling by inhibiting the Gli activators, we demonstrated that Su(fu) controls both Gli activators and repressors, and is a rate-limiting regulatory component in mammalian Hh signaling. Our studies provide novel information for understanding the tumor suppressor function of these Hh signaling components.