CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
R1220

Project Title:
Recruitment of First-Time, Tenure-Track Faculty Members

Award Mechanism:
Recruitment of First-Time, Tenure-Track Faculty Members

Principal Investigator:
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Entity:
The University of Texas Southwestern Medical Center

Lay Summary:

The focus of my current research is to understand mechanisms of cellular signaling at the level of the primary cilia, and its relevance to human health and disease. The first cellular organelle to be described in biology, the primary cilium was long mistaken as a vestigial appendage. The primary cilia are now considered as vital sensory organelles for detection and transmission of a broad range of chemical and mechanical signals in most cells. Signaling mediated by the primary cilia plays fundamental roles in cellular differentiation, polarity and cell cycle control. My current and future research aims at utilizing a variety of biochemical, cell biological and reverse genetic approaches to understanding signaling mediated by cilia, and dissecting their role during cell cycle control and carcinogenesis.

I was initially trained as a physician in Medial College, Calcutta, and Institute of Medical Sciences, Varanasi, India. During my MD years, I studied the role of tyrosine kinases in platelet signal transduction. I then joined Dr. Piali Sengupta's laboratory in Brandeis University as a PhD student. While studying the development of head neurons in the nematode C. elegans, I became interested in the distinctive morphology of the olfactory cilia. Using tools for real time tracking of ciliary assembly in single cells, we showed the differential requirements for building and maintaining specialized olfactory cilia in C. elegans. In addition, we discovered that the membrane architecture of the olfactory sensory cilia in C. elegans are patterned by coincidental signaling inputs, suggesting that cilia are not just static antennae, but organelles whose structures are remodeled by their signaling activities. These findings help us begin understand the remarkable diversity and dynamicity of ciliary architecture in the context of various tissues, an issue extremely important in understanding mechanisms that result in the pathogenesis of multi-syndromic ciliary diseases.

As a postdoctoral fellow in Dr. Peter Jackson's lab in Genentech, I started utilizing an unbiased proteomic approach to build networks of proteins important in ciliary signaling. My initial studies involved studying the role of the tubby family proteins, a family of poorly understood proteins important in neural development and obesity. While generating the tubby family interactome, we discovered that the tubby-like protein, Tulp3 binds to a conserved ciliary complex, called the IFT-A complex. Primary cilia and intraflagellar transport (IFT), an ancient conserved trafficking mechanism within the cilia, are required for optimal sonic hedgehog (Shh) signaling during neural tube differentiation in vertebrates. Paradoxically, mutations in the IFT-A complex, which is implicated in retrograde IFT, cause increased Shh signaling in the neural tube. Similar to the IFT-A

mutants, mutations in Tulp3, also exhibit increased Shh signaling in the neural tube. Our studies on the Tulp3-IFT-A interaction suggested that in addition to its known role in retrograde transport, the core IFT-A sub-complex has a preciliary role in recruiting Tulp3 to the cilia. Tulp3 in turn promotes trafficking of certain rhodopsin family GPCRs to the cilia. Furthermore, using a candidate approach for ciliary GPCRs expressed early during development, we identified an IFT-A regulated ciliary GPCR in repression of Shh signaling. The cAMP-activated protein kinase A (PKA) is pivotal in repressing Shh signaling by the processing of Gli transcription factors into the Gli repressors. However, more than a decade after this was first described, the cAMP regulating pathways that mediate this activation of PKA remain unknown. The processing of Gli3 repressor is blocked in the receptor knockout, and constitutive activity of the receptor results in increased cAMP levels. This suggests that this Tulp3/IFT-A regulated receptor could regulate PKA-mediated processing of Gli3 repressor via cAMP signaling. We have thus discovered a fundamentally new IFT-A/Tulp3- mediated trafficking and signaling pathway for a GPCR in the basal repression machinery of Shh signaling.

Future research in my own laboratory would utilize integrative approaches to dissect the role of this novel repression mechanism in Shh signaling, both in cellular and organismal contexts. Besides, we will utilize a variety of strategies for testing the function of this Tulp3/IFT-A regulated GPCR in establishment of the spatiotemporal basal cAMP gradient in Shh signaling. We would also target this pathway for therapeutic intervention in Shh-dependent tumors, and for bypassing tumor resistance to available drugs. Our studies would thus address the fundamental role of the primary cilium as a regulatable platform in the Shh pathway during tissue homeostasis and disease.