Tata Institute of Fundamental Research
Survey No. 36/P, Gopanpally Village, Serilingampally, Ranga Reddy Dist., Hyderabad – 500 046

Webinar

Tubulin posttranslational modifications: structural and functional implications in mammalian cilia and flagella

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Mammalian cilia and flagella play key roles in cellular signalling, sensory activities, organogenesis (primary cilia), embryonic symmetry (nodal cilia) as well as fluid flow and motility (motile cilia and flagella). Dysfunctions in cilia lead to disorders collectively referred to as ciliopathies. The core structure of cilia and flagella, the axoneme, is a microtubule-based structure that is a hub of various tubulin posttranslational modifications (PTMs) – a key component of the 'tubulin code' that currently emerges as a regulator of microtubule properties and functions.

Among the different PTMs enriched in cilia, glycylation is exclusive to cilia and flagella and while it was evidently observed on motile cilia, it was rarely detected on primary cilia. Developing new antibodies to glycylation, I established that primary cilia do have glycylation, and that similar to motile cilia, it has a role in stabilizing the primary cilia.

To obtain an in-depth molecular and physiological understanding of the role of tubulin glycylation in mammals, I developed a transgenic mouse model knocked out for both the initiating glycylases ($Ttll3^{-/-}$/$Ttll8^{-/-}$). Despite their lack of glycylation in all ciliated tissues, strikingly, the $Ttll3^{-/-}$/$Ttll8^{-/-}$ mice do not show any signs of ciliary dysfunctions characteristic of ciliopathies. However, the male mice were sub-fertile with defects in sperm flagellar beating and overall motility, resulting in majority of the sperm swimming in a circular/helical pattern that impede straight-line swimming, leading to a concomitant loss of progressive motility. In-depth cryo-electron tomography analysis of the molecular alterations within the axoneme determined that lack of glycylation causes abnormal conformations of the dynein arms within sperm axonemes, providing the structural basis for the observed dysfunction. Overall, our work unravels the importance of microtubule glycylation for controlled flagellar beating, directional sperm swimming, and male fertility.

Cilia are enriched with not only glycylation, but also glutamylation and how these two modifications impact the functions of primary cilia in mammals is barely understood. The primary cilia are a hub of various signalling pathways, which are regulated by trafficking of different signalling molecules by intraflagellar transport (IFT). In the future, I propose to determine the molecular link between tubulin PTMs and intraflagellar transport within primary cilia and how this impacts the different signalling pathways. I will also establish how defects in tubulin PTMs can lead to ciliopathies, deciphering the molecular mechanisms and clinical implications of tubulin posttranslational modifications, thus establishing the role of tubulin PTMs as a regulator of organ function and tissue homeostasis.

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3:00 PM