Seminar Announcement

PHYSIOLOGY
National University of Singapore

Title **RNA helicase A mediates 1p36 gene KIF1Bbeta neuroblastoma tumor suppressor function by cooperating in developmental apoptosis during nerve growth factor competition**

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Time 12.00 nn – 1.00 pm

Venue MD6 (Level 4, SMART CLASSROOM)

Abstract

Developmental apoptosis of neuronal precursors is crucial in determining the final number of terminally differentiated cells. During neural development, cells undergo apoptosis as growth factors such as NGF becomes limiting. Abnormal NGF signaling or aberrant developmental apoptosis is implicated in pediatric nervous system tumors. Several genes act upon a developmental apoptotic pathway that is activated when NGF becomes limiting for neuronal progenitors and requires KIF1Bb. KIF1Bb is necessary and sufficient for neuronal apoptosis during NGF withdrawal. KIF1Bb maps to 1p36.2, a region that is frequently deleted in neural crest-derived tumors including neuroblastomas. We identified a transcriptional basis for KIF1Bb-induced cell death, which requires a RNA/DNA helicase known as RNA helicase A (DHX9). KIF1Bb interacts with DHX9 to promote translocation of cytoplasmic DHX9 into the nucleus, resulting in transcription of apoptotic XIAP-associated factor 1 (XAF1). Transcription-impaired or nuclear localization-impaired DHX9 is unable to potentiate KIF1Bb-induced cell death. Knockdown of DHX9 also protects from KIF1Bb-induced cell death whereas KIF1Bb negative mutant is unable to translocate cytoplasmic DHX9 into the nucleus. Furthermore, silencing of XAF1 protects from KIF1Bb-induced cell death. In addition, a genome-wide shRNA library loss-of-function screen revealed a DHX9-interacting transcription factor ZIC2 that is deemed crucial for KIF1Bb-induced apoptosis. This further suggests a DHX9-dependent transcriptional program initiated by KIF1Bb to induce apoptosis in neuroblastomas. Recent literature strongly pointed to KIF1Bb as a bonafide tumor suppressor. Our findings provide a mechanistic understanding of this role, whereby KIF1Bb interacts with cytoplasmic DHX9 leading to its accumulation in the nucleus to initiate a unique transcriptional signature that includes apoptotic effectors such as XAF1.

Convener: **Dr Thai Tran**

All Are Welcome