Cancer, RNA regulation and Therapeutics

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My research background and goals can be summarized into three key words: Cancer, RNA and Therapeutics. In this seminar, I will talk about my research accomplishments on 1) the identification of oncogenic KRAS associated vulnerabilities in lung cancer and 2) the discovery of a novel regulatory mechanism of miRNA arm switching and its association with glioblastoma.

1) The activating mutations in KRAS are frequently involved in the pathogenesis of non-small cell lung cancers (NSCLCs), the most responsible disease for cancer deaths. By employing a multi-genomic data driven approach, we demonstrated oncogenic KRAS-associated selective dependency of NSCLCs on nuclear transport machinery. Chemical perturbation of the nuclear export receptor XPO1 revealed a robust synthetic-lethal interaction with oncogenic KRAS both in vitro and in vivo. The primary mechanism underpinning XPO1 inhibitor sensitivity was intolerance to the accumulation of nuclear IκBα, with consequent inhibition of NFκB transcription factor activity. Intrinsic resistance associated with concurrent FSTL5 mutations was detected and determined to be a consequence of YAP1 activation via a previously unappreciated FSTL5–Hippo pathway regulatory axis, which can be overcome with the co-administration of a YAP1–TEAD inhibitor.

2) Strand selection is a critical step in microRNA (miRNA) biogenesis. Although the dominant strand may change depending on cellular contexts, the molecular mechanism and physiological significance of such alternative strand selection (or "arm switching") remain elusive. We found that miR-324 to be one of the strongly regulated miRNAs by arm switching and identified the terminal uridylyl transferases TUT4 and TUT7 to be the key regulators. Uridylation of pre-miR-324 by TUT4/7 re-positions DICER on the pre-miRNA and shifts the cleavage site, leading to alternative strand selection. In glioblastoma, the TUT4/7 and 3p levels are upregulated, whereas the 5p level is reduced. Manipulation of the strand ratio is sufficient to impair glioblastoma cell proliferation.