Identifying Novel Cell Signaling Components Required for KIF5B-RET-Driven Lung Cancer: A Genetic Approach

Shing, Danny (School: Hunter College High School)

RET (Rearranged During Transfection) is a receptor tyrosine kinase (RTK) that is frequently altered across multiple cancer types. One such alteration is KIF5B-RET, a fusion oncogene that drives a subset of non-small cell lung cancers (NSCLC) and leads to poor prognosis. Treatment of KIF5B-RET-positive NSCLC has been complicated by the recent emergence of a signaling hub model in which KIF5B-RET recruits other RTKs, namely FGFR and EGFR, as alternative avenues of oncogenesis. Furthermore, G810 solvent front mutations have been identified in fusion-positive patients as resistance mechanisms to FDA-approved RET-selective inhibitors, suggesting that additional hub components must be targeted for optimal therapeutic effect. In this study, I used Drosophila melanogaster models to identify key mediators of cancer progression of five KIF5B-RET variants. Through genetic techniques, I knocked down 18 genes transcribing RTKs and Ras/MAPK pathway components. Not only did suppressing multiple RTKs (FGFR, EGFR, IGF1R, ROR) improve KIF5B-RET and G810R fly survival, but knocking down PTPN11, which encodes a key MAPK adaptor protein, substantially rescued both. KIF5B-RET responded more strongly to RET, EGFR, and IGF1R knockdowns while G810R favored FGFR and PTPN11, suggesting that the G810R mutation redirects kinase activity to be more FGFR-centric. Further analysis of pFGFR immunofluorescence in both variants demonstrated strong signaling interdependence between FGFR and multiple RTKs, while suggesting that PTPN11 mediates oncogenesis independently of the FGFR axis. This work expands on the signaling hub model of KIF5B-RET-driven disease and introduces FGFR and PTPN11 inhibition as promising new therapeutic avenues.

Awards Won: