RET oncogene activation in lung adenocarcinoma with neuroendocrine differentiation is mediated through EGFR

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Lung adenocarcinoma (AD) accounts for 40% of all non-small cell lung cancers. Achaete-scute homolog 1 (ASCL1) is a neuroendocrine transcription factor specifically expressed in 10-20% of lung AD with neuroendocrine (NE) differentiation (NED). Our recent data demonstrated that ASCL1 was as an upstream regulator of the RET oncogene in AD with high ASCL1 expression (A+AD). RET is a receptor tyrosine kinase with two main human isoforms; RET9 (short) and RET51 (long). We found that elevated expression of RET51 associated mRNA was highly predictive of poor survival in stage-1 A+AD ($p=0.0057$). Functional studies highlighted the role of RET in promoting invasive properties of A+AD cells. Further, A+AD cells demonstrated close to 10-fold more sensitivity to epidermal growth factor receptor (EGFR) inhibitors, including gefitinib and lapatinib, than AD cells with low ASCL1 expression. Treatment with EGF robustly induced phosphorylation of RET at Tyr-905 in A+AD cells with wild type EGFR. Immunoprecipitation experiments found EGFR in a complex with RET in the presence of EGF and suggested that RET51 was the predominant RET isoform in the complex. In the microarray datasets of stage-1 and all stages of A+AD, high levels of EGFR and RET RNA were significantly associated with poor overall survival ($p<0.01$ in both analyses). These results implicate EGFR as a key regulator of RET activation in A+AD and suggest that EGFR inhibitors may be therapeutic in patients with A+AD tumors even in the absence of an EGFR or RET mutation.

Speaker Biography

Farhad Kosari is an Assistant Professor in the Department of Molecular Medicine at Mayo Clinic. His interests are in the discovery and development of clinically relevant biomarkers for prostate and lung cancers. His domains of expertise are Bioinformatics and Molecular Biology, particularly as related to the development of biomarker based assays. His most recent project focus has been in lung adenocarcinomas with neuroendocrine (NE) differentiation (ND-AD). Characterized by the expression of ASCL1, these ND-ADs are a sizable subset of lung tumors that are largely understudied and underappreciated. His group has recently discovered the main drivers in these tumors and is currently investigating therapeutic options for patients with ND-AD.

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