Novel oncogenic RET mutation found in small cell lung cancer

22 August 2014

For the first time an oncogenic somatic mutation at amino acid 918 in the RET (rearranged during transfection) protein has been identified in small cell lung cancer (SCLC) tumors and enforced expression of this mutation within SCLC cell lines produced increased intracellular signaling and cell growth.

SCLC is a highly malignant form of lung cancer representing 15% of all lung cancers and is strongly associated with tobacco smoking. NSCLC, representing 85% of lung cancer, has been extensively examined for genomic alterations and targeted therapies are approved for patients with certain mutations, however SCLC has not been examined with the same rigor and there are no approved targeted therapies for SCLC.

Investigators at Case Western University examined 6 SCLC tumors, 3 each from primary and metastatic tumors, for 238 somatic mutations across 19 oncogenes. RET wild type and mutant protein was then overexpressed in SCLC cell lines and these cell lines were examined for cell signaling, cell growth and responsiveness to two tyrosine kinase inhibitors of RET.

Results reported in the September issue of the *Journal of Thoracic Oncology*, the official journal of the International Association for the Study of Lung Cancer (IASLC), revealed the RET M918T mutation in a metastatic SCLC tumor and that overexpression of this mutant protein in SCLC cell lines resulted in increased ERK signaling, MYC expression and increased cell proliferation. Likewise, these cell lines overexpressing the RET protein became sensitive to ponatinib and vandetanib, tyrosine kinase inhibitors of RET. Decreased cell growth was the result of this inhibition of RET.

The authors say that their work "suggests that RET mutations play a potential role in some cases of SCLC as no other activating mutations were identified among the 19 oncogenes assayed in the tumor harboring the RET M918T mutation, potentially making M918T the driver mutation in this tumor". However, the authors caution that "the role of oncogenic RET mutations cannot be judged fairly until a larger number of tumors are genomically analyzed, including metastatic tumors".

Provided by International Association for the Study of Lung Cancer