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RON (mst1r) isoforms in lung cancer: Expression and oncogenic function prediction from primary transcript sequences

Ample evidence correlates aberrant RON receptor tyrosine kinase expression to tumor aggressiveness and metastasis in various cancer types. We aimed to understand the molecular aberrations, occurring at the isoform level, of the proto-oncogene RON. We hypothesized that the plethora of tumor enhancing functions of RON, observed in numerous independent studies, may be caused by isoforms formed as a result of increased alternative splicing associated with aberrant expression of RON in tumors. We reasoned that application of methods deficient in isoform-specificity, for both quantification and functional determination of RON, may have hindered our understanding of the precise molecular mechanism linking aberrant RON expression and cancer. Screening RON transcripts from 12 small cell lung cancer (SCLC) and 12 non-small cell lung cancer (NSCLC) cell lines by cDNA sequencing revealed the presence of numerous alternatively spliced RON transcripts as demonstrated by the presence of more than 35 unique exon/intron deletions and insertions. Somatic mutations were not detected in RON coding sequence. Analysis of lysates by Western blotting indicated the presence of several isoforms of RON in most of these cell lines. When probed using different RON antibodies, each recognizing a unique epitope of RON, Western blotting of cell lysates showed different RON specific banding patterns. While isoforms of RON were detected in the lysates of all the cell lines tested, wild type RON was missing in several of them. Analysis of the protein sequences (predicted from transcript sequences) indicated that alternatively spliced isoforms of RON could be localized differently (cytoplasmic, transmembraneous and extracellular) and may exhibit constitutive or dominant negative activities of RON. Besides, the secreted isoforms of RON may interact with intra-tumor ligand, macrophage stimulating protein (MSP) or wild-type RON present on tumor associated macrophages (TAM) and other cells of the tumor microenvironment. Future functional studies of the newly identified transcripts, by cloning and expression of the individual transcripts, are expected to reveal the tumor promoting functions of specific isoforms and eventually leading to develop targeted therapies.

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