Identification of a novel mutant of EPHA4 gene in pancreatic ductal adenocarcinoma

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Mutations in Eph genes (EPHA3, EPHB2) have been reported in several human tumor types. To determine whether these and related genes may be somatically mutated in pancreatic cancer, we sequenced the juxtamembrane segment and tyrosine kinase domain of all fourteen human Eph receptors in >100 samples of primary or metastatic pancreatic cancers corresponding to ~500 Kb of sequence evaluated for potential single base substitutions. We identified two somatic heterozygous missense EPHA4 mutations (p.L771P, p.M814T), both within the highly conserved residues of the tyrosine kinase domain. To determine the potential functional consequences of these mutants, we generated expression vectors encoding each missense mutation and transiently transfected them into 293 cells. Immunoprecipitation-Western assays showed that the L771P mutant had reduced EphA4 kinase activity compared with those cells transfected with a wild-type EPHA4. Additional functional studies are currently in process (cell growth and migration assays). This is the first report of mutations in an Eph gene in pancreatic cancer, and the first report of EPHA4 mutations in any tumor type. While additional studies will be required to determine the functional consequences of these and other Eph mutations, their position within the KD activation segment suggests a functional role could be expected. Our findings suggest that low frequency targets of mutation in pancreatic cancer may have functional consequences.