TARGETING AURORA A AND AURORA B IN LUNG CANCER CELLS REDUCES KRAS-DEPENDENT ONCOGENICITY

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INTRODUCTION. Activating mutations in KRAS are prevalent in lung cancer and have been causally linked to the oncogenic process. However, therapies targeted to oncogenic RAS have been ineffective to date and identification of KRAS targets that impinge on the oncogenic phenotype is warranted. Because Aurora A phosphorylates RAS effector pathway components, and both Aurora A and B cooperate with oncogenic RAS to promote malignant transformation, we hypothesized that mitotic kinases Aurora A and/or B are relevant therapeutic targets in KRAS-induced lung cancer. OBJECTIVES. The main objective of this work is to investigate the roles of Aurora A and B in KRAS-active lung cancer. MATERIALS AND METHODS. We first determined whether oncogenic KRAS induces Aurora kinase expression. For that purpose, we used three different cell-based models: (1) an immortalized primary lung epithelial cell line and its isogenic KRAS-transformed counterpart, (2) H1703 lung cancer cells engineered to express oncogenic KRAS inducibly, and (3) KRAS positive lung cancer cell lines H358 and A549 stably expressing inducible shRNAs targeting KRAS. Second, to validate Aurora A and/or B as therapeutically relevant KRAS targets in lung cancer, we used genetic and/or pharmacological approaches in the abovementioned cells to inactivate Aurora A or B. DISCUSSION AND RESULTS. In all cases, KRAS expression positively correlated with Aurora A and Aurora B expression. KRAS positive H358 and A549 cell lines, inducible shRNA-mediated knockdown of Aurora A or B, as well as treatment with a dual Aurora A and B inhibitor (AI-II), decreased growth, viability, migration, invasion and oncogenicity, and induced apoptosis in vitro. More importantly, AI-II reduced oncogenic properties in vitro in an oncogenic KRAS-dependent manner. Finally, inducible shRNA-mediated knockdown of Aurora A in A549 cells decreased tumor formation in vivo. CONCLUSIONS. Aurora kinase inhibition can specifically target KRAS transformed cells, suggesting Aurora kinase inhibition as a novel approach for KRAS-induced lung cancer therapy.

Key-words: KRAS, Aurora kinases, lung cancer.