Targeting Aurora kinase activity in lung cancer cells driven by oncogenic KRAS impairs lung cancer initiating cell function.

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\textbf{Introduction}: Activating mutations in KRAS are prevalent in cancer and RAS signaling is enhanced in cancer initiating cells (CICs), which are defined as self-renewing tumor cells able to initiate tumor formation, sustain tumor growth and drive tumor dissemination. 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 kinases A and B (AURK) have been implicated both in RAS oncogenesis and in promoting CIC function, we hypothesized that targeting AURK pathways would impair KRAS positive lung CIC function, thereby decreasing lung cancer malignant behavior. \textbf{Objectives}: Our goal was to determine how AURK targeting affects KRAS-positive lung CIC function. \textbf{Materials and Methods}: We targeted AURK in KRAS positive lung cancer H358 and A549 cells by RNA interference or with a dual Aurora A and B inhibitor (Al II) and analyzed tumorsphere formation, clonogenic growth and self-renewal, expression of stem cell surface markers CD44 and CD24 by flow cytometry and expression of stem cell transcription factors by qPCR. \textbf{Results and Conclusions}: A549 and H358 cells formed tumorspheres under low attachment conditions and, when compared to the parental cell lines, sphere-forming cells were able to self-renew and had increased clonogenic ability. Flow cytometry and qPCR analysis revealed that tumorsphere cells displayed increased expression of stem cell surface markers CD44 and CD24, as well as increased expression of stem cell transcription factors Sox2, Oct4, Nanog and Bmi1. Al II treatment decreased the expression of these transcription factors and reduced the number of CD24 positive cells. Furthermore, AURK targeting suppressed tumorsphere formation and growth in both primary and secondary cultures and reduced the clonogenic ability of tumorsphere forming cells. Our results suggest that AURK inhibition therapy can reduce KRAS positive lung CICs, and, therefore might contribute to a more lasting therapeutic effect in KRAS-induced lung cancer.

Aurora kinases, KRAS, cancer initiating cells

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