Identification of microRNA486-5p as a K-Ras Target in Lung Cancer

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K-Ras–induced lung cancer is a very common disease, for which there are currently no effective therapies. Intense efforts are underway to identify K-Ras targets that play a crucial role in oncogenesis. One promising K-Ras-regulated pathway that has sofar been overlooked is the microRNA pathway; microRNAs involved in the malignant transformation triggered by K-Ras remain largely unknown. Our goal was to identify microRNAs regulated by oncogenic K-Ras in lung cells that could contribute to the oncogenic phenotype. Due to a reported positive correlation between microRNA486-5p expression and the presence of K-Ras mutations in colon cancer specimens, we decided to investigate in lung cells whether K-Ras regulates microRNA486-5p. For that purpose we used an immortalized human primary lung epithelial cell line (SALEB) and its isogenic K-Ras-transformed counterpart (SAKRAS). We found that, when compared to SALEB cells, SAKRAS cells express microRNA486-5p at a significantly higher level. SAKRAS cells also express lower levels of the microRNA486-5p target PTEN, a well known tumor suppressor. In order to confirm our results in cell lines derived from lung cancer patients, we used K-Ras positive lung cell lines H358 and A549 to generate stable lines with doxycycline-inducible expression of two different short hairpin RNAs targeting K-Ras. Again K-Ras expression correlated positively with microRNA486-5p expression and negatively with PTEN expression. Taken together, these results suggest that microRNA486-5p is a K-Ras target in lung cancer, modulating PTEN expression, and thereby contributing to cell survival. Further understanding of microRNA486-5p targets could uncover novel targets for lung cancer therapy.

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