Stony Brook University
The Graduate School

Doctoral Defense Announcement

Abstract

Metabolic signatures associated with mutant KRAS in non-small cell lung cancer

By

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Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related deaths worldwide. Oncogenic *KRAS* is among the most frequently mutated driver oncogenes in NSCLC. Patients harboring *KRAS* mutations are associated with a poor prognosis and resistance to therapy. The *KRAS* gene encodes a small GTPase that is well known for its ability to regulate signal transduction, which contributes to its oncogenic properties. It is now appreciated that *KRAS* can promote tumor growth via upregulation of anabolic metabolism. Cancer cells must undergo extensive metabolic reprogramming in order to satisfy the bioenergetics, macromolecular precursors, and redox requirements of a high proliferative state. This prompted us to investigate metabolic signatures associated with mutant *KRAS* in NSCLC with the long-term goal of identifying therapeutic targets. Our initial work showed that mutant *KRAS* promotes a gene expression program of *de novo* lipogenesis in NSCLC. Importantly, pharmacological inhibition of *de novo* lipogenesis resulted in growth inhibition to *KRAS*-expressing tumors and cells. To define the mechanism(s) responsible, we focused on the lipogenic transcription factor sterol regulatory element-binding protein 1 (SREBP1). We observed that *KRAS* increases SREBP1 protein expression in part via MEK signaling, and genetic knockdown of SREBP1 inhibited cell growth. However, lipogenesis was not significantly altered in SREBP1 knockdown cells. RNAseq data revealed a significant decrease in mitochondrial encoded subunits of the electron transport chain (ETC), and subsequent metabolic studies showed a striking decrease in oxidative phosphorylation. Furthermore, ETC impairment resulted in significant decreases to reactive oxygen species (ROS), which were partly responsible for decreased cell growth in SREBP1 knockdown cells. These results suggest a novel role for SREBP1 in *KRAS*-driven NSCLC on mitochondrial function distinct from lipogenesis. Finally, we also demonstrated that mutant *KRAS* significantly alters key metabolites and enzymes in the hexosamine biosynthetic pathway (HBP). Collectively, these studies uncover novel roles for mutant *KRAS* in NSCLC and open a window for potential therapeutic intervention.

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