Increasing therapeutic specificity in cancer by identifying links between specific oncogenic changes and metabolic alterations

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ABSTRACT

It is now appreciated that oncogenes regulate metabolic pathways as part of their mechanism of action. Kras mutations are one of the most common alterations in lung cancer, and are associated with poor response to treatment and survival. These studies show that mutant Kras promotes de novo lipogenesis from glucose. This is in part mediated via MEK1/2 regulation of the lipogenic transcription factor, SREBP1. Importantly, we show in vitro and in vivo that blocking lipogenesis potentiates growth inhibition in the presence of mutant Kras. Using public databases, we show that lung tumors with increased lipogenic gene expression are associated with reduced survival. Furthermore we show a correlation between lipogenic gene expression and mutant Kras. These studies suggest a rationale for stratifying patients and provide a potential therapeutic approach for the treatment resistant mutant Kras lung cancer.

BIOGRAPHY

Dr. Girnun received his PhD from the University of Iowa where he worked on the regulation of gene expression by fatty acids and nuclear receptors. After his graduate work, he did a postdoctoral fellowship at the Dana Farber Cancer Institute and Harvard Medical School in the Laboratory of Dr. Bruce Spiegelman where he worked on the role of PPARgamma and cancer. In 2007 Dr. Girnun was recruited by the University of Maryland School of Medicine in Baltimore where he began working on regulation of metabolic pathways in cancer, with a focus on transcription and the transcriptional coactivator PGC1alpha. In 2013 Dr. Girnun joined Stony Brook University in the Department of Pathology and as Director of Cancer Metabolomics in the Stony Brook Cancer Center. His research has expanded into how specific oncogenic changes can lead to particular metabolic changes. His lab has a strong interest in how these metabolic alterations can be used to identify particular patient populations who would most benefit from therapies targeting pathways that control these metabolic changes.