Letter to the Editor

Cancer Research

STK33 Kinase Is Not Essential in KRAS-Dependent Cells–Response

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Our recently published work (1) was initiated based on the conclusion in Scholl and colleagues that "cells that are dependent on mutant *KRAS* exhibit sensitivity to suppression of STK33, irrespective of tissue of origin" and that "STK33 promotes cancer cell viability in a kinase activity–dependent manner. . ." (2). On the basis of these critical findings, we endeavored to identify small molecule STK33 kinase inhibitors as a potential treatment for *KRAS* mutant cancers.

We also aimed to reproduce some of the key data presented in Scholl and colleagues (2). We believe the points raised by Drs. Scholl and Fröhling are addressed in our article. An additional obstacle of the siRNA/short hairpin RNA (shRNA) approach that we discuss (1) and that is also exemplified by the subsequent work of the authors (3) pertains to the stringency and choice of data analysis method following siRNA/shRNA screens. In the study by Barbie and colleagues, STK33 was not identified among the top 250 candidate genes required for survival of KRAS-dependent cell lines using the Feature Selection method, and it was ranked number 123 using the RIGER analysis (3). In Luo and colleagues, STK33 was not found among the top 379 hits using a stringent statistical method, but was found among the top 1,741 hits using relaxed statistical criteria (4). Drs. Scholl and Fröhling point out in their Letter to the Editor that they also applied "relaxed criteria" to identify STK33 as a hit.

In our work, we addressed directly whether the kinase activity of STK33 plays a role in regulating the p70S6K pathway and/or KRAS-dependent acute myelogenous leukemia cell survival. We identified multiple potent STK33 kinase inhibitors that were used to evaluate the role of STK33 kinase activity. We were not limited by a single tool but, instead, could take advantage of these many molecules to derive activity relationships in multiple assays. It is the collection of our findings that led to our conclusion.

Very little is known about STK33. The lack of known substrate(s), in particular, is a limiting factor in understanding its function in normal and cancer cells. Our extensive, though not exhaustive, attempts at identifying substrates have not been fruitful. Although our article offers an important step forward by identifying STK33 kinase inhibitors, much work will be needed to clarify the function of STK33 in normal physiology and in disease. We hope that the tools available in our article, including the methods to generate recombinant STK33 and the small molecule STK33 kinase inhibitors, as well as future work by others, will take us in that direction.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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