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Two faces of SIVA

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Summary

In non-small cell lung cancer cells (NSCLC) that contain a mutated KRAS gene, SIVA, a p53 target gene that is critical for apoptosis, is overexpressed in a p53-independent manner and promotes tumorigenesis through the stimulation of mTOR signaling. The ablation of SIVA in conditional knock out mice results in an inhibition of tumor development that makes SIVA an interesting new candidate for the treatment of a carcinoma with few therapeutic options.

The contribution of p53 as a sensor of many kinds of stresses that provoke cell cycle arrest and repair, senescence, and apoptosis is undeniable. Diverse conditions that include DNA damage, oncogenic signaling, ribonucleotide and nutrient depletion, or oxidative stress result in the upregulation of a plethora of targets that act either to maintain genomic stability or led to cell elimination (1). What remains unsatisfying is the mechanism by which p53 can act as a tumor suppressor (2,3). The classical view that p53 mediates tumor suppression through target genes that include CDKN1A (p21), BBC3 (Puma), and PMAIP1 (NOXA) has been challenged by recent studies (4). It seems like it is time to dust off these long held notions and look elsewhere for answers. Perhaps the answer will come from studying context-dependent mechanisms and there will be no one size fits all solution to this key question of tumor biology. Perhaps the answer will lie in the identification of novel p53 targets. In this issue of Cancer Discovery the authors, Van Nostrand et al., focus on a novel p53, target gene, SIVA, that has been shown to play a critical role in apoptosis (5). Unlike other such target genes, it has a counterintuitive p53 independent role as a tumor promoter in the context of a non-small cell lung carcinoma (NSCLC) driven by the KRAS^{G12D} mutation. Seeking to define the role of SIVA in tumorigenesis, conditional knock-down of SIVA in mice was surprisingly found to inhibit NSCLC development. Of notable importance is the fact that high levels of SIVA in NSCLC patients correlate with a poor prognosis.

Lung cancers present a formidable challenge for cancer therapeutics. NSCLC can account for approximately 85% of lung cancers. These are mostly adenocarcinomas and squamous cell carcinomas. Treatment options are based on the patients' medical history and the stage of the disease and include surgery, radiation therapy and chemotherapy. The identification of specific genetic alterations in key oncogenes has led to a targeted therapy approach (6). Molecular testing has identified three mutations that are mutually exclusive: EGFR, ALK, and KRAS. Patients whose tumors overexpress EGFR or have activating mutations in its

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potential of these cells. How then, is SIVA promoting tumorigenesis? It is not occurring through p53, because knock-down of SIVA does not result in a change of p53 levels or a change in the expression of p53 targets like Cdkn1a (p21), Bbc3 (Puma), Pmaip1 (Noxa) or Mdm2. It is interesting to note that when the authors knock-down p53, the levels of SIVA by immunoblot are modestly reduced and suggest that the expression is, at least, partially independent of p53 expression. The knock-down of p53 did not alter the percentage of BrdU cells. Perhaps in the spotlight is not the place to look.

The results of gene expression profiling after SIVA knock-down highlight the expression of genes known to regulate NFkB signaling, cell migration and metabolic processes. After ruling out NFkB signaling, the authors focus on increased metabolic activity and show that after SIVA knock-down, there is a reduction in energy production that might very well result in autophagy. Indeed, this was confirmed by an increase in LC3-II, (a modified form of LC3 that gets incorporated into autophagic vesicles) after SIVA knock-down. Using Gene Set Enrichment Analysis (GSEA) the authors narrow the search for a signaling pathway that results in the triggering of autophagy and identified similarities between mTOR and SIVA knock-down signatures. Indeed SIVA is necessary for mTOR activity as its knock-down results in a decrease in the phosphorylation of the substrates, S6K and 4EBP1. mTOR activity is necessary for the proliferation of these cells as witnessed by a decrease in proliferation after mTOR inhibition. A final piece of information is added to show that after SIVA knock-down, phosphorylated TSC2, a marker for the mitogenic arm of the mTOR signaling pathway, is reduced. This fortified the notion that SIVA acts through mitogenic signaling to promote mTOR activity. In the context of cells that contain oncogenic KRAS, SIVA expression is necessary for promoting proliferation and tumorigenesis (Figure 1, right).

The analysis of SIVA expression in KRAS-driven NSCLC has provided unexpected yet provocative results. In the context of these transformed cells that express wild type p53, a bona fide p53 target gene functions in a p53-independent fashion. Surprisingly knockdown of these high levels of SIVA result in death by autophagy. Although the role of autophagy in cancer is still controversial, some studies show that it is an important regulator of tumor development and can also determine successful outcome of anti-tumor therapy (11). The results of this study offer the hope of a tailor-made treatment for patients whose lung cancers contain mutant KRAS and high levels of SIVA. Additionally patients with NSCLC containing mutant EGFR may also benefit from a multipoint therapy approach. In cancer it may be said that the organism is sacrificed for the benefit of deleterious tumor cells. The reverse might be said of autophagy; deleterious cells are sacrificed for the benefit of the organism. And SIVA appears to be a key player in this process.

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Two Faces of Siva: Context dependent outcomes of SIVA overexpression

Figure 1.

Context dependent outcome of SIVA expression. Left, E1A 12S expressing mouse embryo fibroblasts (MEFs) that are wild-type for p53 undergo apoptosis after DNA damage due to upregulation of Bbc3 (Puma), Pmaip1 (Noxa), Bax, and Siva, that are selectively expressed during apoptosis. Right, KRAS^{G12D} mutant NSCLC that also contains a wild-type p53 overexpresses SIVA. These cells proliferate and display a transformed phenotype. Upon SIVA knock-down, cells die by autophagy due to a pronounced reduction of mTOR activity.