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Metabolic dysregulation drives sensitivity after PI3K/mTOR inhibition in HNSCC

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Genomic alterations in the PI3K/mTOR pathway occur in 54% of HNSCC patients. However, clinical trials of PI3K/mTOR pathway inhibitors had limited success even in those tumors with pathway alterations, including *PIK3CA* mutations. To identify mechanisms driving sensitivity in HNSCC, we tested the efficacy of 7 PI3K/mTOR pathway inhibitors in 59 HNSCC cell lines and classified the cell lines as sensitive and resistant to drugs based on C_{max} (peak plasma concentration). After PI3K/mTOR inhibition, the sensitive lines showed significantly reduced clonogenic growth *in vitro* (0.4/ 0.9-fold in HN31/PCI15B; $P<0.05$) and significant tumor growth inhibition *in vivo* using Orthotopic oral xenograft mouse models (1.7 and 2-fold in UMSCC22A and HN31; $P<0.01$). As no canonical pathways account for the underlying mechanism of sensitivity, we measured the level of 301 proteins by reverse phase protein array (RPPA) in 3 sensitive and 3 resistant lines after GSK2126458 treatment. The protein levels of glutaminase and glutamate dehydrogenase were differentially regulated in sensitive lines. Thus, we hypothesized that PI3K/mTOR inhibition in responding cell lines induced reactive oxygen species (ROS)-mediated apoptosis via metabolic alterations. Consistent with this hypothesis, sensitive lines exhibited increased ROS production after GSK2126458 treatment. It also increased the levels of phosphogluconate dehydrogenase (PGD) and decreased levels of glutamate. Metabolic pathway inhibitors targeting glutaminolysis, in combination with GSK2126458 decreased cell viability in resistant cell lines. In addition, we identified that sensitive HNSCC cells that underwent apoptosis after PI3K/mTOR pathway inhibition harbored *NOTCH1* mutation. The underlying mechanism may involve the effect of NOTCH pathway on tumor metabolism and ROS production. This work is significant because inactivating *NOTCH1* mutations, which occur in 18% of HNSCC patients and SCCs of the lung, esophagus, and other sites, may serve as a biomarker for response. Our future work may uncover previously unknown crosstalk between the PI3K/mTOR and NOTCH pathways in SCCs.

Biography

Vaishnavi Sambandam is a Post-doctoral Fellow of The University of Texas MD Anderson Cancer Center and is associated with Dr. Faye Johnson Laboratory.

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