**Abstract**

Non-small cell lung cancer (NSCLC) with concurrent mutations in KRAS and the tumor suppressor LKB1 (KL NSCLC) is refractory to most therapies including immune checkpoint inhibitors and thus, has one of the worst predicted outcomes. Using human NSCLC metabolomics data, we uncovered upregulation of serine-glycine one carbon (SGOC) metabolism via serine hydroxymethyltransferase (SHMT) in KL NSCLC. A prior study in murine pancreatic tumor[1] showed that the LKB1-AMPK axis inhibits SGOC metabolism which is necessary for DNA methylation. Here we report that in NSCLC, LKB1, by collaboration with KEAP1, impedes SGOC metabolism through salt-induced kinase (SIK)-NRF2 axis, and one carbon units are required for antioxidant defense. SHMT suppression increased cellular sensitivity to oxidative stress and cell death. Further, the SHMT inhibitor enhanced the therapeutic efficacy of paclitaxel (first-line NSCLC therapy inducing ROS) in KL tumor growth in vivo. Collectively, the data reveal how KL NSCLC cells fulfill their metabolic requirements and provide insight into therapeutic strategies.