Drug Resistance

Major finding: STAT3 activation contributes to resistance to a broad spectrum of targeted therapies.

Mechanism: RTK/MEK inhibition induces autocrine STAT3 activation through FGFR and JAK kinases.

Impact: Cotargeting FGFRs and JAKs may prevent feedback STAT3 activation and circumvent drug resistance.

FEEDBACK ACTIVATION OF STAT3 IS A WIDESPREAD DRUG-RESISTANCE MECHANISM

An increasing number of nongenetic mechanisms of resistance to targeted therapies in oncogene-addicted cancer cells have been identified. Lee and colleagues hypothesized that oncogene-addicted cells secrete factors upon drug treatment that eventually cause resistance. Indeed, conditioned media from *EGFR*-mutant non–small cell lung cancer (NSCLC) cells treated with the EGFR inhibitor erlotinib increased resistance in treatment-naïve cells. Prolonged erlotinib treatment elevated levels of factors that activate STAT3 and increased STAT3 transcriptional activity, suggesting that feedback activation of STAT3 underlies erlotinib resistance. Consistent with this possibility, STAT3 knockdown augmented erlotinib-induced apoptosis and prevented the emergence of erlotinib-resistant colonies. Gene expression profiling and analysis of secreted factors demonstrated that FGFR and IL6/JAK signaling were upregulated in erlotinib-treated cells, and combined inhibition of FGFRs and JAKs with either PD173074 and ruxolitinib or with ponatinib blocked erlotinib-induced STAT3 phosphorylation and suppressed erlotinib resistance *in vitro*. FGFR- and JAK-driven autocrine activation of STAT3 was dependent on MEK inhibition downstream of EGFR, as either erlotinib or the MEK inhibitor selumetinib increased STAT3 phosphorylation. Notably, increased STAT3 phosphorylation was also observed in response to RTK or MEK inhibition in HER2-, ALK-, and MET-addicted cells, and STAT3 knockdown or combined FGFR and JAK inhibition overcame RTK inhibitor resistance in RTK-addicted cells as well as MEK inhibitor resistance in *KRAS*-mutant NSCLC cells. *In vivo*, combined EGFR, FGFR, and JAK inhibition suppressed STAT3 activation and induced significant regression of *EGFR*-mutant NSCLC xenografts, and combined MEK, FGFR, and JAK inhibition had a similar effect in *KRAS*-mutant NSCLC xenografts. Together with the observation that high STAT3 and FGFR expression was associated with poor response to EGFR-targeted therapy in a small group of patients with NSCLC, these findings implicate feedback upregulation of STAT3 as a common cause of resistance to RTK/MEK–targeted therapy and provide a rationale for combination strategies including inhibitors of STAT3 or its upstream kinases. ■

Lee HJ, Zhuang G, Cao Y, Du P, Kim HJ, Settleman J. Drug resistance via feedback activation of Stat3 in oncogene-addicted cancer cells. Cancer Cell 2014 Jul 24 [Epub ahead of print].

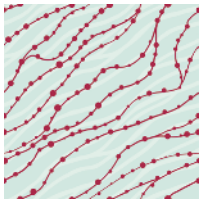
Epigenetics

Major finding: Oncogene-induced metabolic reprogramming alters global histone acetylation during tumorigenesis.

Mechanism: AKT regulates acetyl-CoA production by promoting glucose metabolism and activation of ACLY.

Impact: Therapy directed against metabolic targets may reverse epigenetic deregulation in cancer.

GLOBAL HISTONE ACETYLATION LEVELS IN CANCER ARE DETERMINED BY AKT ACTIVITY



Metabolic rewiring has recently been established as a hallmark of cancer cells and is driven by increased oncogene activity and decreased tumor suppressor activity. Changes in specific metabolic enzymes, such as ATP-citrate lyase (ACLY), alter the activity of chromatin-modifying enzymes in cancer cells, but whether tumor metabolism contributes to broader alterations in the epigenetic landscape remains unclear. Lee, Carrer, Shah, and colleagues found that histone acetylation levels were correlated with glucose availability in several cancer cell lines and that, when deprived of glucose, these cells failed to maintain high acetyl-histone levels. The histone acetyltransferase substrate acetyl-CoA induced the expression of proliferation-related genes and was dynamically regulated with varying glucose levels in glioblastoma cells. Low glucose conditions resulted in decreased acetyl-CoA and elevated levels of reduced CoA (CoASH), and the nuclear ratio of acetyl-CoA and CoASH modulated histone acetylation. Activation of the $Kras^{G12D}$ oncogene in a mouse model of pancreatic cancer increased global histone acetylation prior to tumor formation. Histone acetylation was increased in premalignant and cancer cells as a result of AKT activation, which enhanced glucose uptake and promoted acetyl-CoA production via phosphorylation of ACLY, whereas inhibition of the AKT pathway significantly reduced glucose consumption and histone acetylation *in vitro*. In addition, expression of constitutively activated AKT allowed for sustained histone acetylation in glucose-limited conditions and acutely promoted histone acetylation *in vivo*. Furthermore, phosphorylated AKT was correlated with histone acetylation levels in established human tumors, and low histone acetylation levels were associated with therapeutic failure in prostate cancer. These data suggest that oncogene-induced metabolic reprogramming drives changes in the epigenome of cancer cells, which can in turn influence disease progression. Moreover, these findings establish a rationale for pursuing metabolic targets as a means to pharmacologically reverse epigenetic deregulation in cancer. ■

Lee JV, Carrer A, Shah S, Snyder NW, Wei S, Venneti S, et al. AKT-Dependent Metabolic Reprogramming Regulates Tumor Cell Histone Acetylation. Cell Metab 2014 Jul 3 [Epub ahead of print].

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