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Breast Cancer

Major finding: Lapatinib promotes induction of c-MYC, resulting in reduced lapatinib sensitivity in HER2$^+$ cells.

Mechanism: Lapatinib activates FOXOs, leading to a MLL2/BRD4–dependent increase in c-MYC expression.

Impact: Inhibition of the MLL2/FOXO/BRD4/c-MYC axis may reduce resistance of HER2$^+$ tumors to HER2 inhibitors.

SENSITIVITY TO HER2 INHIBITION IS MODULATED BY EPIGENETIC CONTROL OF FOXOs

HER2 (ERBB2) is commonly overexpressed in breast cancer and associated with poor prognosis. HER2-targeted therapies are available for the treatment of HER2$^+$ breast cancer, including the tyrosine kinase inhibitor lapatinib; however, cancer cells often develop resistance to lapatinib treatment. Lapatinib resistance is associated with increased estrogen receptor signaling and upregulation of prosurvival factors and receptor tyrosine kinases, but the epigenetic mechanisms controlling lapatinib resistance are not well understood. Matkar and colleagues characterized an epigenetic mechanism by which lapatinib promotes c-MYC expression and reduced sensitivity to lapatinib. An shRNA screen identified the mixed lineage leukemia 2 (MLL2) protein, a histone methyltransferase involved in activating gene transcription, as an essential regulator of HER2$^+$ breast cancer cell growth. Lapatinib treatment and MLL2 induced expression of c-MYC, which was required to reduce the sensitivity of HER2$^+$ breast cancer cells to lapatinib. Mechanistically, lapatinib-induced upregulation of c-MYC was mediated by activation of FOXO transcription factors following suppression of the HER2–PI3K–AKT pathway. Lapatinib promoted direct binding of FOXO1/3 to the *MYC* promoter and recruitment of MLL2 to the promoter, which resulted in an increase in activating histone marks and activation of *HER2* gene transcription. Bromodomain-containing 4 (BRD4), another epigenetic regulator, was also bound to the *MYC* promoter in lapatinib-treated cells, further supporting the role of epigenetic regulation in regulating sensitivity to HER2 inhibitors. BRD4 inhibition with a BET inhibitor synergized with lapatinib to suppress c-MYC expression and inhibit HER2$^+$ breast cancer cell growth both *in vitro* and *in vivo*. Taken together, these findings highlight a paradoxical role for the FOXO transcription factors, which normally function as tumor suppressors, in upregulating c-MYC; provide an epigenetic mechanism for the occurrence of HER2 inhibitor resistance; and suggest that inhibiting the MLL2/FOXO/BRD4/c-MYC axis might increase the sensitivity of HER2$^+$ breast cancer cells to lapatinib. ■

Matkar S, Sharma P, Gao S, Gurung B, Katona BW, Liao J, et al. An epigenetic pathway regulates sensitivity of breast cancer cells to HER2 inhibition via FOXO/c-Myc axis. Cancer Cell 2015;28:472–85.

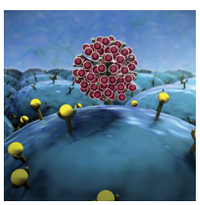
Glioma

Major finding: GBM CSCs require the iron regulators transferrin receptor and ferritin to drive tumorigenesis.

Mechanism: Gain of an epigenetic program enhances CSC iron uptake, and STAT3–FOXM1 signaling drives CSC growth.

Impact: Disrupting iron flux in CSCs is a potential therapeutic strategy for the treatment of GBM.

IRON TRAFFICKING IS ESSENTIAL FOR GLIOBLASTOMA CSC TUMORIGENICITY



Glioblastoma (GBM) is the most common adult brain malignancy and, in spite of highly aggressive treatment, has a poor prognosis. The lack of treatment efficacy may be due in part to the presence of the CD133$^+$ cancer stem-like cell (CSC) subpopulation of GBMs, which has been shown to be radioresistant and chemoresistant and can flourish in the stresses inflicted by the tumor microenvironment. These stresses are mediated in part by aberrant iron metabolism, prompting Schonberg and colleagues to investigate the role of iron regulation in the tumorigenicity of GBM CSCs. Next-generation RNA sequencing identified transferrin (*TF*) as the most differentially expressed gene in GBM CSCs, which secreted high levels of TF compared with non-CSCs. Epigenomic profiling revealed that *TF* enhancers were present in CSCs and in a cell line model of hepatocytes, suggesting that *TF* upregulation in CSCs is mediated by the acquisition of a liver-specific epigenetic mechanism. Consistent with these findings, iron tracing experiments showed increased unbound iron uptake in CSCs compared with non-CSCs. Expression of transferrin receptor (TfR), which mediates intracellular entry of TF-bound iron, and ferritin, which stores excess intracellular iron, was increased in a grade-dependent fashion in gliomas, in particular CSCs, and negatively correlated with patient survival. Furthermore, expression of TfR enhanced tumorsphere formation and tumor initiation, whereas knockdown of ferritin resulted in decreased CSC growth *in vitro* and impaired CSC tumorigenicity *in vivo*. Gene expression profiling revealed that this growth inhibition may be due to regulation of cell-cycle progression by ferritin and identified *STAT3* as the gene most highly correlated with ferritin expression. Knockdown and rescue experiments showed that forkhead box M1 (FOXM1), a STAT3-regulated transcription factor, was critical for ferritin-mediated regulation of CSCs. Together, these results show that GBM CSC tumorigenicity is dependent on the acquisition of an epigenetic mechanism that drives iron metabolism and is potentially targetable. ■

Schonberg DL, Miller TE, Wu Q, Flavahan WA, Das NK, Hale JS, et al. Preferential iron trafficking characterizes glioblastoma stem-like cells. Cancer Cell 2015;28:441–55.

AACR American Association for Cancer Research

CANCER DISCOVERY

Iron Trafficking Is Essential for Glioblastoma CSC Tumorigenicity

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