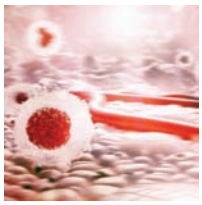
Metastasis

Major finding: PLAG1-mediated GDH1 upregulation promotes LKB1-deficient lung cancer anoikis resistance.

Mechanism: In the absence of LKB1, the GDH1 product α-KG mediates the activation of AMPK by CAMKK2.

Impact: Targeting the PLAG1–GDH1 axis may be a potential therapeutic strategy to prevent metastasis.

GLUTAMINOLYSIS DRIVES LUNG CANCER METASTASIS VIA THE PLAG1–GDH1 AXIS



Loss of liver kinase B1 (LKB1, encoded by *STK11*), which regulates the activation of the metabolic regulator AMPK, is associated with increased metastasis and decreased survival in patients with lung cancer. To elucidate the mechanism underlying the prometastatic role of altered tumor metabolism in lung cancer, Jin and colleagues interrogated the glutaminolysis pathway, which promotes tumor growth and metastasis. The glutaminolytic enzyme glutamate dehydrogenase 1 (GDH1) was shown to confer anoikis resistance, which is required for metastasis, in LKB1-deficient lung cancer cell lines. The transcription factor pleomorphic adenoma gene 1 (PLAG1) was upregulated during anoikis resistance and transactivated the *GDH1* promoter; *PLAG1* knockdown decreased GDH1 expression and increased anoikis. Knockdown of *GDH1* sensitized LKB1-deficient, but not LKB1-proficient, cells to anoikis induction *in vitro* and reduced the metastatic potential of LKB1-deficient cells *in vivo*, whereas the GDH1 product α-KG restored anoikis resistance in *GDH1*-depleted LKB1-deficient cells, suggesting that both GDH1 and α-KG promote anoikis resistance. Similarly, treatment of LKB1-null cells with a small-molecule inhibitor of GDH1 rescued anoikis *in vitro* and attenuated the metastatic potential of LKB1-deficient cell lines and patient-derived xenografts *in vivo*. Further, *GDH1* knockdown resulted in decreased activation of AMPK and its upstream activator calcium/calmodulin-dependent protein kinase kinase 2 (CAMKK2), which were rescued by the addition of α-KG, and diminished cellular ATP levels. *CAMKK2* knockdown resulted in the loss of AMPK activation and anoikis resistance in LKB1-deficient cells; conversely, CAMKK2 overexpression restored anoikis resistance and AMPK activation in *GDH1*-knockdown cells. Mechanistically, α-KG promoted CAMKK2 activation by enhancing the interaction between CAMKK2 and its substrate AMPKα. Consistent with these findings, GDH1 signaling was correlated with metastasis in human LKB1-deficient lung cancers. These results describe the mechanism by which glutaminolysis promotes metastasis and suggest that GDH1 may be a potential antimetastatic target. ■

Jin L, Chun J, Pan C, Kumar A, Zhang G, Ha Y, et al. The PLAG1-GDH1 axis promotes anoikis resistance and tumor metastasis through CamKK2-AMPK signaling in LKB1-deficient lung cancer. Mol Cell 2017;69:87–99.e7.

Gene Expression

Major finding: YY1 preferentially occupies active enhancers and promoters and forms dimers to promote DNA looping.

Concept: YY1 may act analogously to CTCF, which binds insulators to form TADs, to form enhancer–promoter loops.

Impact: YY1 enables enhancer–promoter contacts to control gene expression in malignant and nonmalignant cells.

YY1 FACILITATES ENHANCER–PROMOTER CONTACTS TO PROMOTE GENE EXPRESSION

Transcription factors bind to enhancers and promoters at sites of physical contact created by DNA looping to promote gene transcription, but the proteins that facilitate structural interactions between enhancers and promoters remain poorly understood. CTCF is one such DNA binding protein. CTCF–CTCF interactions are associated with the large DNA loops that create topologically associating domains (TAD) that insulate genes and enhancers within the CTCF–CTCF loop from elements outside the loop. In this manner, CTCF–CTCF loops constrain DNA interactions within the loop to facilitate enhancer–promoter interactions. However, CTCF is not present at the majority of enhancer–promoter interactions and is only occasionally directly involved in enhancer–promoter interactions. Weintraub, Li, and colleagues hypothesized that a bridging protein (similar to CTCF) might facilitate enhancer–promoter contacts and identified Yin Yang 1 (YY1), a zinc-finger transcription factor overexpressed in many cancers, as a candidate protein via chromatin immunoprecipitation with mass spectrometry (ChIP-MS). In embryonic stem cells, YY1 occupied active enhancers and promoters, whereas CTCF preferentially occupied insulator elements and dimerized to facilitate DNA looping. YY1 was also enriched at active enhancers and promoters in mammalian cell lines, including in colorectal cancer, hepatocellular carcinoma, T-cell acute lymphoblastic leukemia, and chronic myeloid leukemia cells. These findings suggested that YY1–YY1 interactions may induce enhancer–promoter loop formation. Indeed, YY1 enhanced the rate of DNA ligation in an *in vitro* circularization assay, indicating that YY1 may directly facilitate DNA interactions. Moreover, deletion of YY1 binding sites reduced the frequency of enhancer–promoter contacts, and depletion of the YY1 protein reduced expression of genes generally occupied by YY1. Collectively, these findings support a direct role for YY1 in facilitating enhancer–promoter interactions that facilitate gene expression in malignant and nonmalignant cells. ■

Weintraub AS, Li CH, Zamudio AV, Sigova AA, Hannett NM, Day DS, et al. YY1 is a structural regulator of enhancer-promoter loops. Cell 2017;171:1573–88.e28.