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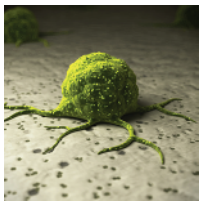
Metastasis

Major finding: LKB1 controls an AMPK-independent pathway to repress SNAIL1 levels and reduce metastatic potential.

Mechanism: The LKB1 substrates MARK1/4 phosphorylate DIXDC1, which inhibits FAK-mediated induction of SNAIL1.

Impact: LKB1 activity connects metabolism to cell polarity and cytoskeletal control in tumor suppression.

LKB1 REGULATES AN AMPK-INDEPENDENT KINASE CASCADE TO SUPPRESS METASTASIS



Loss of serine/threonine kinase 11 (STK11, also known as LKB1) drives tumor initiation and metastasis in multiple cancer types. LKB1 acts as a tumor suppressor by regulating metabolism and cell growth via activation of AMP-activated protein kinase (AMPK). However, it is unknown which effectors of LKB1 are required for its ability to prevent metastasis. Goodwin and colleagues characterized the regulation of epithelial-to-mesenchymal transition (EMT) factors in LKB1-deficient tumor cell lines and found that suppression of LKB1 resulted in increased protein levels of the EMT transcription factor SNAIL1. Depletion of MAP/microtubule affinity-regulating kinase 1 (MARK1) or MARK4, both direct substrates of LKB1, mimicked the deleterious effects of LKB1 loss on SNAIL1 expression, whereas knockdown of AMPK did not affect SNAIL1. *In silico* analysis of MARK1/4 substrates identified the scaffold protein DIX domain-containing 1 (DIXDC1), and silencing of DIXDC1 or mutation of the MARK1/4 phosphorylation site Ser592 upregulated SNAIL1 expression. Phosphorylation of DIXDC1 Ser592 resulted in its localization to focal adhesions, where it contributed to focal adhesion maturation; mutation or depletion of DIXDC1 impaired this maturation process and triggered hyperactivation of focal adhesion kinase (FAK), which stimulated the RAS–MEK–ERK signaling cascade and downstream SNAIL1 expression. Phenotypically, loss of LKB1 or DIXDC1 increased cell migration and invasion, suggesting that LKB1 negatively regulates metastatic potential through MARK1/4 and DIXDC1. Indeed, silencing or mutation of DIXDC1 in lung adenocarcinoma cell lines increased metastatic colonization and tumor burden *in vivo*, similar to the effect of LKB1 loss. Furthermore, *DIXDC1* expression positively correlated with progression-free survival and overall survival in patients with lung adenocarcinoma, and *DIXDC1* was frequently deleted in multiple tumor types. These data define an AMPK-independent signaling pathway by which LKB1 suppresses metastasis and identify DIXDC1 as an endogenous inhibitor of EMT in human cancer. ■

Goodwin JM, Svensson RU, Lou HJ, Winslow MM, Turk BE, Shaw RJ. An AMPK-independent signaling pathway downstream of the LKB1 tumor suppressor controls SNAIL1 and metastatic potential. Mol Cell 2014 Jul 17 [Epub ahead of print].

Targeted Therapy

Major finding: The COX-2–PGE_2 pathway drives angiogenesis, tumor growth, and metastasis independent of VEGF.

Mechanism: PGE_2 promotes angiogenesis via direct stimulation of vasculature and indirect myeloid-cell recruitment.

Impact: COX-2 inhibition may represent a useful strategy to bypass VEGF resistance and prevent metastasis.

DUAL COX2–VEGF BLOCKADE SUPPRESSES TUMOR ANGIOGENESIS AND METASTASIS

Tumor neovascularization is largely driven by VEGF, which has led to the development of small-molecule inhibitors targeting this pathway, including the selective compound axitinib. Despite the clinical activity of these compounds, tumor angiogenesis persists in the presence of VEGF/VEGF receptor (VEGFR) inhibitors; indicating that alternative angiogenic factors are likely to contribute to tumor vascularization. In an effort to identify VEGF-independent angiogenic mechanisms, Xu and colleagues showed that the tumorigenic potential of VEGFR-inhibitor–refractive murine colon cancer cells failed to correlate with VEGF levels, but rather was linked to expression of prostaglandin E2 (PGE_2) and cyclooxygenase 2 (COX-2), a rate-limiting enzyme in PGE_2 production. Inhibition of COX-2 via celecoxib treatment reduced tumor growth *in vivo* without affecting VEGF levels, and forced COX-2 expression in poorly tumorigenic cells enhanced tumor formation and angiogenesis via a VEGF-independent increase in PGE_2 production and myeloid-cell recruitment. Further evidence that COX-2–PGE_2 signaling drives angiogenesis independent of VEGF was provided by the findings that COX-2 expression rescued angiogenesis and tumor growth in VEGF-deficient colon cancer xenografts and that inhibition of VEGF via axitinib or the VEGF blocking antibody DC1O1 was unable to prevent COX-2–PGE_2-induced angiogenesis. Importantly, treatment with celecoxib and DC1O1 or axitinib reduced tumor growth and angiogenesis to a greater extent than that observed with single-agent therapy, suggesting that cotargeting of these pathways leads to a synergistic inhibition of angiogenesis. Furthermore, dual inhibition of the COX-2 and VEGF pathways led to a dramatic reduction in both spontaneous and preexisting tumor metastasis and extended overall survival in several *in vivo* cancer models. Together, these findings emphasize the role of the COX-2–PGE_2 pathway in VEGF-independent angiogenesis and provide a rationale for the clinical use of COX-2 inhibitors in combination with VEGFR blockade in patients with established metastatic disease. ■

Xu L, Stevens J, Hilton MB, Seaman S, Conrads TP, Veenstra TD, et al. COX-2 inhibition potentiates antiangiogenic cancer therapy and prevents metastasis in preclinical models. Sci Transl Med 2014;6:242ra84.

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CANCER DISCOVERY

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