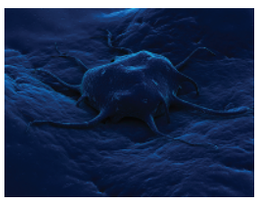
Colorectal Cancer

Major finding: TGF-β–activated signaling in stromal cells enhances metastasis initiation in colon cancer.

Mechanism: TGF-β induces IL-11 secretion by CAFs, which promotes tumor cell survival via GP130/STAT3.

Impact: *TGFB* levels predict cancer relapse, and inhibition of TGF-β signaling may prevent metastasis.

A STROMAL TGF-β RESPONSE PROMOTES COLON CANCER METASTASIS



TGF-β signaling exerts a tumor-suppressive function in colorectal cancer and is frequently inactivated by mutations in epithelial cancer cells. However, serum TGFB1 levels are paradoxically elevated in patients with colorectal cancer and are associated with poor outcome, suggesting that this pathway may promote metastasis, as in the case of breast and prostate cancer. Calon and colleagues hypothesized that activation of the tumor microenvironment by TGF-β may facilitate colorectal cancer progression. In support of this idea, both *TGFB* mRNA levels and TGF-β gene expression signatures derived from stromal cells, in particular cancer-associated fibroblasts (CAF), were predictive of tumor recurrence; high *TGFB* expression or enrichment of these stromal response programs was tightly correlated with relapse after therapy, whereas patients with low *TGFB* levels did not experience disease relapse. Furthermore, increased TGFB1 secretion by colorectal cancer cell lines harboring mutations in the TGF-β pathway activated a stromal TGF-β response that promoted the metastatic colonization of distant organs. This effect was dependent on TGF-β–driven induction of interleukin (IL)-11 in CAFs, which reduced cancer cell clearance during initial colonization and augmented the metastatic potential of colorectal cancer cells, suggesting that stromal TGF-β signaling enhances cancer cell survival. Indeed, IL-11–mediated activation of IL-6 signal transducer (also known as GP130) and STAT3 signaling in tumor epithelial cells promoted the survival of colorectal cancer cells during colonization and was required for efficient metastasis initiation. Importantly, pharmacologic blockade of TGF-β receptor 1 signaling in the tumor stroma decreased primary tumor formation and diminished the engraftment of colorectal cancer cells in the liver. These results identify stromal TGF-β signaling as a critical mediator of colon cancer metastasis and suggest that inhibition of this pathway may suppress tumor relapse. ■

Calon A, Espinet E, Palomo-Ponce S, Tauriello DV, Iglesias M, Céspedes MV, et al. Dependency of colorectal cancer on a TGF-β-driven program in stromal cells for metastasis initiation. Cancer Cell 2012;22:571–84.

Melanoma

Major finding: Relief of ERK-dependent negative feedback reduces RAF inhibitor efficacy in *BRAF*^{V600E} melanoma.

Mechanism: Restoration of ligand-mediated signaling promotes BRAF–CRAF dimerization and ERK activity.

Impact: Combined RAF and MEK inhibitor treatment prevents ERK rebound and enhances tumor suppression.

A FEEDBACK LOOP MODULATES MELANOMA SENSITIVITY TO BRAF INHIBITORS

ERK activity is regulated via negative feedback mechanisms that attenuate ligand-stimulated RAS signaling and downstream RAF dimerization. Elevated ERK activity is characteristic of *BRAF*^{V600E} melanomas and can be inhibited by RAF inhibitors such as vemurafenib that selectively target mutant BRAF monomers; however, acquired resistance to these drugs often develops due to alterations that result in RAF dimerization. Lito and colleagues hypothesized that ERK-dependent feedback suppression of RAS activity prevents RAF dimerization in *BRAF*-mutant melanomas and that relief of this feedback contributes to RAF-inhibitor resistance. Indeed, *BRAF*^{V600E} melanomas exhibited low levels of RAS activity at baseline that were induced following treatment with RAF or MEK inhibitors. This was associated with decreased expression of Sprouty proteins, as well as activation of CRAF and increased ERK phosphorylation, suggesting that RAF inhibitors promote loss of this feedback loop and subsequent reactivation of RAS signaling. The rebound in ERK activity following treatment with RAF inhibitors was dependent on CRAF expression and RAS-mediated formation of BRAF–CRAF heterodimers that retained sensitivity to MEK inhibition but were resistant to vemurafenib retreatment. In addition, relief of ERK-driven feedback potentiated ligand-stimulated RAS signaling and enhanced the response of *BRAF*^{V600E} cells to exogenous growth factors, which diminished the inhibitory effects of vemurafenib. In contrast, treatment with an EGF receptor/HER kinase inhibitor reduced ERK reactivation and BRAF–CRAF dimerization and restored MEK suppression by vemurafenib, suggesting that combined inhibition of receptor tyrosine kinases and BRAF is necessary for maximal antitumor activity. Furthermore, concurrent inhibition of MEK and RAF signaling prevented the rebound of ERK signaling and augmented the suppression of tumor growth in melanoma xenograft models. These findings identify a mechanism of tumor adaptation to ERK inhibition and suggest combinatorial therapeutic strategies that may improve the treatment of melanoma. ■

Lito P, Pratilas CA, Joseph EW, Tadi M, Halilovic E, Zubrowski M, et al. Relief of profound feedback inhibition of mitogenic signaling by RAF inhibitors attenuates their activity in BRAFV600E melanomas. Cancer Cell 2012;22:668–82.

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