Targeted Therapy

Major finding: Selective dissociation of BCL9–β-catenin complexes suppresses WNT-driven tumorigenesis.

Approach: A stapled peptide of BCL9 was used to inhibit pathologic β-catenin activity.

Impact: This approach may be clinically effective in treating cancers with dysregulated WNT signaling.

PEPTIDE TARGETING OF β-CATENIN INHIBITS ONCOGENIC WNT ACTIVITY

WNT signaling plays an important role in development and stem cell homeostasis, and mutations in this pathway have been implicated in multiple cancers. WNT activity is mediated via downstream β-catenin–regulated transcription, but previous attempts to target β-catenin in cancer have been largely unsuccessful due to toxic effects in normal tissues. Takada and colleagues investigated whether targeting β-catenin by harnessing its interface with BCL9, a coactivator that enhances β-catenin activity and is highly expressed in tumors compared with normal cells, could effectively suppress oncogenic WNT signaling. Hydrocarbon stapling was used to generate a cell-permeable peptide representing the domain of BCL9 that binds to a unique site on β-catenin. This stabilized α-helix of BCL9 (SAH-BCL9) was efficiently taken up by cells, localized to the nucleus, and interacted with β-catenin to disrupt BCL9–β-catenin complexes in colorectal carcinoma and multiple myeloma cells. Dissociation of these complexes resulted in reduced β-catenin–dependent transcription and downregulation of WNT target genes involved in proliferation, metastasis, and angiogenesis, suggesting that SAH-BCL9 might have antitumor activity. Indeed, treatment with this peptide decreased cancer cell proliferation, angiogenesis, and invasion *in vitro*. These effects were specific to tumor cells expressing BCL9 and were not observed with a control peptide in which a key binding residue was mutated; SAH-BCL9 also did not affect the interaction of β-catenin with other proteins such as E-cadherin. Furthermore, administration of SAH-BCL9 significantly impaired colorectal cancer and multiple myeloma xenograft growth and metastasis, diminished intratumoral blood vessel formation, and promoted tumor cell apoptosis. These results identify a strategy to selectively inhibit WNT–β-catenin signaling and suggest that this targeted approach may provide therapeutic benefit in cancers that are dependent on aberrant WNT activity. ■

Takada K, Zhu D, Bird GH, Sukhdeo K, Zhao JJ, Mani M, et al. Targeted disruption of the BCL9/β-catenin complex inhibits oncogenic Wnt signaling. Sci Transl Med 2012;4:148ra117.

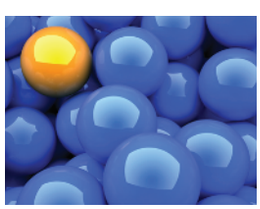
Metastasis

Major finding: Coco promotes reactivation and metastatic outgrowth of dormant breast cancer cells in the lung.

Mechanism: Coco counteracts BMP signaling to enhance the self-renewal of metastasis-initiating cells.

Impact: The Coco gene expression signature may help predict breast cancer relapse to the lung.

A SECRETED BMP INHIBITOR MEDIATES METASTATIC COLONIZATION IN THE LUNG



Cancer cells that disseminate to distant organs must also overcome inhibitory signals within these foreign microenvironments to proliferate and form metastatic outgrowths. Metastatic colonization is thought to be mediated by cancer stem cells, which possess self-renewal ability and are associated with a mesenchymal phenotype, but the molecular mechanisms that trigger their exit from dormancy are unknown. Gao and colleagues used a gain-of-function screen in mammary carcinoma cell lines with different metastatic potentials and identified Coco, a secreted inhibitor of the TGF-β ligand bone morphogenetic protein (BMP), as an important regulator of metastasis-initiating cells in the lung. Expression of Coco enabled nonmetastatic cells to form lung outgrowths, whereas depletion of Coco in metastatic cells prevented lung colonization, indicating that Coco is essential for this step of metastasis. In support of this notion, Coco was necessary and sufficient to stimulate the proliferation of quiescent, solitary tumor cells in the lung. This effect was mediated via inhibition of lung-derived BMP signaling by Coco in metastasis-initiating cells; suppression of BMP activity resulted in reactivation of dormant cells, as was the case with Coco, and rescued the lung-colonizing capability of metastatic cells lacking Coco expression. Furthermore, Coco promoted cancer cell self-renewal, induced the expression of stem cell transcription factors, and augmented primary tumor initiation, suggesting that Coco contributes to colonization by enhancing stem cell characteristics, whereas BMP exerted the opposite effects. Importantly, a Coco-dependent gene expression signature, in particular the genes *NDRG1* and *KIAA1199*, was strongly associated with metastatic relapse to the lung but not metastasis to the bone or brain, which did not express high levels of BMP. These results delineate a mechanism regulating tissue-specific metastatic colonization and suggest that targeting of factors such as Coco may limit metastatic spread. ■

Gao H, Chakraborty G, Lee-Lim AP, Mo Q, Decker M, Vonica A, et al. The BMP inhibitor Coco reactivates breast cancer cells at lung metastatic sites. Cell 2012;150:764–79.