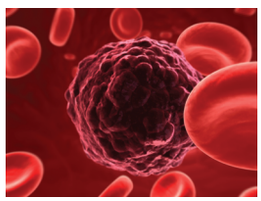
Metastasis

Major finding: *Wnt2* expression in pancreatic CTCs promotes anoikis resistance and metastasis.

Clinical relevance: Inhibition of TAK1 kinase may prevent metastatic spread in pancreatic cancer.

Impact: Analysis of CTC expression profiles may reveal novel drug targets to suppress metastasis.

WNT SIGNALING ENHANCES THE METASTATIC POTENTIAL OF PANCREATIC TUMORS



Circulating tumor cells (CTC) are shed into the circulation from primary tumors and likely give rise to metastases at secondary tissue sites; however, the molecular mechanisms involved in this process have not been well studied. Yu and colleagues describe a candidate signaling pathway important for CTC survival and metastasis in pancreatic cancer. Purified murine pancreatic CTCs were isolated using a microfluidic capture device and then subjected to single-molecule RNA-based sequencing. Comparison of this gene expression profile to that of primary tumors and normal pancreatic tissue yielded a set of genes with enriched expression in CTCs, including *Wnt2*. Overexpression of WNT2 in pancreatic tumor cells resulted in increased lung metastasis, suggesting that this protein may enhance the metastatic potential of CTCs. In support of this possibility, WNT2 expression promoted anchorage-independent tumor sphere formation and reduced anoikis. This prosurvival effect was likely mediated in part through fibronectin (FN1), which was required for WNT2-driven anoikis resistance, and noncanonical WNT signaling, which was elevated in murine pancreatic CTCs. In addition, inhibition of transforming growth factor β–activated kinase 1 (TAK1) decreased FN1 expression and reversed the WNT2 prosurvival phenotype, resulting in abrogation of both tumor sphere formation and metastasis, implicating TAK1 as a central mediator of WNT2 signaling. Importantly, WNT signaling may also be essential to bypass anoikis in human pancreatic tumor cells, as the expression of multiple WNT genes was induced under nonadherent conditions and activation of noncanonical WNT signaling was detected in a subset of patients with metastatic disease. These results support a role for the activation of noncanonical WNT signaling pathways in pancreatic cancer metastasis and identify TAK1 as a potential therapeutic target to suppress metastasis. ■

Yu M, Ting DT, Stott SL, Wittner BS, Ozsolak F, Paul S, et al. RNA sequencing of pancreatic circulating tumour cells implicates WNT signalling in metastasis. Nature 2012 July 1 [Epub ahead of print].

Clinical Trials

Major finding: Dacomitinib significantly improved PFS compared with erlotinib in patients with advanced NSCLC.

Mechanism: Dacomitinib covalently binds and irreversibly inhibits EGFR/HER1, HER2, and HER4.

Impact: Irreversible pan-HER inhibition may be an effective alternative to reversible EGFR inhibition.

IRREVERSIBLE AND REVERSIBLE EGFR INHIBITORS ARE DIRECTLY COMPARED IN NSCLC

Small-molecule reversible inhibitors of human epidermal growth factor receptor 1 (EGFR/HER1), such as erlotinib and gefitinib, are commonly used for the treatment of advanced non–small-cell lung cancers (NSCLC), which frequently harbor activating *EGFR* mutations. Second-generation EGFR inhibitors can irreversibly block receptor activity by covalently binding the ATP-binding pocket, and thus may lead to more potent kinase inhibition and antitumor activity. Ramalingam and colleagues conducted an open-label phase II trial to compare progression-free survival (PFS) in patients with advanced NSCLC who were randomized to receive dacomitinib, a pan-HER irreversible inhibitor targeting EGFR, HER2, and HER4, or erlotinib as a second- or third-line therapy. Dacomitinib led to a significant improvement in PFS compared with erlotinib (2.86 vs. 1.91 months), particularly in wild-type *KRAS* tumors regardless of *EGFR* status (3.71 vs. 1.91 months). However, there was no improvement in PFS among patients with *EGFR*-mutant tumors (7.44 vs. 7.44 months), raising the possibility that the overall improvement in PFS in patients treated with dacomitinib is attributable to permanent blockade of multiple HER family receptors instead of EGFR alone. Overall, compared with erlotinib, dacomitinib also significantly increased the objective response rate (17.0% vs. 5%, including 1 complete response), clinical benefit response rate (29.8% vs. 14.9%), and median duration of response (16.56 vs. 9.23 months), and had a favorable, but non–statistically significant effect on overall survival (9.53 vs. 7.44 months). Dacomitinib was generally well tolerated, with manageable dermatologic and gastrointestinal side effects, and improved patient-reported outcomes pertaining to quality of life and disease-related symptoms. Collectively, these results suggest that irreversible pan-HER inhibitors may be an effective alternative to single-target, reversible HER inhibitors in advanced NSCLC and have led to initiation of a phase III study. ■

Ramalingam SS, Blackhall F, Krzakowski M, Barrios CH, Park K, Bover I, et al. Randomized phase II study of dacomitinib (PF-00299804), an irreversible pan-human epidermal growth factor receptor inhibitor, versus erlotinib in patients with advanced non–small-cell lung cancer. J Clin Oncol 2012 Jul 2 [Epub ahead of print].