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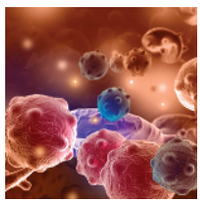
Tumor Microenvironment

Major finding: Stromal cells drive the transcriptional signature of poor-prognosis colorectal cancer subtypes.

Concept: TGFβ signaling in stromal cells promotes colorectal cancer cell tumor initiation and metastasis.

Impact: Stromal gene expression signatures may predict outcome and stratify patients for therapy.

STROMAL CELLS CONTRIBUTE TO POOR PROGNOSIS IN COLORECTAL CANCER



Colorectal cancer is a heterogeneous disease that can be classified into subtypes based on distinct molecular and clinical features. Recent studies have used gene expression profiles to identify a colorectal cancer subtype characterized by expression of stem cell and mesenchymal genes that is associated with poor prognosis. Although it has been suggested that this subtype is comprised of cancer cells that have undergone a switch from an epithelial to a mesenchymal stem cell–like state, it is possible that stromal cells in the tumor microenvironment also contribute to the observed transcriptional profile. Isella and colleagues found that molecular classification of a large cohort of colorectal cancer samples highlighted a poor-prognosis stem/serrated/mesenchymal (SSM) subtype that displayed increased stromal content compared with other colorectal cancer subgroups. SSM signature genes were highly expressed in stromal cell populations within colorectal tumors, including cancer-associated fibroblasts (CAF), leukocytes, and endothelial cells, and species-specific expression profiling of patient-derived xenografts revealed expression of SSM genes in mouse stromal cells. Importantly, high expression of a stromal CAF signature correlated with poor prognosis in untreated patients, whereas upregulation of all three stromal signatures correlated with radiotherapy resistance in rectal cancer. Consistent with these findings, Calon and colleagues showed that genes associated with poor prognosis in colorectal cancer were highly expressed in tumor-associated stromal cells, in particular CAFs, and that high expression of the CAF gene cluster, including TGFβ-regulated genes, defined poor-prognosis tumor subtypes. Elevated TGFβ signaling in CAFs enhanced xenograft formation and tumor-initiating cell frequency. Moreover, inhibition of stromal TGFβ signaling reduced the metastatic potential of patient-derived colorectal cancer organoids, reinforcing the notion that oncogenic crosstalk between cancer cells and the tumor microenvironment contributes to both tumor initiation and progression. Together, these findings indicate that tumor-associated stromal cells contribute to the transcriptome of poor-prognosis colorectal cancer subtypes and drive tumorigenesis via TGFβ-mediated paracrine signaling. ■

Isella C, Terrasi A, Bellomo SE, Petti C, Galatola G, Muratore A, et al. Stromal contribution to the colorectal cancer transcriptome. Nat Genet 2015 Feb 23 [Epub ahead of print].

Calon A, Lonardo E, Berenguer-Llergo A, Espinet E, Hernando-Momblona X, Iglesias M, et al. Stromal gene expression defines poor-prognosis subtypes in colorectal cancer. Nat Genet 2015 Feb 23 [Epub ahead of print].

Clinical Trials

Major finding: The PD-1 inhibitor nivolumab has activity in advanced, refractory squamous NSCLC.

Concept: Nivolumab induces durable objective responses and has a manageable safety profile.

Impact: Further studies of nivolumab as a first-line and second-line treatment in NSCLC are ongoing.

NIVOLUMAB IS ACTIVE IN ADVANCED, REFRACTORY SQUAMOUS NSCLC

Treatment options for patients with advanced squamous non–small cell lung cancer (NSCLC) are limited, and the prognosis for patients with refractory disease is very poor. A phase I clinical trial suggested that treatment with nivolumab, a fully human antibody that inhibits the immune checkpoint protein programmed cell death 1 (PD-1), enhanced antitumor immune responses in patients with NSCLC, prompting Rizvi and colleagues to further evaluate the safety and efficacy of nivolumab in patients with advanced, refractory squamous NSCLC in a single-arm phase II trial. Nivolumab was administered to 117 patients with refractory stage IIIB or stage IV squamous NSCLC, most of whom had previously received at least three systemic treatments. Nivolumab treatment induced a partial response in 17 (14.5%) patients, including two patients with nontarget baseline central nervous system metastases, with a reduction in tumor burden of at least 50% for 11 (65%) of these responding patients. Treatment responses to nivolumab were ongoing in 13 (77%) of 17 responding patients and the median duration of response was not reached, indicative of durable responses. In addition, nivolumab treatment resulted in stable disease in 30 (26%) patients, with a median duration of 6 months. Median overall survival was 8.2 months and overall survival at one year was 40.8%. Analysis of archival pretreatment tumor samples revealed that nivolumab had activity in patients whose tumors expressed the PD-1 ligand PD-L1, as well as in patients with PD-L1–negative tumors. Consistent with phase I data, nivolumab exhibited a manageable safety profile; treatment-related immune-mediated adverse events were generally low grade, and grade 3–4 treatment-related adverse events occurred in 20 (17%) of 117 patients. These findings demonstrate the antitumor activity of nivolumab in advanced, refractory squamous NSCLC and support additional ongoing clinical studies of this inhibitor as first-line and second-line treatment. ■

Rizvi NA, Mazières J, Planchard D, Stinchcombe TE, Dy GK, Antonia SJ, et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. Lancet Oncol 2015;16:257–65.

AACR American Association for Cancer Research

CANCER DISCOVERY

Nivolumab Is Active in Advanced, Refractory Squamous NSCLC

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