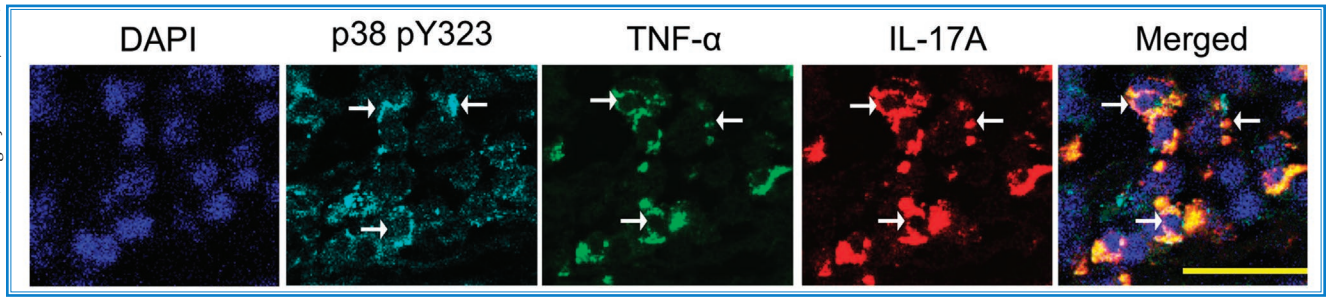
Limiting Inflammation

CCR collaboration suggests new strategy for reducing tumor-promoting cytokines in pancreatic cancer.

(Image: J. Ashwell, CCR)



Human pancreatic ductal adenocarcinoma tissue in which three proteins are fluorescently labeled: p38 pY323 (cyan), TNF-α (green), and IL-17A (red). DAPI was used to stain the nucleus.

Pancreatic tumors, specifically pancreatic ductal adenocarcinomas (PDAC), are among the deadliest of cancers, in part, because of their unique environment. Surrounded by a dense tissue stroma, they develop in a milieu of chemical factors that promotes tumor growth, resistance to chemotherapy, and avoidance of immune targeting. Ironically, the many T cells infiltrating PDACs may promote tumor growth by secreting inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-17A (IL-17A).

Cytokine secretion is regulated by the p38 MAPK pathway, a molecular signaling cascade activated by a variety of cellular stresses via p38 phosphorylation at two classical residues, a threonine at amino acid position 180 and a tyrosine at position 182. Attempts have been made to therapeutically target p38, but toxicities resulting from inhibition of this ubiquitous pathway have thus far proven challenging. However, T-cell receptors also activate p38 through tyrosine phosphorylation at position 323 (pY323). To test whether this specificity might yield a strategy for dampening inflammatory cytokines, Postdoctoral Fellows Muhammad Alam, Ph.D., and Matthias Gaida, M.D., and Jonathan Ashwell, M.D., Chief of CCR's Laboratory of Immune Cell Biology, led a collaboration including Perwez Hussain, Ph.D., Investigator in CCR's Laboratory of Human Carcinogenesis, Serguei Kozlov, Ph.D., Principal Scientist in CCR's Center for Advanced Preclinical Research, as well as researchers in Heidelberg, Germany. Their results were recently published in *Nature Medicine.*

The research team subdivided PDAC patient samples into two groups depending on whether less or more than 10 percent of their T cells stained positively for pY323. The group with greater pY323 levels showed similar T-cell infiltration patterns, but a much greater percentage of TNF-α–, IL-17A–, and IL-21–producing CD4+ T cells. Moreover, this group had a poorer prognosis, with a median survival of 9.8 months as compared to 20.3 months.

In two different mouse models of pancreatic cancer, the researchers then replaced the critical Y323 residue with a phenylalanine residue to prevent phosphorylation. In both cases, they found that this double knock-in substantially reduced disease aggressiveness.

Finally, the team reasoned that a specific inhibitor might be devised to impede p38 activation selectively at Y323, i.e., in T-cell signaling. They designed a peptide based on a known endogenous inhibitor, GADD45-α, that would be taken up by cells and selectively interfere with Y323 signaling. They found that administration of this peptide inhibited tumor growth, in a manner consistent with the inhibition of inflammatory cytokine production by T cells in both mouse models of pancreatic cancer.

"We found that the presence of a high percentage of p38 pY323+ lymphocytes is a very strong negative prognostic factor in human PDAC, and that interference with this pathway in mouse PDAC was beneficial in both preventive and treatment models," said Ashwell. "A potential advantage of targeting the T-cell p38 alternative pathway in the tumor microenvironment, rather than a single cytokine or factor, is that it interferes with multiple downstream proinflammatory events that are involved in tumor progression."

To learn more about Dr. Ashwell's research, please visit his CCR website at https://ccr.cancer.gov/Laboratory-of-Immune-Cell-Biology/jonathan-d-ashwell.