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## RESEARCH ARTICLES

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### Excerpt

**Tumor Cell–Intrinsic USP22 Suppresses Antitumor Immunity in Pancreatic Cancer**

Jinyang Li, Salina Yuan, Robert J. Norgard, Fangxue Yan, Taiji Yamazoe, Andrés Blanco, and Ben Z. Stanger

USP22, a deubiquitinating enzyme, is a tumor-intrinsic factor that can modulate the immune tumor microenvironment in pancreatic cancer. Loss of USP22 sensitizes therapy-resistant tumors, thus, representing a potential target to boost responses of pancreatic tumors to immunotherapy.

**B cell–Derived IL35 Drives STAT3-Dependent CD8+ T-cell Exclusion in Pancreatic Cancer**


Evaluation of pancreatic ductal adenocarcinomas (PDAs) shows that regulatory B cells can drive PDA immune evasion. B cell–derived IL35 activates STAT3 in CD8+ T cells, leading to reduced expression of chemokine receptors and effector function.

**Glypican-3–Specific CAR T Cells Coexpressing IL15 and IL21 Have Superior Expansion and Antitumor Activity against Hepatocellular Carcinoma**

Sai Arun Batra, Purva Rathi, Linjie Guo, Amy N. Courtney, Julien Fleurence, Julien Balzaeu, Rahamthattha S. Shaiq, Thao P. Nguyen, Meng-Fen Wu, Shaun Bulsara, Maxim Mamonkin, Leonid S. Metelitsa, and Andras Heczey

Novel approaches are needed to enhance the efficacy of CAR T cells in solid tumors. Coexpression of IL15 and IL21 improves the antitumor properties of CAR T cells against hepatocellular carcinoma in a TCF-1-mediated manner.

**IL6 Induces an IL22+ CD8+ T-cell Subset with Potent Antitumor Function**


Different subsets of T cells contribute to antitumor immunity. IL22-producing CD8+ T cells (Tc22) are polarized via IL6 and the aryl hydrocarbon receptor, are antitumor, and comprise a large percentage of CD8+ T cells in human ovarian tumors.
Control of Metastases via Myeloid CD39 and NK Cell Effector Function
Juming Yan, Xian-Yang Li, Amelia Roman Aguilera, Christos Xiao, Celia Jacobberger-Foissac, Bianca Nowlan, Simon C. Robson, Courtney Beers, Achim K. Moesta, Nishamol Geetha, Michele W.L. Teng, and Mark J. Smyth

A CD39-targeting monoclonal antibody (B66) has potent activity in experimental and spontaneous metastases models. Myeloid cell, but not NK cell, expression of CD39 is critical for efficacy of the antibody and NK cell-mediated control of metastases.

Matrix-Targeting Immunotherapy Controls Tumor Growth and Spread by Switching Macrophage Phenotype
Claire Deligne, Devadarssen Murdamoothoo, Anis N. Gammage, Martha Gschwandtner, William Erne, Thomas Loustau, Anna M. Marzeda, Raphael Carapito, Nicole De Paul, Inès Velazquez-Quesada, Imogen Mazzier, Zhen Sun, Gertraud Orend, and Kim S. Midwood

Tenascin-C, an extracellular matrix protein, contributes to immune suppression in breast cancer via modulation of macrophage phenotype. Blockade of tenascin-C reverses the phenotypic switch, highlighting the therapeutic potential of targeting the tumor extracellular matrix to alleviate immune-suppressive mechanisms.

Lactic Acidosis Together with GM-CSF and M-CSF Induces Human Macrophages toward an Inflammatory Protumor Phenotype

Tumor-derived lactic acid induces human monocytes to differentiate into macrophages with inflammatory immunoregulatory properties, similar to those of macrophages in established tumors. Drugs targeting the glycolytic metabolism of tumor cells might prevent accumulation of protumor TAMs in tumors.

High-Throughput Prediction of MHC Class I and II Neoantigens with MHCnuggets

An in silico predictor of peptide ligands that can bind to major histocompatibility complex (MHC) proteins is developed and used to assess potential neoantigens and immunogenic missense mutations (IMMs) in 6,613 TCGA patients.

pVACtools: A Computational Toolkit to Identify and Visualize Cancer Neoantigens

Many tumor immune therapies rely on the expression of neoantigens for efficacy, yet uncovering them remains challenging. pVACtools is a sequence analysis toolkit that allows users to identify neoantigens for cancers of interest.
B cells can predict response to immunotherapy, particularly when present in specialized tertiary lymphoid structures (TLSs) or immune aggregates (IAs). Pancreatic ductal adenocarcinoma (PDA), an aggressive cancer with low CD8^+ T-cell infiltration, is commonly refractory to immunotherapy and contains infiltrating regulatory B cells (Bregs). Mirlekar et al. show that IL35-producing B cells in human PDA primarily localize to IA structures. B cell–derived IL35 in a Kras- and p53-driven mouse model acts to hamper CD8^+ T-cell effector function via STAT3 activation, which downregulates key chemotactic and effector molecule expression. Inhibiting STAT3 signaling or deleting B cell–derived IL35 can overcome this suppression, resulting in enhanced antitumor responses and sensitivity to PD-1 blockade. In PDA patients, having high numbers of IL35^+ B cells inversely correlates with low cytotoxic T-cell signatures in tumors. These data highlight how Bregs present at IAs can shape antitumor responses that allow progression of disease and identify possible therapeutic targets to boost efficacy of immunotherapy in PDA. Read more in this issue on page 292. Original image from Supplementary Fig. S6. Artwork by Lewis Long.