

CANCER IMMUNOLOGY RESEARCH

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WHAT WE'RE READING

- 281 **A Sampling of Highlights from the Literature**

PRIORITY BRIEF

- 282 **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.

RESEARCH ARTICLES

- 292 **B cell-Derived IL35 Drives STAT3-Dependent CD8⁺ T-cell Exclusion in Pancreatic Cancer**
A C Bhalchandra Mirlekar, Daniel Michaud, Samuel J. Lee, Nancy P. Kren, Cameron Harris, Kevin Greene, Emily C. Goldman, Gaorav P. Gupta, Ryan C. Fields, William G. Hawkins, David G. DeNardo, Naim U. Rashid, Jen Jen Yeh, Autumn J. McRee, Benjamin G. Vincent, Dario A.A. Vignali, and Yuliya Pylayeva-Gupta
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.
- 309 **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 Balzeau, Rahamthulla S. Shaik, Thao P. Nguyen, Meng-Fen Wu, Shaun Bulsara, Maksim 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.

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

Michael St. Paul, Samuel D. Saibil, Scott C. Lien, SeongJun Han, Azin Sayad, David T. Mulder, Carlos R. Garcia-Batres, Alisha R. Elford, Kavita Israni-Winger, Céline Robert-Tissot, Michael Zon, Sarah Rachel Katz, Patricia A. Shaw, Blaise A. Clarke, Marcus Q. Bernardini, Linh T. Nguyen, Benjamin Haibe-Kains, Trevor J. Pugh, and Pamela S. Ohashi

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.

- 334 **CD4⁺ T-cell Immunity in the Peripheral Blood Correlates with Response to Anti-PD-1 Therapy**

A C Hiroshi Kagamu, Shigehisa Kitano, Ou Yamaguchi, Kenichi Yoshimura, Katsuhisa Horimoto, Masashi Kitazawa, Kazuhiko Fukui, Ayako Shiono, Atsuhito Mouri, Fuyumi Nishihara, Yu Miura, Kosuke Hashimoto, Yoshitake Murayama, Kyoichi Kaira, and Kunihiko Kobayashi

Predictive biomarkers of patient responses to immune checkpoint therapy could help identify patients whose tumors are most amenable to treatment. High numbers of circulating CD62^{low}CD4⁺ T cells positively correlate with responsiveness of NSCLC patients to PD-1 blockade.

- 345 **Combined CD44- and CD25-Targeted Near-Infrared Photoimmunotherapy Selectively Kills Cancer and Regulatory T Cells in Syngeneic Mouse Cancer Models**

Yasuhiro Maruoka, Aki Furusawa, Ryuhei Okada, Fuyuki Inagaki, Daiki Fujimura, Hiroaki Wakiyama, Takuya Kato, Tadanobu Nagaya, Peter L. Choyke, and Hisataka Kobayashi

Near-infrared photoimmunotherapy (NIR-PIT) utilizes antibody-photo-absorber conjugates that can be activated by NIR light. When anti-CD44 and anti-CD25 are both used in this therapy, both cancer cells and Treg cells are selectively depleted, leading to improved antitumor responses.

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- 356 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.
- 368 Matrix-Targeting Immunotherapy Controls Tumor Growth and Spread by Switching Macrophage Phenotype**
Claire Deligne, Devadarssen Murdamoothoo, Anís N. Gammage, Martha Gschwandtner, William Erne, Thomas Loustau, Anna M. Marzeda, Raphael Carapito, Nicodème Paul, Inés 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.
- 383 Lactic Acidosis Together with GM-CSF and M-CSF Induces Human Macrophages toward an Inflammatory Protumor Phenotype**
Léa Paolini, Clément Adam, Céline Beauvillain, Laurence Preisser, Simon Blanchard, Pascale Pignon, Valérie Seegers, Louise-Marie Chevalier, Mario Campone, Romuald Wernert, Véronique Verrielle, Pedro Raro, Norbert Ifrah, Vincent Lavoué, Philippe Descamps, Alain Morel, Véronique Catros, Guillaume Tcherkez, Guy Lenaers, Cinzia Bocca, Judith Kouassi Nzoughet, Vincent Procaccio, Yves Delneste, and Pascale Jeannin
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.
- 396 High-Throughput Prediction of MHC Class I and II Neoantigens with MHCnuggets**
AC Xiaoshan M. Shao, Rohit Bhattacharya, Justin Huang, I.K. Ashok Sivakumar, Collin Tokheim, Lily Zheng, Dylan Hirsch, Benjamin Kaminow, Ashton Omdahl, Maria Bonsack, Angelika B. Riemer, Victor E. Velculescu, Valsamo Anagnostou, Kymberleigh A. Pagel, and Rachel Karchin
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.
- 409 pVACtools: A Computational Toolkit to Identify and Visualize Cancer Neoantigens**
AC Jasreet Hundal, Susanna Kiwala, Joshua McMichael, Christopher A. Miller, Huiming Xia, Alexander T. Wollam, Connor J. Liu, Sidi Zhao, Yang-Yang Feng, Aaron P. Graubert, Amber Z. Wollam, Jonas Neichin, Megan Neveau, Jason Walker, William E. Gillanders, Elaine R. Mardis, Obi L. Griffith, and Malachi Griffith
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.

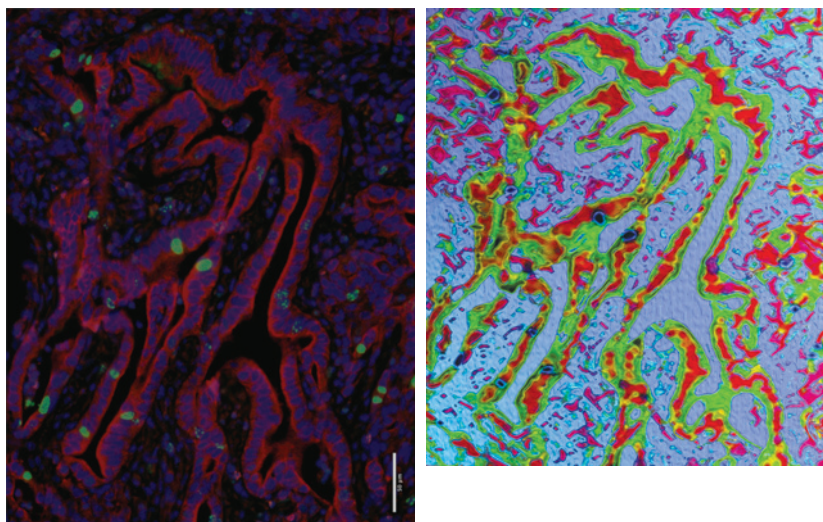
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ABOUT THE COVER

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.



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