

CANCER IMMUNOLOGY RESEARCH

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

IN THE SPOTLIGHT

- 724 **IL11: A Specific Repressor of Tumor-Specific CD4⁺ T Cells**
Sjoerd H. van der Burg
See related article, p. 735
- 725 **Characterizing the Complexities of Neutrophils with Suppressive Properties**
Marco Antonio Cassatella
See related article, p. 790

PRIORITY BRIEF

- 726 **Regulatory T-cell Transcriptomic Reprogramming Characterizes Adverse Events by Checkpoint Inhibitors in Solid Tumors**
Maria Grigoriou, Aggelos Banos, Aikaterini Hatzioannou, Andreas Kloetgen, Panagiotis Kouzidis, Despoina Aggouraki, Roubini Zakopoulou, Giorgos Bamias, Eva Kassi, Dimitrios Mavroudis, Aristotelis Bamias, Dimitrios T. Boumpas, Aristotelis Tsirigos, Helen Gogas, Themis Alissafi, and Panayotis Verginis
Regulatory T cells (Treg) maintain peripheral tolerance. The authors show a common inflammatory signature between Tregs from patients with solid tumors who develop immune-related adverse events and Tregs from patients with autoimmune diseases, suggesting shared underlying mechanisms.

RESEARCH ARTICLES

- 735 **Host IL11 Signaling Suppresses CD4⁺ T cell-Mediated Antitumor Responses to Colon Cancer in Mice**
Jennifer Huynh, David Baloyan, David Chisanga, Wei Shi, Megan O'Brien, Shoukat Afshar-Sterle, Mariah Alorro, Lokman Pang, David S. Williams, Adam C. Parslow, Pathum Thilakasiri, Moritz F. Eissmann, Louis Boon, Frederick Masson, Ashwini L. Chand, and Matthias Ernst
This study shows genetic ablation of IL11 signaling augments production of IFN γ and TNF α by antitumor CD4⁺ T cells, suppressing colon cancer development *in vivo*. The data suggest IL11 as a potential therapeutic target in colon cancer.
See related Spotlight, p. 724

- 748 **MHC Class II Antigen Presentation by Lymphatic Endothelial Cells in Tumors Promotes Intratumoral Regulatory T cell-Suppressive Functions**

A C Anastasia O. Gkoutidi, Laure Garnier, Juan Dubrot, Julien Angelillo, Guillaume Harlé, Dale Brighthouse, Ludovic J. Wrobel, Robert Pick, Christoph Scheiermann, Melody A. Swartz, and Stéphanie Hugues

In this study, tumoral lymphatic endothelial cells are shown to present tumor antigens via MHC class II molecules, promoting a tumor-specific signature in regulatory T cells (Treg) and enhanced Treg suppressive functions, inhibiting antitumor immunity.

- 765 **Exercise Training Improves Tumor Control by Increasing CD8⁺ T-cell Infiltration via CXCR3 Signaling and Sensitizes Breast Cancer to Immune Checkpoint Blockade**

Igor L. Gomes-Santos, Zohreh Amoozgar, Ashwin S. Kumar, William W. Ho, Kangsan Roh, Nilesh P. Talele, Hannah Curtis, Kosuke Kawaguchi, Rakesh K. Jain, and Dai Fukumura

Optimized exercise therapy induces vessel normalization, boosts antitumor effector cell infiltration and function, and delays tumor growth in a CXCR3 pathway/CD8⁺ T cell-dependent manner. This results in sensitization of refractory breast cancer to immune checkpoint blockade.

- 779 **The Chemokine CX3CL1 Improves Trastuzumab Efficacy in HER2 Low-Expressing Cancer *In Vitro* and *In Vivo***

Tobias F. Dreyer, Sabine Kuhn, Christoph Stange, Nadine Heithorst, Daniela Schilling, Jil Jelsma, Wolfgang Sievert, Stefanie Seitz, Stefan Stangl, Alexander Hapfelmeier, Aurelia Noske, Anja K. Wege, Wilko Weichert, Jürgen Ruland, Manfred Schmitt, Julia Dorn, Marion Kiechle, Ute Reuning, Viktor Magdolen, Gabriele Multhoff, and Holger Bronger
CX3CL1 is demonstrated to modulate NK-cell recruitment into the tumor microenvironment of HER2⁺ cancer, increase NK-cell cytotoxicity against HER2⁺ targets, and synergize with trastuzumab therapy. The data highlight CX3CL1 as a potential target molecule to enable anti-HER2 treatment.

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790 Mechanisms Driving Neutrophil-Induced T-cell Immunoparalysis in Ovarian Cancer

Tiffany R. Emmons, Thejaswini Giridharan, Kelly L. Singel, ANM Nazmul H. Khan, Jason Ricciuti, Kaitlyn Howard, Stephanie L. Silva-Del Toro, Ivy L. Debreceni, Cathelijn E.M. Aarts, Mieke C. Brouwer, Sora Suzuki, Taco W. Kuijpers, Ilse Jongerius, Lee-Ann H. Allen, Viviana P. Ferreira, Anna Schubart, Holger Sellner, Jörg Eder, Steven M. Holland, Sanjay Ram, James A. Lederer, Kevin H. Eng, Kirsten B. Moysich, Kunle Odunsi, Michael B. Yaffe, Emese Zsiros, and Brahm H. Segal

The ovarian cancer microenvironment induces suppressor neutrophils that inhibit T-cell signaling and metabolic functions. Acquisition of the suppressor phenotype is dependent on several pathways including complement signaling, which can be targeted therapeutically to enhance antitumor immunity.

See related Spotlight, p. 725

811 Tumor-Associated Neutrophils Drive B-cell Recruitment and Their Differentiation to Plasma Cells

Merav E. Shaul, Asaf Zlotnik, Einat Tidhar, Asaf Schwartz, Ludovica Arpinati, Naomi Kaiser-Iluz, Sojod Mahroum, Inbal Mishalian, and Zvi G. Fridlender

Tumor-associated neutrophils (TAN) are shown to regulate TNF α -mediated B-cell migration into the TME and their differentiation into functional plasma cells, partially mediated by interaction of TAN BAFF and B-cell BAFF-R. The data highlight potential targets for cancer therapy.

825 T Cells Expressing Receptor Recombination/Revision Machinery Are Detected in the Tumor Microenvironment and Expanded in Genomically Over-unstable Models

A C

Gaia Morello, Valeria Cancila, Massimo La Rosa, Giovanni Germano, Daniele Lecis, Vito Amodio, Federica Zanardi, Fabio Iannelli, Daniele Greco, Laura La Paglia, Antonino Fiannaca, Alfonso M. Urso, Giulia Graziano, Francesco Ferrari, Serenella M. Pupa, Sabina Sangaletti, Claudia Chiodoni, Giancarlo Pruneri, Alberto Bardelli, Mario P. Colombo, and Claudio Tripodo

Presence of tumor-infiltrating T cells, characterized by receptor recombinase/revision machinery, is seen in human and mouse tumors. The data highlight *in situ* coexpression of recombinase elements in peripheral T cells, which then play a role in tumor-associated responses.

838 Flightless I Homolog Reverses Enzalutamide Resistance through PD-L1-Mediated Immune Evasion in Prostate Cancer

Hailong Ruan, Lin Bao, Zhen Tao, and Ke Chen

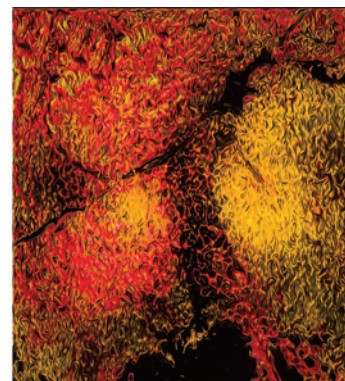
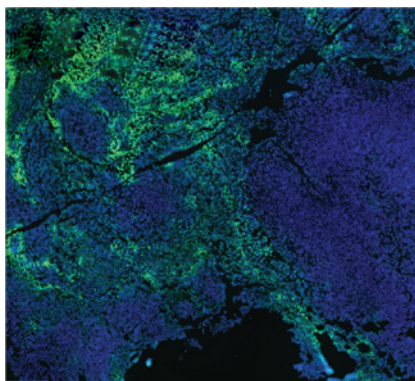
This study reports a functional and biological interaction between enzalutamide resistance and immune evasion through a FLII/YBX1/PD-L1 cascade. The data suggest that combining FLII expression and endocrine therapy may benefit prostate cancer patients by preventing tumor immune evasion.

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ABOUT THE COVER

Exercise can impact immune responses to cancer, but the mechanisms behind this are not fully understood. Gomes-Santos et al. demonstrate in murine models of breast cancer that exercise training contributes to tumor control and response to immune checkpoint blockade (ICB). Mechanistically, exercise training induces vessel normalization, increases effector immune cell infiltration and function, and controls tumor growth in a CXCR3 signaling/CD8⁺ T cell-dependent manner. Because of these effects, ICB-refractory breast cancer becomes sensitized to treatment. Exercise also reduces the incidence of lung metastasis. The data support the use of exercise training to improve antitumor responses and immunotherapy efficacy. Read more in this issue on page 765. Original image from Fig. 2G. Artwork by Lewis Long.



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