WHAT WE'RE READING

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
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 Aloros, 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 IFNγ and TNFα 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
Anastasia O. Gkountiti, Laure Garnier, Ivan Dubrot, Julien Angellillo, Guillaume Harlé, Dale Brighouse, Ludovic J. Wrobel, Robert Pick, Christoph Scheiermann, Melody A. Swift, 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.

754  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, Ashwini 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, Stefa Seitz, Stefan Stangl, Alexander Hapfelmacher, 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.
### Mechanisms Driving Neutrophil-Induced T-cell Immunoparalysis in Ovarian Cancer


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

### 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 Kaisar-Iluz, Sojod Mahroum, Inbal Mishalian, and Zvi G. Fridlender

Tumor-associated neutrophils (TAN) are shown to regulate TNFα-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.

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

Gaia Morello, Valeria Cancila, Massimo La Rosa, Giovanni Germano, Daniele Lecis, Vito Amadio, Federica Zanardi, Fabio Iannelli, Daniele Greco, Laura La Paglia, Antonino Fiannaca, Alfonso M. Urso, Giulia Graziano, Francesco Ferrari, Serenella M. Pupa, Sabina Sangaletti, Claudia Chiudoni, 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.

### 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.