

## CANCER IMMUNOLOGY RESEARCH

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## WHAT WE'RE READING

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

## CANCER IMMUNOLOGY MINIATURES

- 724 **Human NKp44<sup>+</sup> Group 3 Innate Lymphoid Cells Associate with Tumor-Associated Tertiary Lymphoid Structures in Colorectal Cancer**

Atsuyo Ikeda, Takayuki Ogino, Hisako Kayama, Daisuke Okuzaki, Junichi Nishimura, Shiki Fujino, Norikatsu Miyoshi, Hidekazu Takahashi, Mamoru Uemura, Chu Matsuda, Hirofumi Yamamoto, Kiyoshi Takeda, Tsunekazu Mizushima, Masaki Mori, and Yuichiro Doki

Innate lymphoid cells (ILCs) are strategic players in immune responses. Group 3 ILCs (ILC3s) are found in CRC tissue associated with tertiary lymphoid structures (TLSs). Both TLSs and ILCs decrease during CRC progression, suggesting an unsuspected relationship.

## RESEARCH ARTICLES

- 732 **Excessive Costimulation Leads to Dysfunction of Adoptively Transferred T Cells**

**A C** Dinali Wijewarnasuriya, Christina Bebernitz, Andrea V. Lopez, Sarwish Rafiq, and Renier J. Brentjens  
CAR T cells can be driven into a dysfunctional state through excessive costimulation. Understanding the limits of costimulation for CAR T cells will aid design of more efficacious CAR T cells for future clinical trials.

See related article, p. 743

- 743 **Optimization of T-cell Receptor-Modified T Cells for Cancer Therapy**

**A C** Dylan J. Drakes, Sarwish Rafiq, Terence J. Purdon, Andrea V. Lopez, Smita S. Chandran, Christopher A. Klebanoff, and Renier J. Brentjens  
Tumor-directed T cells function better when expressing IL18 rather than IL12. TCR-modified T cells secreting IL18 eradicate established tumors in syngeneic models in combination with sublethal irradiation and in xenograft models, providing evidence to support IL18-boosted T-cell clinical trials.

See related commentary, p. 732

- 756 **Donor Lymphocyte-Derived Natural Killer Cells Control MHC Class I-Negative Melanoma**

Nana Dang, Yuan Lin, Mark Waer, and Ben Sprangers  
Donor lymphocyte infusion after allogeneic bone marrow transplantation can promote antitumor immunity but risks graft-versus-host disease. If there is no prior marrow transplantation, then donor lymphocyte infusion allows donor NK cells to control MHC-negative melanoma without toxicity.

- 769 **Inhibition of MICA and MICB Shedding Elicits NK-Cell-Mediated Immunity against Tumors Resistant to Cytotoxic T Cells**

Lucas Ferrari de Andrade, Sushil Kumar, Adrienne M. Luoma, Yoshinaga Ito, Pedro Henrique Alves da Silva, Deng Pan, Jason W. Pyrdol, Charles H. Yoon, and Kai W. Wucherpennig

Tumor cells evade NK-cell-mediated immunity by proteolytic shedding of the activating MICA/B ligands. Use of a MICA/B antibody inhibits MICA/B proteolytic shedding, leading to NK-cell responses against tumor cells resistant to cytotoxic T cells.

- 781 **CD137/OX40 Bispecific Antibody Induces Potent Antitumor Activity that Is Dependent on Target Coengagement**

**A C** Miguel Gaspar, John Pravin, Leonor Rodrigues, Sandra Uhlenbroich, Katy L. Everett, Francisca Wollerton, Michelle Morrow, Mihriban Tuna, and Neil Brewis

Antibody agonists that target T-cell costimulatory pathways are being tested in the clinic. FS120, a dual agonist antibody specific for CD137 and OX40, delays tumor growth by improving the activation and proliferation of peripheral T cells.

- 794 **Histone Deacetylase Inhibitors and IL21 Cooperate to Reprogram Human Effector CD8<sup>+</sup> T Cells to Memory T Cells**

Junmei Wang, Farah Hasan, Amanda C. Frey, Haiyan S. Li, Jungsun Park, Ke Pan, Cara Haymaker, Chantale Bernatchez, Dean A. Lee, Stephanie S. Watowich, and Cassian Yee

Improving the *in vivo* persistence of adoptive cell therapies correlates to better patient responses. Histone deacetylase inhibitors and IL21 shift CD8<sup>+</sup> T cells to a more persistent, central memory phenotype by increasing CD28 promoter accessibility.

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**806 Anti-VEGF Treatment Enhances CD8<sup>+</sup> T-cell Antitumor Activity by Amplifying Hypoxia**

Patricia E. de Almeida, Judy Mak, Genevive Hernandez, Rajiv Jesudason, Aurelie Herault, Vincent Javinal, Jovencio Borneo, Jeong M. Kim, and Kevin B. Walsh  
Amplification of tumor hypoxia by anti-VEGF treatment enhances CD8<sup>+</sup> T-cell antitumor responses through increased HIF1 $\alpha$  activity. Combining anti-angiogenics and immunotherapeutics may be useful for the treatment of cancer.

**819 Quantification of Early-Stage Myeloid-Derived Suppressor Cells in Cancer Requires Excluding Basophils**

ANM Nazmul H. Khan, Tiffany R. Emmons, Jerry T. Wong, Emad Alqassim, Kelly L. Singel, Jaron Mark, Brandon E. Smith, Joseph D. Tario, Kevin H. Eng, Kirsten B. Moysich, Kunle Odunsi, Scott I. Abrams, and Brahm H. Segal

A substantial proportion of cells with early-stage myeloid-derived suppressor cell (e-MDSC) surface markers in circulation and in ascites of patients with ovarian cancer are basophils. Exclusion of basophils from e-MDSC is required for prognostic and therapeutic studies.

**829 CSF1R Is Required for Differentiation and Migration of Langerhans Cells and Langerhans Cell Histiocytosis**

Silvia Lonardi, Sara Scutera, Sara Licini, Luisa Lorenzi, Anna Maria Cesinaro, Luisa Benerini Gatta, Carlotta Castagnoli, Daniele Bollero, Rosaria Sparti, Michela Tomaselli, Daniela Medicina, Federica Calzetti, Marco Antonio Cassatella, Fabio Facchetti, Tiziana Musso, and William Vermi

CSF1R promotes efficient Langerhans cell (LC) differentiation from hematopoietic progenitors and migration, which may be reduced by CSF1R kinase inhibition. CSF1R expression in clinical LC histiocytosis (LCH) specimens suggests potential for CSF1R blockade in the treatment of LCH.

## CORRECTION

**842 Correction: Extensive Profiling of the Expression of the Indoleamine 2,3-Dioxygenase 1 Protein in Normal and Tumoral Human Tissues**

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## ABOUT THE COVER

Cancer patients are often treated with allogeneic bone marrow transplantation followed by donor lymphocyte infusion (which contains NK cells) in order to induce antitumor responses; however, this therapy is often associated with life-threatening graft-versus-host disease (GvHD). Many strategies have been employed to limit GvHD, such as donor T-cell depletion, but more robust methods are needed. Here, the authors show that without prior bone marrow transplantation, donor lymphocyte infusion controls melanoma tumor growth in mouse models without inducing GvHD; these effects associate with the expansion and activation of tumor-infiltrating NK cells. Blocking IL2 from host CD4<sup>+</sup> T cells inhibits the NK-cell-mediated antitumor effects of donor lymphocyte infusion. Together, these data demonstrate that host CD4<sup>+</sup> T cells support the NK-cell-mediated antitumor effects of donor lymphocyte infusion via IL2. To read more, Dang et al. begins on page 756. Hematoxylin and eosin staining from the Sprangers laboratory. Artwork by Lewis Long.

