HIGHLIGHTS FROM THE LITERATURE

939 What We’re Reading

MILESTONES IN CANCER IMMUNOLOGY

940 2017 William B. Coley Award

CANCER IMMUNOLOGY AT THE CROSSROADS

942 A Blueprint to Advance Colorectal Cancer Immunotherapies


PRIORITY BRIEF

950 Increasing Tumor-Infiltrating T Cells through Inhibition of CXCL12 with NOX-A12 Synergizes with PD-1 Blockade

Dirk Zboralski, Kai Hoehlig, Dirk Eulberg, Anna Frömming, and Axel Vater

Immune checkpoint inhibitors benefit only some patients, perhaps due to exclusion of CTLs by the tumor microenvironment through CXCL12. Treatment with the CXCL12 inhibitor NOX-A12 enhanced infiltration of immune cells and overcame resistance to anti–PD-1 in a murine model.

RESEARCH ARTICLES

957 PI3Kγ Activates Integrin α4 and Promotes Immune Suppressive Myeloid Cell Polarization during Tumor Progression

Philippe Foubert, Megan M. Kaneda, and Judith A. Varner

Myeloid-derived suppressor cells and tumor-associated macrophages, aided by PI3Kγ and integrin α4, accumulate in tumors and block antitumor immune responses. Suppression of PI3Kγ or integrin α4 alleviated the block and supported antitumor immune responses.

969 Melanoma Sequentially Suppresses Different DC Subsets in the Sentinel Lymph Node, Affecting Disease Spread and Recurrence

Mari F.C.M. van den Hout, Bas D. Koster, Berbel J.R. Sluijter, Barbara G. Molenkamp, Rieneke van de Ven, Alfons J.M. van den Eertwegh, Rik J. Scheper, Paul A.M. van Leeuwen, M. Petrousjka van den Tol, and Tanja D. de Grujil

Immunological events accompanying local and regional melanoma progression offer a rationale for the therapeutic targeting of migratory and LN-resident DC subsets to prevent melanoma recurrence. Immunotherapeutic interventions in early-stage melanoma could alter the clinical course of disease.

978 T-cell Localization, Activation, and Clonal Expansion in Human Pancreatic Ductal Adenocarcinoma

Ingunn M. Stromnes, Ayaka Hulbert, Robert H. Pierce, Philip D. Greenberg, and Sunil R. Hingorani

Pancreatic ductal adenocarcinoma resists immune checkpoint blockade. The nature and localization of endogenous CD8+ T cells and suppressive cells infiltrating human pancreatic ductal adenocarcinoma were examined, providing a basis for the design of more effective immunotherapies.

992 Stereotactic Radiotherapy Increases Functionally Suppressive Regulatory T Cells in the Tumor Microenvironment

Emily J. Colbeck, Emma Jones, James P. Hindley, Kathryn Smart, Ralph Schulz, Molly Browne, Scott Cutting, Anwen Williams, Lee Parry, Andrew Godkin, Carl F. Ware, Ann Ager, and Awen Gallimore

Depletion of Tregs lowered the threshold for immune activation, resulting in high endothelial venule (HEV) neogenesis, driven by a T cell–dependent mechanism. A positive feedback loop was formed that allowed T-cell influx and control of carcinogen-induced tumors.
Immunosurveillance and Immunoediting of Breast Cancer via Class I MHC Receptors
Megan M. Tu, Mir Munir A. Rahim, Céline Sayed, Ahmad Bakur Mahmoud, and Andrew P. Makrigiannis
How NK cells are involved in immunosurveillance of solid tumors was examined using mice with and without inhibitory NK receptors. Tumors were molded by environmental immune pressure, editing MHC class I expression as needed to evade immunity.

Subversion of NK-cell and TNFα Immune Surveillance Drives Tumor Recurrence
Tim Kottke, Laura Evgin, Kevin G. Shim, Diana Rommelfänger, Nicolas Boisgerault, Shane Zaidi, Rosa Maria Díaz, Jill Thompson, Elizabeth Hett, Matt Coffey, Peter Selby, Hardev Pandha, Kevin Harrington, Alan Melcher, and Richard Vile
Patients with minimal residual disease are at high risk for relapse. The authors now show how innate immune surveillance mechanisms that normally control infection and the growth of primary tumors are subverted by residual disease to promote recurrence.

Tumor PDCD1LG2 (PD-L2) Expression and the Lymphocytic Reaction to Colorectal Cancer
Yohei Masugi, Reiko Nishihara, Tsuyoshi Hamada, Mingyang Song, Annacarolina da Silva, Keisuke Kosumi, Mancang Gu, Yan Shi, Wanwan Li, Li Liu, Daniel Nevo, Kentaro Inamura, Yin Cao, Xiaoyun Liao, Katsuhiko Nosho, Andrew T. Chan, Marios Giannakis, Adam J. Bass, F. Stephen Hodi, Gordon J. Freeman, Scott J. Rodig, Charles S. Fuchs, Zhi Rong Qian, Jonathan A. Nowak, and Shuji Ogino
Colorectal tumor PDCD1LG2 (PD-L2) expression was inversely associated with Crohn's-like lymphoid reactions, which are a key adaptive antitumor response in colorectal carcinogenesis. This population data can inform the development of immunotherapy strategies targeting immune checkpoint mechanisms.

ABOUT THE COVER
T cells are critical components of the antitumor response but are constrained from action by multiple mechanisms. The interaction of the immune checkpoint PD-1 with its ligand PD-L1 will suppress CD8+ T cells, and in some cancers this effect can be abrogated through antibody blockade. However, pancreatic ductal adenocarcinoma remains nonresponsive when blocking antibodies are administered. To investigate the mechanisms of immunological resistance in pancreatic cancer, Stromnes and colleagues showed that PD-L1 (green) is quite rare in pancreatic tumor cells (magenta), but is expressed in stromal cell clusters. Tumoral T cells in pancreatic tumors had marked variation in their abundance, localization, and phenotype, indicating the multiple and distinct mechanisms of immunotherapy resistance at work. Read more in this issue of Cancer Immunology Research starting on page 978. Original fluorescent micrograph from Stromnes and colleagues. Artwork by Lewis Long.