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 Frömmer, and Axel Vater

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

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. Petrouska van den Tol, and Tanja D. de Gruijl

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

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

1005 Treg Depletion Licenses T Cell–Driven HEV Neogenesis and Promotes Tumor Destruction
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

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.

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.

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.

Stereotactic irradiation of implanted murine tumors increased proliferation of regulatory T cells (Tregs) within tumors. These cells were functionally more suppressive than Tregs derived from unirradiated tumors, highlighting a potential counterbalance to the immunogenic effects of radiotherapy.

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.
1016 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.

1029 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 Coffrey, 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.

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.