Can Targeting Stroma Pave the Way to Enhanced Antitumor Immunity and Immunotherapy of Solid Tumors?
Ellen Puré and Albert Lo


Use of immune checkpoint inhibitors is increasing. Some patients with NSCLC treated with nivolumab develop a radiographic cryptogenic organizing pneumonia (COP) pattern of PD-1 inhibitor–related pneumonitis. Recognition of the radiographic pattern is needed for prompt diagnosis and management.

Synergistic COX2 Induction by IFNγ and TNFα Self-Limiting Type-1 Immunity in the Human Tumor Microenvironment
Jeffrey L. Wong, Natasha Obermajer, Kunle Odunsi, Robert P. Edwards, and Pawel Kalinski
IFNγ and TNFα are primarily antitumor mediators, but unexpectedly synergized to enhance multiple pathways of immune suppression, using COX2 activation as the intermediary. This mechanism limits type-1 antitumor immunity and provides a rationale for targeting the COX2–PGE2 axis.

Post-Sepsis State Induces Tumor-Associated Macrophage Accumulation through CXCR4/CXCL12 and Favors Tumor Progression in Mice
José M. Mota, Caio A. Leite, Lucas E. Souza, Paulo H. Melo, Daniele C. Nascimento, Virginia M. de-Deus-Watatsuma, Jessica Temporal, Florencia Figueiredo, Houtan Noushmehr, José C. Alves-Filho, Fernando Q. Gunha, and Eduardo M. Rego
Patients who recover from sepsis are immunosuppressed and are at higher risk for cancer. Studying melanoma in post-septic-shock mice revealed that tumor composition, progression rate, and microenvironment were biased toward attracting tumor-associated macrophages that support tumor growth.

NK Cell–Mediated Antitumor Effects of a Folate-Conjugated Immunoglobulin Are Enhanced by Cytokines
Many tumors express receptors for the vitamin folate (FRs). Folate-conjugated IgG, which can bind both FR+ tumors and NK-cell receptors for IgG, induced potent NK-cell antitumor responses that were further augmented by cytokine therapy.

A Critical Role of miR-144 in Diffuse Large B-cell Lymphoma Proliferation and Invasion
Haiying Wang, AiHong Wang, Zhenbo Hu, Xin Xu, Zhiqiang Liu, and Zhanju Wang
BCL6 supports the growth of DLBCL. Expression of the microRNA miR-144 in DLBCL cells inversely correlated with BCL6 expression. miR-144 inhibited BCL6 expression, affecting DLBCL proliferation and invasiveness. Thus, miR-144 should be considered in approaches to this cancer.
### Table of Contents

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>354</td>
<td>Mutant KRAS Conversion of Conventional T Cells into Regulatory T Cells</td>
<td>Stephanie Zdanov, Magis Mandapatihal, Rasha Abu Eid, Saudat Adamson-Fadeyi, Willie Wilson, Jialhua Qian, Andrea Carnie, Nadya Tarasova, Mikayel Mkrtichyan, Jay A. Berzofsky, Theresa L. Whiteside, and Samir N. Khleif</td>
</tr>
<tr>
<td>366</td>
<td>Prospective Evaluation of Cetuximab-Mediated Antibody-Dependent Cell Cytotoxicity in Metastatic Colorectal Cancer Patients Predicts Treatment Efficacy</td>
<td>Anna Maria Trotta, Alessandro Ottaiano, Carmela Romano, Guglielmo Nasti, Anna Nappi, Chiara De Divitiis, Maria Napolitano, Serena Zanotta, Rossana Casaretti, Crescenzo D’Alterio, Antonio Avallone, Daniela Califano, Rosario Vincenzo Iaffaioli, and Stefania Scala</td>
</tr>
</tbody>
</table>

### Correction

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>375</td>
<td>Correction: Restoration of miR17/20a in Solid Tumor Cells Enhances the Natural Killer Cell Antitumor Activity by Targeting Mekk2</td>
<td>Anna Maria Trotta, Alessandro Ottaiano, Carmela Romano, Guglielmo Nasti, Anna Nappi, Chiara De Divitiis, Maria Napolitano, Serena Zanotta, Rossana Casaretti, Crescenzo D’Alterio, Antonio Avallone, Daniela Califano, Rosario Vincenzo Iaffaioli, and Stefania Scala</td>
</tr>
</tbody>
</table>

### ABOUT THE COVER

Many tumor types express receptors for folate on their surface, providing a potential target for cancer therapy. NK cells can have potent antitumor activity instigated by their Fc receptors, so Jaime-Ramirez and colleagues tested folate-conjugated IgG as an antitumor agent. Folate bound its receptor on tumor cells, and IgG engaged its Fc receptor on NK cells. Human tumor cells were readily killed in vitro and in mouse models. Cover art (left), rendered by Lewis Long, was inspired by this image of a tumor in normal mice (right) compared with tumors in NK-cell-deficient mice. Read more starting on p. 323 of this issue of Cancer Immunology Research.
ABOUT THE MASTER

Ellen Puré, PhD, is the Grace Lansing Lambert Professor of Biomedical Science and Chair of the Department of Biomedical Sciences at the University of Pennsylvania School of Veterinary Medicine, in Philadelphia. Dr. Puré received her baccalaureate degree from Washington University in St. Louis, MO, where she conducted research on the vascular biology of arachidonic acid metabolites in the laboratory of Philip Needleman. She obtained her doctorate at the University of Texas Southwestern Medical School in Dallas. Her dissertation on antigen receptor and T cell–derived cytokine-mediated activation of B lymphocytes was conducted under the auspices of Ellen Vitetta. She trained as a Damon Runyon–Walter Winchell Postdoctoral Fellow and Leukemia Society Special Fellow and then joined the faculty at the Rockefeller University in New York. In 1992 Dr. Puré moved to Philadelphia, where she was on the faculty of the Wistar Institute until moving to the University of Pennsylvania in 2013.

Dr. Puré’s research focuses on the cellular and molecular basis of inflammation and fibrosis. She studies the basic mechanisms involved in these processes and the contribution of these processes to disease, with an emphasis on cancer in preclinical animal models. A major focus of her laboratory’s work is to define the role of stromal cells, extracellular matrix (ECM), and matrix remodeling in cancer initiation, progression, and metastasis; and to develop novel therapeutic approaches that target the stromal compartment of tumors to use in combination with more conventional therapies that target malignant cells and antiangiogenic therapies.

Two pathways of focus in Dr. Puré’s lab are (i) hyaluronan, a prominent provisional and tumor-associated matrix glycosaminoglycan, and the principle hyaluronan receptor, CD44; and (ii) the cell surface serine protease fibroblast activation protein and the role of this protease in remodeling of collagen-rich provisional and tumor-associated matrix. Her lab established that CD44 promotes atherosclerosis, and they have defined multiple mechanisms by which CD44 promotes inflammation by mediating leukocyte recruitment and leukocyte and mesenchymal cell activation and migration. Her group also established that CD44 is required for intratumoral migration of tumor antigen-specific T cells and optimal antitumor immunity.

Dr. Puré and her colleagues defined fibroblast activation protein, FAP, as a marker of stromal cells and a subset of M2-like macrophages associated with active matrix remodeling in settings of chronic inflammation, tissue fibrosis, and virtually all epithelial-derived solid tumors. They demonstrated that, in human breast cancer, FAP+ stromal cells exhibit subtype-specific gene expression profiles consistent with the co-evolution of tumor cells and stromal cells in the tumor microenvironment. Using an adoptive immunotherapy approach to target tumor stromal cells for deletion, her research group has established that FAP+ stromal cells are required for the generation and maintenance of the desmoplastic response that characterizes many solid human tumors. Dr. Puré’s lab established that disrupting tumor-associated matrix by targeting the stromal compartment at either the molecular or cellular level effectively inhibits tumor growth through both immune-dependent and immune-independent mechanisms as a function of tumor immunogenicity and degree of desmoplasia associated with various tumor types. A current focus of her research is to understand what is emerging as a critical role for ECM composition, organization, and biomechanical signaling in tumor initiation, progression and metastasis, chronic inflammation, and fibrosis.

Dr. Puré was a Pew Scholar, an American Heart Established Fellow, the Crawford-Maynard Established Fellow of the American Heart Association, and recipient of a Distinguished Alumnus Award from the University of Texas Southwestern Medical School, an Asthma and Allergy Foundation of America Investigator Award, and the Arthritis Foundation-Stewart J. McCracken Chapter Award for Research. She has trained numerous undergraduates, predoctoral students, postdoctoral fellows, medical students, and clinical fellows.