EDITORIAL

287 Cancer Immunology Essentials: A Preface

MASTERS OF IMMUNOLOGY

288 The Biology and Medical Implications of Interleukin-6

Toshio Tanaka and Tadamitsu Kishimoto

CANCER IMMUNOLOGY AT THE CROSSROADS: EXPERIMENTAL IMMUNOTHERAPIES

295 Oncolytic Viruses and Their Application to Cancer Immunotherapy

E. Antonio Chiocca and Samuel D. Rabkin

CANCER IMMUNOLOGY MINIATURES

301 JAK2 Expression Is Associated with Tumor-Infiltrating Lymphocytes and Improved Breast Cancer Outcomes: Implications for Evaluating JAK2 Inhibitors


Synopsis: Miller and colleagues analyzed annotated breast tumors and evaluated patient data in three public cohorts; they found an inverse association between JAK2 mRNA and risk of recurrence and a correlation between JAK2 expression, improved outcomes, and infiltrating T cells.

RESEARCH ARTICLES

307 Apoptosis-Regulated Low-Avidity Cancer-Specific CD8+ T Cells Can Be Rescued to Eliminate HER2/neu-Expressing Tumors by Costimulatory Agonists in Tolerized Mice

Chelsea M. Black, Todd D. Armstrong, and Elizabeth M. Jaffee

Synopsis: Black and colleagues identify, for the first time, that low-avidity antitumor T cells are ineffective due to increased expression of proapoptotic proteins promoting activation-induced T-cell death, which can be overcome by TNFR agonists, implicating their use in cancer immunotherapy.

320 PD-1 Expression on Peripheral Blood Cells Increases with Stage in Renal Cell Carcinoma Patients and Is Rapidly Reduced after Surgical Tumor Resection


Synopsis: MacFarlane and colleagues show that tumor resection reverses PD-1 expression on peripheral blood (PB) immune cells and suggest that PD-1 blockade for renal cell carcinoma patients with PD-1 expression on PB cells would be most effective prior to surgery, especially in early-stage cancer.

332 Large-Scale Evaluation of Common Variation in Regulatory T Cell–Related Genes and Ovarian Cancer Outcome

Mary Anne Rossing, Georgia Chenevix-Trench, for the AOCS group, ACS, Paul D.P. Pharoah, Simon A. Gayther, Roberta B. Ness, Kunle Odunsi, Lara E. Sucheston, Keith L. Knutson, and Ellen L. Goode

**Synopsis:** Charbonneau and colleagues analyzed the genotypes and outcomes of 10,084 women from Ovarian Cancer Association Consortium studies and identified polymorphisms in regulatory T-cell genes associated with the survival of patients with endometrioid (IL2RA) and clear cell (CTLA4) invasive epithelial ovarian cancer.

**341** Nonclassical Antigen-Processing Pathways Are Required for MHC Class II–Restricted Direct Tumor Recognition by NY-ESO-1–Specific CD4+ T Cells
Junko Matsuzaki, Takemasa Tsuji, Immanuel Luescher, Lloyd J. Old, Protul Shrikant, Sacha Gnjatic, and Kunle Odunsi

**Synopsis:** Matsuzaki, Tsuji, and colleagues show that a unique subset of NY-ESO-1–specific CD4+ T cells directly recognize cancer cells and short 8-9-mer peptides via nonclassical pathways involving proteasomal degradation, transporter-associated antigen processing (TAP)-mediated peptide transport, and endosomal recycling.

**351** MEK Inhibition, Alone or in Combination with BRAF Inhibition, Affects Multiple Functions of Isolated Normal Human Lymphocytes and Dendritic Cells

**Synopsis:** Vella and colleagues show that inhibition of BRAF (dabrafenib) had no effect on healthy donor T cells and monocyte-derived dendritic cells (MoDC), but that MEK inhibition (trametinib) suppressed T-cell proliferation, cytokine production, antigen-specific expansion, and MoDC cross-presentation.

**361** PD-L1 Expression in Triple-Negative Breast Cancer
Elizabeth A. Mittendorf, Anne V. Philips, Funda Meric-Bernstam, Na Qiao, Yun Wu, Susan Harrington, Xiaoping Su, Ying Wang, Ana M. Gonzalez-Angulo, Argun Akcakanat, Akhil Chawla, Michael Curran, Patrick Hwu, Padmanee Sharma, Jennifer K. Litton, Jeffrey J. Mollodrem, and Gheath Alatrash

**Synopsis:** Using tissue microarrays containing 105 triple-negative breast cancer (TNBC) specimens, Mittendorf and colleagues show that 20% of the TNBC specimens express PD-L1, half have lost PTEN, and inhibitors of PI3K pathway decrease PD-L1 expression, providing a rationale for therapeutic targeting of PD-L1 for TNBC.

**371** Tumor Subtype-Specific Cancer–Testis Antigens as Potential Biomarkers and Immunotherapeutic Targets for Cancers
Jun Yao, Otavia L. Caballero, W.K. Alfred Yung, John N. Weinstein, Gregory J. Riggins, Robert L. Strausberg, and Qi Zhao

**Synopsis:** Yao and colleagues surveyed the expression and methylation of CT antigens and clinicopathologic features of ten cancers in The Cancer Genome Atlas RNAseq datasets, identifying multiple tumor subtype-specific CT antigens to be studied as potential biomarkers and targets for immunotherapy.
ABOUT THE MASTER

Tadamitsu Kishimoto, MD, PhD, is an endowed chair professor at the Immunology Research Center of the Osaka University Graduate School of Frontier Biosciences. He is currently Japan’s leading scientist in the life sciences, specifically in immunology. Dr. Kishimoto has made fundamental contributions to our understanding of cytokine functions through a comprehensive and elegant series of studies on interleukin (IL)-6, its transcription regulatory factors, its receptor and signal-transduction system, and their utilization by the IL-6 family of cytokines. He has developed humanized monoclonal antibodies to the IL-6 receptor and treatments for immune disorders, including cancer. Stability of the IL-6 mRNA is controlled by the binding of microRNAs and RNA-binding proteins to the AU-rich elements at the 3’ untranslated region (UTR). The cover image depicts the regulation of IL-6 synthesis during a pathogenic infection. Bacterial lipopolysaccharide (LPS) binds to the cell-surface Toll-like receptor 4 (TLR4), which activates the synthesis of various proteins, including IL-6, Arid5A, and Regnase-1. Nuclease Regnase-1 binds the 3’UTR of the IL-6 mRNA and accelerates its degradation, while the binding of Arid5A counteracts the destabilizing effect of Regnase-1 on IL-6 mRNA specifically. Therefore, the balance between Arid5A and Regnase-1 plays an important role in IL-6 mRNA stability. When Arid5A dominates the balance of Arid5A and Regnase-1, constitutive overproduction of IL-6 occurs through the stimulation of IL-6R. This positive feedback regulation results in the abnormal production of IL-6 and IL-6–dependent autoimmunity and tumorigenesis. For details, see the Masters of Immunology primer by Tanake and Kishimoto on page 288 of this issue.

ABOUT THE COVER

Cytokines are soluble mediators with redundant and pleiotropic activity that aid cell-to-cell communication. IL-6 is a prototypical cytokine, and it contributes to acute-phase host immune response; its synthesis is induced promptly upon tissue damage or inflammation and ceases when homeostasis is restored. The synthesis of IL-6 is tightly regulated transcriptionally and post-transcriptionally, and its dysregulation has been implicated in the development of autoimmune and chronic inflammatory diseases, including cancer. Stability of the IL-6 mRNA is controlled by the binding of microRNAs and RNA-binding proteins to the AU-rich elements at the 3’ untranslated region (UTR). The cover image depicts the regulation of IL-6 synthesis during a pathogenic infection. Bacterial lipopolysaccharide (LPS) binds to the cell-surface Toll-like receptor 4 (TLR4), which activates the synthesis of various proteins, including IL-6, Arid5A, and Regnase-1. Nuclease Regnase-1 binds the 3’UTR of the IL-6 mRNA and accelerates its degradation, while the binding of Arid5A counteracts the destabilizing effect of Regnase-1 on IL-6 mRNA specifically. Therefore, the balance between Arid5A and Regnase-1 plays an important role in IL-6 mRNA stability. When Arid5A dominates the balance of Arid5A and Regnase-1, constitutive overproduction of IL-6 occurs through the stimulation of IL-6R. This positive feedback regulation results in the abnormal production of IL-6 and IL-6–dependent autoimmunity and tumorigenesis. For details, see the Masters of Immunology primer by Tanake and Kishimoto on page 288 of this issue.