Cancer Immunology Research

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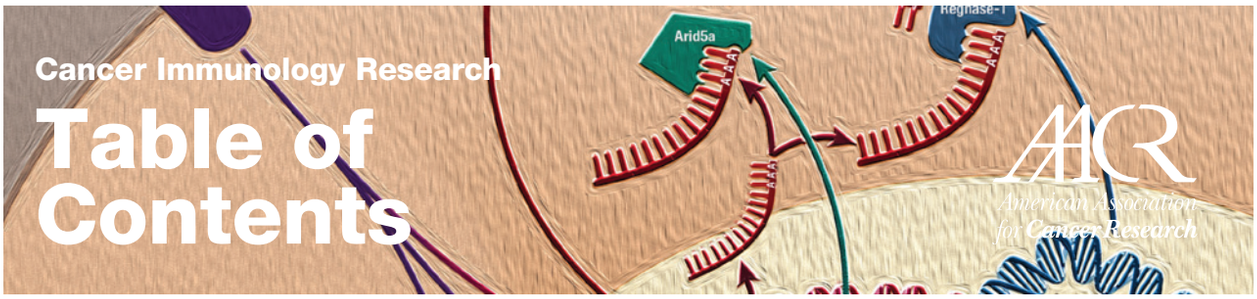

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EDITORIAL

287 **Cancer Immunology Essentials: A Preface**

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288 **The Biology and Medical Implications of Interleukin-6**
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CANCER IMMUNOLOGY AT THE CROSSROADS: EXPERIMENTAL IMMUNOTHERAPIES

295 **Oncolytic Viruses and Their Application to Cancer Immunotherapy**
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CANCER IMMUNOLOGY MINIATURES

301 ***JAK2* Expression Is Associated with Tumor-Infiltrating Lymphocytes and Improved Breast Cancer Outcomes: Implications for Evaluating JAK2 Inhibitors**
Chris P. Miller, Jason D. Thorpe, Amanda N. Kortum, Catherine M. Coy, Wei-Yi Cheng, Tai-Hsien Ou Yang, Dimitris Anastassiou, J. David Beatty, Nicole D. Urban, and C. Anthony Blau
Synopsis: *Miller and colleagues analyzed archived 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**
Alexander W. MacFarlane IV, Mowafaq Jillab, Elizabeth R. Plimack, Gary R. Hudes, Robert G. Uzzo, Samuel Litwin, Essel Dulaimi, Tahseen Al-Saleem, and Kerry S. Campbell
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**
Bridget Charbonneau, Kirsten B. Moysich, Kimberly R. Kalli, Ann L. Oberg, Robert A. Vierkant, Zachary C. Fogarty, Matthew S. Block, Matthew J. Maurer, Krista M. Goergen, Brooke L. Fridley, Julie M. Cunningham, David N. Rider, Claudia Preston, Lynn C. Hartmann, Kate Lawrenson, Chen Wang, Jonathan Tyrer, Honglin Song, Anna deFazio, Sharon E. Johnatty, Jennifer A. Doherty, Catherine M. Phelan, Thomas A. Sellers, Starr M. Ramirez, Allison F. Vitonis, Kathryn L. Terry, David Van Den Berg, Malcolm C. Pike, Anna H. Wu, Andrew Berchuck, Aleksandra Gentry-Maharaj, Susan J. Ramus, Brenda Diergaarde, Howard Shen, Allan Jensen, Janusz Menkiszak, Cezary Cybulski, Jan Lubiński, Argyrios Ziogas, Joseph H. Rothstein, Valerie McGuire, Weiva Sieh, Jenny Lester, Christine Walsh, Ignace Vergote, Sandrina Lambrechts, Evelyn Despierre, Montserrat Garcia-Closas, Hannah Yang, Louise A. Brinton, Beata Spiewankiewicz, Iwona K. Rzepecka, Agnieszka Dansonka-Mieszkowska, Petra Seibold, Anja Rudolph, Lisa E. Paddock, Irene Orlow, Lene Lundvall, Sara H. Olson, Claus K. Hogdall, Ira Schwaab, Andreas du Bois, Philipp Harter, James M. Flanagan, Robert Brown, James Paul, Arif B. Ekici, Matthias W. Beckmann, Alexander Hein, Diana Eccles, Galina Lurie, Laura E. Hays, Yukie T. Bean, Tanja Pejovic, Marc T. Goodman, Ian Campbell, Peter A. Fasching, Gottfried Konecny, Stanley B. Kaye, Florian Heitz, Estrid Hogdall, Elisa V. Bandera, Jenny Chang-Claude, Jolanta Kupryjanczyk, Nicolas Wentzensen, Diether Lambrechts, Beth Y. Karlan, Alice S. Whittemore, Hoda Anton Culver, Jacek Gronwald, Douglas A. Levine, Susanne K. Kjaer, Usha Menon, Joellen M. Schildkraut, Celeste Leigh Pearce, Daniel W. Cramer,

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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**

Laura J. Vella, Anupama Pasam, Nektaria Dimopoulos, Miles Andrews, Ashley Knights, Anne-Laure Puaux, Jamila Louahed, Weisan Chen, Katherine Woods, and Jonathan S. Cebon

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. Molldrem, 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.*

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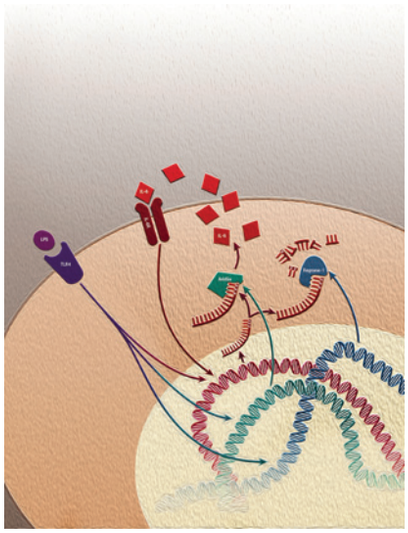
ABOUT THE COVER



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.

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 Castleman disease, rheumatoid arthritis, and juvenile idiopathic arthritis.

Dr. Kishimoto was born in Osaka, Japan, in 1939 and was named an honorary citizen of Tondabayashi City in the Osaka Prefecture in 1992. He received an MD (1964) and a PhD in medicine (1969) from Osaka University. During this period, inspired by Dr. Yuichi Yamamura's work on immunology and medicine, Dr. Kishimoto purified and characterized the structure of human IgM from a patient with Waldenstrom macroglobulinemia. He was a research fellow in Dr. Kimishige Ishizaka's laboratory at the Johns Hopkins University, where he studied the regulation of antibody response in an *in vitro* rabbit lymphocyte system and demonstrated the presence of soluble factors in primed rabbit lymphocytes that enhance antibody production. He showed that the activity inducing the different classes of antibodies is distinct. Dr. Kishimoto returned to his alma mater as a professor and chair of the Department of Medicine, where he discovered and cloned the genes encoding IL-6 and its receptor and delineated the signaling pathway used by the IL-6 family of cytokines. He became the dean of faculty of Osaka University Medical School in 1995. Dr. Kishimoto was the president of Osaka University from 1997 to 2003 and a cabinet member of the Council for Science and Technology Policy Office from 2004 to 2006.

Dr. Kishimoto has received numerous awards, which include the Imperial Prize of the Japan Academy, the Sandoz Prize for Immunology from the International Union of Immunological Society, the Avery-Landsteiner Prize from the German Immunology Society, the Robert Koch Gold Medal, the Crafoord Award from the Royal Swedish Academy of Sciences, and the Japan Prize. He was elected as a Foreign Associate member of both the Institute of Medicine and the U.S. National Academy of Sciences. He is also a member of the Japan Academy and the Deutsche Akademie der Naturforscher Leopoldina and an honorary member of the American Association of Immunologists and the American Society of Hematology. In 1998, Dr. Kishimoto was awarded the Order of Culture from the Emperor of Japan.

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