WHAT WE’RE READING

853  A Sampling of Highlights from the Literature

CANCER IMMUNOLOGY AT THE CROSSROADS

854  Pulling RANK on Cancer: Blocking Aire-Mediated Central Tolerance to Enhance Immunotherapy
Maureen A. Su and Mark S. Anderson

CANCER IMMUNOLOGY MINIATURES

860  IL17A Blockade Successfully Treated Psoriasiform Dermatologic Toxicity from Immunotherapy
Daniel Johnson, Anisha B. Patel, Marc I. Uemura, Van A. Trinh, Natalie Jackson, Chrystia M. Zobniw, Michael T. Tetzlaff, Patrick Hvo, Jonathan L. Curry, and Adi Diab
Patients with skin lesions as a result of immune checkpoint inhibitor therapy are usually treated with corticosteroids. A patient with severe psoriasiform dermatologic toxicity was treated with anti-IL17A instead, which cleared the skin without altering response to pembrolizumab.

866  Phenotypic and Genomic Determinants of Immunotherapy Response Associated with Squamousness
Aaron M. Goodman, Shumei Kato, Ranajoy Chattopadhyay, Byoung Seok Kim, Meagan Montesion, Garrett M. Frampton, Vincent A. Miller, Gregory A. Daniels, and Razelle Kurzrock
Tumor mutational burden (TMB) differs between squamous cell carcinomas (SCCs) and non-SCCs. Amongst SCC subtypes, cutaneous disease has the highest TMB, and both high TMB and cutaneous histology correlate with better outcome in patients after immune checkpoint blockade.

RESEARCH ARTICLES

874  IL1R8 Deficiency Drives Autoimmunity-Associated Lymphoma Development
Federica Riva, Maurilio Ponzoni, Domenico Supino, Maria Teresa Sabrina Bertilaccio, Nadia Polentarutti, Matteo Massara, Fabio Pasqualini, Roberta Carriero, Anna Innocenzi, Achille Anselmo, Tania Veliz-Rodriguez, Giorgia Simonetti, Hans-Joachim Anders, Federico Caligaris-Cappio, Alberto Mantovani, Marta Muzio, and Cecilia Garlanda
Silencing of the regulatory receptor IL1R8 in mice is associated with increased lymphoproliferation in autoimmunity-associated B-cell lymphoma. IL1R8 expression correlates with survival in human diffuse large B-cell lymphoma, suggesting that targeting IL1R8 may present an avenue for future therapies.

886  Programmed Cell Death Ligand-1 (PD-L1) and CD8 Expression Profiling Identify an Immunologic Subtype of Pancreatic Ductal Adenocarcinomas with Favorable Survival
Ludmila Darilova, Won Jin Ho, Qingfeng Zhu, Teena Vithayathil, Ana De Jesus-Acosta, Nilofor S. Azad, Daniel A. Laheru, Elana J. Fertig, Robert Anders, Elizabeth M. Jaffee, and Mark Yarchoan
Two independent cohorts of patients with pancreatic ductal adenocarcinoma (PDAC) were evaluated and a subset of patients with favorable prognosis was identified. These results highlight that in PDAC, the antitumor response is a feature of long-term survival.

896  Function of Human Tumor-Infiltrating Lymphocytes in Early-Stage Non–Small Cell Lung Cancer
Shaun M. O’Brien, Astero Klampatsa, Jeffrey C. Thompson, Marina C. Martinez, Wei-Ting Hwang, Abishek S. Rao, Mark Yarchoan
CD103+ tissue-resident memory (Treg+) T cells are key for antitumor activity in non-small cell lung cancer and are negatively influenced by eomesoderin (Eomes). TIL function may be driven by competition between an antitumor Treg+ program and an Eomes-associated exhaustion program.
910  Endogenous CD4⁺ T Cells Recognize Neoantigens in Lung Cancer Patients, Including Recurrent Oncogenic KRAS and ERBB2 (Her2) Driver Mutations
   It is demonstrated that patients with non-small cell lung cancer commonly have CD4⁺ T-cell responses to neoantigens. These T cells show reactivity to recurrent driver mutations, identifying a potential role for CD4⁺ T cells in immunotherapies.

923  The Tumor Immune Microenvironment Drives a Prognostic Relevance That Correlates with Bladder Cancer Subtypes
   Carolin Pfannstiel, Pamela L. Strissel; on behalf of the BRIDGE Consortium, Germany, Katherine B. Chiappinelli, Danijel Sikic, Sven Wach, Ralph M. Wirtz; on behalf of the BRIDGE Consortium, Germany, Adrian Wulffweber, Helge Taubert, Johannes Breyer, Wolfgang Otto, Thomas Worst, Maximilian Burger, Bernd Wallich, Christian Bollenz; on behalf of the BRIDGE Consortium, Germany, Nicole Fuhrich, Carol I. Geppert, Veronika Weyerer, Robert Stoehr, Simone Bertz, Bastian Keck, Franziska Erlmeier, Philipp Erben, Arndt Hartmann, Reiner Strick, and Markus Eckstein; on behalf of the BRIDGE Consortium, Germany
   Analysis of 542 patients with muscle-invasive bladder cancer shows that spatial organization of immune cells with specific phenotypes correlates with tumor mutational burden and tumor subtypes. These data could predict favorable outcome following cystectomy and adjuvant chemotherapy.

939  CD28 Homolog Is a Strong Activator of Natural Killer Cells for Lysis of B7H7⁺ Tumor Cells
   Xiaoxuan Zhuang and Eric O. Long
   NK cells express CD28H, a CD28 homolog, which enhances cytotoxicity against tumor cells expressing its ligand B7H7. Expression of a CD28H chimeric antigen receptor overrides inhibition by HLA class I receptors and shows promise as immunotherapy.

952  NKT Cell–Driven Enhancement of Antitumor Immunity Induced by Clec9a-Targeted Tailorable Nanoemulsion
   Pui Yeng Lam, Takumi Kobayashi, Megan Soon, Bijuun Zeng, Riccardo Dolcetti, Graham Leggatt, Ranjery Thomas, and Stephen R. Mattarollo
   Antigen and α-galactosylceramide encapsulated in a nanoemulsion improved the function of NKT and dendritic cells, which drove cross-priming of antigen-specific CD8⁺ T cells. Long-term control of solid tumors resulted from a single dose of the emulsion.

963  Coexpression of Inhibitory Receptors Enriches for Activated and Functional CD8⁺ T Cells in Murine Syngeneic Tumor Models
   Huizhong Xiong, Stephanie Mittman, Ryan Rodriguez, Patricia Pacheco-Sanchez, Martina Moskalenko, Yagai Yang, Justin Elstrott, Alex T. Ritter, Sören Müller, Dorothee Nickles, Teresita L. Arenzana, Aude-Hélène Capietto, Lélia Delamarre, Zora Modrusan, Sascha Rutz, Ira Mellman, and Rafael Cubas
   Inhibitory receptor coexpression is thought to serve as a proxy for exhausted T cells, but can define activated T cells responsive to checkpoint blockade. Cells coexpressing inhibitory receptors may thus be responsive to treatment in the clinic.

977  Differential Effects of Depleting versus Programming Tumor-Associated Macrophages on Engineered T Cells in Pancreatic Ductal Adenocarcinoma
   Csf1R blockade in a model of pancreatic ductal adenocarcinoma negatively impacted the function of infused engineered T cells. Addition of a CD40 agonist increased the persistence of the infused T cells but ultimately, did not rescue their function.

990  Farnesoid X Receptor Constructs an Immunosuppressive Microenvironment and Sensitizes FXR⁺PD-L1⁻ NSCLC to Anti–PD-1 Immunotherapy
   Wenjie You, LiJun Li, Deqiao Sun, Xueqing Liu, Zongjun Xia, Shan Xue, Bi Chen, Hui Qin, Jing Ai, and Handong Jiang
   A subtype of non-small cell lung cancer is characterized by immunosuppression through the farnesoid X receptor (FXR) and responsiveness to anti–PD-1 therapy. The combination of high FXR expression and low PD-L1 expression may identify patients receptive to anti–PD-1 immunotherapy.

1001  Tumor-Derived α-Fetoprotein Suppresses Fatty Acid Metabolism and Oxidative Phosphorylation in Dendritic Cells
   Patricia M. Santos, Ashley V. Menk, Jian Shi, Allan Tsung, Greg M. Delgoffe, and Lisa H. Butterfield
   AFP secreted by hepatocellular cancer cells inhibits fatty acid synthesis and oxidative phosphorylation in dendritic cells. These effects on mitochondrial metabolism are mediated through mTORC1, SREBP-1, and PGC1α, resulting in immunosuppression.
MicroRNA-155 Expression Is Enhanced by T-cell Receptor Stimulation Strength and Correlates with Improved Tumor Control in Melanoma

Amaia Martinez-Usatorre, Lorenzo F. Sempere, Santiago J. Carmona, Laura Carretero-Iglesia, Gwennaelle Monnot, Daniel E. Speiser, Nathalie Rufer, Alena Donda, Dietmar Zehn, Camilla Jandus, and Pedro Romero

T-cell receptor stimulation strength dictates microRNA-155 expression in CD8^+ T cells. High miR-155 levels and downregulation of its targets correlate with tumor control in melanoma, suggesting their utility as a CD8^+ T-cell responsiveness biomarker.

Poor Response to Neoadjuvant Chemotherapy Correlates with Mast Cell Infiltration in Inflammatory Breast Cancer


Mast cell infiltration and density correlate with poor clinical outcomes and responses to therapy in patients with inflammatory breast cancer. These cells may be contributing to an immunosuppressive microenvironment and could be targeted to improve therapeutic responses.

ABOUT THE COVER

Development of B-cell lymphoma is associated with chronic inflammation, and autoimmune disease can be a driver of such inflammation. The inhibitory IL1R family member, IL1R8, modulates inflammatory responses. Riva et al. show that a deficiency of IL1R8 in autoimmune-prone mice, that leads to exacerbated autoimmune disease and inflammation, results in B-cell transformation and the development of diffuse large B-cell lymphoma (DLBCL). IL1R8 inhibits MyD88–NF-κB activation, and thus, IL1R8 deficiency led to constitutive signaling of this pathway in splenic B cells, resulting in their uncontrolled expansion. In human DLBCL, IL1R8 expression is downregulated. Higher IL1R8 expression is associated with better outcomes in patients with DLBCL. This study highlights the intersection of cancer and autoimmunity and illustrates how inflammation caused by IL1R8 deficiency can drive the malignant transformation of B cells. Read more in this issue on page 874. Original image from Fig. 3C. Artwork by Lewis Long.