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

866  Phenotypic and Genomic Determinants of Immunotherapy Response Associated with Squamousness
Aaron M. Goodman, Shumei Kato, Ranajoy Chattopadhyay, Ryoosuke Okamura, Ila M. Saunders, Meagan Montesion, Garrett M. Frampton, Vincent A. Miller, Gregory A. Daniels, and Razelle Kurzrock

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

886  Programmed Cell Death Ligand-1 (PD-L1) and CD8 Expression Profiling Identify an Immunologic Subtype of Pancreatic Ductal Adenocarcinomas with Favorable Survival
Ludmila Danilova, Won Jin Ho, Qingfeng Zhu, Teena Vithayathil, Ana De Jesus-Acosta, Nilofer S. Azad, Daniel A. Laheru, Elana J. Fertig, Robert Anders, Elizabeth M. Jaffe, and Mark Yarchoan

896  Function of Human Tumor-Infiltrating Lymphocytes in Early-Stage Non–Small Cell Lung Cancer

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.

CD103+ tissue-resident memory (T EM) 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 T EM program and an Eomes-associated exhaustion program.
NKT Cell

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.

NKT Cell–Driven Enhancement of Antitumor Immunity Induced by Clec9a-Targeted Tailorable Nanoemulsion
Pui Yeng Lam, Takumi Kobayashi, Megan Soon, Bijun Zeng, Riccardo Doletti, 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.

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 expressing inhibitory receptors may thus be responsive to treatment in the clinic.

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.

The Tumor Immune Microenvironment Drives a Prognostic Relevance That Correlates with Bladder Cancer Subtypes
Carolin Pfannstiel, Pamela I. 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 Wulhuber, Helge Taubert, Johannes Breyer, Wolfgang Otto, Thomas Worst, Maximilian Burger, Bernd Wallich, Christian Boleza; 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.

Immunosuppressive Microenvironment and Sensitizes FXRhighPD-L1low NSCLC to Anti–PD-1 Immunotherapy
Wenjie You, Lijun Li, Deqiao Sun, Xuejing 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-1 expression may identify patients receptive to anti–PD-1 immunotherapy.

Farnesoid X Receptor Constructs an Immunosuppressive Microenvironment and Sensitizes FXRhighPD-L1low NSCLC to Anti–PD-1 Immunotherapy
Wenjie You, Lijun Li, Deqiao Sun, Xuejing 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-1 expression may identify patients receptive to anti–PD-1 immunotherapy.

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, Gwennaëlle 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.
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