WHAT WE'RE READING

695  A Sampling of Highlights from the Literature

CANCER IMMUNOLOGY AT THE CROSSROADS

696  The Highs and Lows of Immune-Checkpoint Blockade in Lymphoma
Stephen M. Ansell

CANCER IMMUNOLOGY MINIATURE

701  Responsiveness to PD-1 Blockade in End-Stage Colon Cancer with Gene Locus 9p24.1 Copy-Number Gain

Most patients with metastasis of large bowel cancer do not benefit from immune therapy. This case study shows that a rare gene mutation, termed 9p24.1 copy-number gain, in this otherwise incurable tumor provoked a response to immune therapy.

RESEARCH ARTICLES

707  Siglec-9 Regulates an Effector Memory CD8\(^+\) T-cell Subset That Congregates in the Melanoma Tumor Microenvironment

The lectin Siglec-9 can regulate TCR signaling and effector function of human cytotoxic CD8\(^+\) T cells. Siglec-9 expression defines a subset of effector memory CD8\(^+\) T cells that is prevalent in melanoma tissues.

719  Performance Evaluation of MHC Class-I Binding Prediction Tools Based on an Experimentally Validated MHC–Peptide Binding Data Set
Maria Bonsack, Stephanie Hoppe, Jan Winter, Diana Tichy, Christine Zeller, Marius D. Küpper, Eva C. Schitter, Renata Blatnik, and Angelika B. Riemer

Evaluation of MHC class-I binding predictors based on experimentally validated binders revealed that individual thresholds are needed for different HLA types and peptide lengths to optimize sensitivity and increase the number of epitopes as potential targets for immunotherapy.

737  Tumor Microenvironment Characterization in Gastric Cancer Identifies Prognostic and Immunotherapeutically Relevant Gene Signatures
Dongqiang Zeng, Meiyi Li, Rui Zhou, Jingwen Zhang, Huiying Sun, Min Shi, Jianping Bin, Yulin Liao, Jinjun Rao, and Wangjun Liao

Gastric cancer TME infiltration patterns were determined and systematically correlated with TME cell phenotypes, genomic traits, and patient clinicopathological features to establish the "TME score." This score was a prognostic and predictive factor for immune checkpoint blockade response.

751  Combined Low Densities of FoxP3\(^+\) and CD3\(^+\) Tumor-Infiltrating Lymphocytes Identify Stage II Colorectal Cancer at High Risk of Progression
Tommaso Cavalleri, Paolo Bianchi, Gianluca Baso, Giuseppe Celesti, Fabio Grizzi, Paola Rossi, Luana Greco, Calogero Pitroone, Emanuele Valtorta, Gianluca Mauri, Mauro Truini, Filippo Gustavo Dall’Olio, Giovanni Brandi, Andrea Sartore-Bianchi, Luigi Ricciardiello, Valter Torri, Lorenza Rimassa, Salvatore Siena, Alberto Mantovani, Alberto Malesci, and Luigi Laghi, on behalf of Alleanza contro il Cancro (AICC) Colorectal Cancer Working Group

For nonmetastatic colorectal cancer, FoxP3\(^+\) and CD3\(^+\) T-cell densities have prognostic value up to stage III is reached. Loss of prognostic value at that point indicates that various T-cell subsets are differentially influential as the cancer progresses.

759  IL15 Enhances CAR-T Cell Antitumor Activity by Reducing mTORC1 Activity and Preserving Their Stem Cell Memory Phenotype

IL15 promotes metabolically fit CAR-T cells with a less-differentiated stem cell memory phenotype. Addition of IL15 is a clinically translatable method for improving the antitumor function of ex vivo expanded CAR-T cells, which could improve outcomes for patients.

773  Cancer Immunotherapy with T Cells Carrying Bispecific Receptors That Mimic Antibodies
Sarah Ahn, Jingjing Li, Chuang Sun, Keliang Gao, Koichi Hirabayashi, Hongxia Li, Barbara Savoldo, Ribe Liu, and Gianpietro Doti

CAR T-cell antitumor therapy fails when the tumor loses expression of the chosen epitope. Receptors that mimic antibodies and that recognize two epitopes may reduce the chances for tumor cells to escape immune surveillance.
A Transcriptionally Distinct CXCL13⁺ CD103⁺ CD8⁺ T-cell Population Is Associated with B-cell Recruitment and Neoantigen Load in Human Cancer

Hagma H. Wokel, Joyce M. Lubbers, Roland Arnold, Thalina M. Prins, Pieter van der Vlies, Kim de Lange, Tjalling Bosse, Inge C. van Gool, Florine A. Eggink, Maartje C.A. Wouters, Fenne L. Komdeur, Elisabeth C. van der Slikke, Carien L. Creutzberg, Arjan Kol, Annechien Plat, Mark Claire, David N. Church, Hans W. Nijman, and Marco de Bruyn

TGFβ stimulation of activated CD8⁺ T cells from cancer patients induces upregulation of CD103 and CXCL13, which is important for tertiary lymphoid structure formation. The data highlight a role for TGFβ in coordinating immune responses against tumors.

T Cells Specific for an Unconventional Natural Antigen Fail to Recognize Leukemic Cells

Margot J. Pont, Rimke Oostvogels, Cornelis A.M. van Bergen, Edith D. van der Meiijden, Maria W. Honders, Sophie Bliss, Marlieke L.M. Jongema, Henk M. Lokhorst, J H. Frederik Falkenburg, Tuna Mutis, Marieke Grifftioen, and Robbert M. Spaapen

MHC-bound peptides derived from aberrant proteins may be an immunotherapeutic target on cancer cells. However, T cells recognizing such an antigen failed to react against leukemic cells. Thus, concern is warranted for immunotherapies targeting such antigens.

Multiple Immune-Suppressive Mechanisms in Fibrolamellar Carcinoma

Amy K. Kim, Faiz Gani, Andrew J. Layman, Sepideh Besharati, Qingfeng Zhu, Farah Succaria, Elizabeth L. Engle, Fertyl Bhaijee, Maria B. Goggins, Nicolas J. Llosa, Timothy M. Pawlik, Marios B. Goggins, Elizabeth L. Engle, Sarah L. Johnson, and Robert A. Anders

The expression of immune checkpoint molecules PD-1, PD-L1, B7-H1, and IDO in fibrolamellar carcinoma (FLC) is related to CD8⁺ T-cell density. These checkpoints are clinically targetable with inhibitors. Thus, using immune checkpoint blockade may be efficacious in FLC.

The Pseudogene Olfr29-ps1 Promotes the Suppressive Function and Differentiation of Monocytic MDSCs

Wencong Shang, Yunhuan Gao, Zhenzhen Tang, Yuan Zhang, and Rongguang Yang

A conserved long noncoding RNA (IncRNA), pseudogene Olfr29-ps1, was identified and shown to be induced under inflammatory conditions and in melanomas. Olfr29-ps1 can regulate the immunosuppressive function and differentiation of monocytic MDSCs both in vitro and in vivo.

Suboptimal T-cell Therapy Drives a Tumor Cell Mutator Phenotype That Promotes Escape from First-Line Treatment

Laura Evgin, Amanda L. Huff, Timothy Kottke, Jill Thompson, Amy M. Molan, Christopher B. Driscoll, Matthew Schuinkel, Kevin G. Shin, Phonphimon Wonghilda, Elizabeth J. Ilett, Karen Kaloza Smith, Reuben S. Harris, Matt Coffey, Jose S. Pulido, Hardev Pandha, Peter J. Selby, Kevin J. Harrington, Alan Meicher, and Richard G. Vile

Suboptimal antitumor immunotherapy increases genomic instability in tumor cells by inducing APOBEC3. Resulting mutations can promote tumor cell escape from co-applied therapies. Immunotherapies should be optimized early to prevent a direct enhancement of tumor cell escape.

Accumulation of Circulating CCR7⁺ Natural Killer Cells Marks Melanoma Evolution and Reveals a CCL19-Dependent Metastatic Pathway

Costanza Maria Cristiani, Alice Turdo, Valeria Ventura, Tiziana Apuzzo, Mariaelena Capone, Gabriele Madonna, Domenico Mallardo, Silvia Pesce, Genny Del Zotto, Valter Agosti, Francesco Saverio Costanzo, Elio Gulletta, Aroldo Rizzo, Alessandro Moretta, Francesca C. Costanzo, Klas Karre, Paolo A. Ascienzo, Robert A. Anders, and Ennio Carbone

CCR7⁺ NK cells and CCL19 increased as melanoma progressed. Melanoma-derived cancer stem cells overexpressed CCR7 and were efficiently recognized and killed by NK cells. CCR7 may be a biomarker for metastatic melanoma.
Altered tumor glycosylation is now appreciated to have an immunosuppressive role, whereby immune responses can be downregulated via activity of Siglecs, cell surface proteins that bind sialic acid–containing glycans. Although Siglecs are expressed on some immune cells, T cells rarely express them. Haas et al. report that in melanoma, the majority of tumor-infiltrating, but not circulating, CD8$^+$ T cells express Siglec-9. This subset of Siglec-9$^+$ T cells is highly cytotoxic and proliferative. However, engagement of siglec-9 inhibits the effector functions of the Siglec-9–expressing CD8$^+$ T cells, due to dephosphorylation of the TCR pathway molecules by the SHP-1 phosphatase, which dampens TCR signaling. The majority of primary and metastatic melanoma cells express Siglec-9 ligands. Thus, Siglec-9 receptor-ligand interactions are a glycosylation-dependent inhibitory circuit that suppresses immune responses in the tumor microenvironment. These data suggest that blocking this interaction may enhance antitumor responses, while also confining CD8$^+$ T-cell activation to the tumor microenvironment. Read more in this issue on page 707. Original image from Fig. 2A. Artwork by Lewis Long.
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