WHAT WE'RE READING

1335  A Sampling of Highlights from the Literature

EDITORIAL

1336  Building on Success
Robert D. Schreiber and Philip D. Greenberg

CANCER IMMUNOLOGY AT THE CROSSROADS

1338  Insights into Tumor-Associated Tertiary Lymphoid Structures: Novel Targets for Antitumor Immunity and Cancer Immunotherapy
Anthony B. Rodriguez and Victor H. Engelhard

CANCER IMMUNOLOGY MINIATURES

1346  Tumor Mutation Burden and Structural Chromosomal Aberrations Are Not Associated with T-cell Density or Patient Survival in Acral, Mucosal, and Cutaneous Melanomas

Analysis shows that TMB does not correlate with tumor immune infiltrates, including tumor-resident CD8\(^+\) T cells, in acral, mucosal, and cutaneous melanomas. The data indicate that TMB is not a significant driver of antitumor responses.

RESEARCH ARTICLES

1365  Melanoma Evolves Complete Immunotherapy Resistance through the Acquisition of a Hypermetabolic Phenotype

Under immune pressure from T-cell checkpoint blockade, melanoma evolves a hypermetabolic phenotype conferring complete immunotherapy resistance. Key genes driving enhanced glycolysis and oxidative phosphorylation confer resistance when transferred to the parental melanoma or to a pancreatic cancer.

1381  A DNA-Launched Nanoparticle Vaccine Elicits CD8\(^+\) T-cell Immunity to Promote In Vivo Tumor Control

DNA nanoparticle vaccination plus electroporation robustly induces CD8\(^+\) CTL responses that are able to control, or protect from, melanoma growth in mice. The data demonstrate the utility of this platform and offer a strategy to boost antitumor responses.

1393  Tumor Derives IL33 Promotes Tissue-Resident CD8\(^+\) T Cells and Is Required for Checkpoint Blockade Tumor Immunotherapy
Lujun Chen, Runzi Sun, Junchi Xu, Wensi Zhai, Dachuan Zhang, Min Yang, Cuihua Yue, Yichao Chen, Song Li, Heth Turnquist, Jingting Jiang, and Binfeng Lu

Tumor-derived IL33 mediated ICB efficacy by inducing the accumulation of tumor-resident CD103\(^+\)CD8\(^+\) T cells and CD103\(^+\) dendritic cells.

1388  Tumor-Infiltrating Regulatory T-cell Accumulation in the Tumor Microenvironment Is Mediated by IL33/ST2 Signaling

Tumor infiltrating regulatory T cells (Tregs) suppress antitumor immunity, yet the mechanism for how they accumulate in tumors is unclear. IL33 mediated ICB efficacy by inducing the accumulation of tumor-resident CD103\(^+\)CD8\(^+\) T cells and CD103\(^+\) dendritic cells.
### Glycans as Immune Checkpoints: Removal of Branched N-glycans Enhances Immune Recognition Preventing Cancer Progression

Mariana C. Silva, Angela Fernandes, Maria Oliveira, Carlos Resende, Alexandra Correia, Julio C. de-Feiters-Junior, Aonghus Lavelle, Jéssica Andrade-da-Costa, Magdalena Leander, Helena Xavier-Ferreira, José Bessa, Carina Pereira, Rui M. Henriques, Fátima Carneiro, Márcia Dinis-Ribeiro, Ricardo Marcos-Pinto, Margarida Lima, Bernd Lepenies, Harry Sokol, José C. Machado, Manuel Vilanova, and Salomé S. Pinho

Complex branched N-glycans are identified as glyco-immune checkpoints that are used by colorectal cancer cells to evade immune recognition. The data highlight how inhibiting this glycosylation could be a strategy to improve antitumor responses.

### Blocking P2X7-Mediated Macrophage Polarization Overcomes Treatment Resistance in Lung Cancer

Juliang Qin, Xiaoyu Zhang, Binghe Tan, Su Zhang, Chengcong Yin, Qi Xue, Zhen Zhang, Hua Ren, Jinlian Chen, Mingyao Liu, Min Qian, and Bing Du

P2X7 is expressed in tumor-associated macrophages (TAM), yet its role in lung cancer progression is unknown. Blockade of P2X7 induces antitumor TAMs and rescues the efficacy of anti–PD-1 and chemotherapy against lung cancer.

### Lactate-Modulated Immunosuppression of Myeloid-Derived Suppressor Cells Contributes to the Radioresistance of Pancreatic Cancer

Xuguang Yang, Yun Lu, Junjie Hang, Junfeng Zhang, Tiening Zhang, Yammiao Huo, Jun Liu, Songtao Lai, Dawei Luo, Liwei Wang, Rong Hua, and Yuli Lin

Pancreatic cancer tends to be radioresistant, but the immune-mediated mechanisms behind this resistance are unclear. Lactate secretion from pancreatic tumor cells leads to immune-suppressive MDSCs via HIF-1α signaling in MDSCs, limiting radiotherapy efficacy in pancreatic cancer.

### Infiltration by IL22-Producing T Cells Promotes Neutrophil Recruitment and Predicts Favorable Clinical Outcome in Human Colorectal Cancer

Nadia Tosti, Eleonora Cremonesi, Valeria Governa, Camilla Basso, Venkatesh Kancherla, Mairene Coto-Llerena, Francesca Amicarella, Benjamin Weixler, Silvio Daster, Giuseppe Sconocchia, Pietro Edoardo Majorino, Dimitri Christoforidis, Luigi Tornillo, Luigi Terracciano, Charlotte K.Y. Ng, Salvatore Piscuoglio, Markus von Flië, Giulio Spagnoli, Serenella Eppenberger-Castori, Giandomenica Iezzi, and Raoul Andre Droeser

IL22-producing immune cells are involved in inflammatory gut diseases, yet their role in colorectal cancer (CRC) remains unclear. IL22-secreting T cells recruit neutrophils to CRC tumors, leading to enhanced patient survival.

### ABOUT THE COVER

Although immune checkpoint blockade (ICB) has shown success in prolonging the survival of patients with cancer, the mechanisms behind this are not fully elucidated. Chen et al. find that tumor-derived IL33, whose expression increases after ICB treatment, and ST2 signaling in nontumor cells are key to inducing antitumor responses. IL33 increases functional CD103+CD8+ T cells and CD103+ dendritic cells (DC) in the tumor microenvironment (TME), and the CD103+ DCs are essential for the recruitment of tumor-infiltrating CD8+ T cells into the TME. By treating tumor-bearing mice with IL33 in combination with dual ICB, survival was extended, highlighting the important role of IL33 in mediating the efficacy of ICB. Read more in this issue on page 1381. Original image from Fig. 4F. Artwork by Lewis Long.