A Sampling of Highlights from the Literature

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Lessons Learned from Checkpoint Blockade Targeting PD-1 in Multiple Myeloma
Alexander M. Lesokhin, Susan Bai, and Ashraf Z. Badros

Intrinsic Resistance to Immune Checkpoint Blockade in a Mismatch Repair–Deficient Colorectal Cancer

This case of PD-1 blockade resistance, despite microsatellite instability-high (MSI-H) molecular features, suggests that other biomarkers should be considered. Loss of β2-microglobulin expression and infiltration of NK cells and M2 macrophages may be informative in therapy selection.

Systemic Interferon-γ Increases MHC Class I Expression and T-cell Infiltration in Cold Tumors: Results of a Phase 0 Clinical Trial
Shihong Zhang, Karan Kohli, R. Graeme Black, Lu Yao, Syed M. Spadinger, Qianchuan He, Venu G. Pillarisetty, Lee D. Cranmer, Brian A. Van Tine, Cassian Yee, Robert H. Pierce, Stanley R. Riddell, Robin L. Jones, and Seth M. Pollack

Interferon-γ, an FDA approved drug, can drive inflammation of non-inflamed cancers, potentially facilitating immunotherapy with PD-1 inhibitors. A multicenter trial sponsored by the Cancer Immunotherapy Trials Network is based on these results.

Disrupting LILRB4/APOE Interaction by an Efficacious Humanized Antibody Reverses T-cell Suppression and Blocks AML Development
Xun Gu, Mi Deng, Hao Song, Yuanzhi Chen, Jingjing Xie, Zanling Li, Lici He, Fangfang Huang, Yixiang Xu, Yasuaki Anami, Hai Yu, Chenyi Yu, Leike Li, Zihao Yuan, Xiaoqing Xu, Qihui Wang, Yan Chai, Tao Huang, Yi Shi, Kyoji Tsukihama, X. Charlene Liao, Ningshao Xia, George F. Gao, Ningyuan Zhang, Cheng Cheng Zhang, and Zhiqiang An

When LILRB4 on acute myeloid leukemia cells (AML) binds to its ligand APOE, T-cell activation is suppressed. A humanized mAb to LILRB4 blocks LILRB4/APOE interaction and, through multiple modes of action, blocks AML development in mouse models.

IRF1 Inhibits Antitumor Immunity through the Upregulation of PD-L1 in the Tumor Cell

IFN signaling can mediate antitumor responses, with transcription factor IRF1 involved in tumor suppression. Tumor cell–expressed IRF1 was found to upregulate PD-L1, aiding tumor escape. Thus, tumor cell-specific targeting of IRF1 may be important in immunotherapy.

An Improved Patient-Derived Xenograft Humanized Mouse Model for Evaluation of Lung Cancer Immune Responses
Ismail M. Meraz, Mourad Majidi, Feng Meng, RuPing Shao, Min Jin Ha, Shinya Neri, Bingliang Fang, Steven H. Lin, Peggy T. Tinkey, Elizabeth J. Shpall, Jeffrey Morris, and Jack A. Roth

Often drugs tested in preclinical models fail in the clinic. An improved humanized mouse model derived from nonexpanded CD34+ stem cells from cord blood allowed for robust engraftment and the testing of non-HLA–matched patient tumors with immune therapies.
Histone Deacetylase Inhibition Sensitizes PD1 Activating KIRs on Educated NK Cells Support High Numbers of Circulating CD57 NK Cells Associate with Resistance to HER2-Specific Therapeutic Antibodies in HER2 Primary Breast Cancer

Aurora Manta failing, Sónia Serritosa, Mariona Cabo, Begona Bermejo, Sandra Pèrez-Buiru, Federico Rojo, Marcel Costa-García, Oriol Arpi, Manuela Moraru, Laia Serrano, Ignasi Tusquets, María Teresa Martínez, Gemma Heredia, Andrea Vera, María Martínez-García, Laura Soria, Laura Comerma, Sara Santana-Hernández, Pilar Eroles, Ana Rovira, Carlos Vilches, Ana Lluch, Joan Albanell, and Miguel López-Botet

CD57 NK-cell numbers may be a biomarker to identify breast cancer patients with primary resistance to HER2-specific therapeutic antibodies. NK-cell aging may influence NK-cell antitumor function.

Enriched HLA-E and CD94/NKG2A Interaction Limits Antitumor CD8 T Lymphocyte Responses

Megat Abd Hamid, Ruó-Zheng Wang, Xuan Yao, Peiwen Fan, Xi Li, Xue-Mei Chang, Yaning Feng, Stephanie Jones, David Maldonado-Pérez, Craig Waugh, Clare Verrill, Alison Simmons, Vincenzo Ceredolo, Andrew McMichael, Christopher Conlon, Xiyan Wang, Yanchun Peng, and Tao Dong

Enriched HLA-E expression on carcinomas and tumor-associated macrophages and DCs correlated with coexpression of the CD94/NKG2A inhibitory receptor on PD-1hi TILs. These TILs had impaired responses to IL2 and poor effector function, contributing to immune evasion of tumors.

Activating KIRs on Educated NK Cells Support Downregulation of CD226 and Inefficient Tumor Immunosurveillance

Concepción F. Guillamón, María V. Martínez-Sánchez, Lourdes Gimeno, José A. Campillo, Gerardo Server-Pastor, Jerónimo Martínez-García, Jorge Martínez-Escribano, Amparo Torroba, Belén Férnandez, Daniel J. Abellán, Isabel Legaz, María R. López-Alvarez, Maria R. Moya-Quiles, Manuel Muro, and Alfredo Minguela

Tumors can induce CD226 down-modulation on educated NK cells “sensitized” by activating NK-cell receptors (KIRs). Patients with these hyporesponsive CD226low NK cells had blunted cytokine production and antitumor immunity in a model of colitis-associated tumorigenesis. Without it, Th2 cells had enhanced cytokine production and antitumor immunity was enhanced.

Histone Deacetylase Inhibition Sensitizes PD1 Blockade–Resistant B-cell Lymphomas

Xiaoguang Wang, Brittany C. Waschke, Rachel A. Woolaver, Zhangguo Chen, Can Zhang, Anthony D. Piscopio, Xuedong Liu, and Jing H. Wang

The isoform-selective histone-deacetylase inhibitor OKI-179 has promising pharmacokinetics and immune enhancing effects. Combined treatment with OKI-179/anti-PD1 effectively inhibited poorly immunogenic B-cell lymphomas, providing a rationale for developing combinatorial therapy using epigenetic agents with immune checkpoint inhibitors.

The E3 Ubiquitin Ligase Asb2α in T Helper 2 Cells Negatively Regulates Antitumor Immunity in Colorectal Cancer

Camille A. Spinney, Isabelle Lamsoul, Arnaud Métais, Chanaëlle Febrissy, Christel Moog-Lutz, and Pierre G. Lutz

Tumor cells can evade antitumor responses by altering the balance between Th1 and Th2 cells. Asb2 repressed antitumor responses in a model of colitis-associated tumorigenesis. Without it, Th2 cells had enhanced cytokine production and antitumor immunity was enhanced.

Tumor Lymphatic Function Regulates Tumor Inflammatory and Immunosuppressive Microenvironments

Raghu P. Kataru, Catherine L. Ly, Jinyeon Shin, Hyeung Ju Park, Jung Eun Baik, Sonia Rehal, Sagrarito Ortega, David Lyden, and Babak J. Mehrara

Function of lymphatic vessels near a tumor may contribute to tumor immune evasion and metastasis. Interventions that manipulate lymphatic function may aid control of tumor growth and progression.

Efficient Tumor Clearance and Diversified Immunity through Neoeptiope Vaccines and Combinatorial Immunotherapy


A multifaceted approach utilizing a neoeptiope vaccine in combination with an IL15 superagonist, PD-1 blockade, and a tumor-targeting IL12 molecule promoted the expansion of antitumor T cell responses and efficient tumor clearance in a colon carcinoma mouse model.

Anti–CTLA-4 Activates Intratumoral NK Cells and Combined with IL15/IL15Rα Complexes增强了 Tumor Control

Emilio Sánchez, Erin M. O’Brien, Jenna R. Karras, Tamer B. Shabaneh, Bulent Arman Alysoy, Wei Xu, Cathy Zheng, Xiangfan Yin, Xiaowei Xu, Giorgos C. Karakousis, Ravi K. Amaravadi, Brian Nam, Mary Jo Turk, Jeff Hammerbacher, Mark P. Rubinstein, Lynn M. Schuchter, Tara C. Mitchell, Qin Liu, and Erica L. Stone

Surface expression of CTLA-4 on intratumoral Tregs may facilitate their depletion by NK cells following anti–CTLA-4 therapy, which in combination with IL15/IL15α complexes improves tumor control, compared to either monotherapy, in a mouse model of colon cancer.

CORRECTION

Correction: Automated Analysis of Lymphocytic Infiltration, Tumor Budding, and Their Spatial Relationship Improves Prognostic Accuracy in Colorectal Cancer

Andrew McMichael, Christopher Conlon, Xiyan Wang, Clare Verrill, Alison Simmons, Vincenzo Cerundolo, Peiwen Fan, Xi Li, Xue-Mei Chang, Yaning Feng, Andrea Vera, María Martínez-García, Laura Soria, Laura Comerma, Sara Santana-Hernández, Pilar Eroles, Ana Rovira, Carlos Vilches, Ana Lluch, Joan Albanell, and Miguel López-Botet

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ABOUT THE COVER

Primary breast cancer biopsy tissue is not always available to assess the degree of immune-cell infiltration into HER2+ breast cancer tumors. Thus, one goal for cancer diagnostics is to find reliable measures based on circulating immune cells. Muntasell and Servitja et al. measure the absolute number of circulating CD57+ NK cells before treatment with HER2-specific antibodies and find that the higher the number of NK cells before treatment, the worse the patient’s response to treatment. High amounts of CD57+ NK cells in the blood inversely correlate with their density in tumors, suggestive of a tumor-homing or proliferative deficiency. Indeed, the authors find that CD57+ NK cells in the peripheral blood have both reduced tumor-homing chemokine receptor expression and low proliferation upon activation. The amount of these circulating cells could be used as a diagnostic marker of response to HER2 antibodies. Read more in this issue on page 1280. Original image from Fig. 3B. Artwork by Lewis Long.