WHAT WE'RE READING

1901  A Sampling of Highlights from the Literature

IN THE SPOTLIGHT

1902  Location-Dependent B-cell Function in Glioblastoma
Ferdinando Pucci
See related article, p. 1928.

PRIORITY BRIEF

1903  Phase II Trial of Ipilimumab with Stereotactic Radiation Therapy for Metastatic Disease: Outcomes, Toxicities, and Low-Dose Radiation–Related Abscopal Responses
Determining combination therapies to improve immune checkpoint blockade can benefit patient outcome. In a phase II clinical trial, ipilimumab plus stereotactic radiotherapy provides clinical benefit to metastatic cancer patients.

RESEARCH ARTICLES

1910  Tumor Vessel Normalization, Immunostimulatory Reprogramming, and Improved Survival in Glioblastoma with Combined Inhibition of PD-1, Angiopoietin-2, and VEGF
Mariangela Di Tacchio, Jadranka Macas, Jakob Weissenberger, Kathleen Sommer, Oliver Bahr, Joachim P. Steinbach, Christian Senft, Volker Seifert, Martin Glas, Ulrich Herrlinger, Dietmar Krex, Matthias Meinhardt, Astrid Weyerbrock, Marco Timmer, Roland Goldbrunner, Martina Deckert, Andreas H. Scheel, Reinhard Büttner, Oliver M. Grauer, Jens Schittenhelm, Ghazaleh Tabatabai, Patrick N. Harter, Stefan Günther, Kari Devraj, Karl H. Plate, and Yvonne Reiss
The combination of anti–PD-1 and anti-VEGF/Ang-2 therapy shows efficacy in glioblastoma, a cancer considered to be non-T cell–inflamed. These data highlight how immune therapy efficacy can be improved by also targeting angiogenic factors in this cancer.

1928  Myeloid-Derived Suppressive Cells Promote B cell–Mediated Immunosuppression via Transfer of PD-L1 in Glioblastoma
Catalina Lee-Chang, Aida Rashidi, Jason Miska, Peng Zhang, Katarzyna C. Pitsch, David Hou, Ting Xiao, Mariafausta Fischietti, Seong Jae Kang, Christina L. Appin, Craig Horbinski, Leonidas C. Platanias, Aurora Lopes-Rosas, Yu Han, Irina V. Balyasnikova, and Maciej S. Lesniak
Regulatory B cells (Bregs) can regulate the activation and function of CD8+ T cells in glioblastoma. MDSCs were found to promote Breg differentiation and suppressive function via transfer of PD-L1–bound microvesicles taken up by infiltrating B cells.
See related Spotlight, p. 1902.

1944  IL6 Modulates the Immune Status of the Tumor Microenvironment to Facilitate Metastatic Colonization of Colorectal Cancer Cells
Yujiro Toyoshima, Hidemitsu Kitamura, Huihui Xiang, Youseke Ohno, Shigenori Homma, Hideki Kawamura, Norihiko Takahashi, Toshiya Kamiyama, Yu Han, Irina V. Balyasnikova, and Maciej S. Lesniak
IL6 deficiency reduces colorectal cancer metastasis to the liver and augments the effector functions of CD8+ T cells. Data highlight that IL6 blockade may be a potential strategy for improving antitumor immunity in colorectal cancer.

1958  Trifluridine/Tipiracil plus Oxaliplatin Improves PD-1 Blockade in Colorectal Cancer by Inducing Immunogenic Cell Death and Depleting Macrophages
Emeric Limagne, Marion Thibaudeau, Lisa Nuttin, Vadruenn Spill, Valentin Derangère, Jean-David Fumet, Nadia Amellal, Elisa Peranzoni, Valérie Cattan, and François Girtinghelli

MicroRNAs Affect Complement Regulator Expression and Mitochondrial Activity to Modulate Cell Resistance to Complement-Dependent Cytotoxicity
Yaron Hillman, Mariya Mardamshina, Mitsada Pasmanik-Chot, Lea Ziporen, Tamar Geiger, Noam Shomron, and Zvi Fishelson
Cancer cells respond poorly to antibody-based immunotherapy due to their enhanced resistance to activated complement. MicroRNAs were found to regulate complement resistance in multiple tumor cells, and thus, targeting them may potentiate the success of antibody-based cancer therapy.
1984 ALK and RET Inhibitors Promote HLA Class I Antigen Presentation and Unmask New Antigens within the Tumor Immunopeptidome
Clairwne Y. Oh, Martin G. Klatt, Christopher Bourne, Tao Dao, Megan M. Dacek, Elliott J. Bre, Sung Soo Mun, Aaron Y. Chang, Tatyana Korontsvit, and David A. Scheinberg
Increasing HLA expression in the tumor microenvironment could improve T cell–based immune therapies. ALK and RET inhibition in the appropriate kinase mutant tumors impedes MAPK signaling, leading to an increase in HLA expression and altered epitope presentation.

1998 Tumor-Specific Regulatory T Cells from the Bone Marrow Orchestrate Antitumor Immunity in Breast Cancer
Yingzi Ge, Hans-Henning Böhm, Anchana Rathinasamy, Maria Xydia, Xiaoying Hu, Mudita Pincha, Ludmila Umansky, Christopher Breyer, Michael Hillier, Andreas Bonertz, Alexandra Sevko, Christoph Domschke, Florian Schuetz, Helge Frebel, Steffen Dettling, Christel Herold-Mende, Christoph Reissfelder, Jürgen Weitz, Viktor Umansky, and Philipp Beckhove
Mechanisms for how regulatory T cells (Tregs) inhibit antitumor immune responses are needed to improve therapies. Tumor-specific Tregs from the bone marrow of breast cancer patients migrate to the peripheral blood and inhibit antitumor T-cell responses.

2013 Silencing Fc Domains in T cell–Engaging Bispecific Antibodies Improves T-cell Trafficking and Antitumor Potency
Linlin Wang, Sayed Shahabuddin Hoseini, Hong Xu, Vladimir Ponomarev, and Nai-Kong Cheung
Silencing Fc domains of bispecific antibodies (BsAbs) improves T-cell trafficking and antitumor effects in GD2⁺ and HER2⁺ tumor systems and two mouse models. Future BsAb designs that inactivate Fc domains could improve antitumor efficacy and limit organ toxicities.

2025 T-cell Receptors Engineered De Novo for Peptide Specificity Can Mediate Optimal T-cell Activity without Self Cross-Reactivity
Preeti Sharma, Daniel T. Harris, Jennifer D. Stone, and David M. Kranz
Cancer antigen–specific TCRs generated by directed evolution provide an alternative for adoptive T-cell therapies. A TCR generated by molecular evolution showed similar specificity and less cross-reactivity compared to a TCR generated from a T-cell clone.

2036 Trabectedin Reveals a Strategy of Immunomodulation in Chronic Lymphocytic Leukemia
Priyanka Banerjee, Ronghua Zhang, Cristina Ivan, Giovanni Galletti, Karen Clise-Dwyer, Federica Barbaglio, Lydia Scarfo, Miguel Aracil, Christian Klein, William Wierda, William Plunkett, Federico Caligaris-Cappio, Varsha Gandhi, Michael J. Keating, and Maria Teresa S. Bertilaccio
Chronic lymphocytic leukemia is an incurable disease: Intolerance or resistance to current therapies is often generated by immune cell defects and immunosuppression. Trabectedin inhibits leukemia progression and repairs the immune system.

2052 Mammary Tumor Cells with High Metastatic Potential Are Hypersensitive to Macrophage-Derived HGF
Takanori Kitamura, Yu Kato, Demi Brownlie, Daniel Y.H. Soong, Gaël Sugano, Nicolle Kippen, Jiufeng Li, Dahlia Doughty-Shenton, Neil Carragher, and Jeffrey W. Pollard
Breast cancer cells selected for high metastatic potential have elevated expression of MET and are hyper-responsive to macrophage-derived HGF, which promotes tumor cell extravasation and outgrowth. Blockade of macrophage-mediated HGF/MET signaling could have therapeutic potential for breast cancer.

2065 Tumor Immune Microenvironment and Chemosensitivity Signature for Predicting Response to Chemotherapy in Gastric Cancer
Yuming Jiang, Jingjing Xie, Weicai Huang, Hao Chen, Sujuan Xi, Zhen Han, Lei Huang, Tian Lin, Li-Ying Zhao, Yan-Feng Hu, Jiang Yu, Shi-Rong Cai, Tuanjie Li, and Guoxin Li
An SVM (support vector machine) signature, integrating immune microenvironment and chemosensitivity-related immunohistochemistry features of tumor cells, functions as an independent prognosis predictor. The signature identifies a subgroup of patients with gastric cancer likely to benefit from adjuvant chemotherapy.

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Glioblastoma is considered to be a non-T cell–inflamed cancer and has an immune suppressive tumor microenvironment (TME), creating a hurdle for the efficacy of immunotherapy. Glioblastoma also has high expression of angiogenic factors such as VEGF (vascular endothelial growth factor) and Ang-2 (angiopoietin-2). Di Tacchio et al. demonstrate that targeting VEGF and Ang-2 in combination with anti–PD-1 can overcome glioblastoma’s suppressive TME and allows for enhanced antitumor responses in preclinical models. This triple therapy increases cytotoxic immune cell infiltration and reduces myeloid-derived suppressor cell and regulatory T-cell numbers. Microvessel assessment of tumors shows that triple therapy globally normalizes the tumor vasculature, facilitating immune cell infiltration. These data highlight the importance of targeting angiogenic factors to improve the efficacy of immune checkpoint therapy for glioblastoma. Read more in this issue on page 1910. Original image from Supplementary Fig. S3A. Artwork by Lewis Long.