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827 Reflections on the Histopathology of Tumor-Infiltrating Lymphocytes in Melanoma and the Host Immune Response
Martin C. Mihm Jr and James J. Mulé

Cancer Immunology at the Crossroads: Engineering

836 Engineering New Approaches to Cancer Vaccines
Naveen K. Mehta, Kelly D. Moynihan, and Darrell J. Irvine

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Priority Briefs

849 Ablation of B7-H3 but Not B7-H4 Results in Highly Increased Tumor Burden in a Murine Model of Spontaneous Prostate Cancer
Katharina Kreymborg, Stefan Haak, Rajmohan Murali, Joyce Wei, Rebecca Waite, Georg Gasteiger, Peter A. Savage, Marcel R.M. van den Brink, and James P. Allison
Synopsis: Kreymborg, Haak, and colleagues genetically ablated checkpoint molecules in TRAMP mice to show that deletion of B7-H3 alters the tumor immune infiltrate toward a more suppressive immune environment that supports tumor growth, thus establishing a causal link between B7-H3 and host tumor control.

Research Articles

871 The Killer Cell Ig-like Receptor 2DL4 Expression in Human Mast Cells and Its Potential Role in Breast Cancer Invasion
Chiyuki Ueshima, Tatsuki R. Kataoka, Masahiro Hirata, Ayako Furuhata, Eiji Suzuki, Masakazu Toi, Tatsuaki Tsuoyama, Yoshimichi Okayama, and Hironori Haga
Synopsis: Ueshima, Kataoka, and colleagues show that nonneoplastic human mast cells express NK-cell receptor KIR2DL4, which interacts directly with HLA-G on tumor cells, enhancing MMP-9 production, invasion, and metastasis of HLA-G+ breast cancer cells in vitro and in vivo.
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881 Tumorcidal Effects of Macrophage-Activating Immunotherapy in a Murine Model of Relapsed/Refractory Multiple Myeloma
Jeffrey Lee Jensen, Alexander Rahmilievich, Erika Heninger, Aimee Teo Bromman, Chelsea Hope, Funita Phan, Shigeki Miyamoto, Joanna Matouzlakou, Natalie Callander, Peiman Hematti, Marta Chesi, P. Leif Bergsagel, Paul Sondel, and Fotis Asimakopoulos

Synopsis: Jensen and colleagues report that inhibition of innate immunity checkpoint TPL2 kinase signaling potentiates the efficacy of anti–CD40-based immunotherapy, which expands M1-polarized macrophages in the bone marrow, prolonging survival in an immunocompetent, transplant-based preclinical model of relapsed/refractory multiple myeloma.

902 PolyI:C–Induced, TLR3/RIP3-Dependent Necroptosis Backs Up Immune Effector–Mediated Tumor Elimination In Vivo
Ryo Takemura, Hiromi Takaki, Seiji Okada, Hiroaki Shime, Takashi Akazawa, Hiroyuki Oshiumi, Misako Matsumoto, Takamori Teshima, and Tsukasa Seya

Synopsis: Takemura and colleagues show that polyI:C–zVAD induced CT26 tumor necroptosis and regression in the absence of NK cells and CTLs, and caspase inhibitors directed to the tumor enhanced the efficacy of RNA adjuvant immunotherapy by modulating the tumor microenvironment and dendritic cell–mediated antitumor response.

915 Adenovirus Improves the Efficacy of Adoptive T-cell Therapy by Recruiting Immune Cells to and Promoting Their Activity at the Tumor
Siri Tähtinen, Susanna Grönberg-Vähtäkoskela, Dave Lumen, Maiju Merisalo-Soikkeli, Mikko Siurala, Anu J. Arakkinen, Markus Vähtäkoskela, and Akseli Hermanni

Synopsis: Tähtinen and colleagues report that intratumoral injection of nonreplicating adenovirus can overcome immune tolerance and resistance of B16.OVA murine melanomas to T-cell therapy by recruitment and stimulation of tumor-infiltrating immune cells, thus improving the efficacy of adoptive T-cell therapy in solid tumors.

926 PD-1 and CD103 Are Widely Coexpressed on Prognostically Favorable Intraepithelial CD8 T Cells in Human Ovarian Cancer
John R. Webb, Katy Milne, and Brad H. Nelson

Synopsis: Webb and colleagues evaluated 489 ovarian tumors and found PD-1+ cells in 38.5% of high-grade serous, 17.6% of endometrioid, and 8.6% of clear cell tumors. PD-1 was widely coexpressed with CD103 on intraepithelial CD8 TILs, which were quiescent in situ but functionally competent after polyclonal stimulation in vitro.

936 STAT1-Induced HLA Class I Upregulation Enhances Immunogenicity and Clinical Response to Anti-EGFR mAb Cetuximab Therapy in HNC Patients
Raghvendra M. Srivastava, Sumita Trivedi, Fernando Concha-Beranvete, Jie Hyun-bae, Lin Wang, Raja R. Seethala, Barton F. Branstetter IV, Soldano Ferrone, and Robert L. Ferris

Synopsis: Srivastava and colleagues identify that increase in STAT1–mediated HLA class I upregulation after cetuximab therapy in patients with head and neck cancer correlates with clinical outcome based on results from a prospective clinical trial investigating neoadjuvant treatment with cetuximab; they suggest that the increase may be a biomarker of response to cetuximab treatment.

946 PD-1 or PD-L1 Blockade Restores Antitumor Efficacy Following SSX2 Epitope–Modified DNA Vaccine Immunization
Brian T. Rekoske, Heath A. Smith, Brian M. Olson, Brett B. Maricque, and Douglas G. McNeel

Synopsis: Rekoske and colleagues show that an SSX2 DNA vaccine, optimized for MHC class I binding epitopes, led to increased PD-1 expression on antigen-specific CD8+ T cells and inferior antitumor response in mice bearing tumors expressing SSX2, which was reversed when combined with PD-1/PD-L1 blockade.

956 Melanoma Induces, and Adenosine Suppresses, CXCR3-Cognate Chemokine Production and T-cell Infiltration of Lungs Bearing Metastatic-like Disease
Eleanor Clancy-Thompson, Thomas J. Perekalski, Walburga Croteau, Matthew P. Alexander, Tamer B. Chabanet, Mary Jo Turk, Yina H. Huang, and David W. Mullins

Synopsis: Clancy-Thompson and colleagues show that lung metastatic-like melanoma induces a transient production of CXCR3-cognate chemokines and IFN required for antigen-specific T-cell infiltration into the tumor site, which in part is temporally limited by adenosine signaling and reversible by the adenosine receptor antagonist aminophylline.
This month’s Masters Primer on the histopathology of tumor-infiltrating lymphocytes (TIL) in melanoma and the host immune response is coauthored by two luminaries in immunopathology, Martin C. Mihm Jr and James J. Mulé. Dr. Mihm is a professor of pathology and dermatology at Harvard Medical School (HMS) and the associate director of the melanoma program at the Dana-Farber Brigham and Women’s Cancer Center. Dr. Mulé is the associate center director for translational science, the Michael McGillicuddy Endowed Chair for Melanoma Research and Treatment, and the scientific director of Cell-based Therapies at the Moffitt Cancer Center in Tampa, Florida.

Dr. Mihm was named the 2003 Legend in Dermatopathology of the American Society of Dermatopathology. His research interests have principally been related to malignant melanoma. He began his studies on melanomas with Wallace Clark in 1965 and coauthored the first publication of the classification of malignant melanoma into subtypes. For two decades, Dr. Mihm codirected the WHO melanoma pathology program, which was devoted mainly to the study of TILs in melanoma and has made significant contributions to establishing the importance of TILs as a prognostic factor in primary and metastatic melanoma. In the late 1970s, Dr. Mihm studied delayed hypersensitivity reactions in animals and humans with Harold F. Dvorak, author of the January 2015 Masters primer entitled “Tumors: Wounds That Do Not Heal—Redux.” Dr. Mihm’s collaboration with Dr. Dvorak led to the discovery of the role of basophils in human hypersensitivity reactions, and a definitive description of delayed hypersensitivity in humans that, in turn, led to the first description of the role of the vasculature in human allograft rejection. In the past decade, along with physician-scientist Paula North, Dr. Mihm has begun to study the pathogenesis of vascular anomalies in children and adults. The two researchers discovered a specific phenotype in infantile hemangiomas, and they are investigating the pathogenesis of these lesions. In 1994, Dr. Mihm began collaborations with Glenn Dranoff and F. Stephen Hodi to study vaccine reactions to autologous melanoma cells and the various factors affecting host immune response and survival. This work has led to critical insights in the dynamics of immune function and its regulation. (Continued on the following page.)
ABOUT THE MASTERS

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Dr. Mulé began his studies in tumor immunology and immunopathology under the mentorship of Karl Erik and Ingegerd Hellstrom at the Fred Hutchinson Cancer Research Center (FHCRC) in Seattle, Washington, soon after it opened its doors in 1975. There, he showed for the first time that lymphocytes could selectively localize in tumors in vivo. In 1981, Dr. Mulé moved to the Surgery Branch of NCI to study under Steven A. Rosenberg, publishing a series of studies on the antitumor effect of lymphokine-activated killer cells plus recombinant IL2, the mechanisms operative in high-dose IL2 therapy, and the enhancement of therapeutic potency of cytokine gene-modified tumor cells and TILs. Dr. Mulé’s research group is now involved in characterizing and validating genomic signatures of immunotherapy response, as well as designing and testing novel dendritic cell–based vaccine and adoptive T-cell transfer strategies in preclinical animal tumor models. The aim of their work is to improve these approaches through a focus on breaking tolerance to tumor self-antigens by inhibiting regulatory cells, boosting T-cell costimulation, and administering combinations of recombinant cytokines and other defined molecules with immune-enhancing activities.

Drs. Mihm and Mulé have received numerous awards and recognitions. Dr. Mihm is particularly proud of his teaching and mentoring awards and Dr. Mulé of his trainees who now hold research and teaching positions world-wide. Drs. Mihm and Mulé serve on the editorial boards of leading peer-reviewed journals and on the scientific advisory boards of various academic and health institutions as well as biotechnology and pharmaceutical companies.

Dr. Mihm was born in Pittsburgh, Pennsylvania and graduated summa cum laude from Duquesne University. He obtained his MD from the University of Pittsburgh Medical Center. He completed his residency in dermatology and pathology at the Massachusetts General Hospital (MGH) and subsequently joined the MGH staff. In 1976, he founded one of the first five U.S. residency training programs in dermatopathology. In 1993, he joined the faculty of Albany Medical Center to establish a dermatology and dermatopathology training program. He returned to MGH in 1996 as a clinical professor to continue work in melanoma and to establish a vascular malformation clinic. Dr. Mihm holds five adjunct professorships at different schools in the United States. He cofounded the Rare Tumor Institute of the WHO in Milan, Italy, and was its external coordinator for 5 years. He is currently the codirector of the melanoma pathology program of the European Organisation for the Research and Treatment of Cancer. He has written over 500 articles and authored or coauthored 12 books.

Dr. Mulé was born in Kearny, New Jersey, and graduated from the New Jersey City University; he received a special individual PhD from the FHCRC and the University of Washington, Seattle. He is a long-standing special government employee with the FDA (CBER) and NCI. He chaired the Cellular, Tissue, and Gene Therapy Advisory Committee of CBER, FDA, and was a member of the NCI Director’s Board of Scientific Counselors (BSC-A). He has written over 200 articles and has been a continuously funded investigator for nearly 25 years. Dr. Mulé received postgraduate training at the Surgery Branch of NCI, where he became a senior investigator with tenure. After helping to launch and scientifically direct two biotechnology companies in Palo Alto, California, Dr. Mulé was named the inaugural director of the Graduate Program in Immunology and director of the Tumor Immunology and Immunotherapy Program at the University of Michigan, where he was also the Maude T. Lane Endowed Professor of Surgery and a professor in the Department of Internal Medicine.