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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
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844 The 2015 AACR Joseph H. Burchenal Memorial Award for Outstanding Achievement in Clinical Cancer Research
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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

855 Long-term Benefit of PD-L1 Blockade in Lung Cancer Associated with JAK3 Activation
Synopsis: Van Allen, Golay, Liu, and colleagues genomically profiled tumor and germline samples from a patient with activating JAK3 variants who achieved long-term clinical benefit from anti-PD-L1 therapy, suggesting that alterations in JAK signaling may be immunogenomic modulators of response to PD-L1 immunotherapy.

864 STAT3 in CD8+ T Cells Inhibits Their Tumor Accumulation by Downregulating CXCR3/CXCL10 Axis
Chanyu Yue, Shudan Shen, Jiehui Deng, Saul J. Priceman, Wenzhao Li, Austin Huang, and Hua Yu
Synopsis: Yue, Shen, and colleagues reveal in two mouse tumor models that STAT3 signaling in T cells negatively regulates myeloid-cell/T-cell cross-talk via the IFNγ–CXCR3/CXCL10 axis, which is important for CD8+ T-cell homing to tumors; these findings have implications for cancer immunotherapy and adoptive T-cell strategies.

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 Tsuruhashi, Yoshinichi 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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ABOUT THE COVER

The observation of lymphocytes and mononuclear cells associated with human cancer was first noted more than a century ago, and their importance in host defense against tumors and their potential role in disease prognosis have been studied and characterized extensively in the past half century. The cover image shows lymphocyte infiltration into melanomas. On the upper left is a light microscopy image of a typical tertiary lymphoid structure (large central oval of packed blue-stained lymphocytes) stained by H&E that is associated with melanoma metastases in the lungs of a patient with stage IV disease. These so-called "immune microterritories" are thought to be involved in local B-cell and T-cell reactivity within the melanoma microenvironment. On the lower right is a light microscopy image of the vertical growth phase of a primary malignant melanoma. The tumor (two central melanoma cells shown) is diffusely infiltrated with lymphocytes (dark nuclei) and qualifies as a dense, brisk infiltrate associated with a favorable prognosis. (Image on upper left generated by Jane Messina, a senior member of the Departments of Anatomic Pathology and Cutaneous Oncology, Moffitt Cancer Center, Tampa, FL; image on lower right generated by Labib R. Zakka, Research Fellow, Dermatology Department, Brigham and Women’s Hospital, and Adriano Piris, Instructor in Pathology, Harvard Medical School, and codirector of the Mihm Cutaneous Pathology Consultative Service, Boston, MA.).

ABOUT THE MASTERS

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

(Continued)

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 (CRER) and NCI. He chaired the Cellular, Tissue, and Gene Therapy Advisory Committee of CRER, 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.