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CANCER IMMUNOLOGY AT THE CROSSROADS: EXPERIMENTAL IMMUNOTHERAPIES

598 Hostile, Hypoxia–A2-Adenosinergic Tumor Biology as the Next Barrier to Overcome for Tumor Immunologists
Michail V. Sitkovsky, Stephen Hatfield, Robert Abbott, Bryan Belikoff, Dmitriy Lukashev, and Akio Ohta

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606 The Second Annual AACR–Cancer Research Institute Lloyd J. Old Award in Cancer Immunology

PRIORITY BRIEF

610 A Soluble Form of CD80 Enhances Antitumor Immunity by Neutralizing Programmed Death Ligand-1 and Simultaneously Providing Costimulation
Samuel T. Haile, Lucas A. Horn, and Suzanne Ostrand-Rosenberg
Synopsis: Haile and colleagues report that CD80-Fc effectively maintained PD-1+ T-cell activation and IFNγ production by blocking PD-L1-mediated immune suppression and costimulating CD28, and suggest the development of CD80-Fc as a therapeutic agent.

RESEARCHARTICLES

616 Immunotherapy Converts Nonimmunogenic Pancreatic Tumors into Immunogenic Foci of Immune Regulation
Synopsis: Lutz and colleagues show that an allogeneic vaccine given with or without low-dose cyclophosphamide converted pancreatic cancer into an immunogenic cancer with infiltrating effector lymphocytes and formation of tertiary lymphoid aggregates that are regulatory structures of adaptive immunity.

632 Bevacizumab plus Ipilimumab in Patients with Metastatic Melanoma
Synopsis: Hodi and colleagues report the safety and efficacy of targeting angiogenesis and CTLA-4 in a phase I trial of 46 patients with metastatic melanoma, which revealed the influence of VEGF-A blockade on inflammation, lymphocyte trafficking, and immune regulation, and their synergistic therapeutic effects.

643 Response to BRAF Inhibition in Melanoma Is Enhanced When Combined with Immune Checkpoint Blockade
Synopsis: Cooper, Juneja, Sage, and colleagues show that combining BRAF and PD-1/PD-L1 blockade slowed tumor growth and prolonged survival in a melanoma mouse model, with increased number and activity of tumor-infiltrating lymphocytes similar to that in a human melanoma patient treated with this regimen.
The Tumor Microenvironment Shapes Lineage, Transcriptional, and Functional Diversity of Infiltrating Myeloid Cells
Kutlu G. Elpek, Viviana Cremasco, Hua Shen, Christopher J. Harvey, Kai W. Wucherpfennig, Daniel R. Goldstein, Paul A. Monach, and Shannon J. Turley

Synopsis: Elpek and colleagues analyzed the developmental and transcriptomic signatures of infiltrating myeloid cells in three mouse tumor models and report that tumor-associated macrophages and neutrophils exhibited different frequencies, gene expression profiles, and functions dependent on cancer types but not locations.

Intralesional Treatment of Stage III Metastatic Melanoma Patients with L19–IL2 Results in Sustained Clinical and Systemic Immunologic Responses

Synopsis: Weide and colleagues show that intralesional therapy using the immunocytokine L19–IL2 elicited a high rate of clinical and systemic immune responses in patients with stage III melanoma and report their observation of favorable distant metastasis-free and overall survival in these patients after treatment.

ERK-Dependent Downregulation of the Atypical Chemokine Receptor D6 Drives Tumor Aggressiveness in Kaposi Sarcoma
Benedetta Savino, Nicoletta Caronni, Achille Anselmo, Fabio Pasqualini, Elena Monica Borroni, Gianluca Basso, Giuseppe Celesti, Luigi Laghi, Athanasia Tourlaki, Vinicio Boneschi, Lucia Brambilla, Manuela Nebuloni, Gianluca Vago, Alberto Mantovani, Massimo Locati, and Raffaella Bonecchi

Synopsis: Savino, Caronni, and colleagues report that D6 expression was inversely correlated with increased tumor-associated M2-macrophages and aggressiveness in ERK pathway–activated Kaposi sarcoma (KS), and suggest targeting of CCR2 and the ERK pathway as a therapeutic option for patients with KS.

Programmed Cell Death Ligand 1 Expression in Osteosarcoma

Synopsis: Shen, Cote, and colleagues developed a quantitative RNA-based PD-L1 assay and report PD-L1 expression in 84% of human osteosarcomas, of which 24% were at high levels and correlated with TILs, indicating that this subset of patients may benefit from anti-PD-L1 immunotherapy.

Correction: Oncolytic Viruses and Their Application to Cancer Immunotherapy
ABOUT THE COVER

The thymus is required for the generation of a normal adaptive immune system; thymocyte development and selection are essentially complete prior to sexual maturity. T cells that leave the thymus can recognize peptides presented by the body's class I or class II major histocompatibility complex (MHC1/2). The ordered stages of intrathymic T-cell development include double negative (DN; CD4−CD8−) → double positive (DP; CD4+CD8−) → transitional (CD4+CD8dim) → CD8+ T-killer cells or CD4+ T-helper cells. T-cell receptors for MHC1/2 (TCRα or TCRβ) are expressed on DP thymocytes, which are selected upon encounter with the appropriate MHC molecules. DP cells with TCRs that are not selected for binding to the body's peptides plus MHC1/2 die from "neglect" in the cortex. Thymocytes with too high an affinity for peptides plus MHC1/2 die from "negative selection" in the cortex and medulla. In a healthy person, only ~2% of newly generated thymocytes exit the thymus daily; the rest die in situ during various stages of development. If the transitional (CD4+CD8dim) thymocyte expresses TCRβ, interaction with CD4 and MHC1/2 will activate transcription factor Th-POK to generate CD4+ T-helper cells. If the transitional (CD4+CD8dim) thymocyte expresses TCRα, the weak binding of TCRα and downregulated CD8 with thymic MHC1 in the presence of IL7 will cause coreceptor reversal, i.e. the cell expresses transcription factor RUNX3, which silences the transcription of CD4 and antagonizes Th-POK, enabling the development of CD8+ T-killer cells. For details of thymocyte development, see the Masters of Immunology primer by Harald von Boehmer on page 592 of this issue.

ABOUT THE MASTER

Harald von Boehmer, MD, PhD, is a professor emeritus at the Dana-Farber Cancer Institute (DFCI) and Harvard Medical School (HMS), an adjunct professor at the University of Florida, and a visiting professor in the Institute for Immunology at the Ludwig-Maximilian University of Munich, Germany, where he received his MD in 1968. He subsequently earned a PhD in 1974 from the University of Melbourne, Australia, under the tutelage of Dr. Ken Shortman. Dr. von Boehmer was a member of the Basel Institute for Immunology in Switzerland until 1996, before becoming the director of Unité INSERM 373 at the René Descartes University in Paris, France. He was recruited to join the faculty at DFCI-HMS in 1999, where he served as chief of the Laboratory for Lymphocyte Biology in the DFCI Department of Cancer Immunology and AIDS and a faculty member of the HMS Department of Microbiology and Immunobiology.

The von Boehmer laboratory has contributed significantly to our understanding of T-cell development and its roles in immune responses. Dr. von Boehmer discovered the pre-TCR, cloned the pre-TCRα gene, and defined its role in TCRβ allelic exclusion. Using gene transfer of the TCR, he characterized TCR contribution to recognition by T cells of peptide–MHC complexes. Through analysis of TCR transgenic mice, his favorite experiments, he delineated the role of negative selection in the thymus of developing T cells by peptide–MHC complexes to generation of self-tolerance. He elucidated mechanisms of positive selection in intrathymic generation of CD8+ killer cells, CD4+ helper cells, and FoxP3-expressing CD4+ regulatory cells. His studies on TCR-signaling pathways that permit conversion of naïve T cells into regulatory T cells in vivo have been used to establish antigen-specific tolerance to insulin and prevention of type 1 diabetes. He described the contribution of T-cell development to acute lymphoblastic T-cell leukemia. In particular, his studies of TCR signaling and Notch signaling revealed that T-cell lineage commitment is instructed by the intensity of TCR signals, and that Notch signaling is mandatory for the generation of δβδ but not γδ lineage T cells.

Dr. von Boehmer was born in Guben, Germany; he is an accomplished cellist and has performed with orchestras in Goettingen and Freiburg. His many honors include the Louis-Jeantet Prize for Medicine, jointly with Nicole Le Douarin and Gottfried Schatz (1990), the Avery-Landsteiner prize of the German Society for Immunology (1990), the Paul Ehrlich and Ludwig Darmstädter Prize for Immunology (1993), the Kurt A. Korber Prize for European Science (1997), and most recently the Helmholz International Fellow Award (2013). He also received an honorary medical degree from the Technical University of Munich (2002). Dr. von Boehmer is an elected member of the Academia Europaea (1990), the Institut Universitaire de France (1997), and the German Academy of Sciences Leopoldina (2003).