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Cancer Immunology Research

Illuminating the Interplay of Cancer and the Immune System

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Synopsis: The combination of local radiotherapy to a liver metastasis and systemic anti-CTLA-4 antibody resulted in a sustained complete clinical and radiologic remission in a patient with chemotherapy-refractory metastatic non-small cell lung cancer.

- 373 **Severe Cutaneous and Neurologic Toxicity in Melanoma Patients during Vemurafenib Administration Following Anti-PD-1 Therapy**

Douglas B. Johnson, Erika K. Wallender, Daniel N. Cohen, Sunaina S. Likhari, Jeffrey P. Zwerner, Jennifer G. Powers, Lisa Shinn, Mark C. Kelley, Richard W. Joseph, and Jeffrey A. Sosman

Synopsis: Severe systemic toxicities developed in two patients during vemurafenib therapy following disease progression after treatment with anti-PD-1 agents; these results have important implications for the management of melanoma patients and future clinical trials involving anti-PD-1 and BRAF inhibitors.

PRIORITY BRIEFS

- 378 **Inverse Association between Programmed Death Ligand 1 and Genes in the VEGF Pathway in Primary Clear Cell Renal Cell Carcinoma**

Richard W. Joseph, Mansi Parasramka, Jeanette E. Eckel-Passow, Dan Serie, Kevin Wu, Liuyan Jiang, Krishna Kalari, R. Houston Thompson, Thai Huu Ho, Erik P. Castle, John Cheville, Eugene D. Kwon, E. Aubrey Thompson, and Alexander Parker

Synopsis: In a retrospective, nested, case-control study of 98 primary clear cell renal cell carcinoma tumors, Joseph and colleagues demonstrate an inverse correlation between genes in the VEGF pathway and PD-L1 expression, providing further support of the immunosuppressive role of VEGF on the tumor microenvironment.

- 386 **mTOR Inhibition Improves Antitumor Effects of Vaccination with Antigen-Encoding RNA**

Mustafa Diken, Sebastian Kreiter, Fulvia Vascotto, Abderraouf Selmi, Sebastian Attig, Jan Diekmann, Christoph Huber, Özlem Türeci, and Ugur Sahin

Synopsis: Diken, Kreiter, and colleagues report that treatment of mice in the B16 melanoma model with rapamycin at the effector-to-memory transition phase skews the vaccine-induced immune response toward the memory pool, with alterations of the tumor microenvironment, and prolongs survival.

RESEARCH ARTICLES

- 393 **CD8⁺ T-cell Responses Rapidly Select for Antigen-Negative Tumor Cells in the Prostate**

S. Peter Bak, Mike Stein Barnkob, K. Dane Wittrup, and Jianzhu Chen

Synopsis: Bak, Barnkob, and colleagues show that treatment with antigen-specific CD8⁺ T cells effectively eliminated antigen-expressing prostate cells within the tumor bed, but the antigen-negative tumor cells with downregulated MHC class I continued to grow.

402 **Plasmacytoid Dendritic Cells Support Melanoma Progression by Promoting Th2 and Regulatory Immunity through OX40L and ICOSL**

Caroline Aspod, Marie-Therese Leccia, Julie Charles, and Joel Plumas

Synopsis: Combining the analyses of samples from melanoma patients and from melanoma-bearing humanized mice, the authors delineated the mechanism by which plasmacytoid dendritic cells mediate tumor progression and early relapse and identified potential therapeutic options for patients with metastatic melanoma.

416 **Escalating Regulation of 5T4-Specific IFN- γ ⁺ CD4⁺ T Cells Distinguishes Colorectal Cancer Patients from Healthy Controls and Provides a Target for *In Vivo* Therapy**

Martin Scurr, Anja Bloom, Tom Pembroke, Rohit Srinivasan, Clare Brown, Kathryn Smart, Hayley Bridgeman, Mike Davies, Rachel Hargest, Simon Phillips, Adam Christian, Tom Hockey, Awen Gallimore, and Andrew Godkin

Synopsis: Using overlapping peptides spanning oncofetal antigen 5T4 as targets, Scurr and colleagues identify an inverse correlation between the anti-5T4 CD4⁺ T-cell responses in peripheral blood and colorectal cancer disease progression and show this selective loss is driven in part by regulatory T cells.

426 **Novel Mechanism of Tumor Suppression by Polarity Gene *Discs Large 1 (DLG1)* Revealed in a Murine Model of Pediatric B-ALL**

Gabriel J. Sandoval, Daniel B. Graham, Grzegorz B. Gmyrek, Holly M. Akilesh, Keiko Fujikawa, Benedicte Sammut, Deepta Bhattacharya, Shuba Srivatsan, Alfred Kim, Andrey S. Shaw, Katherine Yang-Iott, Craig H. Bassing, Eric Duncavage, Ramnik J. Xavier, and Wojciech Swat

Synopsis: Using two different murine models of pre-B-cell leukemia, Sandoval and colleagues delineate the mechanism of tumor suppression by the PDZ domain polarity gene DLG1, which interacts with and stabilizes the PTEN protein in early-stage B cells.

CORRECTION

438 **Correction: Ipilimumab Treatment Results in an Early Decrease in the Frequency of Circulating Granulocytic Myeloid Derived Suppressor Cells as well as Their Arginase1 Production**

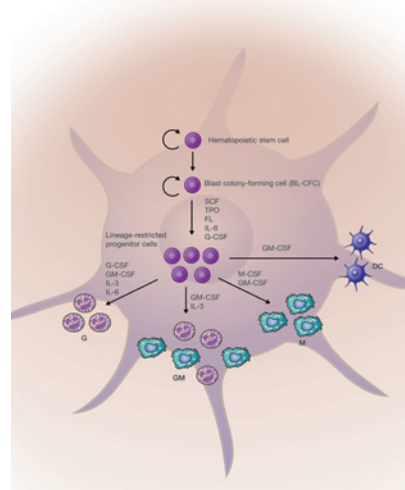
439 **Acknowledgment to Reviewers**

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ABOUT THE COVER

Hematopoietic populations are organized in a hierarchical manner. The cover image shows the family tree of granulocytes and macrophages. A limited number (1 per 10^5 marrow cells) of self-renewing multipotential hematopoietic stem cells serve as the origin of all blood cells. These stem cells can produce 100-fold higher numbers of blast colony-forming cells (BL-CFC), which are likely the progenitors that sustain the daily requirements for new blood cells. Each BL-CFC can self-renew and generate up to several thousand committed, lineage-restricted progenitor cells (only the granulocyte-macrophage and dendritic lineages are shown). In turn, each progenitor cell can generate up to 10^4 maturing progeny. The ability of one stem cell to produce 10^9 progeny is rarely required. The cytokines that control each differentiation/proliferation step are listed: DC, dendritic cell lineage; FL, Flt3 ligand; G, granulocytic lineage; G-CSF, granulocyte colony-stimulating factor; GM, granulocyte-macrophage lineage; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL-3, interleukin 3; IL-6, interleukin-6; M, macrophage lineage; M-CSF, macrophage colony-stimulating factor; SCF, stem cell factor; TPO, thrombopoietin.



ABOUT THE MASTER

Donald Metcalf completed a BSc(Med) in virology and an MD at Sydney University (Sydney, Australia). After an internship at the Royal Prince Alfred Hospital in Sydney, he joined The Walter and Eliza Hall Institute (WEHI) of Medical Research in Melbourne as the Carden Fellow in Cancer Research, a position he has continued to hold since 1954. His work at the WEHI has been interspersed with periods of 1 to 2 years as a visiting scientist at Harvard Medical School (Boston, MA), Roswell Park Memorial Institute (Buffalo, NY), the Swiss Institute for Experimental Cancer Research (Lausanne, Switzerland), the Radiobiological Institute (Rijswijk, the Netherlands), and the University of Cambridge (United Kingdom).

Dr. Metcalf is distinguished for his work on the control of blood cell formation. He discovered the function of the thymus in directing lymphocyte development and, beginning in 1965, developed a series of specialized culture techniques permitting the growth of the various types of blood cells. These cultures led to the discovery of the colony-stimulating factors (CSF), hormones that control the formation of immune cells and the defense against infections. Dr. Metcalf's team purified all four CSFs and characterized their complex functions. His work, along with that of others, led to the cloning of both mouse and human genes encoding the four CSFs and the mass production of these hormones in culture. They showed that the CSFs, when injected into animals, stimulated the formation and activity of immune cells. Metcalf and his colleagues demonstrated the effectiveness of granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) in humans. These CSFs have been used in 10 to 20 million patients around the world as reagents in accelerating the regrowth of blood cells following anticancer treatment, in permitting improved methods for blood cell transplantation, and for increasing resistance to infections.

Dr. Metcalf has published more than 730 scientific papers and nine books on his research, received the highest honors and awards from every industrial nation, and is recognized internationally as the leader in his field. Just to name a few of these accomplishments, Dr. Metcalf is a Fellow of the Australian Academy of Science, a Fellow of the Royal Society London, a Foreign Associate of the U.S. National Academy of Sciences, and a Companion of the Order of Australia. Yet, at the age of 84, Dr. Metcalf continues to work at the bench 8 hours each day. His recent work analyzes the mechanisms by which lineage commitment occurs in hematopoietic populations and the cellular events in oncogene-induced myeloid leukemogenesis.



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