

MASTERS OF IMMUNOLOGY

- 1** Tumors: Wounds That Do Not Heal—Redux
 Harold F. Dvorak

CANCER IMMUNOLOGY AT THE CROSSROADS: HEAD AND NECK CANCER

- 12** Immunity in Head and Neck Cancer
Jonathan D. Schoenfeld

CANCER IMMUNOLOGY MINIATURES

- 18** Lichenoid Dermatitis in Three Patients with Metastatic Melanoma Treated with Anti-PD-1 Therapy
Richard W. Joseph, Mark Cappel, Brent Goedjen, Matthew Gordon, Brandon Kirsch, Cheryl Gilstrap, Sanjay Bagaria, and Anokhi Jambusaria-Pahlajani
Synopsis: Joseph and colleagues describe the immune-mediated rash, lichenoid dermatitis, in three patients treated with anti-PD-1 (MK-3475). These mild rashes are characterized by a marked T-cell infiltrate with ~10% PD-1⁺ T cells.

COMMENTARY

- 23** Cytotoxic T-cell Cytokines Put Cancer Under Arrest
Stanley R. Riddell
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RESEARCH ARTICLES

- 26** Cytotoxic T Lymphocytes Block Tumor Growth Both by Lytic Activity and IFN γ -Dependent Cell-Cycle Arrest
Hirokazu Matsushita, Akihiro Hosoi, Satoshi Ueha, Jun Abe, Nao Fujieda, Michio Tomura, Ryuji Maekawa, Kouji Matsushima, Osamu Ohara, and Kazuhiro Kakimi
Synopsis: Matsushita and colleagues used microarray gene expression analysis coupled with fluorescent ubiquitination-based cell-cycle indicator (fucci) analysis and flow cytometry of a B16 murine model of melanoma to demonstrate that the predominant mechanism of CTL therapy in regulating tumor growth is via IFN γ -mediated cell-cycle arrest.
 See related commentary, p. 23

- 37** Type I Cytokines Synergize with Oncogene Inhibition to Induce Tumor Growth Arrest
Nicolas Acquavella, David Clever, Zhiya Yu, Melody Roelke-Parker, Douglas C. Palmer, Liqiang Xi, Holger Pflücke, Yun Ji, Alena Gros, Ken-ichi Hanada, Ian S. Goldlust, Gautam U. Mehta, Christopher A. Klebanoff, Joseph G. Crompton, Madhusudhanan Sukumar, James J. Morrow, Zulmarie Franco, Luca Gattinoni, Hui Liu, Ena Wang, Francesco Marincola, David F. Stroncek, Chyi-Chia R. Lee, Mark Raffeld, Marcus W. Bosenberg, Rahul Roychoudhuri, and Nicholas P. Restifo
Synopsis: Acquavella, Clever, and colleagues show that IFN γ and TNF α synergize with vemurafenib to induce tumor growth arrest, supporting further study of the intersection between immunologic and oncogenic signaling in cancer cells and of treatment strategies combining vemurafenib and T-cell-based immunotherapy.
 See related commentary, p. 23

- 48** High and Interrelated Rates of PD-L1⁺CD14⁺ Antigen-Presenting Cells and Regulatory T Cells Mark the Microenvironment of Metastatic Lymph Nodes from Patients with Cervical Cancer
A. Marijke Heeren, Bas D. Koster, Sanne Samuels, Debbie M. Ferns, Dafni Chondronasiou, Gemma G. Kenter, Ekaterina S. Jordanova, and Tanja D. de Gruijl
Synopsis: Heeren, Koster, and colleagues performed a comprehensive analysis of the immune-cell subsets and cytokine release profile in tumor-draining lymph nodes from patients with cervical cancer, providing information about the local immunosuppressive mechanisms that promote immune escape and metastatic spread.

- 59** Immunity to the Vacuolar ATPase Complex Accessory Unit ATP6S1 in Patients with Malignant Melanoma
Jun Zhou, Meghna Gupta, Xinqi Wu, Charles Yoon, Anita Giobbie-Hurder, and F. Stephen Hodi
Synopsis: Zhou and colleagues identify broad immune responses to ATP6S1 in the peripheral blood of patients with advanced melanoma; augmented humoral responses from ipilimumab treatment correlated with beneficial clinical outcomes, and the authors propose the development of ATP6S1 as a biomarker and therapeutic target.

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68 T Cells Bearing a Chimeric Antigen Receptor against Prostate-Specific Membrane Antigen Mediate Vascular Disruption and Result in Tumor Regression

Stephen P. Santoro, Soorin Kim, Gregory T. Motz, Dimitrios Alatzoglou, Chunsheng Li, Melita Irving, Daniel J. Powell Jr, and George Coukos

Synopsis: Santoro and colleagues show that CAR T cells directed against the tumor vascular antigen, prostate-specific membrane antigen, directly killed and eliminated tumor endothelial cells in murine cancer models, providing a rationale for using CAR T cells for tumor vascular disruption.

85 Mast Cells Boost Myeloid-Derived Suppressor Cell Activity and Contribute to the Development of Tumor-Favoring Microenvironment

Luca Danelli, Barbara Frossi, Giorgia Gri, Francesca Mion, Carla Guarnotta, Lucia Bongiovanni, Claudio Tripodo, Laura Mariuzzi, Stefania Marzinotto, Alice Rigoni, Ulrich Blank, Mario P. Colombo, and Carlo E. Pucillo

Synopsis: Danelli and colleagues demonstrate interactions between mast cells and myeloid-derived suppressor cells in the mucosa of colon carcinoma patients and in the colon and spleen of tumor-bearing mice and establish the role of CD40/CD40L in the activity of these cells in colon cancer.

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ABOUT THE COVER

Parallels between tumors and wound healing have been recognized for more than a century and continue to intrigue. An integral property shared by both tumors and healing wounds is increased expression of vascular endothelial growth factor (VEGF), also known as vascular permeability factor (VPF). Many types of cancer cells overexpress VEGF, as do parenchymal and inflammatory cells adjacent to sites of tissue injury, whether a cut finger, a stroke, or a myocardial infarct. Wherever it is expressed, VEGF initiates a chain of events that begins with increased vascular permeability to plasma and plasma proteins and is followed by activation of clotting and the laying down of a fibrin gel provisional stroma. Fibroblasts and new blood vessels infiltrate the fibrin stroma, transforming it into granulation tissue, and, ultimately, into dense fibrous connective tissue, called “scar tissue” in wounds and “desmoplasia” in cancer. The new blood vessels that form in tumors and wounds are of six distinctly different types and result from both angiogenesis and arterio-venogenesis. The first angiogenic vessels to form are called “mother” vessels (MV). MVs are large structures, lined only by a single layer of greatly thinned endothelial cells; they are the vessel type that leaks plasma and plasma proteins in both tumors and wounds. MVs derive from preexisting normal venules and capillaries by a three-step process: proteolytic degradation of vascular basement membranes, pericyte detachment, and 4- to 5-fold enlargement driven by intravascular hydrostatic pressure that is no longer opposed by the resistance of intact basement membranes and pericytes.

The cover is an H&E-stained section of a human ovarian carcinoma with three prominent MVs in the tumor stroma. The inset shows a fluorescent image of a rat skin wound at an early stage of healing, demonstrating several MVs that are leaking a circulating macromolecular tracer, FITC-dextran. For details see the Masters of Immunology primer by Harold F. Dvorak on page 1 of this issue.

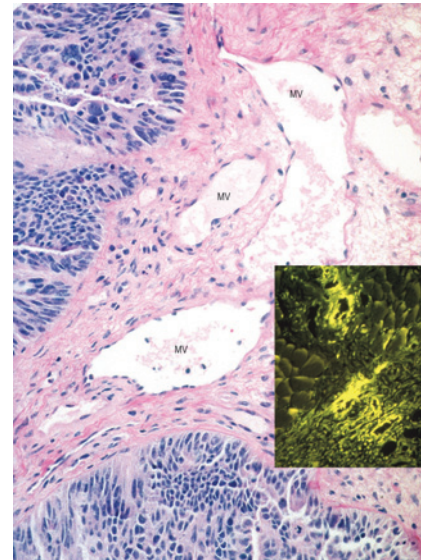


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ABOUT THE MASTER

Harold Fisher Dvorak, MD, was the chief of pathology at the Beth Israel Deaconess Medical Center (BIDMC) and the Mallinckrodt Professor of Pathology at Harvard Medical School (HMS) from 1979 to 2005. He received the 2014 Canada Gairdner International Award for discovering vascular endothelial growth factor (VEGF), a protein that has been effectively targeted in cancer and wet macular degeneration. Dr. Dvorak is a superb classic scientist who enjoys research and pursues science diligently and elegantly. In the early 1970s, Dr. Dvorak and colleagues demonstrated that delayed-type hypersensitivity reactions are heterogeneous, involving various immune-cell populations, and are associated with increased vascular permeability to plasma proteins due to the secretion by macrophages and mast cells of a new factor, which they characterized as the vascular permeability factor (VPF, renamed VEGF).

In 1983, Dr. Dvorak and his colleagues were the first to demonstrate that tumor cells secreted VEGF. This seminal discovery provided the molecular basis for the field of angiogenesis. His research has helped elucidate the nature and composition of tumor stroma and the pathogenesis of its generation. Dr. Dvorak made the critical observation that tumors behave like "wounds that do not heal" in that the vascular and stromal responses they induce closely mimic those of healing wounds. In both settings, and also in chronic inflammatory reactions, the initial sequence of events includes vascular hyperpermeability resulting in plasma fibrinogen extravasation, extravascular fibrin deposition, induction of angiogenesis, and progression to desmoplasia or scar formation. Based on Dr. Dvorak's work and the work of others, VEGF is regarded as the key angiogenic factor contributing to the neovascularization associated with tumor growth and other adaptive or pathologic angiogenic responses. More recently, his work has characterized the different types of blood vessels that tumors generate and the molecular mechanisms by which they form.

Dr. Dvorak has published over 300 original papers and review articles. He is a fellow of the American Association for the Advancement of Science and of the National Foundation for Cancer Research (NFCR). He has served as president of the American Society for Investigative Pathology, which awarded him the 2002 Rous-Whipple award, and in 2013, the Gold-headed Cane award for his scientific accomplishments. In addition to the 2014 Gairdner Award, Dr. Dvorak's many honors include the 2005 Lefoulon-Delalande Grand Prix from the Institut de France and the 2006 inaugural Albert Szent-Gyorgyi Prize for Progress in Cancer Research from the NFCR.

Dr. Dvorak was born in Milwaukee, Wisconsin. He received his bachelor's degree, *magna cum laude*, from Princeton University, and his medical degree, *cum laude*, from HMS. He was trained as a pathology resident at the Massachusetts General Hospital (MGH) and as a postdoctoral fellow at NIH. Dr. Dvorak has served on the HMS faculty since 1967 and is the incumbent Mallinckrodt Distinguished Professor of Pathology at HMS. He has trained many prominent scientists, including Robert Colvin, former chair of MGH pathology and Steven Galli, current chair of pathology at Stanford University. Dr. Dvorak was the founding director of the BIDMC Center for Vascular Biology Research; since 2005, he has focused his efforts on building the Center and continues to pursue his research and share his knowledge by presenting special lectures worldwide.



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