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Partners in Crime: Fledgling Tumors Hijack Inflammation

Balamurugan Kuppusamy
National Cancer Institute at Frederick

Howard A. Young
National Cancer Institute at Frederick, younghow@mail.nih.gov

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EDITORIAL COMMENTARY

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Balamurugan Kuppusamy and Howard A. Young

While inflammation is a normal physiological response after tissue injury, the chemicals/mediators that are released by the damaged tissue can be toxic to the cells. This underlying inflammation increases the likelihood of cellular DNA damage and aberrant cell growth (Kiraly and others 2015). In this scenario, inflammation functions as a ''behind-curtain factor'' for many disorders. Cancer has long been known to be closely tethered to inflammation. Widespread evidence shows that inflammatory diseases such as colitis, pancreatitis, and hepatitis make their respective organs highly susceptible to eventual cancer development (Shalapour and Karin 2015). However, other studies have shown that in due course, a growing cancer starts recruiting and relying on various mediators of inflammation to promote angiogenesis, further proliferating, metastasizing, and subverting the innate and adaptive immune response (Chan and others 2012). While we continue to ponder the chicken or egg scenario of how cancer and inflammation are related, the critical role inflammation plays in cancer progression cannot be denied. For example, some studies demonstrate that anti-inflammatory drugs such as aspirin not only act by reducing inflammation-related disorders, but also decrease the risk of colon cancer and gastrointestinal cancers. In colon cancer, aspirin specifically decreased the incidence of polyps, including advanced polyps, which are the precursors to colorectal cancer (Husain and others 2002; Wang and others 2018). However, experimental data from other cancers, including breast cancer, are not very promising, largely due to the differences in the inflamed tumor microenvironment (Strasser-Weippl and others 2018). Therefore, understanding the intricate cellular signaling pathways and the players involved in the smoldering inflammatory tumor microenvironment is paramount to identifying new strategies for the better management of cancers.

In this special issue, several leaders in the field discuss the latest developments in our understanding of cancer-associated inflammation, with a focus on the role of inflammatory cytokines and interferons. Emphasis is also placed on identifying opportunities and developing road maps for novel treatment approaches to combine immunotherapies with direct modulation of cytokine levels in the host.

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Address correspondence to:
Dr. Balamurugan Kuppusamy
Center for Cancer Research
National Cancer Institute
Building 560, Room 22-45
Frederick, MD 21702

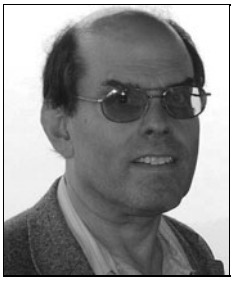
E-mail: kuppusamyb@mail.nih.gov

Dr. Howard A. Young
Center for Cancer Research
National Cancer Institute
Building 560, Room 31-23 (Office)
Frederick, MD 21702-1201

E-mail: younghow@mail.nih.gov

National Cancer Institute, Frederick, Maryland.

Guest Editors



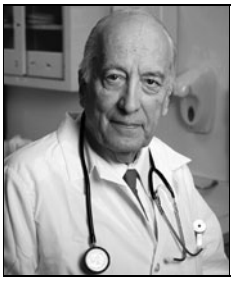
Howard Young, PhD

Dr. Howard Young obtained his PhD in microbiology at the University of Washington and carried out postdoctoral research at the National Cancer Institute (NCI) under Drs. Edward Scolnick and Wade Parks. He was a member of the Laboratory of Molecular Immunoregulation at NCI from 1983 to 1989 prior to joining the Laboratory of Experimental Immunology in 1989. He was President of the International Society for Interferon and Cytokine Research (2004–2005) and served as Chair of the Immunology Division of the American Society for Microbiology. He has also served as Chair of the National Institutes of Health (NIH) Cytokine Interest Group and Co-Chair of the NIH Immunology Interest Group. He is a three-time recipient of the NIH Director's Award for Mentoring (2000, 2006, and 2018), and in 2006 he received the National Public Service Award. Dr. Young has expertise in the regulation and characterization of cytokine gene expression with a special emphasis on interferons. The Young laboratory has as its major focus how disruption of the control of interferon-γ gene expression during development and maturation of the cellular immune system impacts the host inflammatory response and the development of autoimmune disease and cancer. His laboratory has developed a mouse model of chronic interferon-γ expression that results in three different autoimmune diseases resembling lupus, aplastic anemia, and primary biliary cholangitis. This model may provide new insight into the initiation and progression of these diseases.

Balamurugan Kuppusamy, PhD

Dr. Balamurugan Kuppusamy obtained his PhD from the University of Madras, Chennai, India. Dr. Kuppusamy pursued his postdoctoral studies at the University of Zurich, Switzerland, and at the NCI. Since March 2015, he has served as a staff scientist in the Laboratory of Cell and Developmental Signaling (NCI/CCR). Dr. Kuppusamy is a recipient of the NCI Cancer Genetics and Signaling Fellowship. In 2011 and 2012, he received the NIH ''Fellows Award for Research Excellence'' and NCI Fellows and Young Investigators ''Outstanding Achievement in Science Award,'' respectively. In 2015, he was awarded a research grant from the METAvivor Foundation to study signaling pathways in inflammatory breast cancer, an aggressive subtype of breast cancer. Dr. Kuppusamy has published 20+ peer-reviewed research articles. His areas of expertise include hypoxia, signal transduction, cancer stem cells, mouse models, breast cancer, CEBPD transcription factor, FBXW7, and inflammation.

Lead Authors



Thomas A. Waldmann, MD

Dr. Waldman received his MD degree from Harvard Medical School. Following an internship at Massachusetts General Hospital, he joined the Metabolism Branch of the National Cancer Institute (NCI) in 1956. Since 1973, he has been Chief of the Metabolism Branch, CCR of the NCI, National Institutes of Health (NIH), now named the Lymphoid Malignancies Branch. Over the past quarter century, Dr. Waldmann's work has focused on the biology of interleukin-2 (IL-2) and IL-15 with implications for cancer therapy and vaccine design. He reported the production of the monoclonal antibody anti-Tac that identified the IL-2 receptor alpha subunit. The humanized form of this antibody, daclizumab (Zenapax), was approved by the Food and Drug Administration (FDA) for use in the prevention of renal allograft rejection and is of value in the treatment of multiple sclerosis. Dr. Waldmann showed that although IL-2 and IL-15 that he co-discovered have heterotrimeric receptors with two subunits in common, these two cytokines have contrasting roles in the adaptive immune response. The unique role of IL-2 is in the elimination of self-reactive T cells to prevent autoimmunity. By contrast, IL-15 is dedicated to the prolonged maintenance of memory T-cell responses to invading pathogens. Dr. Waldmann has taken advantage of this difference to produce IL-15 under current Good Manufacturing Practice for use in the treatment of patients with metastatic malignant melanoma and renal cell cancer. Furthermore, he is incorporating IL-15 and its receptor, IL-15R alpha, in molecular vaccines for cancer and AIDS. Dr. Waldmann has been awarded the Lila Gruber Cancer Research Award, the CIBA-Geigy Drew Award in Biomedical Research, the Milken Family Medical Foundation Distinguished Basic Scientist Award, the Artois-Baillet Latour Health

Prize, the Bristol-Myers Squibb Award for Distinguished Achievement in Cancer Research, the Paul Ehrlich Medal, Paul Ehrlich Institute, the Debrecen Prize in Molecular Medicine, and the AAI-Dana Foundation Award in Human Immunology Research. He has been elected as a member of the National Academy of Sciences USA, American Academy of Arts and Sciences, the Institute of Medicine of the NAS, Association of American Physicians, and the Hungarian Academy of Sciences, and is an Honorary Fellow of the Royal Society of Medical Sciences (United Kingdom). Furthermore, he has been appointed as a NIH Distinguished Investigator.

Kevin C. Conlon, MD

Dr. Kevin Conlon graduated from Rush Medical College and completed his residency in Internal Medicine at Rush University Medical Center (RUMC). After serving as Chief Medical Resident at RUMC, he received his medical oncology training at the NCI and subsequently joined the Biological Response Modifier Program at the Frederick Cancer Research Center (BRMP/FCRF) to continue his translational immunotherapy research. After leaving the BRMP, Dr. Conlon was a medical officer at the Center for Biologics Evaluation and Research (CBER) at the FDA and later a clinical director of the IL-12 program at the Genetics Institute in Cambridge, Massachusetts. Dr. Conlon joined the Rush University Section of Medical Oncology in 2000 to continue his clinical and translational immunotherapy efforts as the Director of Clinical Research and the Oncology Inpatient Unit for the section. He returned to the NCI in 2009, initially joining the Investigational Drug Branch of Cancer Therapy Evaluation Program (IDB/CTEP), and since 2011 he has been responsible for directing clinical trials derived from the preclinical research of the laboratory of Dr. Thomas A. Waldmann, the chief of the Lymphoid Malignancy Branch (LyMB). He has been the principal investigator on many of the Branch's IL-15 and other clinical trials. While at the BRMP, Dr. Conlon worked in the Laboratory of Dr. Augusto Ochoa evaluating adoptive cellular immunotherapy strategies, and later in collaboration with Drs. Howard Young and John Ortaldo, he examined functional differences in T-cell subsets. These laboratory investigations defined differences in cytokine secretion, chemokine production, as well as differences in NF-κB family transcriptional factor signaling for CD4 and CD8 naïve and memory subsets. Dr. Conlon also continued to assess preclinical immunotherapy models in collaboration with Drs. William Murphy and Robert Wiltrout. His clinical efforts at the BRMP included pilot studies with anti-CD3 activated T cells and recombinant human cytokines. In his time at the Genetics Institute, RUMC Medical Oncology, and since returning to the NCI, Dr. Conlon's research focus has been clinical immunotherapy trials. Under his direction, the Clinical Trials Team completed the first-in-human trial with recombinant human IL-15 (rhIL-15) and continues to develop combination immunotherapy trials with rhIL-15. He is also collaborating with Dr. Liyanage Perera of LyMB to develop cellular immunotherapy trials with chimeric antigen receptor T cells against a variety of tumor target antigens. The other focus of Dr. Conlon's clinical research is HTLV-1 related adult T-cell leukemia lymphoma, which is a continuation of Dr. Waldmann's long-standing research interest in immune-based treatments for this disease.

Ahmed Lasfar, PhD

Dr. Ahmed Lasfar is a member of the Cancer Institute of New Jersey and Principal Investigator and a faculty member at Ernest Mario School of Pharmacy, Rutgers University, New Jersey. He serves as editor, board member, and reviewer of several international journals and foundations. Dr. Lasfar graduated in France from Paris Rene Descartes University in medical and applied science. He completed his doctoral studies in immunology at Paris Diderot University and his postdoctoral training in cancer immunology at Robert Wood Johnson Medical School, New Jersey.

M. Raza Zaidi, PhD

M. Raza Zaidi received his PhD in biochemistry and molecular biology from Robert Wood Johnson Medical School, Rutgers University, New Jersey, and completed his postdoctoral training at Columbia University and the NCI. He is currently an associate professor at the Fels Institute for Cancer Research and Molecular Biology, Lewis Katz School of Medicine at Temple University. The overarching goal of his research program is to elucidate the molecular mechanisms of ultraviolet radiation (UV)-induced melanomagenesis. In this respect, his specific interest is in gene–environment–microenvironment interactions and how inflammatory and epigenetic mechanisms play pro-melanomagenic roles in the context of UV insult to the skin.

Jorge Morales-Montor, PhD

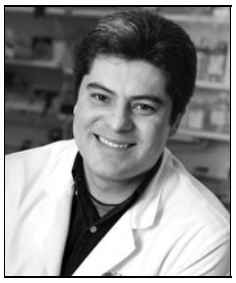
Dr. Jorge Morales-Montor is a full-time professor at the Departamento de Inmunología, Instituto de Investigaciones Biomèdicas, Universidad Nacional Autonoma de México. He is the chief editor of *Advances in Neuroirmmune Biology* and member of the editorial board of 20 journals. He has published more than 120 scientific articles. One of his contributions, published in the *Journal of Interferon and Cytokine Research*, is the journal's most downloaded and cited article since 2015. He is a member of the Mexican Academy of Sciences, the Latin America Academy of Sciences, the New York Academy of Sciences, and the American Association of Immunologists.

Ayten Nalbant, PhD

After graduating from Istanbul University with a biology major, Dr. Ayten Nalbant did a master's and PhD at the University of Southern California, Los Angeles. After completing her doctoral studies, Dr. Nalbant began working as an assistant professor in the Department of Molecular Biology and Genetics at the Izmir Institute of Technology (IYTE), and she continues to work at this institution. She has also worked as acting head and head of the Molecular Biology and Genetics Department and as deputy dean of the Faculty of Science at the IYTE. She teaches undergraduate and graduate courses in immunology, cell biology, signal transduction, and apoptosis. She is a founder and director of the molecular immunology laboratory at the Molecular Biology and Genetics Department of IYTE. Dr. Nalbant's ongoing scientific research is in the field of molecular cellular immunology, in particular differentiation of T helper 17 cells and immune response regulation. The research in her laboratory is supported by the Scientific and Technological Research Council of Turkey. She is a principle investigator of the 1001-Scientific and Technological Research Projects funding program. She has published numerous national and international abstracts and research and review articles in T-cell immunology.

Jaewoo Hong, PhD

Dr. Jaewoo Hong graduated from Konkuk University in Seoul, South Korea, with a DVM in 2006 and a PhD in immunology in 2012. He then completed a dissertation on cytokine immunology. He joined Dr. Richard Lee's lab at Brigham and Women's Hospital/Harvard Medical School in 2012 as a postdoctoral research fellow to study the role of IL-33 in the cardiovascular system. He joined Dr. Charles Lin's lab at the NCI in 2013 as a Cancer Research Training Award fellow.



Julio Valencia, MD

Dr. Julio C. Valencia is a staff scientist at the Cancer and Inflammation Program (CIP), NCI, in Frederick, Maryland. He earned a MPH degree (2018) from the University of Maryland—College Park and a MD degree (1997) from the Universidad Nacional Mayor de San Marcos (UNMSM), Lima, Peru. He began actively working on the biology of interferons (IFNs) and autoimmunity with Dr. Howard Young after joining the CIP group late in 2014. Previously, Dr. Valencia worked on several areas related to skin biology, pigmentation, and melanoma as part of the Pigment Cell Biology Section in the Laboratory of Cell Biology, NCI, in Bethesda, Maryland. There, Dr. Valencia explored the effects of IFNs on skin cells and pigmentation. In 2006, Dr. Valencia spearheaded the completion of the first melanosome proteome that identified novel biomarkers for melanoma and elucidated the role of melanosomes in drug resistance (2009). From 2012 to 2015, he served as an elected council member of the Pan American Society of Pigment Cell Research (2013–2015) and served as co-chair of the Pigment Cell Interest group at the NIH (2012–2014). Currently, Dr. Valencia's focus is on understanding cancer development and immunotherapy options in the context of autoimmunity. The mini-review presented here covers the adaptation mechanisms acquired by immune cells during autoimmunity, current and experimental anticancer therapies, and the most common preclinical mouse models available for research on autoimmune diseases.