Cancer Immunology Research

The 2013 William B. Coley Award for Distinguished Research in Basic and Tumor Immunology

The Coley Award was presented to Dr. Michael Karin (right) by Dr. Glenn Dranoff on September 30, 2013.

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William Bradley Coley (1862–1936) was a prominent New York cancer surgeon, who developed the first immunological treatment of cancer. In 1891, after one of his patients died of bone cancer despite having had aggressive surgery, Coley decided to find a better way. He searched through hospital records and discovered the remarkable case of a patient whose sarcoma had regressed following a severe erysipelas skin infection with high fever. He reasoned that the infection had somehow caused the tumor to regress. To test his hypothesis, Coley infected a terminally ill cancer patient with live erysipelas and saw the patient's cancer disappear. He then produced mixtures of dead bacteria, known as Coley's mixed bacterial toxins, and inoculated many more cancer patients, achieving lasting remissions in some cases. Coley's work marks the start of the modern era of harnessing the immune system to combat diseases, and Dr. Coley is known as the "Father of Cancer Immunotherapy."

The Cancer Research Institute (CRI) was founded in 1953 by Dr. Coley's daughter, Helen Coley Nauts, to advance the science of cancer immunology. In 1975, CRI established the William B. Coley Award for Distinguished Research in Basic and Tumor Immunology, which is presented annually to scientists who have made outstanding achievements in the field. The 2013 Coley Award was given to Dr. Michael Karin of the University of California, San Diego (UCSD). The award ceremony took place at CRI's annual awards dinner, held on September 30, 2013, in New York City, in conjunction with the 21st annual CRI symposium on cancer immunotherapy.

Dr. Karin is a world expert on signal transduction, who has made pioneering contributions to our understanding of the relationship between inflammation and cancer. Dr. Glenn Dranoff, Associate Director of CRI's Scientific Advisory Council and Editor-in-Chief of this journal, said in his introductory remarks that Karin's work has "transformed the way we think about the origins of cancer, and the forces that drive its progression from an unruly beginning to a full-blown lethal disorder."

Scientists have suspected for more than a century that inflammation might participate in tumor development, going back at least to Rudolf Virchow, who first noticed that tumors were infiltrated with immune cells (1). Today, much epidemiologic data link inflammation with cancer, and inflammation is recognized as one of the "enabling characteristics" of cancer, along with genome instability (2). Dr. Karin was among the first to delineate a specific mechanism by which inflammation could lead to cancer.

Dr. Karin gave the inaugural William B. Coley lecture on the first day of the CRI symposium. In his lecture, entitled "Making the Switch: How to convert (one day. . .) tumor-promoting inflammation to antitumor immunity—ongoing lessons from basic studies," Karin presented evidence from basic research in his laboratory linking inflammation with the promotion and progression of colon cancer, and discussed efforts in translating basic discoveries into effective therapies for cancer.

Colorectal cancer is the third leading cause of cancer-related death in the world. There are three major types of colorectal cancer: colitis-associated cancer that arises from preexisting inflammatory bowel disease, and familial and sporadic colorectal cancer, known collectively as colorectal cancer that do not involve inflammatory bowel disease. The association between chronic inflammation and cancer development is well established in colitis-associated cancer, but even in cases of sporadic colorectal cancer, Karin and colleagues have found a surprising role for inflammatory signaling pathways in cancer progression.

Much of Dr. Karin's work on colorectal cancer centers on the transcription factor NF-κB. NF-κB was identified and characterized in the early 1980s by Dr. David Baltimore's group at the Massachusetts Institute of Technology in the context of immunoglobulin gene rearrangement and B lymphocyte development; NF-κB binds to the immunoglobulin κ light-chain enhancer, and can be induced by bacterial lipopolysaccharide (3). NF-κB is now known to function as a "hub" of transcriptional regulation involved in both the inflammatory and innate immune responses, stimulating release of inflammatory cytokines such as IL-1, IL-6, and TNF. Dr. Karin's work has extended the role of NF-κB even further, moving it from an "innocent bystander to a major culprit of cancer" (4), a suspicion Karin developed after finding that NF-κB can inhibit programmed cell death (5).

Using a colitis-associated mouse cancer model, the Karin laboratory identified the molecular link between inflammation-induced activation of NF-κB and the development of colitis-associated cancer—specifically through the production of proinflammatory cytokine IL-6, a potent activator of STAT3 (6, 7). Concurrently, Pikarsky, Porat, Stein, Ben-Neriah, and

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colleagues used a mouse model of inflammatory hepatitis that progresses to liver cancer to show that NF-κB similarly functions as a tumor promoter in this system, enabling the progression of premalignant liver cells to hepatocellular carcinoma (8). Together these studies confirmed that NF-κB is a critical link between chronic inflammation and cancer development. In recent work, Dr. Karin has shown that NF-κB plays a role in colorectal cancer even where chronic inflammation is not present. Based on microarray expression profiling analysis, both colitis-associated cancer and colorectal cancer have the same inflammatory gene signature, which depends on the activation of NF-κB and STAT3 (9).

The NF-κB pathway normally functions in the immune system to stimulate inflammatory responses against infections and to maintain homeostasis under conditions of stress; however, persistent stimulation of this same pathway with unopposed production of proinflammatory signals can contribute to tumorigenesis, highlighting the dialogue between tumor cells and components of the immune system. Chronic inflammation mediated by NF-κB can inhibit apoptosis of transformed cells, promote angiogenesis, reshape the extracellular matrix, and increase production of reactive oxygen species that further damage DNA. Evidence also suggests that NF-κB is constitutively activated in most tumors (10). Thus, NF-κB may be the "missing link" between inflammation and cancer progression.

In his Coley lecture, Dr. Karin presented recent work focused on the inflammatory cytokines IL-23 and IL-17. Both cytokines are upregulated in sporadic colorectal cancer, and higher levels of expression correlate with decreased survival in human patients with colorectal cancer (9). The major source of IL-23 expression in developing colorectal tumors is tumor-associated macrophages. The mechanism of macrophage activation appears to depend on their Toll-like receptors, which are stimulated by colonic microflora penetrating the incipient tumors. Experiments in mice demonstrated that both IL-23 and its receptor are required for colorectal cancer tumorigenesis, and for inducing the expression of IL-17. The ablation of the IL-17 receptor also results in lower tumor burden, raising the possibility that blocking antibodies to one or both cytokines might be effective in cancer treatment, particularly when combined with chemotherapy (11). Indeed, preliminary studies in the Karin laboratory support this concept.

Dr. Karin's work highlights the nature of the immune response to cancer: it is a balance between tumor-fighting immunity and tumor-promoting inflammation. Efforts to develop effective immunotherapies, including cancer vaccines, must therefore incorporate a sophisticated understanding of the role that inflammation can play as both an instigator of tumorigenesis and a promoter of tumor progression, locking the tumor microenvironment into an immunosuppressive state that preferentially nurtures tumor cell growth, survival, and spreading. In deciphering the molecular signals involved in inflammation, Dr. Karin's work opens up new avenues for treatment, providing us with, as Dr. Dranoff said, "the blueprints for crafting new therapies that reprogram the immune response to restrain and then destroy tumors." The 2013 Coley Award recognizes this accomplishment and what it is likely to mean for the field of immunotherapy in the coming years.

Dr. Karin received his BS in biology and microbiology from the Tel Aviv University, and his PhD in molecular biology from the University of California, Los Angeles, where he worked in Dr. Harvey Herschman's laboratory studying the regulation of the expression of metallothionein mRNAs by glucocorticoid hormones and heavy metals. He did postdoctoral studies in the laboratory of Dr. Beatrice Mintz at the Fox Chase Institute for Cancer Research in Philadelphia, where he studied the biochemical mechanism of iron-transport using totipotent mouse teratocarcinoma cells with the goal of generating a mouse model with transferrin receptor deficiency. Dr. Karin continued postdoctoral training in Dr. John Baxter's laboratory at the University of California, San Francisco, where he cloned the gene encoding human metallothionein IIA and studied hormonal regulation of the metallothionein gene transcription. In 1982, Dr. Karin established his independent laboratory as an assistant professor in the Department of Microbiology at the University of Southern California. He joined the faculty of UCSD in 1986, where he is currently Distinguished Professor of Pharmacology and Pathology at the UCSD School of Medicine, and holds the Ben and Wanda Hildyard Chair for Mitochondrial and Metabolic Diseases.

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