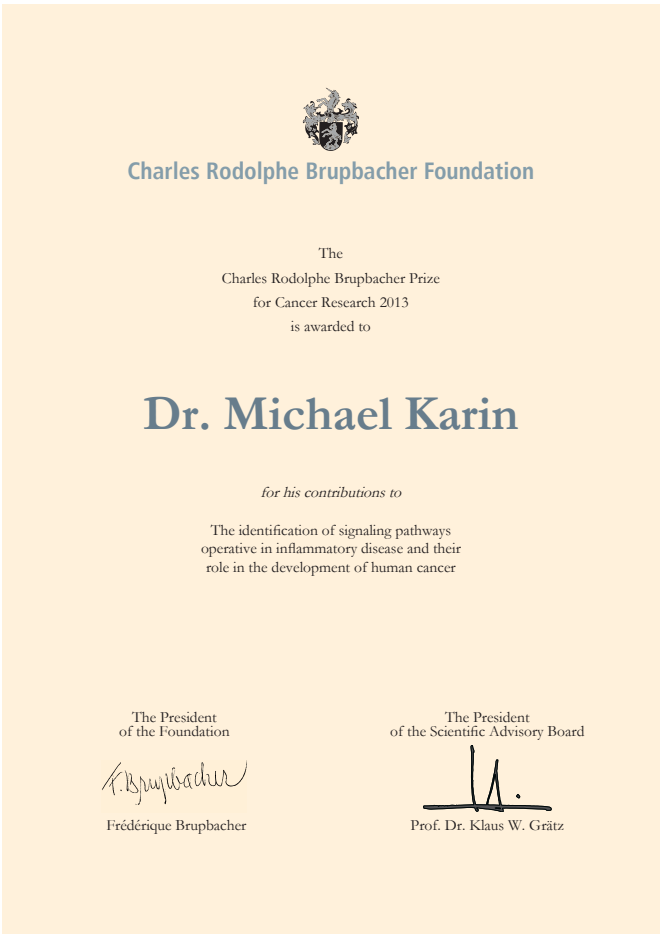

Laudatio

Klaus Rajewsky

The notion of a link between cancer and inflammation, famously put forward by Rudolf Virchow in his academic lectures on "die krankhaften Geschwülste" in the winter semester 1862/63 in Berlin, has a long and rich tradition. Inflammation, a hallmark of innate immunity, represents a defense of the organism against tissue damage and pathogen invasion. It involves the death and regeneration of cells and usually resolves within a short time. However, inflammatory processes often develop into a chronic, pathological condition, and it appears plausible that this can be accompanied by a deregulation of cellular proliferation, and, ultimately, malignant growth – "wounds that won't heal".

Only recently, however, with the advent of modern methods of molecular biology and in particular, mouse genetics, has a picture emerged in which we begin to mechanistically understand the complex ways in which chronic inflammatory processes and malignant growth can go hand-in-hand and promote each other. It is in this general context that we celebrate Michael Karin today as a scientific pioneer of the highest caliber.

Michael Karin was born in Israel, studied biology at Tel Aviv University and then moved to the United States to work on his PhD thesis at the University of California at Los Angeles. After two short postdoctoral stays with Beatrice Mintz and John Baxter from 1979 to 1981 he began his independent scientific career, settling in 1986 at the University of California in San Diego, where he is a professor in the Department of Pharmacology since 1989.

His first scientific publication, resulting from his thesis work with Harvey Herschman, was a paper in Science on the induction of metallothionein synthesis in HeLa cells by dexamethasone. Control of gene expression by external stimuli through cellular receptors, intracellular signaling cascades and transcription factors & transcriptional control became his obsession, combining methods of biochemistry, molecular biology and imaginatively, as they became available, mouse genetics. This led him from the analysis of basic molecular mechanisms to the study of pathophysiology in animals. In an amazing, steady stream of publications in top scientific journals to this day he and his colleagues have contributed a truly overwhelming wealth of discoveries and new insights relating to diverse biological processes, ranging from the role of protein phosphorylation in transcriptional control and basic principles of signal transduction to signaling cascades involved in cellular stress, innate immunity, inflammation and cancer. This included the discovery or in-depth characterization of key protein kinases, namely Jun kinase (JNK) that controls stress responses, and IκB kinase (IKK), a protein complex with a central role in the activation of the NF-κB pathway. This latter pathway is the main player in the control of inflammatory processes and innate immunity, and it is here that genetically tailored mouse models provided direct mechanistic links between inflammation and cancer.

Two papers published in 2004, one from Michael Karin's group and the other from Yinon Ben-Neriah and colleagues, described mouse models of two classical inflammation-associated human malignancies, colitis-associated colon cancer on the one hand, and hepatocellular carcinoma on the other. In both cases NF-κB activity was critical for cancer pathogenesis, amazingly in both the cancer cells themselves and

inflammatory cells in the cancer environment. In this complex scenario, anti-apoptotic proteins encoded by NF-κB target genes in the tumor cells cooperate with NF-κB controlled cytokines produced by neighboring myeloid and endothelial cells and promoting tumor cell growth and survival. One of these factors is interleukin 6, which Karin and colleagues demonstrated to play a role in both colon cancer and hepatocellular carcinoma, contributing in the latter case to the preferential occurrence of this malignancy in males, as also observed in the human. Additional complexity of this cellular interplay comes from the requirement for NF-κB activity at distinct phases of tumor development, and distinct functional activities of NF-κB transcription factors in different cell types and cellular contexts. In the past few years, the Karin laboratory has uncovered fascinating facets of these matters. To name just a few, NF-κB driven lymphotoxin production in B lymphocytes is required for the development of castration-resistant prostate cancer, through upregulation of IKKα in the tumor cells; and IKKα is also required for prostate cancer metastasis. Karin and colleagues have also provided compelling evidence that obesity predisposes for hepatocellular carcinoma through chronic inflammation, caused by fat deposition in the liver and resulting in the overproduction of cytokines like interleukin 6 and tumor necrosis factor.

I will just mention in passing that all of the above work is clearly of utmost clinical relevance and indispensable for the development of new therapies in this general area, and close by saying that Michael Karin is a true scientific giant in the biomedical field, who took rigorous basic research right into the realm of human disease, in particular the cancer field. He did this by an insatiable curiosity, energy and ambition, none of which he has lost even a bit over the years. My own first contact with him taught me all about scientific competition; while it fortunately ended in a draw, my lesson was to better not compete with him. He is a master of generating new ideas and concepts by bringing together elements from diverse fields, based on an enzyclopedic knowledge of the literature. No greater fun than to discuss science (or, for that matter, other matters) with him, and to have him as a participant in a scientific meeting. Congratulations, Michael, for this highly deserved honor!

Michael Karin

Summary Curicculum vitae

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La Jolla, California 92093-0723

Date of Birth May 25, 1951

Education Tel Aviv University, Tel Aviv, Israel
B.Sc. Biology, 1975
University of California, Los Angeles
Ph.D. Molecular Biology, 1979

Professional Appointments

1975 – 1979	Graduate Student, Molecular Biology Institute, UCLA. Supervisor: Dr. Harvey Herschman
1979 – 1980	Postdoctoral Fellow, Fox Chase Institute for Cancer Research, Philadelphia. Supervisor: Dr. Beatrice Mintz
1980 – 1981	Postdoctoral Fellow, Department of Medicine and Biochemistry, University of California, San Francisco. Supervisor: Dr. John Baxter

1981 – 1982	Assistant Research Biochemist, Metabolic Research Unit, University of California, San Francisco
1982 – 1985	Assistant Professor of Microbiology, School of Medicine, University of Southern California
1986 –1987	Associate Professor, Department of Medicine, University of California, San Diego
1987 – 1989	Associate Professor, Department of Pharma cology, University of California, San Diego
1989 – Present	Professor, Department of Pharmacology, University of California, San Diego
1993 – 2005	Founder and Consultant, Signal Pharmaceuticals (currently Celgene Pharma ceuticals), San Diego, CA

Editorial Boards

DNA & Cell Biology; Molecular Carcinogenesis; Genes, Chromosomes & Cancer; Molecular & Cellular Biology; Chemistry & Biology; Cell Growth & Differentiation; Critical Review of Eukaryotic Gene Expression; Mol. Cell. Biol. Res. Comm.; IUBMB-Life; Current Molecular Medicine; Molecular Pharmacology; Current Molecular Medicine, Molecular Cell; Cell Death and Disease; Journal of Experimental Medicine; Current Signal Transduction Therapy; Immunity; Proceedings of the National Academy of Sciences; Gastroenterology; Cell Metabolism; Oncogene; Free Radical Biology and Medicine; Cancer Discovery

U.S. Patents:	**Examples include**
6,863,888 (US)	Oncoprotein protein kinase
5,643,720 (US)	Method of inhibiting transcription utilizing nuclear receptors
5,534,426 (US)	Oncoprotein protein kinase
4,601,978 (US)	Mammalian metallothionein promoter system
7,189,832 (US)	Gamma Subunit of Cytokine Responsive IκB Alpha Kinase Complex and methods
7,314,615 (US)	IκB Kinase-β (IKKβ) Binding Antibodies and Methods of Using Same
7,319,134 (US)	Regulation of Transcription Factor, NF-IL6/ LAP
7,388,071 (US)	Methods for Identifying and Using IKK Inhibi tors
7,399,606 (US)	Methods for Identifying IκB Kinase (IKK) Inhibitors
7,491,506 B2	(US) Inhibition of B-cell Maturation and Anti body Production
7,695,921 (US)	Method for Detecting the Presence of Pros tate Cancer

Honors (Limited listing only)

1984 – 1987	Searle Scholars Award
1990	Oppenheimer Award for Excellence in Research from Endocrine Society
1999 – 2008	Frank and Else Schilling-American Cancer Society Research Professor
2005	Elected Member, National Academy of Sciences
2010	The Harvey Prize in Human Health
2011	Elected Member, Institute of Medicine, The National Academies

Publications (Limited listing only)

Grivennikov SI, Wang K, Mucida D, Stewart CA, Schnabl B, Jauch D, Taniguchi K, Yu GY, Osterreicher CH, Hung KE, Datz C, Feng Y, Fearon ER, Oukka M, Tessarollo L, Coppola V, Yarovinsky F, Cheroutre H, Eckmann L, Trinchieri G, Karin M. Adenoma-linked barrier defects and microbial products drive IL-23/IL-17-mediated tumour growth. Nature. 2012 Nov 8;491(7423):254-8.

Shaked H, Hofseth LJ, Chumanevich A, Chumanevich AA, Wang J, Wang Y, Taniguchi K, Guma M, Shenouda S, Clevers H, Harris CC, Karin M. Chronic epithelial NF-κB activation accelerates APC loss and intestinal tumor initiation through iNOS up-regulation. Proc Natl Acad Sci U S A. 2012 Aug 28;109(35):14007-12.

DiDonato JA, Mercurio F, Karin M. NF-κB and the link between inflammation and cancer. Immunol Rev. 2012 Mar;246(1):379-400.

Monica Guma M, Stepniak D, Shaked H, Spehlmann ME, Shenouda S, Cheroutre H, Vicente-Suarez I, Eckmann L, Kagnoff MF, Karin M. Constitutive intestinal NF-κB does not trigger destructive inflammation unless accompanied by MAPK activation. J Exp Med 2011 208:1889-1900

Chang L, Karin M. Mammalian MAP kinase signalling cascades. Nature. 2001 Mar 1;410(6824):37-40.

Karin M, Ben-Neriah Y. Phosphorylation meets ubiquitination: the control of NF-[kappa]B activity. Annu Rev Immunol. 2000;18:621-63.

Liu ZG, Hsu H, Goeddel DV, Karin M. Dissection of TNF receptor 1 effector functions: JNK activation is not linked to apoptosis while NF-kappaB activation prevents cell death. Cell. 1996 Nov 1;87(3):565-76.

Angel P, Karin M. The role of Jun, Fos and the AP-1 complex in cell-proliferation and transformation. Biochim Biophys Acta. 1991 Dec 10;1072(2-3):129-57.

Angel P, Imagawa M, Chiu R, Stein B, Imbra RJ, Rahmsdorf HJ, Jonat C, Herrlich P, Karin M. Phorbol ester-inducible genes contain a common cis element recognized by a TPA-modulated trans-acting factor. Cell. 1987 Jun 19;49(6):729-39.

Inflammation and Cancer: Effects, Mechanisms and Therapeutic Implications

Michael Karin

A century and a half ago, equipped with what was then state-of-the-art technology – a microscope and histochemical stains, Rudolph Virchow made the astounding finding that most cancers contain inflammatory infiltrates, an observation that led him to postulate that cancer may be caused by constant irritation. Indeed, the word tumor, meaning "swelling", that is used describe cancer, also refers to one of the five cardinal signs of inflammation. Although it has been known to many other pathologists, that followed Virchow, that solid malignancies contain inflammatory infiltrates composed of monocytes, macrophages, neutrophils and different types of lymphocytes, the suggestion that inflammation and cancer are mechanistically linked has been largely ignored until twenty years ago when newly emerging epidemiological data led to the estimate that about 15% of all cancer-related deaths are linked to persistent infections, such as Helicobacter pylori and Hepatitis B and C viruses, and chronic inflammatory diseases, such as ulcerative colitis. Much of the delay in recognizing and studying the role of inflammation in tumorigenesis has probably been due to the view that cancer is a cell autonomous process governed by activation of oncogenes and loss of tumor suppressors. This dogma, of course, has been dropped in recent years and it is now well acknowledged that the tumor microenvironment also plays a very important role in cancer development and progression and inflammation has been recognized as an enabling characteristic of cancer. Major components of the tumor microenvironment are inflammatory cells, such as tumor associated macrophages (TAM), which play multiple pro-tumorigenic functions, as demonstrated by the Pollard and Montovani groups, including the production of inflammatory cytokines. The general view regarding the role of such cytokines in tumor development and progression has also seen a major revision. Initially, it was expected that the prototypical inflammatory cytokine TNF (tumor necrosis factor) plays a major role in cancer control, as its namesake indicates. Although in high doses TNF can be used in cancer therapy (albeit to a rather limited extent due to its toxicity), chronic production of low amounts of TNF promotes tumor development, as first shown by Balkwill and co-workers

in skin cancer. Other members of the TNF family, lymphotoxin (LT) and RANK ligand (RANKL) produced by B and T lymphocytes, also play important pro-tumorigenic functions in prostate and breast cancers, respectively, as shown in my laboratory. Another very important tumor promoting cytokine affecting the development of both colon and liver cancers is IL-6, whose pro-tumorigenic function was first detected in mouse models but is now supported by strong circumstantial evidence obtained in human studies.

Despite the accumulation of multiple lines of evidence supporting the pathogenic function of inflammatory processes in tumorigenesis, it has not been too obvious what comes first – inflammation or cancer? It is now clear that the answer to this "chicken and the egg" question is – both. We first addressed this question in the classic model of colitis associated cancer (CAC), a form of colorectal cancer (CRC), that appears in patients suffering from ulcerative colitis or Crohn's disease and accounts for about 2% of all cases of CRC. By genetic ablation of IKKβ, a protein kinase that is required for activation of transcription factor NF-κB, a master regulator of inflammatory processes and cell survival, in either intestinal epithelial cells (IEC) or myeloid cells, we have shown that activation of NF-κB in both cell types, which occurs prior to the appearance of malignant colonic tumors, is critical for CAC development. Whereas in pre- malignant IEC, in which β catenin signaling has been activated by oncogenic mutations, IKKβ-driven NF-κB exerts its tumor promoting function through the upregulation of genes that maintain cell survival, in lamina propria myeloid cells NF-κB activation controls the production of tumor promoting cytokines, including TNF and IL-6, that drive the proliferation of pre-malignant IEC. In addition, persistent inflammation can also accelerate the initiation of CAC through upregulation of inducible nitric oxide synthase (iNOS), an enzyme whose product can cause nitrosative stress and genomic instability. However, inflammation can also be the consequence of cancer. Indeed, in the 98% of CRC that does not develop in the context of pre-existing inflammation, we found that formation of colonic adenomas triggers an inflammatory response, referred to as tumor-elicited inflammation, that drives adenoma to carcinoma progression. Tumor-elicited inflammation in CRC occurs early in the tumorigenic pathway and is due to a localized loss of the intestinal permeability barrier, resulting in invasion of the adenomas by commensal microbes or their components (e.g. endotoxin) that trigger the activation of Toll-like receptors and induce the production of the inflammatory cytokine IL-23 by TAMs and intra-tumoral dendritic cells. IL-23 fulfills its pro-tumorigenic function through the upregulation of two other inflammatory cytokines: IL-17 and IL-6. Importantly, elevated expression of a so-called "IL-23-Th17" signature in stage I and II human CRC, as found by Galon and Fridman, is a bad prognostic indicator that is associated with a marked decrease in disease free survival. Two other cancers where inflammation can act both before and after tumor development are liver and pancreatic cancers, two of the most fatal cancers that are refractory to most currently available therapeutics. Pre-existing inflammation, hepatitis caused by viral infections (HBV, HCV), alcohol exposure or excessive consumption of fatty foods or chronic pancreatitis with unknown etiology can greatly increase liver and pancreatic cancer risk. As we first found in mouse models of liver cancer, a major tumor promoting mechanism that can act in both organs is "death-induced inflammation" which is caused by chronic tissue damage. Another important pro-tumorigenic mediator acting in the liver, is LT whose expression can be induced upon HCV infection through a mechanism that involves the IKKβ-dependent activation of NF-κB. The role of NF-κB in liver cancer development, however, is somewhat complex as strong inhibition of NF-κB can augment cell death and thereby lead to "death-induced inflammation" and enhanced tumorigenesis.

While the nascent "inflammation and cancer" field has grown rapidly in the past 10 years, it has yet to reach maturity. It is also facing major challenges, including the therapeutic application of the basic knowledge discussed above. It is currently well established that broad acting anti-inflammatory drugs such as aspirin can reduce cancer risk. The question is whether more specific and more potent anti-inflammatory drugs will be more effective than aspirin? However, the cost associated with such drugs prohibits their use in cancer prevention and economic considerations restrict their application to cancer treatment. In addition to increasing the use of broad acting and cheap anti-inflammatory drugs and anti-oxidants in cancer prevention, I firmly believe that newly approved anti-cytokine drugs, such as neutralizing antibodies and decoy receptors that target IL-6, IL-17 or IL-23 as well as small molecule inhibitors of

Th17 differentiation need to be evaluated for their efficacy in conjunction with currently approved anti-cancer drugs. By inhibiting pro-tumorigenic inflammation, such drugs may greatly enhance the cytocidal effect of conventional therapeutics. In addition, drugs that target pro-tumorigenic cytokines may increase the efficacy of newly developed therapies, such as the anti-CTLA-4 and anti-PD1 antibodies that potentiate the activation of tumor-killing cytotoxic T cells. It is my hope that in the next five years we will see much progress in the translational arena, but this will require a concerted effort between academia, drug companies and regulatory agencies.

References:

Greten, F.R., Eckmann, L., Greten, T.F., Park, J.M., Li, Z-W, Egan, L.J., Kagnoff, M.F. and Karin, M.(2004) IKKβ links inflammation and tumorigenesis in a mouse model of colitis associated cancer. Cell 118:285-296.

Naugler, W.E., Sakurai, T., Kim, S., Maeda, S., Kim, K., Elsharkawy, A.M., Karin, M. (2007). Gender disparity in liver cancer due to sex differences in MyD88-dependent IL-6 production. Science 317:121-124.

Park, E.J., Lee, J.H., Yu, G.Y., He, G., Ali, S., Holzer, R., Österreicher, C., Takahashi, H., Karin, M. (2010) Dietary andgenetic obesity promote liver inflammation and tumorigenesis by enhancing IL-6 and TNF expression. Cell 140:197-208.

Ammirante, M., Luo, J.-L., Grivennikov, S., Nedospasov, S., Karin, M., (2010) B cell-derived lymphotoxin promotes castration-resistant prostate cancer. Nature 464:303-305.

Grivennikov, S., Greten, F., Karin, M. (2010) Immunity, Inflammation and Cancer. Cell 140:883-899

Tan, W., Zhang, W.Z., Strasner, A., Grivennikov, S.I., Cheng, J.Q., Hoffman, R.M., Karin, M. (2011) Tumour-infiltrating T regulatory cells stimulate mammary cancer metastasis through RANKL-RANK signalling. Nature 470: 548-553.

Kuraishy, A., Karin, M., Grivennikov, S.I. (2011) Tumor promotion via injury- and death-induced inflammation. Immunity 35: 467-477.

Grivennikov, S., Wang, K., Mucida, D., Stewart, C-A., Schnabl, B., Jauch, D., Taniguchi, K., Yu, G., Österreicher, C.H., Hung, K.E., Datz, C., Feng, Y., Fearon, E.R., Oukka, M., Tessarollo, L., Coppola, V., Yarovinsky, F., Cheroutre, H., Eckmann, L., Trinchieri, G., Karin, M. (2012) Adenoma-linked barrier defects and microbial products drive IL-23/IL-17-mediated tumour growth. Nature in press