► *As a clinical scientist, I like the interdisciplinary character of this Cancer Encyclopedia. The concise, yet comprehensive Essays written by experts from leading institutions throughout the world make it possible to easily keep track of important developments in the rapidly developing area of cancer research. It will be particularly useful for the oncology specialist, focussed on one area of the cancer problem to be able to gather information on other topics in the cancer field.* ► **Judah Folkman †,** Director, Vascular Biology Program, Andrus Professor of Pediatric Sugery and Professor of Cell Biology, Childen's Hospital, Boston, MA, USA

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► *These days we are overloaded with data from a wide range of disciplines that all impact on cancer research. In an era when the transfer of basic science knowledge into patient treatment is a dominant agenda, the ability to access and understand information from many areas is critical to success. The Cancer Encyclopedia is a landmark achievement in covering a wide range of important information in a readily accessible form. I am pleased having been asked to participate in this timely project as the Encyclopedia will set new standards and will serve as a valuable information source for basic and clinical scientists in the area of oncology.*
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► *The past three decades have witnessed an explosion of knowledge in the field of cancer research. Recent developments are seeing a dynamic merging of basic and clinical science, with basic science as the provider of instrumental and analytical tools that allow the assessment of the role of environmental factors in cancer, the refinement of diagnostics, the presymptomatic diagnostics, the evaluation of patients prognosis and, hopefully in the future, new strategies for causal therapies. Translational research is increasingly becoming a new paradigm in cancer research. The Cancer Encyclopedia is a comprehensive reference source both as a tool to close the language gap between clinical and basic science investigators and as a platform of information for students and informed laymen alike.* ► **Irene O.L. Ng,** MBBS, MD, PhD, FRCPath, FHKCPath, FHKAM Professor, Dept. of Pathology, The University of Hong Kong

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► *As in many other fields, knowledge and access to knowledge are key ingredients for success. That is why I welcome this second edition of the Encyclopedia of Cancer so much. In the field of cancer medicine, many scientists and clinicians around the world will be excited about this and will recognize their own prime area but also many others. This is not only a reference text, it is a text that gives you enormous excitement about the progress made in so few years.*
► **Ernest Pauwels,** Socrates Professor of Nuclear Medicine, Department of Oncology, Transplantation and New Technology in Medicine, Pisa University, Pisa, Italy

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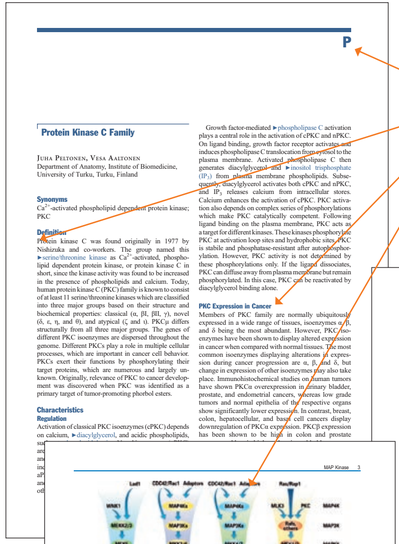


P

Protein Kinase C Family

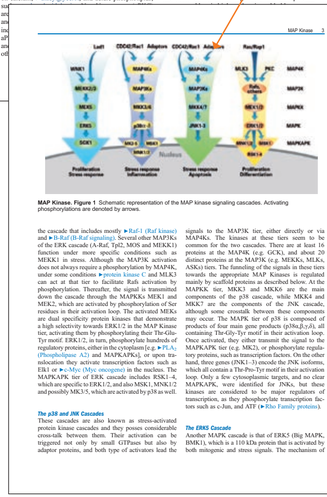
Juha Peltonen, Vesa Aaltonen
Department of Anatomy, Institute of Biomedicine, University of Turku, Turku, Finland

Synonyms
Ca^{2+}-activated phospholipid dependent protein kinase; PKC

Definition
Protein kinase C was found originally in 1977 by Nishizuka and co-workers. The group named this ►serine/threonine kinase as Ca^{2+}-activated, phospholipid dependent protein kinase, or protein kinase C in short, since the kinase activity was found to be increased in the presence of phospholipids and calcium. Today, human protein kinase C (PKC) family is known to consist of at least 11 serine/threonine kinases which are classified into three major groups based on their structure and biochemical properties: classical (α, βI, βII, γ), novel (δ, ε, η, and θ), and atypical (ζ and ι). PKCs differs structurally from all three major groups. The genes of different PKC isoenzymes are dispersed throughout the genome. Different PKCs play a role in multiple cellular processes, which are important in cancer cell behavior. PKCs exert their functions by phosphorylating their target proteins, which are numerous and largely unknown. Originally, relevance of PKC to cancer development was discovered when PKC was identified as a primary target of tumor-promoting phorbol esters.

Characteristics
Regulation
Activation of classical PKC isoenzymes (cPKC) depends on calcium, ►diacylglycerol, and acidic phospholipids, such as ►phosphatidylserine. Growth factor-mediated ►phospholipase C activation plays a central role in the activation of cPKC and nPKC. On ligand binding, growth factor receptor activates and induces phospholipase C translocation from cytosol to the plasma membrane. Activated phospholipase C then generates diacylglycerol and ►inositol trisphosphate (IP_3) from plasma membrane phospholipids. Subsequently, diacylglycerol activates both cPKC and nPKC, and IP_3 releases calcium from intracellular stores. Calcium enhances the activation of cPKC. PKC activation also depends on complex series of phosphorylations which make PKC catalytically competent. Following ligand binding on the plasma membrane, PKC acts as a target for different kinases. These kinases phosphorylate PKC at activation loop sites and hydrophobic sites. PKC is stable and phosphatase-resistant after autophosphorylation. However, PKC activity is not determined by these phosphorylations only. If the ligand dissociates, PKC can diffuse away from plasma membrane but remain phosphorylated. In this case, PKC can be reactivated by diacylglycerol binding alone.

PKC Expression in Cancer
Members of PKC family are normally ubiquitously expressed in a wide range of tissues, isoenzymes α, βI, and δ being the most abundant. However, PKC isoenzymes have been shown to display altered expression in cancer when compared with normal tissues. The most common isoenzymes displaying alterations of expression during cancer progression are α, βI, and δ, but change in expression of other isoenzymes may also take place. Immunohistochemical studies on human tumors have shown PKCα overexpression in primary bladder, prostate, and endometrial cancers, whereas low grade tumors and normal epithelia of the respective organs show significantly lower expression. In contrast, breast, colon, hepatocellular, and head and neck cancers display downregulation of PKCα expression. PKCβI expression has been shown to be high in colon and prostate



MAP Kinase. Figure 1 Schematic representation of the MAP kinase signaling cascades. Activating phosphorylations are denoted by arrows.

the cascade that includes mostly ►Raf-1 (Raf kinase) and ►B-Raf (B-Raf signaling). Several other MAP3Ks of the ERK cascade (A-Raf, Tpl2, MOS and MEKK1) function under more specific conditions such as MEKK1 in stress. Although the MAP3K activation does not always require a phosphorylation by MAP4K, under some conditions ►protein kinase C and MLK3 can act at that tier to facilitate Ras activation by phosphorylation. Thereafter, the signal is transmitted down the cascade through the MAP2Ks MEK1 and MEK2, which are activated by phosphorylation of Ser residues in their activation loop. The activated MEKs are dual specificity protein kinases that demonstrate a high selectivity towards ERK1/2 in the MAP Kinase tier, activating them by phosphorylating their Thr-Glu-Tyr motif. ERK1/2, in turn, phosphorylate hundreds of regulatory proteins, either in the cytoplasm [e.g. ►PLA$_2$ (Phospholipase A2) and MAPKAPKs], or upon translocation they activate transcription factors such as Elk1 or ►c-Myc (Myc oncogene) in the nucleus. The MAPKAPK tier of ERK cascade includes RSK1–4, which are specific to ERK1/2, and also MSK1, MNK1/2 and possibly MK5/5, which are activated by p38 as well.

The p38 and JNK Cascades
These cascades are also known as stress-activated protein kinase cascades and they posses considerable cross-talk between them. Their activation can be triggered not only by small GTPases but also by adaptor proteins, and both type of activators lead the signals to the MAP3K tier, either directly or via MAP4Ks. The kinases at these tiers seem to be common for the two cascades. There are at least 16 proteins at the MAP4K (e.g. GCKs), and about 20 distinct proteins at the MAP3K (e.g. MEKKs, MLKs, ASKs) tiers. The funneling of the signals in these tiers towards the appropriate MAP Kinases is regulated mainly by scaffold proteins as described below. At the MAP2K tier, MKK3 and MKK6 are the main components of the p38 cascade, while MKK4 and MKK7 are the components of the JNK cascade, although some crosstalk between these components may occur. The MAPK tier of p38 is composed of products of four main gene products (p38α,β,γ,δ, all containing Thr-Gly-Tyr motif in their activation loop. Once activated, they either transmit the signal to the MAPKAPK tier (e.g. MK2), or phosphorylate regulatory proteins, such as transcription factors. On the other hand, three genes (JNK1–3) encode the JNK isoforms, which all contain a Thr-Pro-Tyr motif in their activation loop. Only a few cytosoplasmic targets, and no clear MAPKAPK, were identified for JNKs, but these kinases are considered to be major regulators of transcription, as they phosphorylate transcription factors such as c-Jun, and ATF (►Rho Family proteins).

The ERK5 Cascade
Another MAPK cascade is that of ERK5 (Big MAPK, BMK1), which is a 110 kDa protein that is activated by both mitogenic and stress signals. The mechanism of

2 Human T-cell Leukemia Virus

concomitant HIV infection. However in contrast to HTLV-I, an etiological role for HTLV-II in hematologic malignancy has not been shown in epidemiologic studies.

Pathology
HTLV, by infecting CD4+ helper T cells, establishes a chronic infection that over time develops into leukemia. The glucose transporter 1 (GLUT-1) protein is most likely the receptor for HTLV-I and is expressed on the surface of many different cells. This finding can explain the ability of HTLV to infect a wide variety of human cells. The mechanism for cell transformation is not fully explained but appears to be related to expression of the X region viral proteins particularly Tax. This transcriptional transactivator protein enhances the activity of cellular transcription factors and activates various promoters including NFkB. Tax can also block the activity of the tumor suppressor protein p53 and inhibit apoptosis. These effects result in immortalization of cells in culture and eventual tumor development. Some investigators believe that the production of the lymphocyte growth factor interleukin-2 (IL-2) drives the CD4+ lymphocytes to proliferate, particularly since there is an up-regulation of IL-2 production and expression of the IL-2 receptor on the infected cell surface. The leukemic cells, once proliferating, spread through the body and can induce a variety of syndromes including bone lesions due to osteoclastic activity. Hypercalcemia is frequently found in patients with acute ATL in association with an increased number of osteoclasts possibly induced through cytokine effects on hematopoietic precursor cells. ATL differs from cutaneous T cell leukemia by the absence of leukemic cell infiltration of the epidermis despite presence of tumor cells in the dermis and subcutaneous tissue. Moreover, the bone marrow and lungs are usually not involved in ATL. ATL treatment includes IFNα and zidovudine, as well as inhibitors of NFkB activity, but the median survival with ATL is about a year even with therapy.

Neurologic Disease
Clinical Presentation
Cases of tropical spastic paraparesis (TSP) have occurred in the Caribbean (e.g., Jamaica, Dominican Republic, Martinique, Trinidad) in Latin America, Africa and India. In Japan, a similar disease, called HTLV-associated myelopathy (HAM), is frequently diagnosed in HTLV-I endemic areas. This neurologic disease occurs in up to two percent of infected individuals, most commonly between ages 35 and 45; it is observed more often in females than in males. This finding can reflect either sex-related acquired infection or a female predilection for the immunologic basis for its pathology. A neurologic syndrome identical to TSP/HTLV-I, an etiological role for HTLV-II in hematologic malignancy has not been shown in epidemiologic studies.

Pathology
Because of the very high titer of antibody to HTLV-I and the presence of lymphocytes within the central nervous system, TSP has been considered to result from an autoimmune-like response of the host. The neuropathology can be caused by inflammation of nerve roots from HTLV-1 infected cells infiltrating the spinal cord, or by direct infection of glial cells by HTLV-1. Cellular and cytokine-mediated inflammatory responses directed at HTLV-I initiate the damage to neural tissue, followed by gliosis in advanced cases. Treatment with corticosteroids has shown some improvement but generally TSP has a slow unremitting course.

►Cancer, cancer causes and control, transduction of oncogenes, virology

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Editor-in-Chief

Dr. Schwab is the Director of the Division of Tumour Genetics at the German Cancer Research Center (DKFZ) in Heidelberg, with joint Professorships at the Universities of Heidelberg and Kaiserslautern.. His scientific career started by working out the genetics of hereditary cancer susceptibility in the fish Xiphophorus, where pigment cell tumors develop spontaneously after introgressive interspecies hybridization. Subsequently, he changed his research focus to the development of human cancers. He is well-known for his first application of parallel oncogene expression analysis (array analysis) of human tumor cells that led to the identification of the amplified MYCN gene in the children's cancer neuroblastoma. Amplified MYCN has been the first prognosis-associated molecular marker for human cancer, today the determination of MYCN-status is an established parameter worldwide for therapy design of neuroblastoma. More recently, the interest of Dr. Schwab has expanded to the molecular analysis of human fragile sites, which are predetermined chromosome breakage regions related to chromosomal damage in cancer and, possibly, also in other forms of human disease. Dr. Schwab is author, or co-author, of approximately 150 peer-reviewed publications plus a large number of review articles and book chapters. He is Associate Editor for Cancer Research, Oncogene and British Journal of Cancer, and Managing Editor of Cancer Letters.

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