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REVIEW

Protein kinase C and cancer: what we know and what we do not

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Since their discovery in the late 1970s, protein kinase C (PKC) isozymes represent one of the most extensively studied signaling kinases. PKCs signal through multiple pathways and control the expression of genes relevant for cell cycle progression, tumorigenesis and metastatic dissemination. Despite the vast amount of information concerning the mechanisms that control PKC activation and function in cellular models, the relevance of individual PKC isozymes in the progression of human cancer is still a matter of controversy. Although the expression of PKC isozymes is altered in multiple cancer types, the causal relationship between such changes and the initiation and progression of the disease remains poorly defined. Animal models developed in the last years helped to better understand the involvement of individual PKCs in various cancer types and in the context of specific oncogenic alterations. Unraveling the enormous complexity in the mechanisms by which PKC isozymes have an impact on tumorigenesis and metastasis is key for reassessing their potential as pharmacological targets for cancer treatment.

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INTRODUCTION

Protein kinase C (PKC), a prototypical class of serine/threonine kinases, exemplifies specific signaling molecules that link multiple cellular processes to cancer. Originally identified as a cellular receptor for the phorbol ester tumor promoters more than 30 years ago,[1–2] PKC became the subject of intense studies by academic laboratories and pharmaceutical companies (>50 000 citations in PubMed, which is even more than other ABC kinases such as PKA or PKB/Akt). Extensive work established these kinases as pleiotropic regulators of cell function, including proliferation, differentiation, survival and motility.[3] To date, it is clear that PKCs are associated with a number of diseases, including cancer, cardiovascular dysfunctions and metabolic disorders. The complexity in PKC signaling arises from the fact that PKC is a multifamily of structurally related kinases with diverse biological functions. Indeed, mammalian PKCs encompass 10 members that represent the products of nine different genes located in different chromosomes. PKC isozymes have been classified into three groups: 'conventional' or 'classical' PKCs (cPKCs) that are composed of PKCα, two splice variants of PKCβ (PKCβI and PKCβII) and PKCγ; 'novel' PKCs (nPKCs), a group that includes PKCδ, PKCε, PKCη and PKCθ; and 'atypical' PKCs (aPKCs) ζ and ι (λ). cPKCs and nPKCs are activated by diacylglycerol (DAG), a lipid second messenger transiently generated upon stimulation of membrane receptors such as tyrosine-kinase and G-protein-coupled receptors. DAG mimics the action of phorbol esters, as they bind to the C1 domains in the regulatory region. Only the cPKCs are calcium-sensitive, as they have a calcium-binding C2 domain (the C2 domain in nPKCs is calcium-insensitive). aPKCs display unique regulatory properties: they are unable to bind DAG or calcium and rather depend on protein–protein interactions and phosphorylation for their activation[3] (Figure 1).

In the last years we have witnessed major advances in our understanding of the roles of PKCs in tumor development and progression, including in late stages of the disease and metastasis. This review summarizes the knowledge on PKC isozymes in cancer progression and highlights the most recent advances in the field, particularly using genetically modified mouse models in the context of specific oncogenic alterations.

PKC ISOZYME EXPRESSION IN CANCER: CHANCE OR CAUSALITY?

Expression levels of PKC isozymes change in neoplastic diseases. The overall picture is, however, confusing, partly due to potential issues of antibody specificity in immunohistochemical studies and lack of appropriate validation controls in many reports. The standing question is whether those changes in expression have any causal relationship with disease progression. An additional complication is that, in an era when microarray mRNA databases are routinely used, there are significant discrepancies between the available information on PKC expression at the mRNA and protein levels. This can be epitomized for PKCε, an isozyme that is markedly upregulated in most epithelial cancers at the protein level,[4–7] but shows only marginal or no changes in mRNA databases (Figure 2). Whereas high expression of PKCε in tumors may involve changes at a transcriptional level, expression underestimation by databases may relate to post-translational events that ultimately modify protein stability. Modeling expression patterns from mRNA expression databases, which in most cases have not been generated from microdissected tissues, can distort the actual profile of PKC protein expression in tumors and ultimately mislead our efforts to correlate those changes with clinicopathological outcomes.

Another important issue that received little attention is the activation status of PKC isozymes in cancer. There is little experimental evidence supporting either hyperactivation or hypoactivation of PKCs in human tumors. Unlike other important kinases implicated in cancer progression, such as Erk, JNK or Akt, phosphorylation of PKCs does not necessarily correlate with activation status. One impediment to address this important matter is the lack of reliable readouts associated with the

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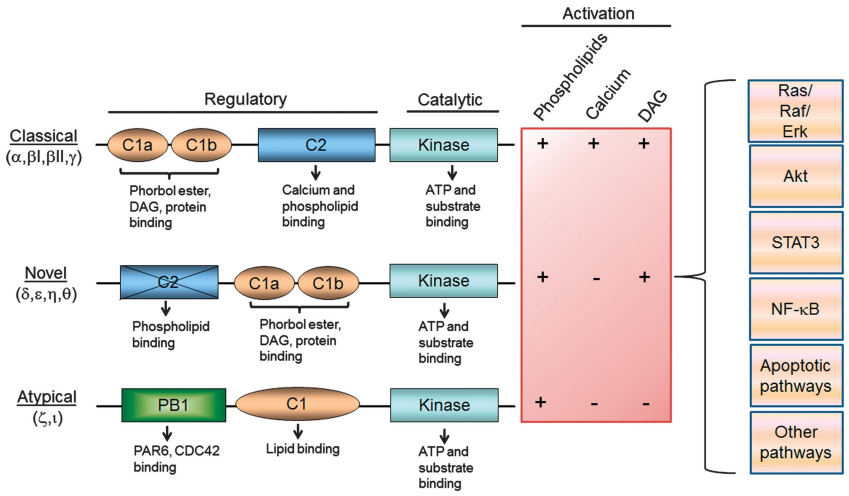

Figure 1. Structure of PKC isozymes. PKCs are multidomain proteins that are regulated by lipids and protein–protein interactions. DAG generated upon activation of receptors causes the activation of cPKCs and nPKCs, and its actions are mimicked by phorbol esters. aPKCs do not respond to DAG or phorbol esters. PKCs activate a number of signal transduction pathways that regulate tumorigenesis and metastasis.

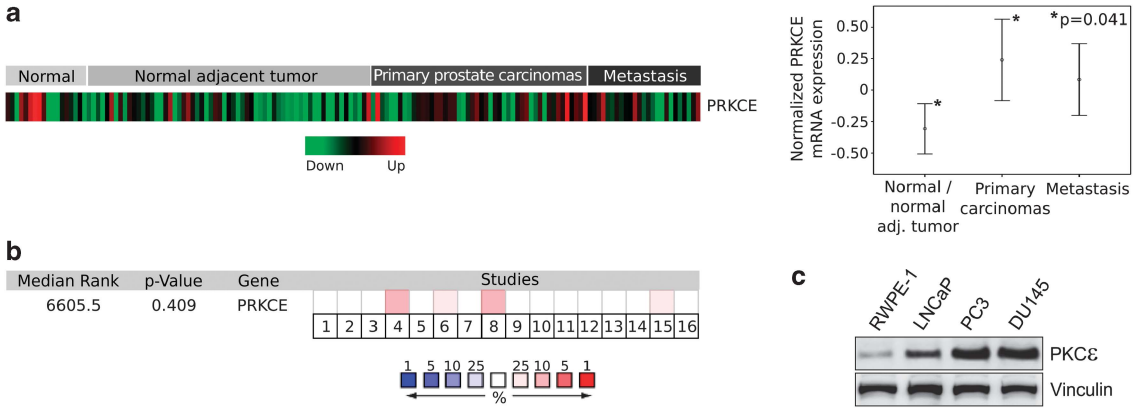

Figure 2. Expression of PKCε in prostate cancer. (**a**) *In silico* PKCε mRNA expression profiling in 81 normal/normal adjacent prostate tumors, 48 primary prostate carcinomas and 25 prostate cancer metastasis obtained from a publicly available data set (GSE6919). *PRKCE*, PKCε gene. (**b**) Meta-analysis of PRKCE mRNA expression across 16 prostate microarray studies from the Oncomine database. This meta-analysis shows non-statistically significant differences in PRKCE mRNA expression (combined *P*-value = 0.41) between normal and prostate cancer groups. Red intensity is a representative of the statistical significance in mean difference between normal and prostate cancer for each study. (**c**) Expression of PKCε in 'normal' immortalized prostate epithelial RWPE-1 cells versus prostate cancer cells. This figure was originally published by Garg *et al.*,[176] The American Society for Biochemistry and Molecular Biology.

activated status of individual PKCs, in particular PKC isozyme-specific substrates that could be detected in human tumors. Genetically encoded reporters for PKC isozymes reliably detect enzyme activation and substrate phosphorylation in cellular models in culture;[8–12] however, we still lack tools to detect activated PKCs or their specific substrates in tumors by immunohistochemistry. The association of PKCs to membranes is a requisite for the activation of DAG/phorbol ester-regulated PKCs.[3] Whereas some exceptions have been reported, such as the activation by proteolytic cleavage,[13] cPKCs and nPKCs translocate to the plasma membrane in response to stimuli such as growth factor receptor activation. Although less understood at a mechanistic level, cPKCs and nPKCs can also redistribute to a number of intracellular compartments, including the translocation to the mitochondria, Golgi, endoplasmic reticulum and nuclear membrane. Constitutive association of PKCs to internal membranes has also been reported.[14–17] At present, we do not understand well the significance of such compartmentalization and whether PKCs are fully activated in discrete intracellular locations due to differential membrane compositions, DAG availability, and/or the presence of isozyme-specific protein partners that cooperate for the transition to an activated status. All these factors conspire against a full appreciation on how PKC activation contributes to disease progression.

PKCα: TUMOR PROMOTER OR TUMOR SUPPRESSOR?

PKCα has been long recognized as a regulator of multiple aspects of tumor growth, including proliferation, survival, differentiation and motility. As several studies linked PKCα to enhanced proliferation and anti-apoptotic signals,[18–22] there has been significant interest in this kinase as a potential target for cancer therapy. However, PKCα had limited success as a drug target for cancer. Indeed, due to its very complex and highly tissue-specific functions, PKCα acts as a tumor promoter or a tumor suppressor depending on the context. To add another level of complexity, PKCα is upregulated in some

cancers (such as bladder, endometrial and breast cancer) and downregulated in others (such as colorectal tumors and malignant renal cell carcinomas[23,24]). There is little information on substrates specifically phosphorylated by PKCα or genetic programs controlled by PKCα, thus rendering our comprehension of the molecular basis of this functional diversity incomplete.

Early studies in glioma cellular models established that PKCα is upregulated relative to astrocytes. Antisense oligonucleotides against PKCα inhibit the proliferation of glioma cells.[25] Consistent with these results, overexpression of PKCα in U87 glioblastoma cells enhances proliferation. Although overexpression of PKCα did not protect U87 cells from apoptosis by etoposide, other studies documented that PKCα renders enhanced resistance to apoptosis in response to radiation and chemotherapy.[18,26,27] In U1242 glioblastoma cells, PKCα regulates the activation of nuclear factor kappa B (NF-κB), which results in a pro-survival phenotype.[28] Aprinocarsen (Ly900003, ISIS 3521), an antisense oligonucleotide directed against the 3′-untranslated region of PKCα, arrests A172 glioma cells and induces p53. Aprinocarsen also impairs tumor growth in xenograft models. In combination with other chemotherapeutic agents, aprinocarsen was shown to have additive or super-additive antitumor effects.[29–31] Despite encouraging responses in early clinical trials, this anti-PKCα agent failed to make it into phase III clinical trials either alone or in combination with other agents.[29] Another PKCα inhibitor, the staurosporine analogue UCN-01[32] proved to be a potent antitumor agent in preclinical models, but its effect cannot be explained simply by PKCα inhibition.[33] It is also intriguing that PKCα RNA interference depletion but not PKCα inhibition impairs the growth of glioma cell lines, suggesting that the effect is independent of the catalytic phosphotransferase activity of the enzyme.[18]

Another interesting link between PKCα and cancer progression has been established in breast. Ways *et al.*[34] showed that ectopic overexpression of PKCα in MCF-7 breast cancer cells (which express low levels of PKCα) enhances proliferative rate, confers anchorage-independent growth and tumorigenic potential in nude mice, and drastically alters cell shape by inducing loss of an epithelioid morphology. PKCα overexpressing MCF-7 cells have reduced estrogen receptor (ER) levels, suggesting that PKCα contributes to the switch from ER-positive to ER-negative status. Likewise, Tonetti *et al.*[35] found that stable overexpression of PKCα in T47-D breast cancer cells is accompanied by downregulation of ER function and confers hormone-independent tumor growth that cannot be inhibited by tamoxifen.[36] A recent study suggests that this effect may be mediated by Notch-4.[37] Elevated PKCα expression was suggested to be a predictor of tamoxifen treatment failure, which fits with the observation that patient tumor samples with elevated PKCα levels are generally negative for ER expression, and these patients respond less to endocrine therapy.[38,39] A recent study by Larsson and coworkers[40] demonstrated that PKCα levels correlates with ER and progesterone receptor negativity, proliferative activity and tumor grade. Thus, altogether it seems that PKCα is a biomarker for poor prognosis and endocrine therapy resistance in breast cancer. PKCα is also an effector of ErbB2 in breast cancer cells, and ErbB2 small interfering RNA depletion decreases PKCα protein levels. Moreover, ErbB2 overexpression correlates with membrane-associated staining of PKCα in human breast cancer specimens, suggesting that ErbB2 drives the constitutive activation of PKCα.[41] Go6976, a pharmacological inhibitor of cPKCs,[42] abrogates ErbB2-mediated upregulation of urokinase-type plasminogen activator and cell invasion.[43] Whereas PKCα expression is higher in triple-negative breast cancers than in other subtypes,[44] we still need to underscore meaningful associations of this PKC with genetic alterations specific for each breast cancer subtype.

In a very recent study by the Weinberg laboratory, PKCα was found to be enriched in epithelial-to-mesenchymal-induced mammary cells.[45] Interestingly, inhibitors targeting PKCα preferentially kill mesenchymal cells relative to epithelial cell lines, and likewise, depletion of PKCα using small hairpin RNA results in a substantial loss of mesenchymal cells. A PKCα signaling network is activated preferentially in cancer stem cells by platelet-derived growth factor and involves the transcription factor FRA1 (Fos-related antigen 1). The activation of the PDGFR-PKCα-FRA1 pathway in breast cancer stem cells makes them particularly susceptible to pharmacological inhibition of PKCα. Whereas the relevance of this pathway has to be established in other cancer types, this study certainly shed light into the potential therapeutic value of targeting PKCα in epithelial cancers.

Despite the reported pro-tumorigenic effects of PKCα, it has been also described as a growth inhibitory kinase in several cell types. For example, activation of PKCα in non-small cell lung cancer (NSCLC) cells leads to $p21^{Cip1}$ upregulation, inhibition of cell growth and senescence.[46] Not surprisingly, aprinocarsen showed no significant benefit for NSCLC patients, either alone or in combination with other chemotherapeutic agents.[29]

Years ago, Black and coworkers[47,48] reported that PKCα activation triggers a program of cell cycle exit-specific events in intestinal crypts through the repression of cyclin D1 translation. This effect implicates the activation of the translational repressor 4E-BP1 through a phosphatase 2A-dependent mechanism and in a PI3K/Akt-independent manner.[49] PKCα also inhibits the Wnt/β-catenin pathway in colon cancer cells and represses the expression of β-catenin target genes such as c-Myc,[50] a mechanism that may involve receptor-related orphan receptor alpha RORα.[51] Interestingly, a small-molecule screening identified a compound (CGK062) that promotes PKCα-mediated phosphorylation of β-catenin, leading to its proteasomal degradation. This compound has antitumor effects in nude mice.[52] The expression of PKCα in proliferating intestinal epithelial cells is repressed both *in vitro* and *in vivo* by the SOX9 transcription factor.[53] All neoplasm arising in $APC^{-/+}$ mice, which develop multiple intestinal neoplasia, express low levels of PKCα. Remarkably, loss of PKCα directly correlates with aggressiveness of intestinal tumors. Furthermore, tumor formation and aggressiveness are enhanced in double transgenic $APC^{Min/+}$; $PKC\alpha^{-/-}$ mice (Figure 3a). Interestingly, spontaneous intestinal tumors develop in $PKC\alpha^{-/-}$ mice.[54,55] PKCα also suppresses skin tumor formation induced by DMBA (7,12-dimethylbenz[a]anthracene). However, PKCα deficiency does not alter the size or malignancy of skin tumors.[56]

PKCα activation by phorbol esters contributes to cell death in androgen-dependent prostate cancer cells. Activation of PKCα in

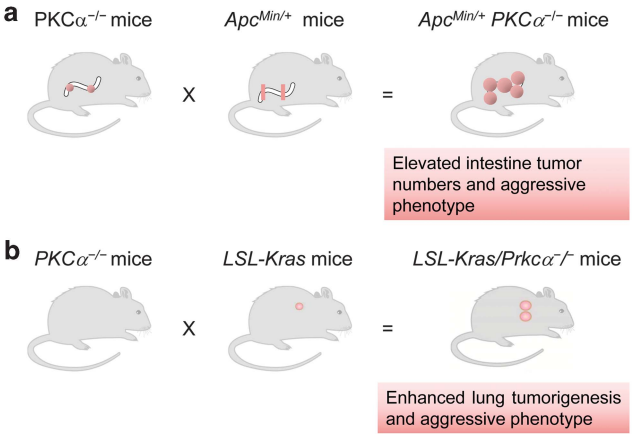

Figure 3. Loss of PKCα gene enhances tumor progression. (**a**) Deletion of the PKCα gene enhances the formation of tumors in $APC^{Min/+}$ mice, and those tumors show a more aggressive phenotype. (**b**) Deletion of PKCα in K-Ras mutant mice resulted in progression of benign tumors to adenocarcinoma. Tumors exhibit high frequency and grade, and are bigger in size.

LNCaP cells leads to a rapid and reversible dephosphorylation of Akt possibly via activation of a protein phosphatase 2A phosphatase.[57] Stable DAG analogues with preferred selectivity for PKCα also induce apoptosis in LNCaP cells.[58] A kinase-dead PKCα mutant blocks the apoptotic response elicited by a combination of phorbol 12-myristate 13-acetate (PMA) treatment and radiation, and a constitutively active PKCα mutant sensitizes cells to radiation treatment. Although radiation alone reduces initial LNCaP tumor growth and serum prostate-specific antigen levels in mice, combinatorial treatment with PMA or a specific PKCα DAG activator eliminates tumor growth and drastically reduces prostate-specific antigen levels.[59]

A very interesting recent study by the group of Alan Fields reported that PKCα has a key role in K-Ras-mediated lung tumorigenesis.[60] There is an evident loss of expression of PKCα in primary human NSCLC tumors. Remarkably, PKCα-knockout mice display enhanced K-Ras lung tumorigenesis (Figure 3b) and bypass oncogene-induced senescence. The tumor promoting effect caused by loss of PKCα may involve the expansion of bronchoalveolar stem cells. Mechanistic analysis determined that loss of PKCα reduces the activation of p38 mitogen-activated protein kinase in bronchoalveolar stem cells from K-Ras tumors and augments transforming growth factor β1 (TGFβ1) mRNA levels. Moreover, a TGFβ receptor inhibitor reversed the effect of PKCα loss in K-Ras/PKCα-depleted tumors. This study reported the inhibitors of DNA binding (Id) Id1-3 as potential downstream targets of PKCα-dependent tumor suppressor activity, as also observed in other intestinal cells and fibroblasts.[61,62] Therefore, PKCα suppresses tumor initiation and progression in the K-Ras lung cancer mouse model through a p38 mitogen-activated protein kinase/TGFβ signaling axis.

PKCα has been implicated in invasion and metastasis, mostly as a positive regulator.[63–68] In breast cancer cells, ErbB2-dependent activation of PKCα promotes cell invasion.[41] PKCα overexpressing MCF-7 breast cancer cells display enhanced motility, which was attributed to decreased expression of E-cadherin and β-catenin and high expression of matrix metalloprotease (MMP)-2/MMP-9.[69,70] A specific PKCα peptide inhibitor significantly reduced metastasis of mouse mammary cancer cells to the lungs. Analysis of highly metastatic (4T1) and non-metastatic (JC) mouse mammary cells indicates that the basal activation of PKCα is higher in the former. Treatment with this PKCα antagonistic peptide did not affect tumor growth but blocked metastasis of 4T1 cells to the lungs. PKCα inhibition blocks metastasis by inhibiting the activation of MMPs in combination with decreased NF-κB activity and CXCL12 receptor levels.[71]

PKCβ ISOZYMES: SPLICED VARIANTS WITH DISTINCT INVOLVEMENT IN CANCER

PKCβI and PKCβII, spliced variants encoded by the *PRKCB* gene have differential tissue expression and a distinct involvement in cancer. PKCβ isoforms have been implicated in the progression of many cancer types, including lymphoma, glioblastoma, breast, prostate and colorectal cancers.[72–76] It is not fully understood why PKCβ isoforms have in some cases different functions. This may relate to unique lipid- and protein interactions via their different C-terminal domains that confer distinctive localization properties.[77–79] However, many studies using pharmacological agents do not distinguish between PKCβ subtypes.

Early studies reported elevated PKCβII levels both during the initial stages of tumorigenesis and in colonic carcinomas relative to normal colonic tissue.[80–82] Spindler *et al*.[83] reported that 18% of primary adenocarcinomas exhibit very high levels of PKCβII, which correlates with poor survival rates. PKCβII has been implicated in colon cancer cell proliferation *in vitro*.[84,85] Murray *et al*.[86] generated a transgenic mouse model overexpressing PKCβII in the intestinal epithelium. In addition to epithelial hyperproliferation, these mice display increased susceptibility to carcinogen-induced preneoplastic lesions in the colon. The phenotype has been linked to repression of TGFβ signaling and elevated COX-2 expression.[72] In the proximal colon, activated K-Ras induces the expression of PKCβII, activation of the Mek/Erk signaling axis and increased epithelial cell proliferation.[87] In a cellular model of intestinal cells, stable overexpression of PKCβII confers an invasive phenotype mediated by a Ras/Mek/PKCι/Rac1-dependent pathway.[88] The role of PKCβI in the colon is less clear. Overexpression of PKCβI suppresses the growth of HT29 and SW480 colon cancer cell xenograft.[89] However, other report shows that expression of PKCβI confers resistance to apoptosis by tumor necrosis factor α (TNFα) and paclitaxel.[90]

PKCβI expression positively correlates with high Gleason scores in prostate carcinomas, and inhibition of this kinase blocks androgen receptor-induced tumor cell proliferation *in vitro* and xenograft growth *in vivo*. Notably, PKCβI phosphorylates histone H3 and inhibits androgen-dependent transcription.[91] A study using a specific PKCβII peptide inhibitor showed that this isoform is involved in prostate cancer cell proliferation. PKCβII also has an important role in endothelial cell proliferation, and inhibition of PKCβII reduces angiogenesis. These effects were linked to dysregulation of cytokinesis and microtubule organization.[73] Enzastaurin, an inhibitor with some degree of specificity toward PKCβ, displays antiproliferative effects in PC-3 cells.[92]

Overexpression of either PKCβI or PKCβII in MCF-7 breast cancer cells promotes cell growth and enhances cyclin D1 levels, whereas dominant-negative PKCβ mutants inhibit growth.[93] On the other hand, another report showed that PKCβI overexpression induces a less aggressive biological behavior in MCF-7 cells characterized by reduced tumor formation.[94] In a murine mammary model, PKCβI inhibits tumorigenesis despite having a positive effect on growth in culture. Moreover, tumor cells that overexpress PKCβI have attenuated metastatic capacity to the lungs.[95] Enzastaurin has significant effects on the growth of breast cancer cells *in vitro* and *in vivo*.[96,97] High levels of PKCβII have been reported in several breast cancer cell lines and patient samples. The levels of cytoplasmic PKCβII expression positively correlate with ErbB2/Her2 levels, whereas nuclear PKCβII positively correlates with ER levels.[98]

PKCβII is expressed in human NSCLC specimens with significant variability, both in tumor cells and the stroma.[99] Enzastaurin in combination with the antifolate pemetrexed causes G2/M checkpoint abrogation and apoptosis in lung cancer cells.[100] In cell culture, enzastaurin is a potent inhibitor of vascular endothelial growth factor-stimulated proliferation of endothelial cells, and *in vivo* this inhibitor causes a significant reduction in intratumoral vessels that parallels a delay in lung cancer tumor growth.[99] Enzastaurin also enhances the anti-angiogenic effects of radiation in NSCLC models.[101] The PKCβ inhibitor, Enzastaurin, regulates proliferation of glioblastoma cells by supporting the activity of GSK3, S6 kinase and Akt.[102] The effect of the PKCβ inhibitor was also shown in U87MG human glioblastoma cells inoculated into nude mice. Enzastaurin proved to be efficient as an anti-angiogenic compound in models of glioblastoma,[76] however clinical trials in patients with recurrent high-grade glioma show limited success when this inhibitor was used as a monotherapy.[103]

Patients with diffuse large B-cell lymphoma that express PKCβ have reduced overall survival compared with those that are negative for this kinase.[104,105] Enzastaurin displays pro-apoptotic properties in T-cell and B-cell lymphoma cell lines.[106,107] There is significant interest in using this PKCβ inhibitor for the treatment of various types of lymphomas, both as a single agent and in combination therapies.[108,109] Taking advantage of a PKCβ-knockout mouse model, it has been recently demonstrated that stromal PKCβII is indispensable for the survival of chronic lymphocytic leukemia B cells. The fact that stromal PKCβII is upregulated in biopsies from patients with chronic lymphocytic

leukemia , and that chronic lymphocytic leukemia cells induce the expression of stromal PKCβ,[110] highlights the need to better understand how this PKC contributes to cancer development in the context of the different tumor microenvironments.

PKCδ: COMPLEX ROLES IN APOPTOSIS, TUMOR GROWTH AND METASTASIS

PKCδ has been widely characterized as a pro-apoptotic and antiproliferative kinase. In addition, PKCδ has been broadly implicated as a death mediator of chemotherapeutic agents and radiotherapy.[111–114] PKCδ is involved both in DNA damage and receptor-mediated cell death.[3,114,115] Initial work from the Reyland lab showed that PKCδ is cleaved by caspase-3 and mobilizes from the cytoplasm to the nucleus after treatment with genotoxic agents.[13] Other studies showed that PKCδ-mediated apoptosis involves the allosteric activation of the enzyme rather than proteolytic cleavage. For example, in androgen-dependent prostate cancer cells, PKCδ activation triggers an apoptotic response without the generation of a constitutively active catalytic fragment.[116] This effect involves the activation of the p38 mitogen-activated protein kinase cascade[57] and is mediated by a RhoA/ROCK/p21^{Cip1}-dependent pathway.[117] PKCδ-mediated apoptosis in androgen-dependent prostate cancer cells occurs through the autocrine secretion of TNFα and TNF-related apoptosis-inducing ligand, which induce caspase-8 cleavage through the JNK and p38 mitogen-activated protein kinase cascades.[118–120] The discrepancies in the mechanisms of PKCδ activation among the various studies may be explained by cell type differences and nature of the stimulus.

An inhibitory role for PKCδ in proliferation has been reported in a number of cellular models. The initial observations by Mischak *et al.*[121] that ectopic overexpression of PKCδ confers growth inhibitory properties to NIH 3T3 cells, were later recapitulated in many other cell lines. Depending on the cell type, activation of PKCδ can induce cell cycle arrest either in G1 or G2.[48,122] Our laboratory showed that treatment of lung cancer cells with phorbol esters induces cell cycle arrest in G1 through the induction of p21^{cip1} and Rb dephosphorylation.[123] However, it has been also noted that ectopic expression of PKCδ stimulates quiescent cells to initiate the G1 phase cell cycle progression. Notably, PKCδ-overexpressing cells arrest in S-phase rather than completing the cell cycle.[124]

It is important to mention that studies ascribed pro-survival properties to PKCδ in a number of tumor models, including breast, lung, pancreatic and liver cancer.[115] Moreover, ectopic expression of PKCδ in mammary cells confers anchorage-independent growth properties and enhances the resistance to apoptotic stimuli.[125] The scenario that PKCδ could be a tumor promoting kinase rather than a tumor suppressor began to shape new paradigms in PKC isozyme function, and clearly points to an exquisite cell type selectivity.

Data from patients cannot point to a clear link between PKCδ expression levels and clinical outcome. Loss of PKCδ expression has been reported in a few cancer types,[126–128] but this downregulation could not be unambiguously linked to tumorigenesis. PKCδ is upregulated in some cancer types.[129,130] PKCδ is barely detected in normal prostate epithelial cells; however, high PKCδ expression could be observed in prostate preneoplastic lesions and carcinomas.[131,132] In breast cancer specimens, PKCδ mRNA levels are significantly higher in ER-positive tumors and a positive correlation between high PKCδ mRNA levels and reduced overall survival has been reported.[133] Interestingly, the expression of PKCθ, an isozyme related to PKCδ, is dysregulated in some cancers.[130,134–136]

Emerging studies using genetically engineered mice began to shed light into the involvement of PKCδ in tumorigenesis. PKCδ skin transgenic mice are resistant to tumor promotion by DMBA/PMA.[137] Studies using PKCδ-knockout mice revealed contrasting effects particularly in the context of specific genetic alterations. Reyland and coworkers[138] investigated the involvement of PKCδ in K-Ras-dependent tumorigenesis and found that the incidence of urethane-induced lung tumors (which display activating mutations in K-Ras) is reduced in a PKCδ-null background. Moreover, PKCδ RNA interference depletion inhibits anchorage-independent growth, invasion, migration and tumorigenesis in K-Ras-dependent NSCLC cells. The Reyland lab also described a positive role for PKCδ in mammary tumorigenesis in the context of ErbB2 overexpression. A meta-analysis of ErbB2-positive breast cancers shows increased PKCδ expression and a negative correlation between PKCδ expression and prognosis. Most remarkably, there is a significant delay in tumor onset in MMTV-ErbB2(Neu) in a PKCδ-null background.[139] A tumorigenic role for PKCδ has been also reported in a model of pancreatic cancer. Indeed, overexpression of PKCδ (as observed in human ductal carcinomas) leads to increased anchorage-independent growth and tumorigenesis *in vivo*.[140] In addition, in a PC-3 xenograft model, PKCδ activation promotes tumor growth and increases angiogenesis through a mechanism that involves reactive oxygen species, nicotinamide adenine dinucleotide phosphate and hypoxia-inducible factor 1α.[141]

PKCδ generally has a positive role in migration and invasiveness.[142–145] In prostate cancer cellular models, PKCδ has been implicated in invasiveness and the control of collagen secretion induced by overexpression of the oncoprotein PCPH.[132] Breast cancer models provided controversial evidence for the involvement of PKCδ in invasion. Whereas a study showed that PKCδ overexpression in highly motile BT-549 breast cancer cells reduces migration and PKCδ downregulation enhances motility and MMP-9 secretion in MCF-7 cells[146] other study reported that enhanced migration induced by forced epidermal growth factor receptor overexpression in MCF-7 cells requires PKCδ.[147] PKCδ was found to inhibit the production of proteolytic enzymes in murine mammary cells, possibly limiting metastatic dissemination.[125] Downregulation of PKCδ suppresses lung colonization in the murine mammary breast cancer model MTLn3 without affecting the growth of primary tumor.[148] Studies performed in BL6 murine melanoma cells showed that PKCδ overexpression increases their metastatic capacity *in vivo*, possibly due to an increase in the plasma levels of TGF-β1.[149,150] A similar pro-metastatic effect of PKCδ has been shown in the human pancreatic cell line PANC1.[140]

The multiplicity of effects regulated by PKCδ and the complexity of the effects in cell cycle regulation, cell motility, tumorigenicity and metastasis, both in positive and negative manners (Figure 4), would argue that this kinase is not a likely candidate for the therapy of cancer.

PKCε: AN ONCOGENIC AND METASTATIC KINASE

PKCε has been originally described as an oncogenic kinase[121,151,152] and is known to signal via the Ras-Raf-1 signaling pathway[153–156] as well as other pathways. PKCε-transformed fibroblasts secrete increased amounts of TGF-β and possibly other mitogens, an indication that growth autocrine loops may account for its oncogenic activity[157,158] PKCε is overexpressed in a large number of cancers. For example, PKCε is overexpressed in ~75% of primary tumors from invasive ductal breast cancer patients. Increased PKCε staining correlates with high histological grade, positive ErbB2/Her2 status and negative estrogen and progesterone receptor status.[7] Overexpression of PKCε has been reported in the majority (>90%) of primary NSCLC cancers relative to normal lung epithelium.[5] PKCε levels are elevated in prostate cancer relative to benign prostatic epithelia,[159] and a correlation with aggressiveness of human prostate cancer has been found.[4] PKCη, an isoform related to PKCε, has also been shown to be upregulated in some cancers,[160,161] but downregulated in others.[162]

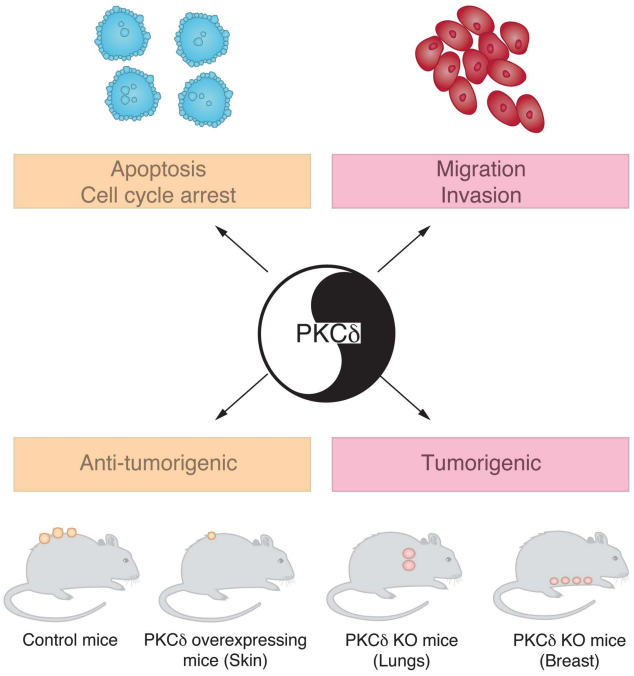

Figure 4. Multiple biological functions regulated by PKCδ. Studies in cellular models established important roles for PKCδ in apoptosis and as a negative regulator of cell cycle progression. PKCδ has been also implicated in cancer cell motility and invasiveness. Studies using animal models showed that PKCδ can either act as a tumor suppressor or contribute to tumorigenesis depending on the context.

Not surprisingly, studies from several laboratories highlight a role for PKCε in cell cycle control, specifically in G1 to S progression.[163–165] In addition, PKCε promotes survival in many cell types.[6,166–168] The survival activity of PKCε involves the modulation of caspases and Bcl-2 family members.[166,169–171] Forced expression of PKCε in LNCaP prostate cancer cells confers resistance to PMA-induce apoptosis by preventing Bax oligomerization; moreover, it leads to accelerated proliferation of LNCaP cells due to constitutive activation of the Erk cascade.[167] Our laboratory recently demonstrated that PKCε modulates Bad phosphorylation at Ser112 to protect LNCaP prostate cancer cells against apoptosis induced by PMA or TNFα.[170] PKCε protects glioma and lung cancer cells from TNF-related apoptosis-inducing ligand-induced apoptosis.[168,172,173] Subsequent studies by Basu and coworkers[174] revealed that PKCε inhibits cell death in breast cancer cells, partly by preventing the activation and translocation of Bax to the mitochondria. PKCε inhibition/depletion impairs proliferation and anchorage-independent growth of human NSCLC cells.[5,175] Many pro-apoptotic genes upregulated upon PKCε RNA interference depletion in lung cancer cells are also downregulated in human lung adenocarcinomas.[175] RWPE-1 cells, a model of normal immortalized prostate epithelial cells, express very low levels of PKCε as compared with different human prostate cancer lines, and ectopic expression of PKCε in RWPE-1 cells confers growth advantage and leads to Erk and Akt activation.[6] Recently, our laboratory identified a key role for PKCε as a mediator of NF-κB signaling in prostate cancer.[176] PKCε inhibition/depletion impairs constitutive and TNFα-dependent activation of NF-κB as well as the induction of NF-κB responsive genes pertaining to cell survival, proliferation, metastasis and invasion, such as COX-2, MMP-9, vascular endothelial growth factor and interleukin-6.[176]

Overexpression of PKCε in androgen-dependent LNCaP cells initiates tumor growth *in vivo* both in intact and castrated athymic nude mice,[177] thereby indicating that PKCε has the potential to advance the progression of prostate cancer and initiate recurrent tumor growth in the absence of androgens. In concordance, another study found that PKCε overexpression in breast cancer cells causes tumor growth in BALB/c mice with significant increase in the incidence and number of spontaneous experimental lung metastases.[95] In line with these results, depletion of PKCε from lung cancer cells using small hairpin RNA markedly inhibited xenograft growth in nude mice. Furthermore, the PKCε translocation inhibitor peptide εV1-2 blocks NSCLC tumor growth in nude mice. Moreover, both small hairpin RNA depletion and pharmacological inhibition of PKCε causes a strong induction of cell death in xenograft tumors.[175]

Unfortunately, there has been little work intending to recapitulate PKCε overexpression as observed in human cancer. Our laboratory developed prostate-specific transgenic mice that overexpress PKCε in the normal prostate *in vivo* under the control of the androgen-responsive probasin (PB) promoter, which leads to the formation of preneoplastic lesions (Figure 5). Conversely, similar mouse models for other PKCs (PB-PKCα and PB-PKCδ mice) do not display any noticeable phenotypic changes in the prostate. Furthermore, elevated phospho-Akt as well as hyperactivation of Akt effectors S6 and mTOR could be detected in hyperplasia and prostatic intraepithelial neoplastic (PIN) lesions from PB-PKCε transgenic mice. Besides, PKCε overexpression confers resistance to apoptosis induced by androgen ablation, highlighting a pro-survival role of PKCε in the mouse prostate.[6] Hyperactivation of NF-κB and Stat3 were evident in the PIN lesions of PB-PKCε transgenic mice relative to the normal areas or regions with mild hyperplasia.[6,176]

Prostates of TRAMP mice (a model that spontaneously develops progressive invasive prostate cancer) have very high PKCε protein levels compared with prostates of control mice.[4] A recent study demonstrated that genetic ablation of PKCε in TRAMP mice inhibits prostate cancer development and metastasis.[178] Deletion of PKCε in TRAMP mice decreases the phosphorylation/activation of Stat3 as well as its nuclear translocation and DNA-binding activity. It has been proposed that loss of PKCε in TRAMP transgenic mice reduces the expression of proliferation, survival and metastasis markers, including COX-2, Bcl-xL, cyclin D1 and vascular endothelial growth factor as well as it decreases serum interleukin-6 levels.

A growing body of evidence indicates that PKCε is implicated in tumor cell invasion and metastasis. Enhanced PKCε levels are associated with invasion and/or metastasis of human breast, glioma and renal cell carcinoma.[7,164,179] PKCε contains an actin-binding motif that positions this kinase within a cytoskeletal matrix where many PKC substrates are localized.[180–183] Deletion of this motif abrogates invasion and metastatic spread of tumors driven by PKCε overexpression.[184] In human glioma cells, the PKC-interacting protein RACK1 appears to link activated PKCε to the integrin β chain at focal adhesions, and PKCε mediates the adhesion and motility of cells via Erk phosphorylation.[185] PKCε also promotes the assembly of matrix adhesions containing actin filaments and β1-integrins, and integrin signaling links PKCε to the Akt survival pathway in recurrent prostate cancer cells.[186] In models of breast and head and neck cancer, PKCε regulates motility and invasion, at least in part due to the activation of small Rho GTPases, specifically RhoA and/or RhoC.[7,187] Very recent work from our laboratory showed that targeted disruption of PKCε in lung cancer cells reduces motility through Rac1 inactivation. Several extracellular matrix proteases are downregulated in PKCε-depleted lung cancer cells.[188] Consistent with a role for PKCε in metastatic dissemination, PKCε-depleted NSCLC cells fail to colonize lungs after tail vein injection in mice.[188] Likewise, a study from the Urtreger's laboratory showed that inoculation of

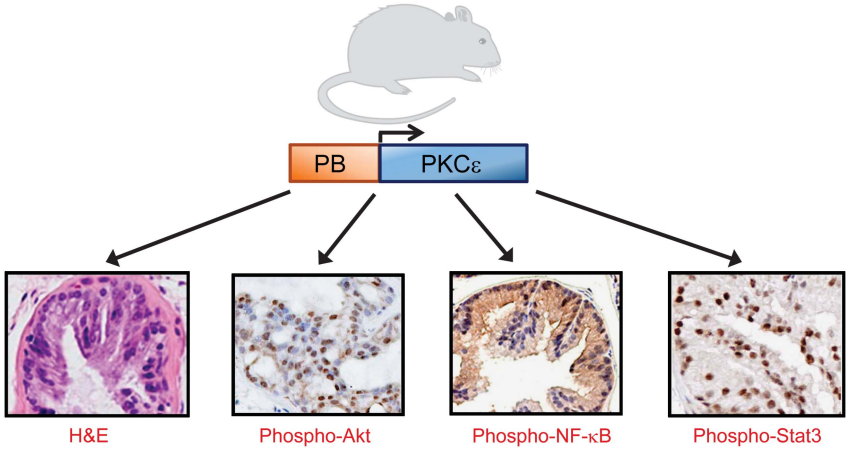

Figure 5. Phenotype of prostate-specific PKCε transgenic mice. Prostate-specific overexpression of PKCε in mice under the control of the probasin (PB) promoter leads to a preneoplastic phenotype. Representative photomicrographs for hematoxylin and eosin (H&E), phospho-Akt, phospho-NF-κB and phospho-Stat3 staining in ventral prostates from 12-month-old male PB-PKCε mice are shown.

PKCε overexpressing breast cancer cells in mice enhances the incidence and number of spontaneous and experimental lung metastases.[95]

Verma and coworkers[189,190] generated skin transgenic mice expressing PKCε under the control of the human K14 promoter, which exhibit phenotypic abnormalities including inflammation, hyperkeratosis, hyperplasia, cellular hypertrophy and ulceration. Highly malignant and metastatic squamous cell carcinomas develop in the skin of PKCε transgenic mice. Additionally, PKCε overexpression has been shown to sensitize the mouse skin to UVR-induced carcinogenesis.[191] A subsequent study demonstrated that skin transgenic PKCε mice develop a myeloproliferative-like disease.[192]

Altogether, these observations establish that PKCε overexpression is linked to an aggressive phenotype and suggest that targeting PKCε could be an effective anticancer strategy. Whereas the development of PKCε inhibitors targeting the ATP-binding site may be challenging due to the high homology of this site among PKCs, agents directed against domains implicated in translocation may be valuable. In that regard, the PKCε translocation inhibitor εV1-2 has anti-tumorigenic activity in NSCLC cells[175] and a bifunctional peptide in which εV1-2 has been linked to the 12-mer cancer homing peptide HN1 impairs the growth of head and neck squamous cell carcinoma cells in xenografts.[193] Lastly, Ras-driven and epithelial-to-mesenchymal-dependent phenotypes in breast cancer cells could be reversed by PF-526355, an ATP mimetic inhibitor with selectivity for PKCε and PKCθ. This inhibitor impairs the growth of MDA-MB-231 breast cancer xenografts in mice, thus representing a promising agent for cancer therapy.[194]

ATYPICAL PKCS ζ AND ι: OPPOSITE ROLES IN CANCER

aPKC isozymes, which comprise PKCζ and PKCι (PKCλ), are structurally and functionally distinct from other PKCs in that they have a single DAG/phorbol ester unresponsive C1 domain and lack a C2 domain.[195,196] Regardless of controversies in the literature largely due to the use of non-specific approaches such as inhibitory peptides and dominant-negative mutants, many studies point to a tumor suppressor function of PKCζ, whereas PKCι essentially fulfills the criteria of an oncogenic kinase (Figure 6).

Both up and downregulation of PKCζ has been shown in human cancer. PKCζ upregulation has been reported in prostate cancer, bladder cancer and lymphomas,[197–202] whereas downregulated

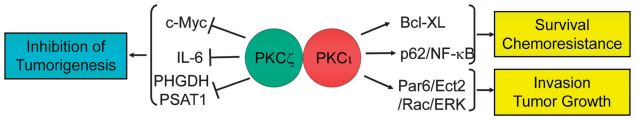

Figure 6. Roles of atypical PKCs in cancer. Most evidence points to PKCζ as a tumor suppressor protein and PKCι as an oncogenic kinase.

expression of PKCζ has been shown in glioblastoma, lung cancer, kidney, renal clear cell carcinoma, melanoma and pancreatic cancer.[203–212] A pro-apoptotic function for PKCζ has been described in several cancer models. For example, PKCζ inhibits growth and promotes differentiation and apoptosis in colon cancer cells. The inhibitory effect of PKCζ on the transformed phenotype of these cells suggests that downregulation of PKCζ may contribute to colon tumorigenesis.[213] PKCζ also exhibits a pro-apoptotic function in ovarian cancer.[214] In murine TRAMP prostate cancer cells, expression of a constitutively activated PKCζ mutant enhances proliferation, whereas PKCζ inhibition leads to Akt activation and enhanced cell survival.[215] There are several reports, however, highlighting a pro-survival role for PKCζ.[216–220]

PKCζ-deficient mice display increased Ras-induced lung carcinogenesis, arguing for a role for this aPKC as a tumor suppressor *in vivo*. It has been postulated that the tumor suppressor activity of PKCζ occurs through its ability to downregulate Ras-induced interleukin-6 production. The enhanced secretion of interleukin-6 in PKCζ-deficient Ras-transformed cells is essential for growth under conditions of limited nutrients and mitogens.[209] Genetic inactivation of PKCζ in mice in a Pten-deficient background leads to invasive prostate carcinoma. A significant correlation between PKCζ and Pten levels exists in human prostate tumors, and PKCζ is significantly reduced in metastatic versus primary tumors with low Pten. Analysis of gene signatures in PKCζ-deficient cells revealed a link with c-Myc. Indeed, c-Myc is a contributor to the more aggressive phenotype associated with PKCζ loss.[221] Loss of PKCζ also allows glucose-addicted human cancer cells to reprogram their metabolism in response to glucose deprivation by augmenting the utilization of glutamine through the serine biosynthetic pathway.[222]

Accumulating evidence established that PKCι is an oncogenic kinase and that it contributes to the transformed phenotype. Overexpression of PKCι is observed in many human cancers,

including colon, lung, pancreas, breast, prostate and ovarian cancer. The PKCι gene (*PRKCI*) is amplified in some human cancers,[223–225] although PKCι overexpression is not always associated with gene amplification.[226–228] This has been well summarized in a review by Murray *et al.*[229]

PKCι expression is elevated in NSCLC tumors and cell lines, and is required for the transformed phenotype of NSCLC cells harboring oncogenic K-Ras mutation.[230–233] NSCLC cell lines without Ras mutation also depend on PKCι for their malignant phenotype if they harbor *PRKCI* gene amplification.[233] PKCι mediates its effects through a Rac1-Pak-Mek-Erk-dependent mechanism.[88] By means of a proteomics approach, Justilien *et al.*[234] identified the Rho-GEF Ect2 as a component of the PKCι–Par6 complex that is required for transformed growth. The Ect2 gene co-amplifies with *PRKCI* suggesting a coordinated mechanism for tumorigenesis. Disruption of the PKCι–Par6 interaction, as caused with the anti-rheumatic agent aurothiomalate, potently inhibits growth of PKCι-overexpressing cell lines. Anti-rheumatic agent aurothiomalate inhibits K-Ras-mediated expansion of bronchoalveolar stem cells and lung tumor growth *in vivo*.[231,235] On the other hand, aPKCs appear to be dispensable for mammalian hematopoietic stem cell function.[236] PKCι has been also implicated in colon and pancreatic cancer using cell lines and animal models.[227,228] PKCι is required for hedgehog signaling in basal cell carcinomas. Indeed, PKCι functions downstream of smoothened (SMO) to phosphorylate and activate the GLI1 transcription factor. Moreover, PKCι is upregulated in tumors resistant to SMO inhibitors, and targeting PKCι suppresses the growth of resistant basal carcinoma cell lines.[237] Other interesting signaling connections have been established for PKCι, including mutually antagonistic regulation with RhoB in glioblastoma cell invasion,[238] links with the NF-κB pathway[239,240] as well as association with cell cycle proteins cyclin E in ovarian cancer,[224] and S-phase kinase-associated protein 2 in esophageal cancer.[241]

FINAL REMARKS

Tangible progress has been made in the last 30 years in understanding the regulation and cellular functions of PKC isozymes in cancer. The picture that emerged, however, is less than clear. What we have learned over the last years is that the biology of PKC isozymes is exceptionally complex, and that many studies in cell lines do not necessarily apply to *in vivo* models. For the next wave of studies on PKC function, the generation of animal models recapitulating the scenarios observed in different cancer types should be a priority. However, it is still not known whether the activation status of different members of the PKC family is altered in cancer and whether activated PKCs functionally interact with oncogenes and tumor suppressors genes driving the tumorigenic and metastatic phenotype.

One would expect that PKC is a promising target for cancer therapy, but only for specific PKC isozymes that display oncogenic activity, such as PKCε and PKCι. The portfolio of available PKC inhibitors remains narrow, and unfortunately the majority of compounds lack specificity among members of the PKC family or even with other kinases unrelated to PKC. Hence, there is a great need to design selective small-molecule inhibitors for PKC isozymes that have sufficient potency to impair PKC function *in vivo*. There may be concrete opportunities to rationally design inhibitors against the ATP-binding site, but this is still challenging due to the high homology among PKCs in that region. Some examples of small molecules capable of disrupting protein–protein interactions for PKC isozymes provided proof-of-principle for alternative approaches in the design of PKC modulators.[175,235,242] C1 domain ligands, such as the bryostatins,[243,244] did not show major beneficial effects in patients despite their anti-tumor effects in mice.[242] One may envision that PKC isozyme-specific inhibitors may possibly work in combined therapies with chemotherapeutic agents for discrete cancer types. Translating PKC modulators into a clinical setting remains a formidable challenge that we face for the next years.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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