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Editorial
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PKC: An Ambiguous Target in Cancer Therapy

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Editorial

The normal physiological status of living cells mainly depends on their interacting ability with neighboring cells and extracellular stimuli. In response to the extracellular stimuli, cells processed the signals and produce an appropriate response [1]. These signals amplitudes are controlled by various protein kinases. Among them, PKC family represents 2% of kinome and control myriad signaling pathways, and thus, regulates multiple cellular functions like apoptosis, migration, metabolism, and so on. Therefore, modulation in the PKC signaling pathways causes diseasesd conditions, including cancer [2]. The PKC family with 10 different isoforms activated by variety of stimulators such as hormones, growth factors, and neurotransmitters activate phospholipase C to induce diacylglycerol (DAG) generation. The member of classical PKC isoform (cPKC: α, βI, βII and γ) comprises C1 and C2 domain binds with DAG and Ca^{2+} respectively for enzyme activation. The novel PKC isoform (nPKC: δ, ε, θ and η) consists of C1 domain and a novel C2 domain, therefore, nPKC not sensitive to Ca^{2+} is activated by DAG alone. Atypical PKC (aPKC: ζ, λ/ι) contains an atypical C1 domain and therefore, activated in the absence of DAG and Ca^{2+}. All the PKC isoform comprises highly conserved catalytic domain that includes ATP binding region (C3) and protein kinase domain (C4) at carboxyl terminal. In addition, a pseudo substrate sequence is present in all the PKC isoform at their regulatory region to maintain the inactive state of the enzyme [3,4]. PKC was first discovered as a kinase in 1977 by Nishizuka and coworkers et al. [5], but later on, it was found that PKC could be activated by phorbol ester; a tumor promoting factor, opened the door for designing and developing a better anticancer drug targeting PKC [6]. In addition, numerous studies from basic and clinical trials revealed that PKC efficiently regulates multiple cellular functions such as uncontrolled growth, morphological changes, and invasion during neoplastic growth [4]. For instance, PKC-α regulate transformation of non-stem cancer cells to cancer stem cells during breast cancer progression, melanoma vasculogenic mimicry and melanoma cell survival [7-9]. Moreover, PKC-α also implicated in P-glycoprotein (Pgp) mediated MDR in the various cancer cells such as colon cancer, gastric cancer, leukemia, and breast cancer [10]. Besides, higher level of PKC-α is expression detected in malignant glioma cells and non-small-cell lung cancer (NSCLC) [11,12]. However, selective inhibition of PKC-α by αV5-3 reduces 90% metastasis of mammary tumor to lungs in a mouse model [13]. The two splice variant of PKC-β, especially PKC-βII is a critical factor for vascular endothelial growth factor-induced tumor angiogenesis and metastasis of breast cancer cell [14]. In addition, PKC-β found to regulate various aspect of cancer progression in colon, human prostate, lymphoma, breast and glioblastoma [15-19]. Generally, PKC-δ has long been known as a pro-apoptotic factor, but accumulating data indicated that PKC-δ acts as a survival factor in various cancer cell lines including lung, breast, liver and pancreatic cancer [20]. Overexpression of PKC-ε, the first identified oncogenic isoform of PKC has been found in the lung cancer, thyroid cancer, breast cancer, and colon cancer [21]. Numerous studies have established that PKC-η is responsible for tumor aggression and sustained proliferation in non-small cell lung cancer, whereas, PKC-θ exhibit oncogenic properties in stromal tumors [22,23]. Despite the anti-apoptotic and pro-proliferative activity of PKC, several studies have discussed the tumor suppressive role of PKC in various cancer cell lines [3,4,24-26]. In a comprehensive study, A.C. Newton and coworkers revealed that out of the total mutation in PKC identified during cancer progression in human, 61% mutation were the Loss of Function (LOF), suggesting the importance of PKC as a tumor suppressor factor [27]. Pharmaceutical and academic researchers have developed a healthy list of PKC regulators after extensive work on the role of PKC and their regulation during disease condition. Unfortunately, only few of them like Aprinocarsen, UCN01, AEB071, Enzastaurin, Midostaurin and Riluzole went for clinical trials, and after Phase I & II clinical trials, all of them have failed to give satisfactory results, but few have shown their anticancer efficacy [3,28] (Table 1). The reason is not very clear yet, one can assume that the PKC regulators used are non-specific in nature and therefore, have failed to manage the activity of PKC. However, several new PKC regulators like decursin, curcumin,

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Table 1: A list of PKC modulators running under clinical trials.

Drug	Disease	Phase	Status	Identifier
Aprinocarsen	Breast Cancer	2	Completed	NCT00003236
Enzastaurin	Breast Cancer	2	Active	NCT00451555
UCN01	Pancreatic Cancer	2	Completed	NCT00045747
AEB071	Uveal Melanoma	1	Active	NCT02273219
Curcumin	Breast Cancer	2	Active	NCT03072992
Disulfiram	Breast Cancer	2	Active	NCT03323346

alkyl cinnamates and diosmetin have been recently tested in the labs and shown good result in multiple cancer cell lines [29-32]. Further, a group of miRNAs including miR220b and premiR24-2 have been identified to regulate PKC expression during tumor progression [33]. Although, we have succeeded to some extent, there are several challenges like, inadequate preclinical studies, enrichment of adequate dose of the drug to the target site, targeted delivery of specific drug, and lack of selectivity that hampered the development of an effective PKC regulator are still needed to be addressed properly [34].

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