Protein Kinase C: The Drug Target One Must See

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Five years ago, the 30th birth anniversary of protein kinase C (PKC) was celebrated with much grandeur [1]. While it is difficult to say how small or big is the period of thirty five years in the life of a family of enzymes, more than 55,000 research articles have been published on PKCs ever since the discovery this family of enzymes in 1977 [2,3]. This means, on an average 1500 publications on PKCs were published every year. This speaks in itself regarding the importance of PKCs.

PKC belongs to the family of serine/threonine kinases involved in the regulation of various aspects of cell functions, including cell growth, differentiation, metabolism, and apoptosis [4]. PKC’s role has been implicated in the pathophysiology of several diseases such as cancer, diabetes, stroke, heart failure, and Alzheimer’s disease. PKC has been a subject of intensive research in the area of various types of cancers [5]. The PKCs comprise of a super family consisting of 11 subtypes, which have been categorized as typical and atypical. Typical PKCs bind to endogenous lipid messenger diacylglycerol (DAG) or the ultrapotent phorbol esters isolated from plant origin (Figure 1), whereas atypical ones are DAG insensitive. The typical PKCs are further divided into the conventional (α, βI, βII and γ) and novel (δ, ε, θ and η) classes, each having four primary domains. C1 domain binds DAG/phorbol ester. The C2 domain binds Ca\(^{2+}\) and/or phosphatidylserine (PS). C3 is the ATP-binding domain and C4 is the catalytic domain. The combined C3 and C4 can also be called the kinase domain. DAG is sufficient to activate the novel PKCs whereas the conventional PKCs additionally require Ca\(^{2+}\) for their activation. In both conventional and novel PKCs, the DAG/phorbol ester responsive C1 domain consists of a tandem repeat of highly conserved cysteine-rich zinc-finger subdomains known as C1A and C1B. These subdomains show significant differences in their binding affinities for phorbol esters and DAG [6]. Atypical PKCs (ζ and ι/λ) have a single non-DAG binding C1 domain.

PKC’s life of thirty five years has been quite eventful. Some of these important events are: discovery that phorbol esters, isolated from plants, activate PKC much more that the endogenous DAG [7,8], elucidation of the primary sequence of PKC in 1986 [9,10], crystal structure of an activator-bound C1 domain in 1995 [11], crystal structure of the ligand-bound kinase domain in 2004 [12], and at a time when the notion was that the full length structure of a PKC was nearly impossible because of its poor solubility and stability, the full length...
structure (Figure 2) was published in 2011 [13]. Now that, the structures are known, functions are more or less defined, and their role in disease states are established, why can’t PKC be used as a drug target for controlling disease? In fact, tremendous research efforts are underway to develop PKC-based drugs with several compounds currently on clinical trials. These are compounds targeting the activator binding C1 domain (bryostatin 1, ingenol 3-angelate, prostratin), ATP-competing compounds targeting kinase domain (straurosporine and its derivatives, enzastaurin, midostaurin and others), antisense oligonucleoside (ISIS 3521), phospholipid analogs (edelfosine, ilmofosine, miltfosine, N, N, dimethylsphingosine etc.). However, not a single PKC based drug is in the market at present!

This brings us to the core issue of selectivity. Most of the PKC domains show high sequence and structural similarity amongst its isoforms, making it difficult to design molecules targeting isoform selectively. Not only that, a possible design of PKC inhibitor targeting the attractive kinase domain lacks selectivity, due to high degree of homology in kinase region among more than 500 kinases in the human genome [14,15]. On the other hand, there are fewer C1 domains (a total of 67 C1 domains and only 17 of PKC C1 domains), which makes C1 domain a major focus for PKC based drug discovery in recent years [15].

Past thirty five years in the life of PKCs have revealed many complex relationships and interactions. These complexities have made PKC based drug discovery quite challenging [16]. For example, one particular isoform may be involved in different diseases. And, several isoforms may be involved in one particular disease while for a particular disease, two PKC isoforms may show opposing effects. Relevant to this, PKCα, and PKCδ play opposite roles in the proliferation and apoptosis of glioma cells [17], PKCe and PKCγ in alcoholism [18] and PKCe and PKCd in cardioprotection [19].

The fallout of these complications has been that several pharmaceutical companies have turned their focus away from PKC based drug discovery. While the enthusiasm of the biopharmaceutical companies is not very high at this moment, PKC’s affair with academia is going strong. It is only reasonable to suggest that it would take only a few more innovations that can bring PKCs back to the forefront of the drug discovery field.

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Figure 1.
Chemical structures of DAG (top) and phorbol ester, TPA (bottom).
Figure 2.
Crystal structure of full length PKCβII.