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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 (staurosporine and its derivatives, enzastaurin, midostaurin and others), antisense oligonucleoside (ISIS 3521), phospholipid analogs (edelfosine, ilmofosine, miltefosine, N, N, dimethylsphingosine etc.). However, not a single PKC based drug is in the market at present!

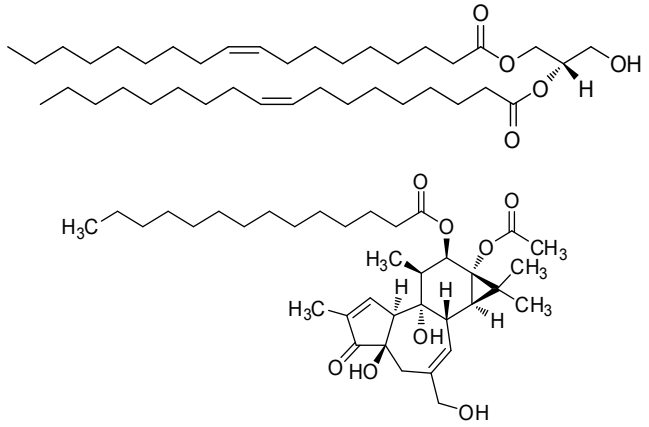

Figure 1: Chemical structures of DAG (top) and phorbol ester, TPA (bottom).

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].

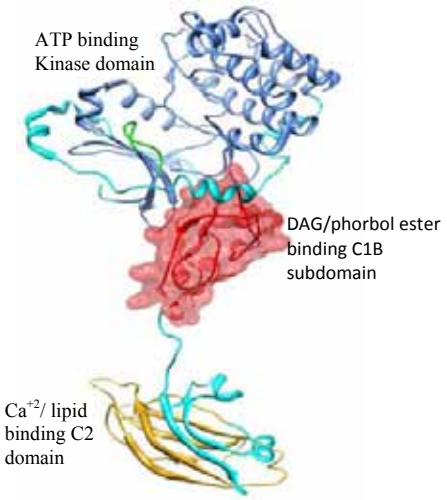

Figure 2: Crystal structure of full length PKCβII.

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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], PKCε and PKCγ in alcoholism [18] and PKCδ and PKCε 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.

References

1. Battaini F, Mochly-Rosen D (2007) Happy birthday protein kinase C: past, present and future of a superfamily. Pharmacol Res 55: 461-466.
2. Takai Y, Kishimoto A, Inoue M, Nishizuka Y (1977) Studies on a cyclic nucleotide-independent protein kinase and its proenzyme in mammalian tissues. I. Purification and characterization of an active enzyme from bovine cerebellum. J Biol Chem 252: 7603-7609.
3. Inoue M, Kishimoto A, Takai Y, Nishizuka Y (1977) Studies on a cyclic nucleotide-independent protein kinase and its proenzyme in mammalian tissues. II. Proenzyme and its activation by calcium-dependent protease from rat brain. J Biol Chem 252: 7610-7616.
4. Newton AC (2001) Protein kinase C: structural and spatial regulation by phosphorylation, cofactors, and macromolecular interactions. Chem Rev 101: 2353-2364.
5. Hofmann J (2004) Protein kinase C isozymes as potential targets for anticancer therapy. Curr Cancer Drug Targets 4: 125-146.
6. Irie K, Oie K, Nakahara A, Yanai Y, Ohigashi H, et al. (1998) Molecular basis for Protein Kinase C isozyme-selective binding: the systhesis, folding, and phorbol ester binding of the cysteine-rich domains of all Protein Kinase C isozymes. J Am Chem Soc 120: 9159-9167.
7. Castagna M, Takai Y, Kaibuchi K, Sano K, Kikkawa U, et al. (1982) Direct activation of calcium-activated, phospholipid-dependent protein kinase by tumor-promoting phorbol esters. J Biol Chem 257: 7847-7851.
8. Kraft AS, Anderson WB, Cooper HL, Sando JJ (1982) Decrease in cytosolic calcium/phospholipid-dependent protein kinase activity following phorbol ester treatment of EL4 thymoma cells. J Biol Chem 257: 13193-13196.
9. Parker PJ, Coussens L, Totty N, Rhee L, Young S, et al. (1986) The complete primary structure of protein kinase C--the major phorbol ester receptor. Science 233: 853-859.
10. Coussens L, Parker PJ, Rhee L, Yang-Feng TL, Chen E, et al. (1986) Multiple, distinct forms of bovine and human protein kinase C suggest diversity in cellular signaling pathways. Science 233: 859-866.
11. Zhang G, Kazanietz MG, Blumberg PM, Hurley JH (1995) Crystal structure of the cys2 activator-binding domain of protein kinase C delta in complex with phorbol ester. Cell 81: 917-924.
12. Xu ZB, Chaudhary D, Olland S, Wolfrom S, Czerwinski R, et al. (2004) Catalytic domain crystal structure of protein kinase C-theta (PKCtheta). J Biol Chem 279: 50401-50409.
13. Leonard TA, Różycki B, Saidi LF, Hummer G, Hurley JH (2011) Crystal structure and allosteric activation of protein kinase C βII. Cell 144: 55-66.
14. Manning G, Whyte DB, Martinez R, Hunter T, Sudarsanam S (2002) The protein kinase complement of the human genome. Science 298: 1912-1934.
15. Blumberg PM, Kedei N, Lewin NE, Yang D, Czifra G, et al. (2008) Wealth of opportunity - the C1 domain as a target for drug development. Curr Drug Targets 9: 641-652.
16. Mackay HJ, Twelves CJ (2007) Targeting the protein kinase C family: are we there yet? Nat Rev Cancer 7: 554-562.
17. Mandil R, Ashkenazi E, Blass M, Kronfeld I, Kazimirsky G, et al. (2001) Protein kinase Calpha and protein kinase Cdelta play opposite roles in the proliferation and apoptosis of glioma cells. Cancer Res 61: 4612-4619.
18. Newton PM, Ron D (2007) Protein kinase C and alcohol addiction. Pharmacol Res 55: 570-577.
19. Churchill EN, Mochly-Rosen D (2007) The roles of PKCdelta and epsilon isoenzymes in the regulation of myocardial ischaemia/reperfusion injury. Biochem Soc Trans 35: 1040-1042.