PKC at a glance

Peter J. Parker[1,*] and Judith Murray-Rust[2]

[1]Protein Phosphorylation Laboratory, and
[2]Structural Biology Laboratory, Cancer Research UK, London Research Institute, 44 Lincoln's Inn Fields, London, WC2A 3PX, UK

*Author for correspondence (e-mail: p.parker@cancer.org.uk)

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The protein kinase C (PKC) family is represented in all eukaryotes and in *Homo sapiens* comprises the related PKCα through PKCι gene products (Dempsey et al., 2000). The kinase domains are closely related, as illustrated in the dendrogram, and form part of the AGC kinase superfamily. For clarity, the PKC-related kinases (PRK/PKN) are not included here; similarly excluded is the PKD/PKCμ family, members of which have distinct kinase domains but some related regulatory properties. The three PKC subgroups shown are structurally and functionally distinguished. The conventional, cPKC, isoforms (PKCα, PKCβ and PKCγ) are diacylglycerol (DAG) sensitive and Ca^{2+} responsive (responding through an archetypal C2 domain). The novel, nPKC, isoforms (PKCδ, PKCε, PKCη and PKCθ) are DAG sensitive but Ca^{2+} insensitive; their C2-related domains do not retain Ca^{2+}-coordinating residues. The atypical, aPKC, isoforms (PKCζ and PKCι/λ) have altered C1 domains and are not DAG sensitive; regulation occurs in part through the N-terminal PB1 domain. Structures for C1 domains and C2 domains have been determined (examples are illustrated for PKCδ), and kinase domain models based on the highly related PKA have been built (that for PKCα is shown here).

Genetic studies in the mouse indicate that particular PKC isoforms are essential in a number of specific contexts, some of which are highlighted here (Abeliovich et al., 1993; Leitges et al., 1996; Hodge et al., 1999; Castrillo et al., 2001; Leitges et al., 2001; Martin et al., 2002; Mecklenbrauker et al., 2002; Miyamoto et al., 2002). However, this is a very much narrower phenotypic profile than is reflected in the rather broad pattern of expression for most of these proteins. Thus it is likely that some functional redundancy exists.

The activation of cPKC and nPKC isoforms typically involves recruitment to membranes and interaction with or allosteric activation by DAG. Agonist-induced production of DAG is effected by multiple mechanisms. For receptor tyrosine kinases and receptors linked to non-receptor tyrosine kinases, this involves the recruitment of phosphatidylinositol (4,5)-bisphosphate [PtdIns(4,5)P_2]-specific phospholipases C$\gamma_{1/2}$ (PtdIns-PLC$\gamma_{1/2}$) through their SH2 domains. For serpentine receptors, coupling is effected by PtdIns-PLCβ family members through Gα_q-GTP and Gβγ family member allosteric interactions. Additionally, PtdIns-PLCε is a target for the small GTPase Ras (not illustrated). For cPKC isoforms, the initial recruitment event is the Ca^{2+}-sensitive step, which is driven by C2 domain interactions with Ca^{2+} and anionic-phospholipids. For nPKC isoforms, no equivalent mechanism promoting interaction with DAG has been elucidated. For aPKC isoforms activation can be driven in part by interaction with the Cdc42-GTP–Par6 complex, which binds the PB1 domain of aPKC. In each case, the allosteric effects of these lipids/proteins on PKC isoforms lead to a loss of the

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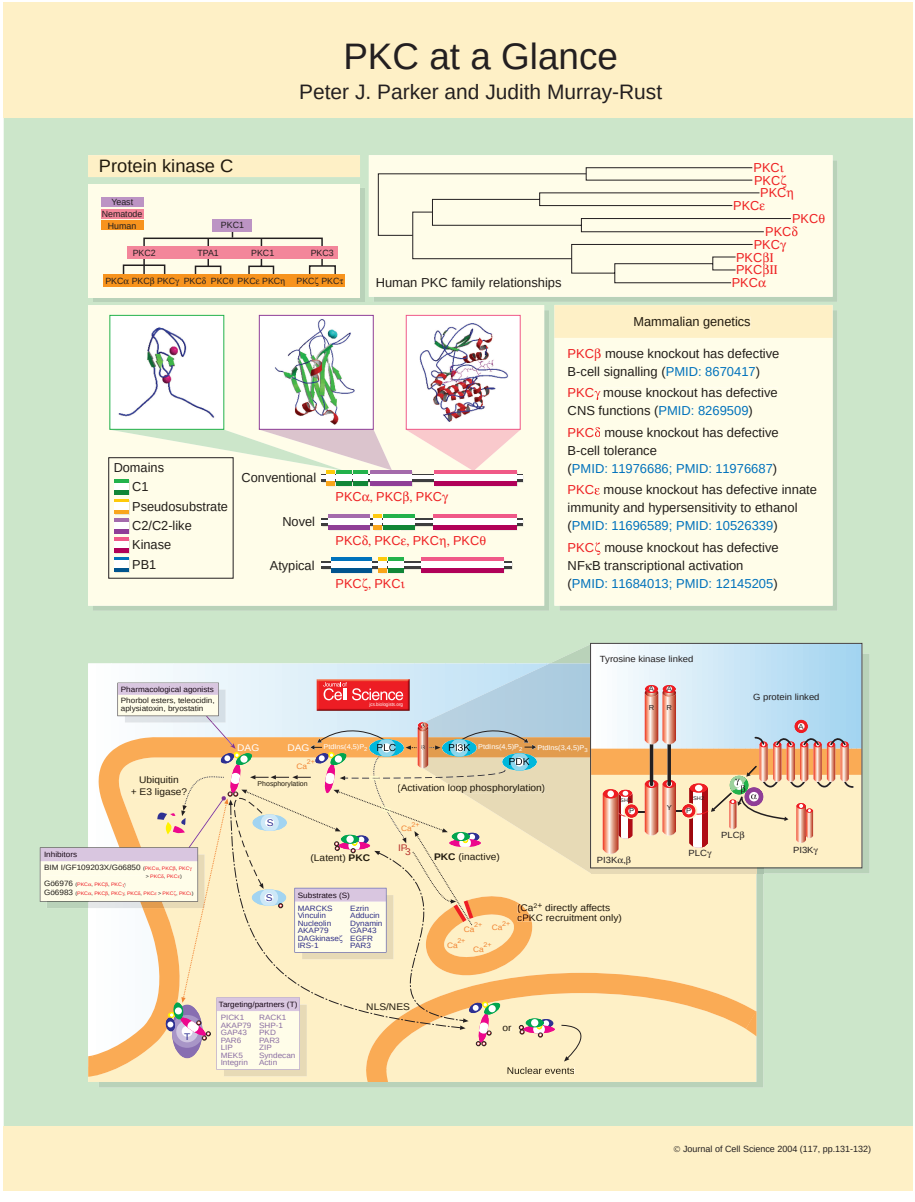

inhibition exerted by the inhibitory pseudosubstrate sequence that otherwise occupies the active site.

For optimum catalytic output all the PKC family members appear to require phosphorylation in their activation loops at a TFCGT motif conserved in many members of the AGC kinase superfamily (Parekh et al., 2000). This is catalysed by phosphoinositide-dependent kinase 1 (PDK1), which is itself recruited to membranes by PtdIns(3,4,5)P_3. The upstream enzyme PI 3-kinase is, similarly to PtdIns-PLC, coupled to receptors through tyrosine kinases, heterotrimeric G proteins and/or Ras proteins. The PDK1-dependent activation loop phosphorylation occurs in conjunction with C-terminal phosphorylations to lock the kinase domains in their active conformations; there remains some debate as to the order and requirements for these phosphorylations.

In the membrane-bound, open, active conformations, substrate phosphorylation is efficient. Some examples of PKC substrates are shown and include a number of cytoskeleton-associated proteins that contribute to localised cytoskeletal reorganisation (Jaken and Parker, 2000). For many substrates – the so-called STICKs (substrates that interact with C-kinases) – direct kinase-substrate interaction contributes to specificity/efficiency of action. Some of the complexes involve scaffolding proteins termed RICKs (receptors for inactive C-kinases), which can operate prior to PKC activation, restricting membrane and substrate access; other complexes form post-activation, such as RACKs (receptors for activated C-kinases), determining substrate access (Mochly-Rosen and Gordon, 1998).

Pharmacological probes for the action of PKC family proteins include membrane-permeant allosteric activators (e.g. phorbol esters) and catalytic inhibitors. In general these do not distinguish isoforms and, furthermore, they can modulate other C1-domain-containing proteins (e.g. phorbol esters) or protein kinases (catalytic site inhibitors). However, their combined use is a helpful guide to PKC involvement in cellular processes.

PKC action can be localised to multiple compartments, including the plasma membrane, (recycling) endosomes, the Golgi and the nucleus. Location is determined in part by the scaffolds but also by targeting information intrinsic to individual isoforms – for example, nuclear localisation/export sequences (NLS/NES). The requirements for the individual isoforms are in part revealed by those non-redundant properties manifest in the mouse knockout phenotypes. It remains to be determined how specific actions relate to these patterns of behaviour at a molecular level.

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