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Protein Kinase C

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Synonyms

C kinase; PKC

Definition

Protein kinase C (PKC) is an enzyme family whose members are activated by agonists that cause receptor-mediated generation of lipid second messengers. The activated enzymes transduce information from such agonists by phosphorylating relevant downstream substrates.

Basic Characteristics

PKC is a family of enzymes whose members play central roles in transducing information from external stimuli to cellular responses. Members of this family of serine/threonine kinases respond to signals that cause lipid hydrolysis. PKC isozymes phosphorylate an abundance of substrates, leading to both short-term cellular responses such as regulation of membrane transport and long-term responses such as memory and learning. They generally function as tumor suppressors, with loss-of-function mutations associated with diverse cancers. Conversely, gain-of-function mutations have been identified in degenerative diseases. Thus, homeostatic control of PKC is essential to avoid pathophysiologies.

The PKC Family

There are nine genes encoding PKC isozymes in mammals, and they fall into three classes: conventional (α, β (with two common splice variants, βI and βII) and γ), novel (δ, ε, η, and θ), and atypical (ζ and ι/λ) PKC isozymes (Newton 2018). As shown in Fig. 1, all isozymes comprise an N-terminal regulatory moiety and a C-terminal kinase core. The regulatory moiety contains two important functional segments: an autoinhibitory pseudosubstrate sequence that allosterically regulates access to the substrate-binding cavity and one or more membrane-targeting modules. It is the nature of the membrane-targeting modules that defines the classes of PKC isozymes. All PKC isozymes have a version of the C1 domain, the diacylglycerol sensor. This domain binds diacylglycerol, the natural agonist, as well as phorbol esters, potent functional analogues, in all isozymes except atypical PKC isozymes. For these isozymes, an impaired ligand-binding pocket does not support the binding of diacylglycerol or phorbol esters, and, as a consequence, the hallmark of atypical PKC isozymes is their complete lack of response to phorbol esters. Rather, these isozymes are regulated by binding

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protein partners through their PB1 (for Phox and Bem1p) protein interaction domain. Conventional and novel PKC isozymes have a C2 domain. For conventional PKC isozymes, this domain binds phosphatidylinositol-4,5-bisphosphate in the plasma membrane in a Ca^{2+}-dependent manner, serving as a plasma membrane-sensing module. An impaired Ca^{2+}-binding pocket in the novel PKC isozymes makes them unresponsive to Ca^{2+}. In one novel isozyme, PKC δ, phosphorylation on tyrosine controls protein interactions of this domain.

Regulation

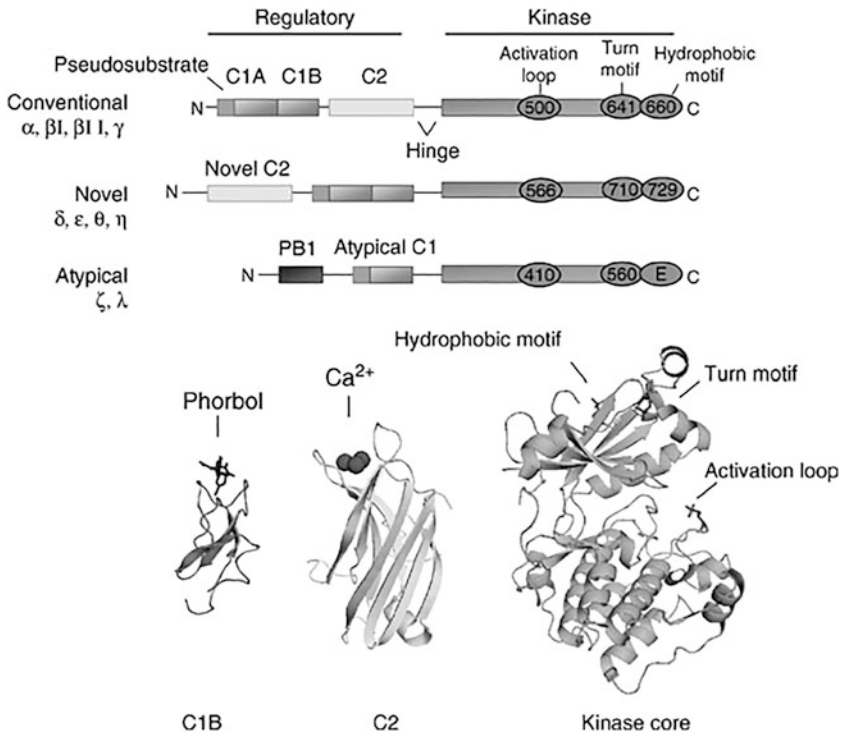
PKC isozymes are regulated by three mechanisms: phosphorylation, second messenger binding, and protein–protein interactions. First, a series of ordered phosphorylations renders newly synthesized PKC catalytically competent. The upstream kinase, phosphatidylinositol-dependent kinase-1 (PDK-1), phosphorylates the activation loop of PKC, triggering phosphorylation at two conserved sites in the C-terminus, the turn motif and the hydrophobic motif, by a mechanism that is facilitated by mTORC2. Phosphorylation of the hydrophobic motif occurs via intramolecular autophosphorylation. The positions of these sites on structure of the kinase domain of PKCβII are shown in Fig. 1. These phosphorylations are essential to lock PKC in a stable and autoinhibited conformation. Second, the mature, fully phosphorylated species of PKC is allosterically activated following engagement of the membrane-targeting modules to the membrane. For conventional PKC isozymes, Ca^{2+} pretargets PKC to the membranes by binding the C2 domain and increasing this domain's affinity for anionic lipids. At the membrane, the C1 domain binds diacylglycerol, an event that provides the energy to release the autoinhibitory pseudosubstrate sequence from the substrate-binding cavity. Novel PKC isoforms respond to diacylglycerol alone because their C1 domain has a sufficiently high-affinity binding to diacylglycerol such that pretargeting by the C2 domain is not required. Third, scaffold proteins position PKC near its activators or substrates, allowing specificity in signaling by distinct isoforms.

Signaling by PKC is terminated by concentrations of its ligands dropping to basal levels (i.e., Ca^{2+} and diacylglycerol). Prolonged activation also results in the dephosphorylation and degradation of PKC. Dephosphorylation is controlled, in part, by PHLPP (for PH domain leucine-rich repeat protein phosphatase), which dephosphorylates the hydrophobic motif of conventional and novel PKC isozymes, initiating their downregulation.

Function in Health and Disease

Conventional and novel PKC isozymes generally function to suppress proliferative and survival pathways, with recent evidence converging on roles as tumor suppressors (Newton 2018). Analysis of somatic mutations throughout the PKC family has revealed that the majority are loss of function. In contrast, germ-line mutations that enhance activity are associated with degenerative diseases such as Alzheimer's disease and cerebellar ataxia. For a number of cancers, including pancreatic and colon, patients with high levels of PKC have significantly better prognosis than those with relatively low levels. One exception is PKCι, an atypical PKC, which functions as an oncogene in cancers such as that of the lung (Yin et al. 2019).

Because the levels of PKC in cells control the amplitude of PKC signaling pathways, defects in PKC regulation that result in altered levels of the kinase are associated with disease. One mechanism that controls the levels of PKC is a quality control pathway by which the phosphatase PHLPP regulates how much newly synthesized PKC progresses to the stable, phosphorylated form: low levels of the phosphatase allow more accumulation of phosphorylated (and thus stable) PKC, whereas high levels promote dephosphorylation and degradation of PKC. This quality control mechanism is particularly important in pancreatic cancer, where patients with low PHLPP and high PKC have considerably better prognosis than ones with high PHLPP and low PKC (Baffi et al. 2019).



Protein Kinase C, Fig. 1 Domain structure of PKC family members showing regulatory modules (pseudosubstrate sequence and C1, C2, and PB1 domains) and the kinase core. Shown below are the structures of the C1 domain of PKCδ with bound phorbol, the C2 domain of PKCβ with bound Ca^{2+}, and the kinase domain of PKCβII solved by Grant and coworkers (Grodsky et al. 2006) with three processing phosphorylation sites labeled. Figure adapted from (Newton 2003)

Drugs

Activators

Conventional and novel PKC isozymes are potently activated by phorbol esters, heterocyclic compounds found in the milky sap exuded by plants of the Euphorbiaceae family. This sap was used medicinally as a counterirritant and cathartic agent over the millennia; we now know that the active ingredients, phorbol esters, specifically bind to the C1 domain, the diacylglycerol sensor described above. In fact, their ability to recruit PKC to membranes is so effective that phorbol esters cause maximal activation of conventional PKC isozymes, bypassing the requirement for Ca^{2+}. This module is found in a number of other proteins in addition to PKC, so the profound effects of phorbol esters on cells are mediated by other proteins as well. Bryostatins are another class of compounds that bind to the C1 domain and result in acute activation of PKC. Note that these molecules are not readily metabolized and result in the constitutive activation of PKC, triggering PHLPP-mediated dephosphorylation and subsequent downregulation. Thus, while these molecules acutely activate PKC isozymes, they cause the chronic loss of the enzymes. This paradox accounted for confusion as to whether to inhibit or activate PKC in cancer therapies.

Inhibitors

A number of inhibitors directed toward the active site of PKC have been developed (Yin et al. 2019). While these failed in clinical trials for cancer (where, in general, PKC activity should be restored, not inhibited), they may prove useful for neurodegenerative diseases, where inhibiting overly active PKC could be beneficial.

Cross-References

- ▶ Diacylglycerol
- ▶ PHLPP
- ▶ Phorbol Esters
- ▶ Phospholipases
- ▶ Protein Kinase C

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