PKCα and PKCδ: Friends and Rivals

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Jennifer D. Black[1,*], **Trisiani Affandi**[2], **Adrian R. Black**[1], **and Mary E. Reyland**[2,*]

From the [1]*Eppley Institute for Research in Cancer and Allied Diseases, University of Nebraska Medical Center, Omaha, Nebraska, USA;* [2]*Department of Craniofacial Biology, School of Dental Medicine, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA*

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PKC comprises a large family of serine/threonine kinases that share a requirement for allosteric activation by lipids. While PKC isoforms have significant homology, functional divergence is evident among subfamilies and between individual PKC isoforms within a subfamily. Here, we highlight these differences by comparing the regulation and function of representative PKC isoforms from the conventional (PKCα) and novel (PKCδ) subfamilies. We discuss how unique structural features of PKCα and PKCδ underlie differences in activation and highlight the similar, divergent, and even opposing biological functions of these kinases. We also consider how PKCα and PKCδ can contribute to pathophysiological conditions and discuss challenges to targeting these kinases therapeutically.

PKC was discovered nearly 45 years ago based on its unique dependence on lipids and Ca^{2+} for activation (1, 2). Further studies revealed 10 PKC isoforms that are founding members of the larger AGC (collective name for cAMP-dependent PKA, cGMP-dependent protein kinase G, and PKC) superfamily of protein kinases (3–5). PKC subfamilies have been defined based on specific requirements for activation by lipids and Ca^{2+}. These subfamilies include conventional PKCs (cPKCs; PKCα, PKCβ, and PKCγ), which require diacylglycerol (DAG) and Ca^{2+} for activation, novel PKCs (nPKCs; PKCδ, PKCε, PKCη, and PKCθ), which are Ca^{2+} independent, and atypical PKCs (PKCζ and PKCι), which do not require DAG or Ca^{2+} and are activated by protein–protein interactions (6). As many isoforms are ubiquitously expressed, targeting these kinases in disease has been daunting due in part to concerns about specificity and redundancy. This is the first review we are aware of that compares activation and function of representative isoforms of the cPKC (PKCα) and nPKC (PKCδ) subfamilies. Our goal is to highlight novel and unique aspects of the regulation and signaling functions of these isoforms to encourage their exploration as drug targets in cancer and other diseases.

PKC isoforms participate in "outside–in" signaling by transducing signals from a variety of cell surface receptors including receptor tyrosine kinases (RTKs) and G protein–coupled receptors. Indeed, the identification of lipid-regulated kinases such as PKC was a turning point that linked hydrolysis of membrane inositol lipids, described decades earlier, to regulation of intracellular functions (7, 8). These receptors, as well as other physiologic activators of PKC, were shown to stimulate breakdown of membrane phosphatidylinositol 4,5-bisphosphate (PIP_2) to generate the signaling lipids DAG and inositol 3-phosphate (IP_3) (9) (Fig. 1). DAG tethers PKC to the membrane, whereas IP_3 induces release of Ca^{2+} from the endoplasmic reticulum (ER). Interaction of PKCs with the membrane induces conformational changes that lead to release of autoinhibition and activation. Thus, membrane localization is considered the hallmark of PKC activation (10) (see later and Refs. (4, 11) for a detailed description of PKC activation events).

All PKC isoforms have highly conserved C-terminal catalytic domains and similar N-terminal regulatory domains (4). However, divergence in critical motifs results in differences in cofactor requirements, mode of membrane recruitment, mechanisms of noncanonical activation, spatial distribution, desensitization, and protein–protein interactions. These differences underly the divergent functions that have been ascribed to PKC subfamilies and to isozymes within subfamilies (Fig. 2*A*). Later, we will discuss the unique structural features and known functions of PKCα (conventional subfamily) and PKCδ (novel subfamily) in diverse biological processes, highlighting contexts in which these kinases have contrasting and similar roles.

Distinct structural features of PKCα and PKCδ

Unique structural features and modes of activation

The N-terminal domain of cPKC and nPKC isoforms includes a tandem repeat C1 domain comprising C1a and C1b subdomains that bind DAG, albeit with varying affinity, a membrane lipid–binding C2 domain, and a pseudosubstrate motif that blocks access to the substrate-binding pocket (12). However, PKCs differ in the nature and arrangement of these domains. For example, in PKCα, the C2 domain lies between the C1 and catalytic domains, whereas in PKCδ, the C2 domain lies between the N terminus and the C1 domain (Fig. 2*A*). Elegant studies by several groups have revealed differences in the maturation, activation, and downregulation (inactivation) of PKCα and PKCδ that are thought to contribute to specification of function.

* For correspondence: Mary E. Reyland, Mary.Reyland@cuanschutz.edu; Jennifer D. Black, Jennifer.Black@unmc.edu.

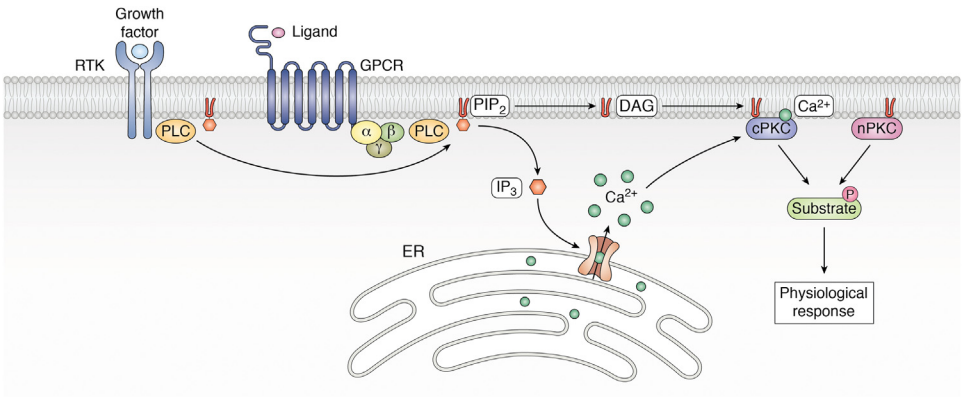

Figure 1. Diagrammatic representation of PKC-mediated signal transduction. Activation of phospholipase C (PLC) through ligand binding of receptor tyrosine kinases (RTKs) or G protein–coupled receptors (GPCRs) results in hydrolysis of phosphatidylinositol 4,5-biphosphate (PIP_2), generating diacylglycerol (DAG) and inositol trisphosphate (IP_3). IP_3 releases Ca^{2+} stored in the endoplasmic reticulum (ER). The accumulation of DAG and Ca^{2+} results in membrane recruitment of conventional PKC isozymes (cPKCs), whereas recruitment of novel PKCs (nPKCs) is DAG dependent but Ca^{2+} independent. Activated PKCs phosphorylate their substrates to trigger downstream physiological responses.

Kinase phosphorylation and maturation

Many AGC kinases share a requirement for serine/threonine phosphorylation at three conserved sites in the C-terminal domain for activity (3, 13). In PKCs, constitutive phosphorylation in the activation loop by the PIP_3-regulated kinase, 3-phosphoinositide-dependent protein kinase 1, trans-phosphorylation at the "turn" motif, typically by mammalian target of rapamycin complex 2 (mTORC2), and autophosphorylation at the hydrophobic motif (13–15) is required for catalytic competence and protection from degradation. It is important to emphasize that, in contrast to other AGC kinases that are acutely activated by phosphorylation (*e.g.*, Akt (13)), phosphorylation of the three "priming" sites is seen in inactive PKC (Fig. 2, *B* and *C*, step 2) and is, therefore, not indicative of PKC activation *per se*. Instead, membrane localization and substrate phosphorylation are the only reliable indicators of kinase activation. Comparison of the regulation and function of PKCα and PKCδ priming phosphorylation has revealed two important differences. First, unlike PKCα, which is dependent on activation loop phosphorylation for activity (14), the T505A activation loop mutant of PKCδ is still partially active (16). This difference may have consequences for modulation of kinase activity as well as kinase degradation. Second, a recent study from the Newton laboratory has identified a fourth priming phosphorylation motif, the mTOR interaction motif, in some mTORC2–regulated AGC kinases, including PKCα (17, 18). Phosphorylation of this motif (S631 in PKCα) by the mTORC2 complex allosterically regulates PIP_3-regulated kinase, 3-phosphoinositide-dependent protein kinase 1 binding, activation loop phosphorylation, and autophosphorylation of the hydrophobic motif. Curiously, select nPKC isoforms, including PKCδ, are mTORC2 independent for priming and lack this conserved threonine (19). Additional serine and threonine phosphorylation events may fine-tune activation of PKCδ in response to specific signals (20). As discussed later, tyrosine phosphorylation may in addition play a role in modulating the activity of PKCα and PKCδ.

PKCα and PKCδ have unique C1, C2, and phosphotyrosine-binding domains

Divergence in the C2 and C1 domains of PKCα and PKCδ accounts for important differences in Ca^{2+} dependence and mechanism of activation (Fig. 2). C2 domains are evolutionary conserved lipid-and protein-binding motifs (21). PKCα has a topology I (S family) C2 domain that requires Ca^{2+} for lipid binding (21, 22). Since membrane binding of the C2 domain is required for membrane recruitment of PKCα by DAG, PKCα activation is Ca^{2+} dependent. In contrast, PKCδ has a topology II (P family) C2 domain that lacks the critical structural requirements for Ca^{2+} binding (21, 22); thus, PKCδ activation is Ca^{2+} independent (23, 24). The C2 domain of PKCδ also differs from that of PKCα in its ability to mediate protein–protein interactions (22–24). Benes *et al.* (22) have identified a novel high-affinity phosphotyrosine-binding (PTB) motif in the PKCδ C2 domain, which is not found in PKCα or other PKC isozymes. This PTB domain is distinct from both Src-homology 2 and previously described PTB domains in that it interacts with residues in the phosphorylated peptide both C-terminal and N-terminal to pTyr (22). Binding of the C2 PTB domain to phosphotyrosine-containing proteins in *trans* could drive the formation of PKCδ-specific signaling modules, whereas *cis* interactions could contribute to regulation of PKCδ by binding to tyrosine-phosphorylated residues within the kinase domain, for example, as induced by hydrogen peroxide (25).

cPKC and nPKC C1a and C1b domains differ in their affinity for DAG and play unique roles in isoform activation (26). In PKCα, the C1a domain has a higher affinity for DAG compared with the C1b domain (26). However, the C1a domain is masked in unstimulated PKCα by interaction with the C2 and catalytic domains and is only released following Ca^{2+}-dependent interaction of the C2 domain with anionic lipids in the plasma membrane (27–31) (Fig. 2*B*). Thus, activation of PKCα requires a multistep process in which the C2 domain initially interacts with the membrane, with subsequent

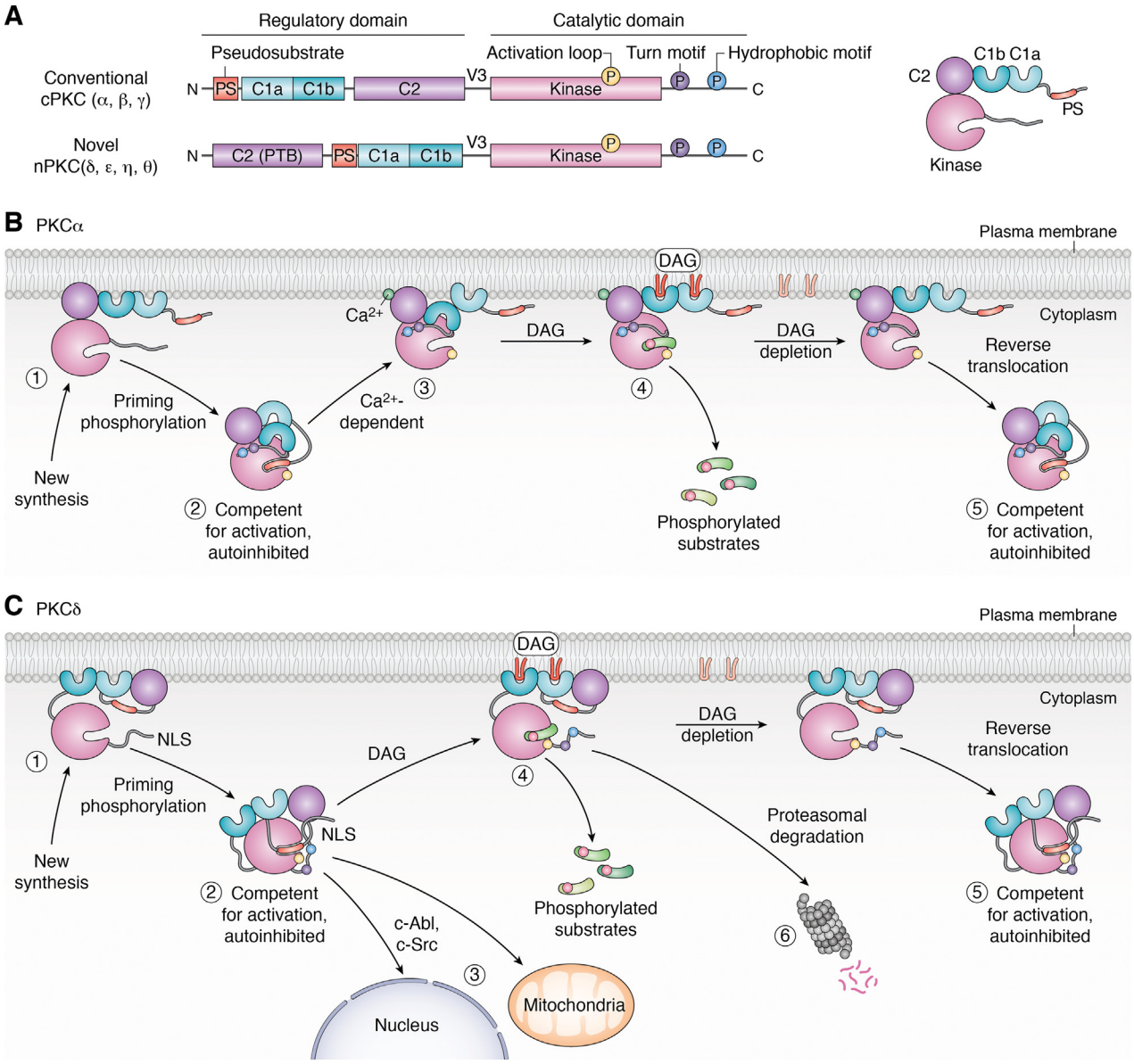

Figure 2. Structural features and mechanisms of activation of PKCα and PKCδ. *A*, protein domains of the cPKC and nPKC isoform subfamilies. The N-terminal regulatory domain contains the pseudosubstrate domain (PS, *brick red*), the lipid-binding C1 domain (C1a and C1b, *light and dark green*), and the lipid-binding C2 domain (*purple*), which in PKCα also binds Ca^{2+}. The phosphotyrosine-binding (PTB) motif in the C2 domain of PKCδ is indicated. The C-terminal catalytic domain contains the kinase core (*pink*) and phosphorylation sites in the activation loop (*yellow circle*), the turn motif (*purple circle*), and the hydrophobic motif (*blue circle*). Phosphorylation at these sites is required for catalytic competence. The regulatory domain and the catalytic domain are connected by the flexible V3 hinge region, which contains a protease cleavage site. *B* and *C*, newly synthesized PKCα (*B*) and PKCδ (*C*) are in an open conformation at the plasma membrane (step 1). Upon phosphorylation at three "priming" sites, they are released into the cytosol. Cytosolic PKCα and PKCδ are competent for activation but in an autoinhibited conformation with the PS embedded in the substrate-binding site (step 2). *B*, activation of PKCα in response to physiological signals involves a two-step process. Initial interaction of PKCα with the plasma membrane is mediated by Ca^{2+}-dependent lipid binding of the C2 domain (step 3), which enables interaction with DAG (*red U shape*) through the C1 domain (step 4). DAG-induced membrane interaction results in a conformational change allowing PKCα to phosphorylate its substrates. Upon DAG depletion, PKCα undergoes reverse translocation into the cytosol where it assumes its autoinhibited state and is available for reactivation (step 5). *C*, PKCδ is directly recruited to the plasma membrane or other subcellular organelles in response to DAG or other activation signals such as tyrosine phosphorylation by c-Abl and c-Src (steps 3 and 4). Membrane interaction induces a conformational change that results in PKCδ activation and phosphorylation of substrates (step 4). Signal termination of PKCδ can occur through reverse translocation following DAG depletion (step 5). Alternatively, long-term inactivation of PKCδ signaling can occur through proteasomal degradation of the enzyme (step 6). cPKC, conventional PKC; DAG, diacylglycerol; nPKC, novel PKC.

release of the C1a domain for membrane penetration and DAG binding (30–32). Notably, although the C2 domain of PKCα has low intrinsic affinity for Ca^{2+}, its Ca^{2+} binding is enhanced by PIP_2, phosphatidylserine, and DAG in the plasma membrane, allowing for enzyme activation by DAG even at subphysiological intracellular Ca^{2+} levels (21, 29, 33–35). Nonetheless, while activation of PKCα by DAG does not require release of intracellular calcium stores, elevated intracellular Ca^{2+} concentrations increase the rate of PKCα activation in the presence of DAG (29); thus, PKCα activation may be targeted to local areas of Ca^{2+} generation, consistent with spatially restricted signaling (36).

The mechanism of PKCδ activation is similar to that of PKCα, except that PKCδ does not bind calcium and is targeted to the membrane primarily through high-affinity binding of the C1 domains to membrane DAG (37) (Fig. 2*C*). However, the relative contribution of the C1a and C1b domains to membrane DAG binding remains to be resolved. It has been reported that, as in PKCα, the C1a domain of PKCδ has high affinity for DAG, whereas the C1b domain fails to bind DAG but has high affinity for phorbol esters (38). In contrast, other studies have shown that the C1b domain of PKCδ binds to DAG with an affinity that is two orders of magnitude greater than that of cPKCs, and that mutation of the C1a domain has minimal effects on binding of PKCδ to DAG-containing membranes (37, 39). Nonetheless, the high affinity of the C1 domain of PKCδ for DAG compensates for the lack of membrane binding of its C2 domain, allowing for direct C2 domain–independent membrane recruitment and activation of the kinase by signal-generated DAG (37). DAG-independent functions of the C1b domain may also contribute to targeting and activation of PKCδ (37). For instance, Wang *et al.* (40) have shown that the C1b domain of PKCδ mediates its association with the Golgi/ER protein, p23/Tmp21, to regulate apoptosis.

Noncanonical activation of PKC

In addition to the plasma membrane, it is now clear that PKC isoforms can be activated in a variety of subcellular locations and can respond to stimuli that do not promote hydrolysis of membrane lipids (41). One well-documented mechanism of noncanonical activation of both cPKCs and nPKCs is through reactive oxygen species (ROS) (42). The cysteine-rich zinc-binding finger of C1 domains is highly sensitive to oxidation by ROS, which destroys the conformation of the DAG-binding site. For PKC, oxidation by ROS typically relieves autoinhibition and activates the kinase (43). While redox-dependent conformational changes can activate both cPKCs and nPKCs, PKCδ can also be regulated by oxidative stress through changes in phosphorylation of specific tyrosine residues unique to this isoform (25, 44). There are at least two explanations for redox regulation *via* tyrosine phosphorylation (42). First, cysteine residues in the active site of protein tyrosine phosphatases are very sensitive to redox inactivation, and the inhibition of dephosphorylation manifests as an overall increase in tyrosine phosphorylation (45). Second, redox activation of RTKs (*e.g.*, epidermal growth factor receptor [EGFR]) and non-RTKs (*e.g.*, c-Abl, c-Src, and Src-family kinases) results in increased phosphorylation on tyrosine residues in PKCδ (42, 46). The most extensively studied of these residues are Tyr311 (rodent; 313 human), Tyr155 (rodent and human), and Tyr64 (rodent and human), which can be phosphorylated by c-Lck, c-Abl, and c-Src (25, 42, 44, 47, 48). PKCα is also tyrosine phosphorylated in response to oxidative stress (25), and tyrosine phosphorylation of Tyr195, Tyr285/286, Tyr365, Tyr504, Tyr512, and Tyr515 (human) has been reported in multiple studies https://www.phosphosite.org/proteinAction.action?id=1773.

Tyrosine phosphorylation is essential for activation of PKCδ in response to death signals. The Reyland laboratory has described a noncanonical activation scheme for PKCδ in which progressive phosphorylation at Tyr155 and Tyr64 by c-Abl and c-Src, respectively, allosterically activates the kinase while also promoting its nuclear translocation (48, 49). Tyrosine phosphorylation reveals a cryptic bipartite nuclear localization signal in the C terminus of PKCδ allowing importin-α binding and nuclear import (47, 50, 51) (Fig. 2*C*; also see the "Apoptosis" section). Phosphorylation of PKCδ at Tyr155 and Tyr64 appears to be a general response to agents that cause DNA damage (48). Phosphorylation at Tyr311 and Tyr187 can also promote the apoptotic function of PKCδ (52–54), suggesting that multiple tyrosine phosphorylation events may coordinate activation of this function of the kinase.

Other examples of noncanonical activation include Ca^{2+} overload in the ischemic heart, where the cysteine protease calpain cleaves PKCα in the V3 region to generate a constitutively active cytosolic C-terminal catalytic fragment (CF) that negatively regulates myocardial function (55). Likewise, PKCδ can be activated by caspase-3-mediated cleavage (56). In both cases, cleavage activates the kinase by releasing the CF from inhibitory interactions with the regulatory domain. Finally, in the context of cell migration, PKCα can be activated by oligomerized syndecan-4 (57), a transmembrane proteoglycan that serves as a receptor for heparan sulphate–binding growth factors and extracellular matrix (ECM) components such as fibronectin and vitronectin (see later).

Signal termination

PKC signal termination is mediated by acute inactivation and long-term desensitization mechanisms. For PKCα and PKCδ, this is accomplished largely through rapid metabolism of DAG (58), which leads to activity-dependent dissociation of PKC from the membrane and restoration of the autoinhibited protein in the cytosol (Fig. 2, *B* and *C*, step 5, and (59, 60)). However, prolonged activation by ligands that are not readily metabolized (*e.g.*, phorbol esters, bryostatin) and, in the case of PKCδ, by physiological stimuli (*e.g.*, growth factors), can result in activity-dependent downregulation/loss of PKCα and PKCδ protein, with loss of associated signaling in the continued presence of agonists (Fig. 2*C*, step 6). Multiple mechanisms of downregulation have been implicated, with subcellular localization playing an important role in dictating the engagement of processing pathways (61). While ubiquitin-mediated proteasomal degradation is a major mechanism of PKC downregulation (62–65), endomembrane trafficking and lysosomal processing have also been shown to play a role, at least for PKCα (66–68).

Multisite dephosphorylation of PKC by PH domain leucine-rich repeat protein phosphatase (69) and protein phosphatase 2A (PP2A) (65, 70), which appears to occur in an intracellular compartment (66–68, 70), may serve as a trigger for PKC degradation in some contexts (63, 70). For cPKCs, peptidyl-prolyl isomerization of the turn motif–priming site by peptidyl-prolyl *cis*/*trans* isomerase (PIN1) is required for

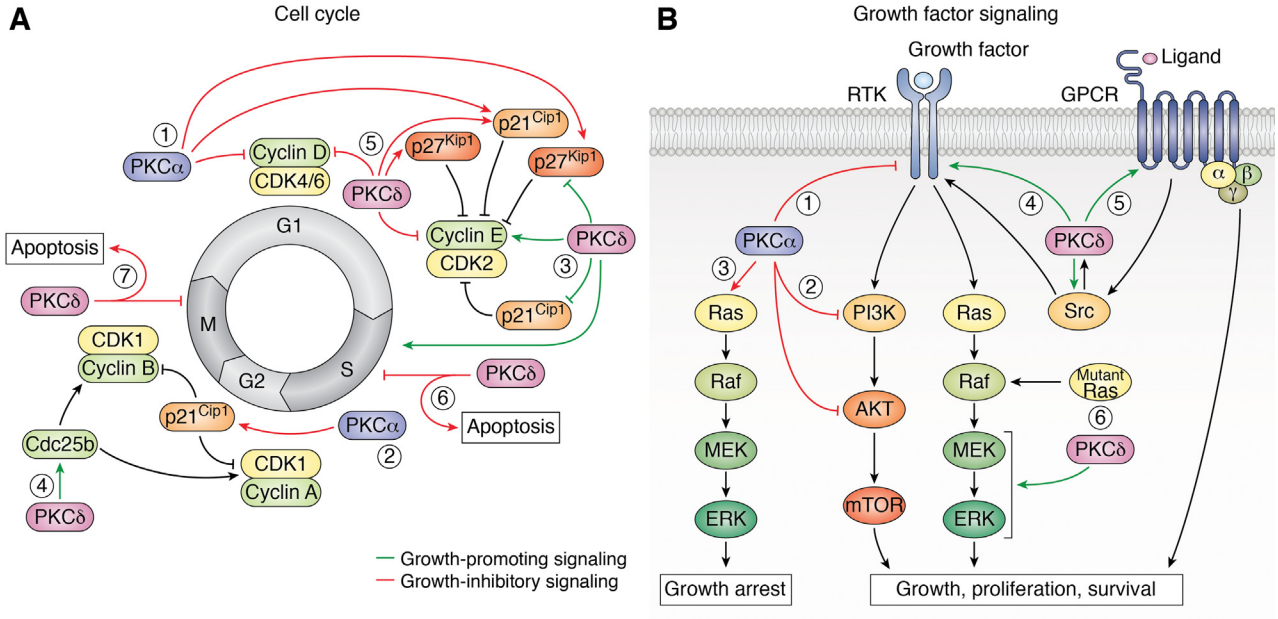

Figure 3. Growth regulation by PKCα and PKCδ. *A*, PKCα signaling predominantly inhibits cell cycle progression. In G_1, PKCα induces cell cycle withdrawal by inhibiting CDK4/6 and CDK2 activity through downregulation of cyclin D and upregulation of $p21^{Cip1}$ and $p27^{Kip1}$ (1). PKCα activation in S phase induces senescence as a result of $p21^{Cip1}$ upregulation in G_2/M (2). In contrast, PKCδ both promotes and inhibits cell cycle progression. Positive effects of PKCδ on G_1/S progression involve cyclin E upregulation and downregulation of $p21^{Cip1}$ and $p27^{Kip1}$ (3). PKCδ can also promote S-phase transit (3) and can enhance the G_2/M transition by activating CDK1 through phosphorylation of Cdc25b (4). Conversely, PKCδ inhibits G_1 progression by downregulating cyclin D and cyclin E and upregulating $p21^{Cip1}$ and $p27^{Kip1}$ (5). PKCδ can also inhibit cell cycle progression in S phase (6) and G_2/M (7), which results in apoptosis. *B*, PKCα can inhibit proliferation by suppressing the activity of receptor tyrosine kinases (RTKs) (1) such as EGFR, and by inhibiting multiple steps in the PI3K–AKT pathway (2). In addition, PKCα induces growth-inhibitory ERK signaling (3) that is dominant over growth-promoting signals. In contrast, PKCδ promotes proliferation and survival through positive regulation of receptor and non-RTKs (4) and G protein–coupled receptors (GPCRs) (5) and by promoting oncogenic ERK signaling downstream of mutant K-Ras (6). CDK, cyclin-dependent kinase; EGFR, epidermal growth factor receptor; ERK, extracellular signal–regulated kinase.

dephosphorylation of priming sites (71). However, fully phosphorylated mature PKC (Fig. 2, *B* and *C*, step 5) is the major substrate for the proteasome in many cell types (61, 65, 67, 72, 73). Parker *et al.* (73) showed that hyperphosphorylated PKCδ is rapidly degraded in phorbol ester–treated cells and at the G_1/S boundary during the cell cycle. The Black laboratory confirmed degradation of fully phosphorylated PKCδ using short-chain DAGs such as 1,2-dioctanoyl-*sn*-glycerol (DiC_8) (61). In the case of PKCα, proteasomal degradation of the fully primed active form following prolonged activation with phorbol esters or bryostatins requires the molecular chaperone heat shock protein 70 (72), which can, paradoxically, also serve to stabilize the dephosphorylated enzyme by binding to the turn motif, promoting its rephosphorylation and reentry into the pool of signaling competent enzyme (74). Maintenance of priming site phosphorylation on activated PKCα is also facilitated by heat shock protein 90 (72), with nucleotide occupancy of the active site within these kinases further contributing to phosphatase resistance (75). Although few studies have addressed lysosomal pathways of PKC downregulation, the Black group and others have determined that PKCα is targeted to lysosomes by phorbol esters *via* at least two distinct lipid raft–dependent pathways, and that the fully primed protein is also the major target for lysosomal degradation (66–68).

While PKCα and PKCδ are both degraded in response to prolonged activation by phorbol esters, studies with other PKC agonists have identified at least two important differences in activation-induced desensitization of these isoforms. PKCδ is readily degraded in response to prolonged activation by membrane-permeant short-chain DAGs (61) or physiological signals that stimulate the production of DAG (*e.g.*, gonadotropin-releasing enzyme (76), bombesin (77), and platelet-activated growth factor (77)). In contrast, chronic activation of PKCα by DiC_8 (61) or physiological agonists (*e.g.*, thyrotropin-releasing enzyme (78), angiotensin II (79)) fails to engage desensitization mechanisms, such as dephosphorylation, ubiquitination, internalization, or degradation, with the enzyme remaining membrane associated and able to support downstream signaling for prolonged periods (*e.g.*, 12 h (61, 77)). Differences in Ca^{2+} sensitivity and DAG affinity of PKCα and PKCδ failed to explain the selective resistance of PKCα. Thus, although an effect of different membrane domains was observed, underlying mechanisms remain to be determined (61). Another notable difference is seen in the response of these isoforms to bryostatin 1. While concentrations from 0.1 to 1 μM bryostatin promote proteasomal and lysosomal degradation of PKCα (61, 63), these doses fail to downregulate PKCδ (80, 81). Interestingly, these low concentrations of bryostatin also block the ability of phorbol esters to induce PKCδ degradation when the two agonists are coapplied, suggesting that bryostatin directs PKCδ to a subcellular compartment that is not accessible to phorbol esters.

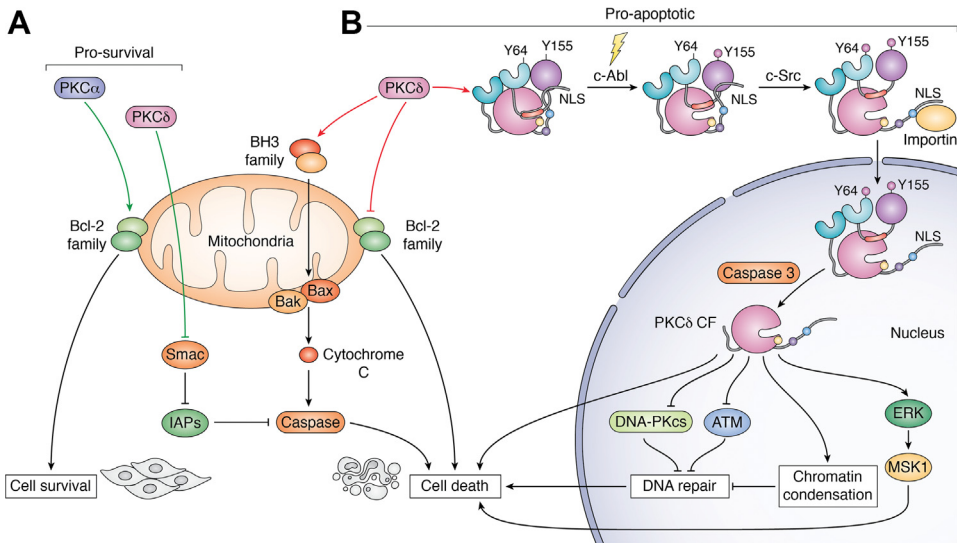

Figure 4. Regulation of cell survival and apoptosis by PKCα and PKCδ. *A*, PKCα predominantly promotes cell survival through activation of Bcl-2 family proteins. While PKCδ is primarily a proapoptotic kinase, it can drive cell survival by sequestering Smac, thus allowing IAPs to inhibit caspase activation. *B*, PKCδ drives cell death by downregulating antiapoptotic Bcl-2 family proteins or by upregulating the proapoptotic BH3 family proteins, which allows the formation of Bax/Bak channels, release of cytochrome *c*, and activation of caspase. Upon DNA-damaging signals (*yellow lightning bolt*), PKCδ undergoes noncanonical activation involving sequential phosphorylation of Y155 and Y64 by c-Abl and c-Src, respectively. These phosphorylation events result in a conformational change that releases the C-terminal tail from the C2 and kinase domains, revealing a cryptic NLS to allow importin binding and nuclear transport. In the nucleus, active caspase-3 cleaves PKCδ to generate active C-terminal catalytic domain (PKCδ CF). Potential mechanisms of PKCδ-dependent cell death include suppression of the DNA damage response, alterations in chromatin structure, and inhibition of DNA repair. The ERK–MSK1 pathway is important for regulation of the proapoptotic response of PKCδ. Prosurvival proteins are in *green*, and proapoptotic proteins are in *orange*. CF, catalytic fragment; ERK, extracellular signal–regulated kinase; IAP, inhibitor-of-apoptosis protein; MSK1, mitogen- and stress-activated protein kinase 1; NLS, nuclear localization signal.

Subcellular localization of PKCα and PKCδ

The differential effects of PKC agonists on PKCα and PKCδ may reflect their activation at different cellular locations (82), with PKCα translocating mainly to the plasma membrane, whereas PKCδ accumulates in a variety of additional compartments, including the plasma membrane, Golgi membranes, the ER, mitochondria, and the nucleus (50, 83, 84). Localization-specific functions of PKC may be regulated by spatially restricted generation of second messengers such as Ca^{2+} and/or DAG or by protein–protein interactions that facilitate access to unique substrates (85), among other mechanisms.

The almost exclusive localization of activated PKCα at the plasma membrane (65, 86–88) may explain the important role of this isoform in regulating cell growth, differentiation, and migration. As discussed further, extensive evidence supports the ability of both PKCα and PKCδ to regulate the activity of RTKs and downstream effectors that reside at the plasma membrane (89–97). PKCα also coordinately regulates plasma membrane–associated Rho-GTPases, as well as integrins and the actin cytoskeleton, to regulate cell spreading, focal contact formation, and migration (see later).

The wide subcellular distribution of activated PKCδ is consistent with its diverse functions in proliferation, migration, DNA repair, apoptosis, and metabolism. Agonist-induced changes in the intracellular distribution and activity of PKCδ have been investigated using FRET-based fluorescence reporters (41, 83). These studies demonstrate a unique two-step mechanism for recruitment and retention of PKCδ at the mitochondria, where the kinase regulates respiration and promotes apoptosis (98–100). In other studies, Gomel *et al.* (101) targeted exogenous active PKCδ to the cytosol, ER, nucleus, or mitochondria. Their studies showed that ER-targeted PKCδ is antiapoptotic, whereas nuclear-, cytoplasmic-, and mitochondrial-targeted PKCδ is proapoptotic.

The Reyland laboratory has shown that nuclear localization of PKCδ is highly regulated and linked to cell death signals such as activation of c-Abl and caspase-3 (47, 50). Nuclear localization is in addition controlled by c-Src and Src-family kinases (83), suggesting a potential link between growth factor signaling and cell death. In addition to PKCδ, caspase-3 also accumulates in the nucleus in response to apoptotic signals, where it can cleave PKCδ in the V3 region to generate a constitutively activated CF (PKCδ CF) (51, 56), which is also constitutively nuclear because of exposure of its nuclear localization signal. Whether PKCδ CF is functionally distinct from full-length PKCδ is unclear since both forms of PKCδ can induce apoptosis when overexpressed, albeit with different kinetics (51, 102).

Proliferation and differentiation

In-depth studies of the growth regulatory functions of PKCα in normal cells have been performed in the hematopoietic system and in regenerating epithelial tissues, including the intestinal epithelium, epidermis, and endometrium. While PKCα signaling can promote (103–105) or inhibit (106, 107) proliferation in cells of the immune system, the kinase is predominantly antiproliferative and prodifferentiation in regenerating epithelia (86–88, 108–115). PKCδ can also promote (116–121) or inhibit (122–126) proliferation in normal

and cancer cells (127–129). Curiously, in some cases, PKCα and PKCδ regulate similar cell functions, albeit with different outcomes. For example, while cell cycle arrest by PKCα can lead to cell differentiation (86–88, 108–115), cell cycle arrest by PKCδ is more likely to drive cell death (130, 131). PKCα and PKCδ diverge significantly in their regulation of growth factor signaling, with PKCα inhibiting growth factor receptor activity and downstream pathways, and PKCδ generally propagating growth factor signaling by regulating downstream pathways such as the MEK (mitogen-activated protein kinase kinase)–ERK (extracellular signal–regulated kinase) cascade (102, 132, 133). Here, we will discuss what is known about mechanism(s) underlying the overlapping and divergent effects of these PKC isozymes on growth regulatory targets.

Cell cycle regulation

Compelling evidence for growth-suppressive and differentiation-inducing functions of PKCα comes from immunohistochemical analysis of unperturbed epithelial tissues. PKCα is cytosolic and inactive in proliferating cells of intestinal and colonic crypts (88, 110), the basal layer of the epidermis (112, 113), and the endometrium (86). However, coincident with cell growth arrest and differentiation in these tissues, PKCα robustly localizes to the plasma membrane, a hallmark of PKC activation (10). More specifically, PKCα is cleared from the cytosol and appears at the plasma membrane in the upper crypt region of the intestinal epithelium, the first suprabasal layer (spinous layer) of the epidermis, and in non-proliferating estrus phase endometrial cells. Remarkably, PKCα remains membrane associated and presumably active for prolonged periods in postmitotic cells, for example, 2 to 3 days in the intestine and 8 to 10 days in the skin, consistent with the requirement for sustained activation of the enzyme for maintenance of physiological responses such as growth arrest and differentiation (134, 135). Strikingly, *in vivo* studies in genetically engineered mice largely support a growth suppressive role for PKCα. While PKCα knockout mice are viable, fertile, and have no overt phenotype, Oster and Leitges (136) reported increased crypt cell mitotic index in the intestinal epithelium of these mice. The Farese group further showed that insulin signaling through PI3K is enhanced in PKCα-deficient skeletal muscle and adipocytes and that PKCα acts as a physiological feedback inhibitor of the insulin pathway (137), a finding that has been confirmed in multiple systems (138–140).

A direct role for PKCα activity in driving growth arrest was established by *in vitro* studies in intestinal crypt–like cells (108, 109) and keratinocytes (87, 112), which demonstrated that PKCα can trigger hallmark events of cell cycle withdrawal into G_0. Evidence from these and other systems points to D-type cyclins and the cyclin-dependent kinase (CDK) inhibitory proteins, $p21^{Cip1}$ and $p27^{Kip1}$, as critical cell cycle regulatory targets of PKCα (Fig. 3*A*). PKCα induces rapid downregulation of cyclins D1, D2, and D3 and/or induction of $p21^{Cip1}$/$p27^{Kip1}$, inhibition of G_1/S cyclin/CDK complex activity, and changes in the pocket proteins, p107, pRb, and p130, characteristic of G_1 arrest and cell cycle withdrawal in multiple cell types (87, 108, 109, 112, 141, 142). PKCα-induced downregulation of D-type cyclins is mediated by at least two mechanisms: inhibition of cyclin D translation through PP2A-mediated activation of the translational repressor 4E-BP1 (143–145), and transcriptional repression, likely through a MEK–ERK-dependent mechanism (135, 143, 145). PKCα induces $p21^{Cip1}$ at the level of transcription *via* p53-dependent (146) and p53-independent mechanisms (141, 143). Consistent with its ability to trigger cell cycle withdrawal, activation of PKCα can induce $p21^{Cip1}$-dependent cell senescence (147). Studies in lung cancer cells by the Kazanietz group showed that activation of PKCα in S phase results in irreversible G_2/M cell cycle arrest, which was not observed when PKCα was activated in G_1 phase (147).

In contrast to PKCα, which largely restrains cell growth and cell cycle progression, PKCδ can promote or suppress proliferation depending on the context. Perhaps not surprisingly, PKCδ regulates many of the same targets as PKCα. Studies from Kitamura *et al.* (130) demonstrate biphasic activation of PKCδ in response to serum and a requirement for PKCδ activation for DNA synthesis. PKCδ can promote cell cycle progression in G_1 by increasing cyclin levels or by reducing expression or nuclear levels of $p21^{Cip1}$ and/or $p27^{Kip1}$ (130, 131), and can enhance G_2/M transition through phosphorylation of Cdc25b (148) (Fig. 3*A*). In contrast, vascular endothelial cells and B cells derived from PKCδ knockout mice show an increase in proliferation (149, 150) consistent with studies by Watanabe *et al.* (122, 151–153) that have linked PKCδ to growth arrest. As shown for PKCα, induction of G_1 or G_1/S arrest can occur through upregulation of $p21^{Cip1}$ or $p27^{Kip1}$ or through downregulation of cyclin D and/or cyclin E (123, 131, 151, 154–158). Several mechanisms have been identified for regulation of $p21^{Cip1}$ by PKCδ including (a) transcriptional induction through KLF4 (124), (b) regulation of $p21^{Cip1}$ phosphorylation (159), and (c) regulation of the interaction of $p21^{Cip1}$ with CDK2 (160). PKCδ can in addition regulate the interaction of $p27^{Kip1}$ with CDK4 to inhibit proliferation (123).

Cell cycle arrest by PKCδ may have important implications for cell death decisions. Notably, in some studies, PKCδ promotes G_1 transition and causes cells to arrest in S or G_2/M (130, 131). Using a PKCδ overexpression model, Ohno *et al.* (130) showed that phosphorylation of PKCδ at Thr505 is required for the serum-induced transition from G_1 to S phase; however, in the same study, PKCδ induced a block in G_2/M progression. Similarly, expression of the PKCδ CF induced a strong G_2/M block in primary human keratinocytes and immortalized HaCaT cells coincident with induction of apoptosis (161). Other studies show that overexpression of PKCδ stimulates $G_1 \rightarrow S$ transition, but the cells then arrest in S phase and undergo apoptosis (131). Thus, $G_1 \rightarrow S$ promotion under these conditions is not proproliferative but proapoptotic.

Finally, like PKCα, increasing evidence points to a role for PKCδ in cell senescence (161–165). Studies in adipocyte stem cells show that PKCδ can induce senescence through regulation of human telomerase reverse transcriptase (162, 163).

Similar studies identified PKCδ as a mediator of transforming growth factor-β–induced senescence through repression of human telomerase reverse transcriptase (165) or inactivation of glycogen synthase kinase 3β (166). PKCδ can also function in cell senescence downstream of $p16^{INK4a}$ and Rb (164). An interesting question is whether induction of senescence by PKCδ is a survival mechanism under conditions where DNA repair is inhibited (see the "Cell survival and cell death" section).

Regulation of growth factor signaling

Inhibitory effects of PKCα on cell cycle progression also reflect its ability to suppress the activity of tyrosine kinase receptors, including EGFR (89–95), ErbB2 (Erb-B2 RTK 2) (HER2 [human epidermal growth factor receptor 2]/neu) (93, 96, 97), c-Met (hepatocyte growth factor receptor) (167), and RET (rearranged during transfection) (168) (Fig. 3*B*). PKCα can inhibit tyrosine kinase receptor signaling by reducing ligand-binding affinity though direct receptor phosphorylation and by altering cell surface expression of receptors by modulating receptor trafficking (93–95, 167–175). PKCα also regulates cell proliferation by acting downstream of growth factor receptors, as exemplified by its ability to suppress insulin action through inhibition of PI3K–Akt and MEK–ERK signaling downstream of the insulin receptor (138–140). PKCα-mediated inhibition of PI3K–Akt signaling has been observed in multiple systems (*e.g.*, (86, 145, 176, 177)) and can be accomplished *via* distinct mechanisms, including suppression of the catalytic activity of PI3K by phosphorylation of the p84α regulatory subunit (177) or direct phosphorylation of the catalytic subunit (178) and by PP2A-dependent dephosphorylation of Akt (86). Interestingly, PKCα can also induce growth arrest *via* strong and sustained activation, rather than inhibition, of the MEK–ERK pathway (135). PKCα-induced growth inhibitory ERK signaling is dominant over proproliferative ERK signaling from serum-regulated growth factors (111, 135, 179–181), further supporting the ability of PKCα to drive growth arrest in epithelial tissues.

In direct contrast to PKCα, PKCδ promotes signaling through tyrosine kinase and G protein–coupled receptors, including receptors for EGF, fibroblast growth factor (FGF), hepatocyte growth factor, insulin-like growth factor 1, and vascular endothelial growth factor (102, 132, 133, 182–188) (Fig. 3*B*). PKCδ can drive growth factor signaling as part of an active receptor complex, through regulation of A disintegrin and metalloprotease 17–mediated shedding of ligands such as EGF (189), and by controlling recycling and degradation of activated cell surface receptors (170, 190–192). Ligand binding to EGFR and other receptors in this family frequently results in activation of a PKCδ–Src–ERK pathway (127, 132, 133, 193). The Reyland laboratory has shown that in Her2/ErbB2-positive breast cancer cells, loss of PKCδ disrupts the association of Src with ErbB2 and inhibits ERK activation (127). In addition to acute regulation, PKCδ contributes to sustained ERK activation both downstream of growth factors and through growth factor–independent mechanisms (118, 190, 194–197). For example, sustained activation of ERK in response to DNA damage is PKCδ dependent but EGFR independent (197). PKCδ is required for maintenance of ERK activation downstream of mutant K-Ras in some non–small cell lung cancer (NSCLC) cells and may be a mechanism of resistance to tyrosine kinase inhibitors (TKIs) (128, 198–200). PKCδ can also activate MEK–ERK by inhibiting Raf kinase inhibitory protein (RKIP), a negative regulator of ERK activation (201). Regulation of growth factor signaling by PKCδ could potentially also be mediated by its ability to bind phosphotyrosine and assemble signaling complexes (22).

Cell differentiation

Elegant studies by the Fields laboraotory showed that PKCα promotes cytostasis and megakaryocytic differentiation of K562 human erythroleukemia cells and that this effect is mediated by isozyme-specific sequences within the catalytic domain (202–204). The Schwende group (205) demonstrated the ability of PKCα to promote differentiation of THP-1 monocyte-like cells into macrophage-like cells, and Nishizuka *et al.* (134) showed that sustained activation of PKCα is required for differentiation of HL-60 promyelocytic leukemia cells into macrophages. The link between PKCα signaling and cell differentiation is clearly illustrated by studies in keratinocytes. Early work by Yuspa *et al.* identified PKCα as a major player in the induction of differentiation markers during Ca^{2+}-induced keratinocyte differentiation (114), findings that were subsequently confirmed by others (87, 113, 115). Using human keratinocyte organotypic raft cultures, Denning *et al.* (87) demonstrated that PKCα deficiency results in decreased cell differentiation, indicated by reduced expression of the late granular layer differentiation marker, loricrin, and impaired epidermal stratification. PKCα has also been shown to play a major role in the differentiation program of mouse keratinocytes by promoting Ca^{2+}-dependent activation of AP-1 transcription factors (206). Studies from the Rosato laboratory (207) investigated the involvement of PKCα and PKCδ in FGF receptor 2b–induced keratinocyte differentiation. Their work showed that PKCδ is necessary at the onset of differentiation, whereas PKCα is necessary for the terminal stages of differentiation. Consistent with this role, PKCδ promotes differentiation in a variety of cells and tissue types (208–210).

Cell survival and cell death

While PKCα provides a strong antiproliferative signal, multiple studies have also linked PKCα to cell survival. In contrast, while PKCδ supports cell survival in some contexts, it is more commonly a regulator of cell death (211). Interestingly, PKCα and PKCδ have been shown to have opposing effects on cell survival in the same cell (212–214). For example, in salivary acinar cells, apoptosis induced by loss of PKCα requires PKCδ activity (214).

Cell survival

An early report by Parker *et al.* (215) described a causal relationship between loss of PKCα function and induction of

apoptosis in COS cells, pointing to the ability of PKCα to mediate survival signaling. Subsequent studies in a broad range of cell types further support this role (214, 216–218). The prosurvival functions of PKCα are modulated primarily through Bcl-2 (B cell lymphoma 2 apoptosis regulator) family members (Fig. 4*A*). Induction of cell death in glioma cell lines and rat hepatic epithelial cells by PKCα knockdown is associated with significant downregulation of the survival protein, Bcl-xL (B cell lymphoma–extra large apoptosis regulator) (216, 219). Ruvolo *et al.* (220) determined that PKCα can phosphorylate Bcl-2 on Ser70 *in vitro*, a modification linked to enhanced Bcl-2 antiapoptotic activity (221), and PKCα-mediated phosphorylation of Bcl-2 was subsequently confirmed in multiple studies using a variety of cell types (220, 222–225). Importantly, PKCα can associate with mitochondrial membranes (221, 222) *via* a mechanism that may involve anchorage by protein interacting with PRKCA 1 (PICK1) (222), for appropriate positioning to regulate Bcl-2. Additional mechanisms associated with the prosurvival effects of PKCα include (a) suppression of apoptosis mediators FEM1b and apoptotic protease activating factor-1 (APAF-1) in T-cell acute lymphoblastic leukemia cells (226), (b) modulation of the proapoptotic BH3 protein, BAD (BCL-2-associated death promoter), in lymphoma cells (227), (c) induction of nuclear translocation of NFκB in bladder cancer cells (228), (d) cytoplasmic localization of p53 in melanoma cells (229), and (e) upregulation of Dicer in bladder cancer cells (230).

Prosurvival signaling by PKCδ is somewhat surprising given its well-established role in regulating cell death. In particular, many studies have shown an essential role for PKCδ in the survival of cells that are dependent on activated K-Ras. These include neuroendocrine tumor cells (116), cancer stem cells in pancreatic and prostate tumors (117), and a subset of lung cancer cells (117, 128, 198). In NIH 3T3 cells engineered to express activated K-Ras (199) and pancreatic cancer cell lines with activated K-Ras (186), PKCδ is required to maintain Akt prosurvival signaling. However, in K-Ras–addicted NSCLC cells, PKCδ is required for ERK activation downstream of mutant K-Ras but not Akt activation (128, 198, 199). PKCδ supports the survival of cancer stem cells in multiple human tumor types (117, 121, 231) and facilitates maintenance of tumor-initiating cells (232). Muselli *et al.* (233) have recently shown that PKCδ regulates expression of the protein Bmi1 (B cell–specific Moloney murine leukemia virus integration site 1), which is required for stem cell renewal. Other prosurvival mechanisms include sequestration of Smac, an antagonist of inhibitor-of-apoptosis proteins (Fig. 4*A*) (234, 235), and regulation of the phosphorylation and inactivation of the proapoptotic protein Bim (BCL-2-like protein 11) (236, 237) (186, 198, 237).

Contrary to its prosurvival roles, overexpression of PKCδ is associated with decreased survival in colon cancer cells, keratinocytes, and many nontransformed cells (124, 125, 238). Consistent with a dual role for PKCδ in regulation of cell viability, functional proteomic analysis of PKCδ-depleted salivary epithelial cells reveals upregulation of signaling pathways that promote cell survival as well as cell death (239). In particular, ERK signaling, energy sensing, the DNA damage response, and apoptosis were identified as key pathways dependent on PKCδ (187, 194–197, 240–242). These seemingly paradoxical functions of PKCδ may reflect cell- and context-specific integration of different signaling pathways.

Apoptosis

The preponderance of evidence supports opposite roles for PKCα and PKCδ in cell death, with PKCα suppressing and PKCδ inducing apoptosis (211, 238) (Fig. 4*B*). However, PKCα can also play a proapoptotic role. In hormone-dependent LNCaP prostate cancer cells, prolonged association of PKCα with non-nuclear membranes leads to apoptosis (243), and PKCα mediates apoptosis induced by DAG-lactones (244). In renal tubular cells, PKCα mediates cell death induced by polychlorinated biphenyls, *via* a mechanism that involves downregulation of Bcl-2 and activation of caspase-3 (245).

Extensive studies from the Reyland laboratory and others have shown that PKCδ plays a central role in activation of cell death pathways under conditions of cell stress and DNA damage (149, 246, 247) (Fig. 4*B*). Depletion of PKCδ suppresses DNA damage–induced cell death in most nontransformed cells and some cancer cells, PKCδ knockout mice are protected from irradiation-induced damage to the salivary gland and thymus, and salivary epithelial cells from PKCδ knockout mice are resistant to multiple apoptotic stimuli (211, 247). PKCδ also regulates apoptosis through TRAIL (tumor necrosis factor (TNF)–related apoptosis-inducing ligand) and TNFα (248, 249). In this context, PKCδ can regulate secretion of death receptor ligands in response to phorbol ester (250) and death receptor expression in the context of ER stress (251, 252).

Nuclear PKCδ is the primary inducer of cell death, although localization of PKCδ to the mitochondria may also contribute to apoptosis (50, 51, 253, 254). Nuclear localization of PKCδ is tightly regulated to prevent inappropriate activation of cell death pathways (see the "Distinct structural features of PKCα and PKCδ" section) (47, 50). Once in the nucleus, PKCδ is cleaved by nuclear caspase-3 to generate a 42 kD CF (PKCδ CF), which is constitutively nuclear and a potent inducer of apoptosis (51). Interestingly, caspase-3 cleavage of PKCδ *per se* is not required for this mechanism of apoptosis, but nuclear translocation of PKCδ and PKCδ kinase activity are essential (51). Defining the critical role tyrosine phosphorylation plays in activating PKCδ in response to DNA damage led to the prediction that TKIs could be protective against irradiation damage. The Reyland laboratory has subsequently shown that TKIs block PKCδ activation and provide robust protection against radiation-induced damage to the salivary gland *in vivo* (49, 255). Furthermore, PKCδ-targeted siRNAs reduce cytotoxin-induced renal cell injury in mice as well as irradiation-induced salivary gland damage (256, 257). Thus, PKCδ-targeted therapies could be used to provide protection from damage during radiation and/or chemotherapy treatment.

Mechanistically, PKCδ can regulate the apoptotic machinery through downregulation of prosurvival Bcl-2 proteins, such as Mcl-1 (myeloid cell leukemia-1 antiapoptotic BCL-2 family

protein), or upregulation of proapoptotic Bcl-2 proteins, including BIM, BAD, BAX (BCL-2 associated X protein), and BAK (BCL-2 antagonist/killer 1) (236, 258–261). However, Bcl-2 proteins have not been identified as direct substrates of PKCδ. More likely, PKCδ regulates these apoptotic players indirectly through p38, c-Jun N-terminal kinase, ERK, and mitogen- and stress-activated protein kinase 1 (MSK1), Akt, and other pathways that control cell survival in response to damage (176, 196, 197, 262, 263). In addition, there is evidence that PKCδ regulates the DNA damage response and cell cycle checkpoints (264–270). For example, PKCδ can regulate activation of the DNA damage sensors DNA-PK (DNA-dependent protein kinase) and ATM (ataxia–telangiectasia mutated) as well as phosphorylation of RAD9 and γH2AX (264–266, 268, 269). In the case of DNA-PK, PKCδ inactivates the catalytic subunit, suppressing DNA repair and inducing apoptosis (265). Phosphorylation of histone H3 Ser10 by PKCδ has also been described, which is accompanied by chromatin condensation and increased apoptosis (271). Similarly, the Reyland laboratory has shown that MSK1 is required for apoptosis through a PKCδ → ERK → MSK1 pathway (197). Cell cycle checkpoints in S phase and G_2/M phase may also be targets for induction of cell death by PKCδ (266, 267, 269) as loss of the G_2/M checkpoint is associated with increased radiation sensitivity and apoptosis (267). Whether these checkpoints are directly regulated by PKCδ or induce cell death secondary to accumulation of DNA damage has not been fully elucidated.

Regulation of cell motility and migration

While the biological effects of PKCα and PKCδ often diverge, a notable exception is seen in the regulation of cell motility and migration where both isoforms generally act as positive regulators, although the mechanisms underlying this regulation often differ (Fig. 5). A large body of evidence points to PKCα as a positive regulator of epithelial-to-mesenchymal transition (EMT), a dynamic process in which polarized epithelial cells assume a mesenchymal phenotype characterized by enhanced migratory capacity and invasiveness. EMT plays important roles during normal development as well as pathological processes such as tumor metastasis (272–275). PKCα regulates the expression of transcription factors that play key roles in EMT, including FRA1 (276), SNAIL (274, 277), TWIST1 (277, 278), ZEB1 (zinc finger E-box–binding homeobox 1) (273), and ZEB2 (277). For example, TWIST1 is a PKCα substrate, and PKCα-mediated phosphorylation leads to accumulation of TWIST1 through inhibition of its ubiquitination and proteasomal degradation (278). Knockdown of PKCα leads to downregulation of ZEB1 and accompanying upregulation of E-cadherin mRNA, as well as inhibition of cell migration and invasion (273). PKCα is also likely to affect EMT and E-cadherin expression through negative regulation of p120-catenin by direct inhibitory phosphorylation (279, 280). In contrast to PKCα, few studies have reported regulation of EMT by PKCδ; however, PKCδ activity has been linked to EMT based on its ability to mediate effects of EGF on E-cadherin and adherens junctions in primary keratinocytes (281).

In addition to regulating EMT, PKCα has direct effects on cell migration and invasion, predominantly mediated by coordinated regulation of Rho-GTPases (282). PKCα binds to syndecan-4, a ubiquitously expressed heparan sulphate proteoglycan that acts as a receptor for growth factors such as FGF2, vascular endothelial growth factor, and PGDF, and ECM components, including fibronectin and vitronectin (283). Following engagement with heparan sulphate–binding proteins, syndecan-4 undergoes PIP_2-dependent oligomerization, which results in activation of PKCα through a noncanonical mechanism that is independent of DAG and Ca^{2+} (57, 282, 284–286). In the resting state, syndecan-4 represses the

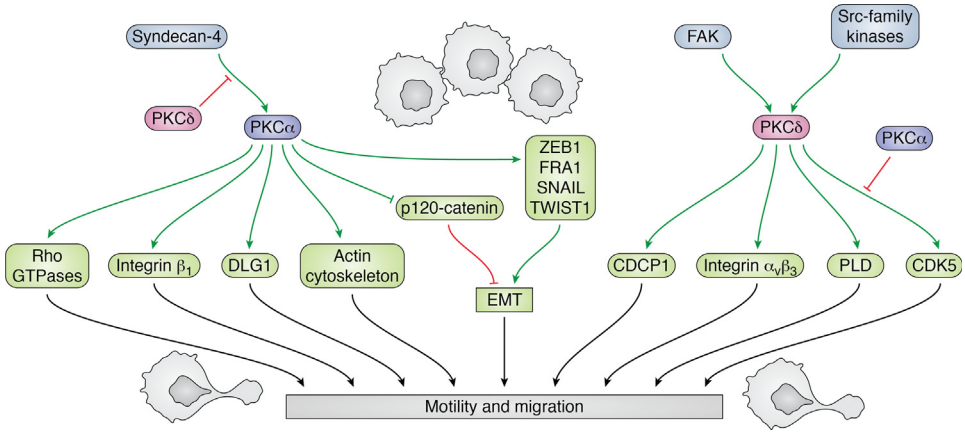

Figure 5. Effects of PKCα and PKCδ on motility and migration. PKCα and PKCδ have predominantly positive effects on cell motility and migration, although they generally regulate these processes through different mechanisms. Activation of PKCα following its interaction with syndecan-4 promotes migration through regulation of Rho-GTPases. PKCα can also enhance migration through regulation of the Scribble–LGL–DLG polarity complex and remodeling of the actin cytoskeleton. PKCα regulation of ZEB1, FRA1, SNAIL, and TWIST1 enhances EMT and promotes cellular motility. PKCδ mediates effects of FAK and Src family kinases on migration, acting through PLD, CDK5, and CDCP1. Integrin signaling represents a common target for PKCα and PKCδ, although the specific integrins targeted differ. Finally, syndecan-4 and CDK5 represent nodes where PKCα and PKCδ can regulate each other's effects on migration. Positive effects are shown in *green arrows*, and negative effects are shown in *red*. CDCP1, CUB domain–containing protein 1; CDK5, cyclin-dependent kinase 5; DLG, discs large MAGUK (membrane-associated guanylate kinase homologs) scaffold protein; EMT, epithelial-to-mesenchymal transition; FAK, focal adhesion kinase ; LGL, lethal giant larvae protein; PLD, phospholipase D; ZEB1, zinc finger E-box–binding homeobox 1.

activity of Rho-family small GTPases, RhoA and Rac1, through interaction with and activation of the Rho GDP–dissociation inhibitor, RhoGDI1. However, following activation, syndecan-4-bound PKCα phosphorylates RhoGDI1, leading to release and activation of RhoA and Rac1 (287–290). Thus, syndecan-4-mediated activation of PKCα supports directional migration through activation of RhoA and Rac1 at sites of matrix and/or growth factor binding (291). PKCα also supports migration through phosphorylation of p190RhoGAP (GTPase-activating protein) (292), which leads to inhibition of RhoA but not Rac1, and thus regulates the phasic activation of Rho-GTPases that is required for migration (292, 293). Notably, PKCδ signaling can oppose the effects of PKCα on RhoA and Rac1. While PKCδ does not interact with syndecan-4 (282), the kinase can phosphorylate syndecan-4 on Ser183, which inhibits PIP_2 binding and oligomerization to prevent PKCα activation by heparan sulphate–binding proteins (294).

Modulation of migration by PKCα can also involve direct effects on components of the actin cytoskeleton. For example, phosphorylation by PKCα protects the actin crosslinking protein, filamin A, from degradation and enhances cytoskeletal remodeling and cell migration (295, 296). PKCα also binds and phosphorylates vinculin (297) and fascin (298) to regulate cell spreading and focal adhesion. The Scribble–LGL (lethal giant larvae protein)–DLG (discs large MAGUK [membrane-associated guanylate kinase homologs] scaffold protein) polarity complex has also been implicated in the ability of PKCα to control directed migration (299–301). PKCα interacts with DLG1 at the leading edge, and blockade of this interaction reduces the ability of PKCα to promote migration (299). Notably, regulation of DLG1 is unique to PKCα since it is mediated by a PDZ ligand motif in the C terminus of the kinase that is not present in PKCδ or other PKC isozymes.

Both PKCα and PKCδ regulate motility and invasion through modulation of integrin function. PKCα interacts with the cytoplasmic tail of β1 integrin to promote its internalization, and inhibition of this interaction suppresses migration (302, 303). Effects on integrin internalization can be mediated by PKCα phosphorylation of formin-like receptor 2 in lamellipodia and filopodia to promote actin-dependent internalization of formin-like receptor 2/α integrin/β1 integrin complexes (304, 305). While PKCα regulates integrin recycling, PKCδ is important for linking integrins to downstream effectors including phospholipase D, Src, focal adhesion kinase, and mitogen-activated protein kinase (306–308). In addition, PKCδ can control migration through regulation of integrin expression (309, 310).

PKCδ also has effects on migration that are distinct from those of PKCα. Limited evidence supports a role for PKCδ in controlling the stability of the actin cytoskeleton and enhancing migration through phosphorylation of myosin light chain (311–313). PKCδ also plays an important role in regulating smooth muscle cell and neutrophil migration (314–317). Soroush *et al.* (318, 319) have shown that PKCδ regulation of neutrophil–endothelial cell interactions and neutrophil migration is dependent on phosphorylation of PKCδ on Tyr155. A role for PKCδ in cortical neuron migration has also been shown, with PKCδ promoting cell migration by stabilizing the CDK5 activator, p35 (320). In contrast, PKCα has been reported to be a negative regulator of CDK5 activity (321). Another mechanism unique to PKCδ involves regulation of cell migration through interaction of the enzyme with the transmembrane CUB domain–containing protein 1 (CDCP1) (322–324). As discussed previously, this protein interacts with the PTB in the C2 domain of PKCδ (22). Upregulation of CDCP1 is seen in many types of cancer where it is associated with progressive disease and poor survival (323, 325). In pancreatic cancer, CDCP1 regulates cell migration, invasion, and ECM degradation through a mechanism that requires association with PKCδ and recruitment of Src (323). Hepatocellular carcinoma and renal carcinoma cells can upregulate CDCP1 *via* a hypoxia-inducible factor–dependent mechanism to drive PKCδ-dependent migration (322, 324), and a novel small-molecule inhibitor that blocks association of PKCδ and CDCP1 was shown to inhibit metastasis of gastric carcinoma cells (326).

PKCα and PKCδ in disease

Functions of PKCα and PKCδ in cell proliferation, cell survival, cell death, and migration are often subverted in disease. Disease phenotypes likely reflect the sum of individual phenotypes, in the context of their relative contribution to the specific disease process. Here, we will discuss what is known about the contribution of PKCα and PKCδ to cancer, immune, and neurodegenerative disorders.

Roles in tumorigenesis

Analysis of mouse models of cancer clearly reveals opposing phenotypes for PKCα and PKCδ in tumor development and progression. The antiproliferative activity of PKCα (see the "Proliferation and differentiation" section) is reflected in a predominantly tumor suppressive role of the enzyme, supported by frequent downregulation of PKCα mRNA and protein in most cancer types (327) and by the fact that PKCα knockout or inhibition enhances tumorigenesis in all murine cancer models reported to date (*i.e.*, models of intestinal (136), skin (328), endometrial (86), and lung (329) cancer as well as B-CLL (330)). Oster and Leitges (136) showed that loss of PKCα in the $Apc^{Min/+}$ mouse model of intestinal neoplasia enhances tumor formation in the intestine, with lesions displaying a more aggressive histopathological phenotype and mice dying significantly earlier than their PKCα-expressing littermates. Hara *et al.* (328) showed that PKCα knockout mice subjected to the two-stage protocol of skin carcinogenesis develop significantly more papillomas, and the Black laboratory has shown that PKCα deficiency accelerates tumor formation in a mutant PTEN (phosphatase and tensin homolog)–driven model of endometrial tumorigenesis (86). Similarly, genetic deletion of PKCα in three murine lung adenocarcinoma models (*LSL-Kras, LA2-Kras*, and urethane exposure) by the Fields group (329) significantly increased tumor number, size, and aggressiveness, while promoting progression from adenoma to carcinoma and reducing mouse survival.

Consistent with a role of PKCα in regulating cell senescence (147), PKCα deficiency resulted in bypass of oncogene-induced senescence in these lung cancer models (329). Loss of PKCα also resulted in expansion of the tumor-initiating bronchioalveolar stem cell population, facilitated by enhanced expression of inhibitor of DNA binding proteins 1–3 (Id1–3), an effect of PKCα deficiency also identified by the Black group (86, 111) in intestinal epithelial and endometrial cells. Finally, Michie *et al.* (330) reported that deficiency of PKCα in hematopoietic progenitor cells results in B-CLL-like disease in mice. It should be noted that, aside from studies in hematopoietic progenitor cells (330), all PKCα-deficient mouse models referenced here harbored organism-wide loss of the kinase. Thus, additional studies are needed to exclude a role for PKCα deficiency in tumor-associated stromal and immune cells in observed tumor-suppressive effects. Nevertheless, analysis of patient tumors supports findings in animal models, with PKCα loss correlating with advanced disease in many human tumor types (86, 329, 331, 332). In addition, while mutations in PKCα are rare in tumors, a loss-of-function PKCα mutant (D463H) is a hallmark of chordoid gliomas, present in 100% of cases examined to date (333, 334).

Both increased (16, 17) and decreased (335–339) expression of PKCδ has been observed in human tumors; however, functional genomic alterations of PKCδ are rare, and none have been mechanistically linked to cancer (340). While increased expression of PKCδ correlated with poor prognosis in a subset of human breast tumors (127, 341), expression of PKCδ was shown to decrease with increasing tumor grade in urinary bladder cancer (336). The variable expression of PKCδ in human tumors argues for context-dependent roles in tumor promotion and tumor suppression, consistent with the dual functions of PKCδ in proliferation and cell death that have been demonstrated *in vitro*. This contrasts with the finding that PKCδ largely functions as a tumor promoter in mouse models of cancer, including mammary gland, pancreatic, and lung (127–129). An exception are studies in transgenic mice where overexpression of PKCδ suppresses phorbol ester– but not UV irradiation–induced skin cancer (342, 343).

It should be noted that the PKCδ-deficient mouse cancer models in which PKCδ functions as a tumor promoter are all likely to be K-Ras dependent and, as discussed previously, PKCδ is required for survival of cells with activated K-Ras (128, 129, 186, 199) (see the "Cell survival and cell death" section). This is in direct contrast to PKCα, which functions as a tumor suppressor in K-Ras-driven tumor models (329). Studies by the Reyland laboratory in K-Ras mutant NSCLC cell lines support the notion that PKCδ function may be dependent on oncogenic context. In these studies, PKCδ function was investigated in two subpopulations of K-Ras mutant NSCLC cells defined based on dependence on K-Ras for survival (128, 198). NSCLC cells functionally dependent on K-Ras were found to require PKCδ for survival, whereas those not functionally dependent on K-Ras used PKCδ for apoptosis (128, 198). Studies in additional cancer models are clearly needed to delineate the roles of PKCδ in tumorigenesis and to understand how oncogenic context contributes to the function of this kinase.

Involvement in resistance to cancer therapeutics

Interestingly, both PKCα and PKCδ can promote resistance of cancer cells to chemotherapeutic agents, perhaps reflecting mechanistic overlap in their signaling functions. The ability of these kinases to protect cells from the cytotoxic effects of chemotherapeutic agents likely reflects their well-established prosurvival functions (see the "Cell survival and cell death" section). Increased expression of PKCα confers resistance of tumor cells to adriamycin (344), tamoxifen (345), etoposide, and cytosine arabinoside (220, 223), and protective effects have been linked to enhanced Bcl-2 phosphorylation in some contexts (220, 223). Conversely, reduced levels of PKCα sensitize T-acute lymphoblastic leukemia cells to vincristine and prednisone by preventing the downregulation of proapoptotic factors, FEM1b and Apaf-1 (226). Reduced expression of PKCα also sensitizes tumor cells to cisplatin, taxol (224, 346, 347), erlotinib (277), and mitomycin-C plus 5-fluorouracil (217). The clinical relevance of these findings is highlighted by evidence that PKCα expression correlates with resistance to antiestrogen therapy in breast cancer patients (348).

As might be expected, PKCδ has been validated as a synthetic lethal target in some cancers with mutant K-Ras (200, 349) and is required for resistance to TKIs in a subset of K-Ras mutant NSCLC cells (116, 186, 199). In addition, a recent study by Chen *et al.* (350) showed that PKCδ contributes to acquired resistance to EGFR inhibitors by stabilizing interaction of sodium/glucose cotransporter 1 (SGLT1) with EGFR and increasing glucose uptake. PKCδ expression is increased in NSCLC cells that are dependent on K-Ras for survival, and this correlates with increased nuclear abundance of PKCδ and resistance to chemotherapy-induced apoptosis (198). In this model, nuclear accumulation of PKCδ correlates with resistance to TKIs (200) rather than apoptosis.

Roles in invasion and metastasis

Consistent with their ability to promote cell migration (see the "Regulation of cell motility and migration" section), both PKCα and PKCδ have been implicated in tumor cell invasion and metastasis. Evidence points to PKCα, but not PKCδ, acting as a positive regulator of EMT through regulation of transcription factors such as TWIST and SNAIL (274, 277, 278). PKCα can also regulate Rho-GTPases and the actin cytoskeleton to promote cell spreading, migration and invasion, and both isoforms can regulate degradation of the ECM. PKCα promotes tumor cell invasion in multiple cancer types, including colon cancer (351), hepatocellular carcinoma (352), pancreatic cancer (274), endometrial cancer (353), melanoma (354), and glioblastoma (355). Furthermore, reduced expression/activity of PKCα inhibits metastasis in xenograft models of breast cancer (356, 357), ovarian cancer (358), and melanoma (355). In addition to effects on migration, this activity is associated with the ability of PKCα to increase matrix metalloproteinase (MMP) secretion in breast cancer (357),

glioblastoma (355), and lung cancer cells (359). Interestingly, PKCδ suppresses MMP9 secretion and migration in breast and colon cancer cells (360–362); however, it is required for chemomigration and MMP9 expression in prostate cancer cells (363) and for MMP9 expression in thrombin-stimulated astrocytes (364).

Early studies by the Jaken laboratory suggested a relationship between high expression of PKCδ and metastasis (361). They showed that mammary tumor cells that are engineered to overexpress the regulatory domain of PKCδ, which inhibits the activity of endogenous PKCδ, have reduced metastasis when transplanted into the mammary fat pad of mice (361). More recently, PKCδ has been linked to metastatic phenotypes such as migration and invasion in many *in vitro* models, including thyroid (365), hepatocellular (322), breast (127, 366), lung (128, 310), prostate (363), pancreatic (323), and renal cell (324) cancer. While confirmation using *in vivo* models and human tumors is needed, therapeutic targeting of PKCα or PKCδ may hold promise for suppression of metastatic disease; however, the potential role for these kinases as tumor suppressors would need to be taken into consideration in any clinical applications.

Contribution to autoimmune disease, inflammation, and neurodegeneration

PKCδ knockout mice develop a lupus-like autoimmune disease with age, which has been linked to a defect in the establishment of B-cell tolerance and aberrant accumulation of subpopulations of B cells (126, 150, 195, 367, 368). Notably, a similar autoimmune phenotype has been described in a patient with a rare loss-of-function mutation in the *PRKCD* gene (369, 370). *In vivo* studies reveal a role for PKCδ in promoting inflammation, as PKCδ knockout mice show defects in macrophage function (371, 372), platelet activation (373), and expression of proinflammatory cytokines (374, 375). Limited evidence also supports a role for PKCα in regulation of inflammatory responses, which can be positive or negative in different contexts. PKCα overexpression in mouse epidermis promotes marked intraepidermal neutrophilic inflammation and expression of inflammation-related genes such as cyclooxygenase 2 and TNFα (376, 377). Conversely, PKCα is protective against lipopolysaccharide-induced lung inflammation likely through inhibition of proinflammatory cytokine release by macrophages (378).

Given its role in inflammation, it is not surprising that disruption of PKCδ *in vivo* can be protective in tissue injury models and mouse models of disease. For example, PKCδ knockout mice show improved pathogen clearance and increased survival in rat models of sepsis (379–381). Both PKCα and PKCδ have been implicated in neurodegenerative disease (248, 382–385). The discovery of rare gain-of-function PKCα variants in families with late-onset Alzheimer's disease supports a causative role for PKCα in the disease (386). In the case of PKCδ, loss or downregulation is protective in Alzheimer's and Parkinson's disease and is associated with increased survival in Huntington's disease (248, 383–385). In some cases, these effects are associated with alterations in cell death, consistent with the known role of PKCδ in promoting apoptosis (247, 384, 385).

Summary and perspective

In this review, we have compared the structure, activation, and subcellular localization of PKCα and PKCδ and discussed their unique and sometimes opposing functions (Fig. 6). Our goal was to identify important gaps in knowledge and to stimulate new questions, particularly as they relate to human disease and therapy. Here, we highlight major themes in the regulation of biological functions by PKCα and PKCδ and discuss implications for the pathogenesis of diseases such as cancer.

PKCα and PKCδ can regulate the same or similar biological functions but with opposing outcomes

The contrasting functions of PKCα and PKCδ are often mediated by regulation of the same target molecules or pathway. This dichotomy is well exemplified by the growth-regulatory functions of these kinases. While PKCα is primarily involved in antiproliferative and prodifferentiation activities, PKCδ has both proproliferative and antiproliferative functions. Remarkably, both kinases regulate the same cell cycle proteins and growth factor signaling pathways, albeit in different ways. In the case of growth factor signaling, the specific pathway targets diverge, with PKCα regulating ligand binding, receptor trafficking, and downstream pathways, whereas PKCδ primarily regulates the activation of proproliferative pathways downstream of growth factor receptors. The observation that PKCα and PKCδ can control similar (or the same) biological pathways with different outcomes indicates that output is likely to be highly dependent on tissue, cellular, and signaling context.

		PKCα	PKCδ
Structure	DAG	Yes	Yes
	Ca^{2+}	Yes	No
	Subcellular localization	Plasma membrane	Plasma membrane, Golgi, ER, mitochondria, nucleus
Function	Proliferation	−−−/+	++/−
	Differentiation	+++	+
	Survival	++	+
	Death	−	+++
	Motility/migration	+++	+
Disease	Tumorigenesis	−−−	++
	Metastasis	++	+
	Chemoresistance	++	+
	Autoimmunity/ inflammation	+/−	++
	Neurodegeneration	+	+

Figure 6. Summary of the regulation and functions of PKCα and PKCδ signaling. The regulation and predominant roles of PKCα and PKCδ are indicated. + and − indicate positive and negative effects on the indicated cellular processes, with multiple +/− symbols indicating the relative prevalence of indicated effects based on the literature.

PKCα and PKCδ have largely opposing roles in cell survival and cell death

In most, but not all cases, PKCα activates prosurvival pathways, whereas PKCδ promotes cell death. In some contexts, contrasting functions are mediated by opposing effects on the same target proteins, with one example being the Bcl-2 family proteins. However, PKCδ can exert proapoptotic roles through regulation of targets not shared by PKCα, as seen in response to cell stress or DNA damage. The ability of PKCδ to regulate cell proliferation and cell death raises the important question of how these functions are segregated. Evidence points to subcellular localization of PKCδ as a determinant of function. When primarily cytoplasmic, PKCδ appears to be proproliferative, whereas nuclear translocation is tightly associated with cell death. However, some cancer cells may have high levels of nuclear PKCδ but not induce apoptosis, consistent with evasion of apoptosis being a hallmark of cancer. An interesting question is whether proproliferative signaling and cell death signaling by PKCδ are linked, and if so, how. A possible connection is EGFR and MEK–ERK, which can regulate both biological outcomes. Studies in cells with specific oncogenic drivers and lessons from drug resistance models suggest that PKCδ "rewiring" is likely an adaptive response to promote tumor cell survival.

In mouse models of tumorigenesis, PKCα is uniformly tumor suppressive, whereas PKCδ usually functions as a tumor promoter

The largely tumor-suppressive effects of PKCα suggest that antiproliferative signaling is dominant over the prosurvival functions of the kinase. The largely tumor-promoting effects of PKCδ, on the ther hand, point to dominant effects of PKCδ-regulated proproliferative and prosurvival pathways. It is notable that both PKCα and PKCδ generally act as positive regulators of migration and invasion, and both kinases have been implicated in tumor metastasis. The well-documented ability of PKCα to promote cell motility, EMT, invasion, and survival likely explains the seemingly contradictory tumor-promoting activity of this kinase in some cancer types, such as breast tumors. It should be appreciated that *in vivo* cancer models are largely limited to studies in whole animal knockouts of PKCα or PKCδ and to a select group of tumor models. Analysis of the role of these kinases in models with tissue-specific gene disruption, and in the context of other cancer driving mutations, will be required to more fully understand how these enzymes contribute to tumorigenesis and tumor progression.

The well-documented roles of PKCα and PKCδ in disease pathogenesis support their potential as therapeutic targets

While efforts are underway to target individual PKC isoforms, isozyme-specific targeting is a challenging task because of structural similarity and overlapping functions. There are also important concerns about whether therapeutic strategies should focus on rescuing or inhibiting PKC signaling given the complex phenotypes observed. In addition, both PKCα and PKCδ can promote resistance of cancer cells to the effects of chemotherapeutic agents, further complicating approaches to targeting these enzymes in cancer. A deeper understanding of the functions of each isoform in specific disease settings will be essential for the development of effective drug strategies.

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Abbreviations—The abbreviations used are: BIM, BCL-2-like protein 11; BCL-2, B cell lymphoma 2 apoptosis regulator; CDCP1, CUB domain–containing protein 1; CDK, cyclin-dependent kinase; CF, catalytic fragment; cPKC, conventional PKC; DAG, diacylglycerol; DLG, discs large MAGUK (membrane-associated guanylate kinase homologs) scaffold protein; ECM, extracellular matrix; EGFR, epidermal growth factor receptor; EMT, epithelial-to-mesenchymal transition; ER, endoplasmic reticulum; ERK, extracellular signal–regulated kinase; FGF, fibroblast growth factor; IP3, inositol 3-phosphate; MEK, mitogen-activated protein kinase kinase; MMP, matrix metalloproteinase; MSK1, mitogen- and stress-activated protein kinase 1; mTORC2, mammalian target of rapamycin complex 2; nPKC, novel PKC; NSCLC, non–small cell lung cancer; PIP2, phosphatidylinositol 4,5-bisphosphate; PP2A, protein phosphatase 2A; PTB, phosphotyrosine-binding motif; ROS, reactive oxygen species; RTK, receptor tyrosine kinase; TKI, tyrosine kinase inhibitor; TNF, tumor necrosis factor; ZEB, zinc finger E-box-binding homeobox.

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