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review

The atypical protein kinase Cs

Functional specificity mediated by specific protein adapters

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Since its discovery more than 10 years ago, the atypical PKC (aPKC) subfamily has attracted great interest. A number of reports have shown that the kinases of this subfamily play critical roles in signaling pathways that control cell growth, differentiation and survival. Recently, several investigators have identified a number of aPKC-interacting proteins whose characterization is helping to unravel the mechanisms of action and functions of these kinases. These interactors include p62, Par-6, MEK5 and Par-4. The details of how these adapters serve to link the aPKCs to different receptor signaling pathways and substrates in response to specific stimuli are crucial not only for developing an understanding of the roles and functions of the aPKCs themselves, but also for more generally establishing a view of how specificity in signal transduction is achieved.

Introduction

The atypical protein kinase C (aPKC) subfamily of kinases is composed of two members, ζPKC and λ/ιPKC. These proteins are highly related, with a 72% overall amino acid identity (Nishizuka, 1995). The conservation is most striking in the catalytic domain, which is also conserved among the other PKC isotypes that belong to the classical and novel subfamilies. In contrast, the regulatory domain of the aPKCs is clearly different from those of the other members of the PKC superfamily; it has only one zinc finger whereas the others have two (Nishizuka, 1995). Like the novel PKCs, the aPKCs lack the characteristic C2 domain that is present in the classical isoforms. These important structural differences may explain why the aPKCs are insensitive to Ca^{2+}, diacylglycerol and phorbol esters, which are potent activators of the other isoforms (Nishizuka, 1995). The exact mechanism of activation of the aPKCs is still largely unclear. However, there is abundant evidence that they play important roles in controlling cell growth and survival (Berra *et al.*, 1993; Diaz-Meco *et al.*, 1996a; Bjorkoy *et al.*, 1997; Murray and Fields, 1997; Wooten, 1999), most likely through their regulation of critical signaling pathways including those that activate the AP-1 and NF-κB transcription factors (Diaz-Meco *et al.*, 1993; Berra *et al.*, 1995; Akimoto *et al.*, 1996; Liao *et al.*, 1997; Sontag *et al.*, 1997; Takeda *et al.*, 1999; Wooten, 1999). Although the participation of the aPKCs in these cascades was initially linked to Ras signaling (Berra *et al.*, 1993; Diaz-Meco *et al.*, 1994; Bjorkoy *et al.*, 1997; Liao *et al.*, 1997), further developments in this field have revealed a complex set of interactions with a number of proteins that are not known to participate in the Ras pathway, suggesting that sophisticated regulatory mechanisms are involved in aPKC signaling.

Of scaffolds and adapters

A critical issue concerning the involvement of the aPKCs in these pathways is what the connection between these kinases and the receptor signaling complexes is. In this regard, the protein p62 may provide some insight. p62 was isolated independently by two groups as a novel and selective aPKC-interacting protein, and it binds the aPKC V1 sequence, which comprises the first 126 amino acids upstream of the zinc finger domain (Puls *et al.*, 1997; Sanchez *et al.*, 1998). The site of p62 to which the aPCKs bind has been narrowed down to a short stretch of acidic amino acids (Figure 1) termed AID (for atypical PKC-interaction domain). p62 also has a novel cysteine-rich sequence that forms an atypical zinc finger termed the ZZ domain (Sanchez *et al.*, 1998). Recent evidence strongly suggests that p62 provides a scaffold linking the aPKCs to the tumor necrosis factor α (TNFα) and interleukin-1 (IL-1) receptor signaling complexes through its interactions with RIP and TRAF6, respectively (Figure 2A and B). Both of these proteins are important mediators of the inflammatory response activated by the cytokines TNFα and IL-1 (Sanz *et al.*,

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P62 ^{66}HYRDEDGDLVAFSSDEEL^{83}
MEK5 ^{61}EYEDEDGDRITVRSDEEM^{78}
Par-6 ^{60}GYTDAHGDLLPLTNDDSL^{77}

Fig. 1. The AID sequences of p62 and MEK5 aligned with the corresponding putative region of Par-6. Identical and closely related residues are shown in gray.

1999, 2000). This implicates protein–protein interactions involving the aPKCs as critical events in the transduction of TNFα and IL-1 signaling.

The main transducer of TNFα signaling is the TNFR1 molecule, a 55 kDa transmembrane protein with an intracellular death domain (DD) that serves to recruit the DD-containing protein TRADD. The simultaneous binding of TRADD to TRAF2 and RIP gives rise to an interconnected, activated complex in whose context RIP is necessary and sufficient for NF-κB activation (Goeddel, 1999). The interaction of p62–aPKC with RIP may offer a mechanistic explanation for the involvement of aPKCs in TNFα signaling downstream of RIP (Sanz *et al.*, 1999). Exactly how the aPKCs are activated by their presence in these complexes is not yet understood. This could potentially involve conformational changes that make the aPKCs accessible to their substrates, or possibly the recruitment of an unidentified activator.

Interestingly, there is a certain parallelism between the TNFα and IL-1 signaling cascades. In the latter case, the intracellular domain of the IL-1 receptor interacts with MyD88, a functional analog of TRADD. MyD88 then recruits a kinase, IRAK, which interacts with TRAF6. In this case, both the kinase and the TRAF are required intermediaries for NF-κB activation (Lomaga *et al.*, 1999; Thomas *et al.*, 1999), with TRAF6 serving as the adapter that makes the connection with the p62–aPKC complex. aPKC activity is required for IL-1 and TRAF6 activation of NF-κB (Sanz *et al.*, 2000). p62, then, appears to act as a point of convergence of the IL-1 and the TNFα signaling pathways. Its functional importance in NF-κB activation has been highlighted by the observation that its depletion severely abrogates NF-κB activation by both TNFα and IL-1 (Sanz *et al.*, 2000). It is not yet clear whether p62 is also required for the activation of NF-κB by Ras or if, on the contrary, Ras can target the aPKCs through an independent pathway. In any event, an essential component of the NF-κB pathway is the IκB kinase (IKK) complex, which phosphorylates and triggers the degradation of IκB to release NF-κB from its cytosolic state, allowing its nuclear translocation (Karin, 1999). Recent results suggest that the aPKCs that are somehow activated by the complexes described above target the IKK β subunit, possibly through a direct interaction (Lallena *et al.*,

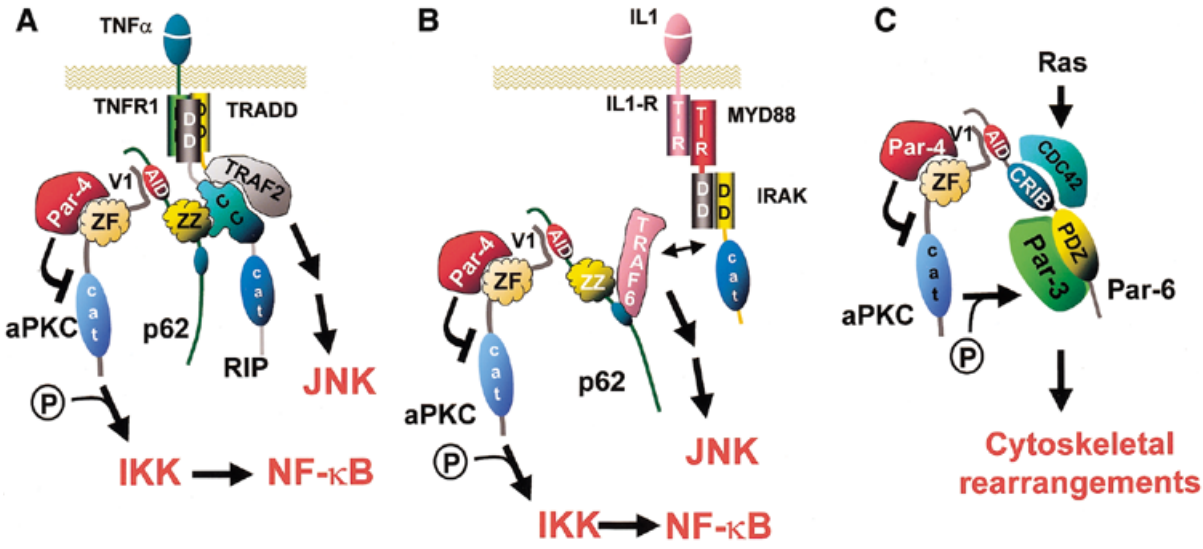

Fig. 2. The modulation of aPKC function by different protein complexes. (**A**) In response to TNFα receptor stimulation, the death domain (DD) of the corresponding receptor binds the adapter TRADD, which serves to recruit RIP. The coiled-coil (CC) region of RIP interacts with the atypical zinc finger (ZZ) of p62. The AID sequence of p62 interacts with the V1 domain of the aPKCs and serves to recruit them to the receptor signaling complex, and to activate them through an unknown mechanism. The inhibitory protein Par-4 can target the zinc finger (ZF) of the aPKCs, provoking their inhibition and the subsequent induction of apoptosis. (**B**) TRAF6 also interacts with p62, linking the aPKCs to the IL-1 signaling cascade. IRAK, after it is recruited to the IL-1 signaling complex, is hyperphosphorylated and released to interact with TRAF6. The recruitment of IRAK to the IL-1 receptor complex takes place through its interaction with the adapter MyD88, which binds the IL-1 receptor through the TIR domain. IKK can be recruited to these complexes through RIP or the TRAFs where its β subunit can be phosphorylated and activated by the aPKCs. (**C**) CDC42 or Rac may stimulate Par-6 (AID site), which forms a complex with the aPKCs (V1 site) in close proximity to Par-3, which interacts with the PDZ domain of Par-6. This results in the phosphorylation of Par-3 by the aPKCs, leading to downstream effects on cytoskeletal arrangement. The interaction between Par-6 and CDC42 may explain the role of the aPKCs in cytoskeletal remodeling during Ras transformation, since Ras is known to activate CDC42.

1999; Wooten *et al.*, 2000). Thus, p62 may serve to bring together RIP, TRAF6 (upstream components of the cytokine signaling pathways) and the aPKCs, an event that most likely serves to transmit a signal to the IKK complex.

Recently, another protein, the α isoform of the kinase MEK5, was identified as a second AID-containing molecule (M.T. Diaz-Meco and J. Moscat, unpublished observations). MEK5 is the upstream regulator of the kinase BMK1/ERK5, and both proteins are important in the control of cell growth (English *et al.*, 1998; Kamakura *et al.*, 1999). The aPKCs have been shown to interact with the AID site of MEK5 via their V1 domain. These interactions are mitogen inducible and important for the activation of the MEK5/ERK5 pathway. Therefore, it seems that p62 and MEK5 serve to direct the aPKCs into different signaling cascades using their respective AID sequences.

The V1 domains of the aPKCs also interact with Par-6 (partitioning-defective-6), a scaffold protein with yet another function: the control of cell polarity (Watts *et al.*, 1996; Qiu *et al.*, 2000). Par-6 has a CRIB-like domain that is responsible for its interactions with CDC42 and Rac (Qiu *et al.*, 2000), and a PDZ domain that has been implicated in the interaction with Par-3. The mammalian Par-3, called ASIP, has been reported to interact with the catalytic domain of the aPKCs and to be a relatively good substrate (Izumi *et al.*, 1998). Both the *Caenorhabditis elegans* aPKC homolog, PKC-3, and Par-3 are required for the proper control of embryonic polarity (Tabuse *et al.*, 1998). In mammalian cells, ASIP appears to be involved in the establishment/maintenance of epithelial cell polarity (Izumi *et al.*, 1998; Qiu *et al.*, 2000). The *Drosophila* homolog of Par-3 is Bazooka and recent evidence demonstrates that the aPKC binds to Bazooka and is required for the control of polarity of epithelia and neuroblasts in this system (Wodarz *et al.*, 2000). The aPKCs bind to a region of Par-6 that maps to residues 15–110 (Qiu *et al.*, 2000). We have noted that this region contains a short amino acid sequence that displays significant homology with the AIDs of p62 and MEK5 (Figure 1). It is therefore very likely that Par-6 uses its putative AID site to interact with the V1 domain of the aPKCs. It seems then, that there is an outstanding parallelism between p62 and Par-6: p62 responds to cytokine signaling by linking the aPKCs to the NF-κB pathway and Par-6 seems to respond to CDC42 signaling by linking the aPKCs with the actin cytoskeletal structure (Figure 2). This provides a potential mechanistic explanation for the requirement of the aPKCs in both Ras- and CDC42-induced cell transformation (Bjorkoy *et al.*, 1997; Qiu *et al.*, 2000).

In summary, the V1 domain of the aPKCs is a region to which as many as three different adapters/effectors may bind. A particular interaction may result in the placement of an aPKC into a specific signaling complex where it interacts, either directly or indirectly, with the appropriate sets of both upstream and downstream effectors. Such interactions could thereby confer specificity to the actions of the aPKCs, allowing a single enzyme to serve different functional purposes in a context-dependent manner. This is an important issue, especially when, as in the case of PKCs, the kinase catalytic domains are highly similar and the cell has to devise mechanisms to impose specificity.

Par-4, a negative regulator

In addition to having distinct V1 site binding partners, the aPKCs are also reported to have two zinc finger domain binding partners: LIP (lambda-interacting protein) (Diaz-Meco *et al.*, 1996b) and Par-4 (prostate androgen response-4) (Diaz-Meco *et al.*, 1996a). In the cases of the novel and classical PKC isotypes, the zinc finger domains are targeted by lipid cofactors that influence kinase activity (Nishizuka, 1995). Not surprisingly, both LIP and Par-4 are able to modulate aPKC enzymatic activity, LIP being an activator (Diaz-Meco *et al.*, 1996b) and Par-4 an inhibitor (Diaz-Meco *et al.*, 1996a). Little is known about the precise mechanism of action of LIP or about its role in the cell. However, Par-4 emerges as an important molecule from a cell functional point of view (Diaz-Meco *et al.*, 1996a), as it was previously identified as a gene induced in prostate cancer cells undergoing apoptosis (Sells *et al.*, 1994). Subsequent studies have demonstrated that Par-4 levels increase during neuronal cell death (Guo *et al.*, 1998), and the overexpression of Par-4 causes cells to undergo apoptosis in a manner that depends on its ability to block aPKC activity (Diaz-Meco *et al.*, 1996a). Interestingly, the expression of Par-4 inhibits IKK and the ensuing activation of NF-κB by TNFα, making cells that are normally resistant to apoptosis susceptible to TNFα-induced death (Diaz-Meco *et al.*, 1999). Par-4 levels are downregulated in Ras-transformed cells (Barradas *et al.*, 1999), which has physiological implications for cancer. Indeed, restoration of Par-4 to normal parental levels makes these cells more sensitive to pro-apoptotic insults, including the action of chemotherapeutic agents (Barradas *et al.*, 1999). Strikingly, experiments *in vivo* demonstrate that the progression of tumors derived from Ras-transformed cells expressing Par-4 is much more effectively reduced than those from Ras-transformed cells in which Par-4 levels are depleted (Barradas *et al.*, 1999). This is reminiscent of what has been shown by others (Wang *et al.*, 1999) and indicates that the blockage of NF-κB activity in Ras-transformed cells makes them more sensitive to the actions of chemotherapy. Altogether, these observations support an important role for the aPKCs in cell survival. Interestingly, recent evidence from *Drosophila* aPKC loss-of-function indicates that embryos die before cellularization is complete, showing premature cell death and increased TUNEL labeling (Wodarz *et al.*, 2000).

Perspectives

The observations described above allow us to draw novel and exciting models that may begin to explain how the aPKCs contribute to the regulation of cell function. However, they also raise many questions that need to be addressed. For example, what determines which of the aPKCs interact with p62, Par-6 or MEK5 in a given situation? In this regard, the distinct cellular localization of the three adapters may contribute an additional level of specificity. Consistent with this notion, immunofluorescence analysis reveals that p62 displays punctate staining colocalizing with certain endosomal markers (Sanchez *et al.*, 1998). Par-3, which constitutively associates with Par-6, localizes to the tight junctions in epithelial cells (Izumi *et al.*, 1998). The localization of endogenous Par-6 has not been reported and is an important issue, as the ectopic expression of Par-6 disrupts tight junctions (Joberty *et al.*, 2000); this finding seems to be inconsistent with its proposed role in maintaining cell polarity. What actually causes the activation of the aPKCs within the complexes? How do activated aPKCs phosphorylate the appropriate targets in reponse to a particular stimulus? From a broader

perspective, what are the contributions of the aPKCs to NF-κB activation as compared with those of other putative IKK kinases? Is Par-3 the only transducer of the aPKC signals in the control of the cytoskeletal architecture? How does Par-6 orchestrate the signaling events that control cell polarity? What transcription factors are involved in the downregulation of Par-4 during oncogenic transformation?

Genetic models, including knock-out mice, need to be generated for the aPKCs and for their adapters. Analyses of these may provide a better understanding of the physiological implications of aPKC inactivation in a whole animal. Nevertheless, it is already apparent that, through their complex interactions with a variety of adapters, the aPKCs form part of distinct signaling complexes that endow promiscuous kinases with functional specificity.

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