Complex Formation and Cooperation of Protein Kinase Cθ and Akt1/Protein Kinase Bα in the NF-κB Transactivation Cascade in Jurkat T Cells*

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Protein kinase Cθ (PKCθ) is known to induce NF-κB, an essential transcriptional element in T cell receptor/CD28-mediated interleukin-2 production but also T cell survival. Here we provide evidence that PKCθ is physically and functionally coupled to Akt1 in this signaling pathway. First, T cell receptor/CD3 ligation was sufficient to induce activation as well as plasma membrane recruitment of PKCθ. Second, PKCθ selectively cooperated with Akt1, known to act downstream of CD28 co-receptor signaling, in activating a NF-κB reporter in T cells. Third, Akt1 function was shown to be required for PKCθ-mediated NF-κB transactivation. Fourth, PKCθ co-immunoprecipitated with Akt1; however, neither Akt1 nor PKCθ served as a prominent substrate for each other in vitro as well as in intact T cells. Finally, plasma membrane targeting of PKCθ and Akt1 exerted synergistic transactivation of the IκB kinase β/inhibitor of NF-κB/NF-κB signaling cascade independent of T cell activation. Taken together, these findings suggest a direct cross-talk between PKCθ and Akt1 in Jurkat T cells.

PKCθ isoenzymes are thought to reside in the cytosol in an inactive conformation and translocate to the plasma membrane upon cell activation (1). PKCθ was shown to co-localize selectively with the TCR to the T cell synapse when antigen-specific T cells are engaged by their physiological ligand (2, 3). The isoenzyme-selective recruitment of PKCθ to the plasma membrane was shown to be dependent on the Vav-1/Rac-mediated pathway (4, 5). Functional studies of PKCθ revealed an early and essential role in the TCR/CD28-induced stimulation of mitogen-activated protein kinase c-Jun NH2-terminal kinase/AP-1 and nuclear factor of activated T cells but also the IKKβ/IκBα/NF-κB signaling cascade (for review see Ref. 6). Consistently, PKCθ was found to associate with an activated IKK complex in GM1-enriched lipid rafts during TCR/CD28-mediated T cell activation (7). Mouse genetic evidence (employing PKCθ-KO mice (8)) identified the TCR/CD28-induced activation of NF-κB in the IL-2 gene promoter as the major physiological function of PKCθ; however, its biochemical relevance as well as the manner in which PKCθ becomes coupled to the TCR during antigen stimulation have been largely undefined.

Similarly to PKCθ, the serine/threonine kinase Akt (also known as protein kinase B) has been shown to contribute to NF-κB (9). In peripheral mouse T cells, Akt could be activated in response to TCR stimulation and led to enhanced NF-κB activation via accelerated degradation of the NF-κB inhibitory protein IκBα (10). In Jurkat T cells, Akt was shown to be activated enzymatically in TCR/CD3 signal transduction involving Rac and PI3K function (11). Additionally, CD28 ligation has been reported to result in the strong association with, and activation of, PI3K, subsequently recruiting and enzymatically activating Akt in both the leukemic T cell line Jurkat and freshly isolated human peripheral blood-derived normal T lymphocytes (12). Consistently, Akt function was recently shown to provide the CD28 co-stimulatory signal in T cells (13).

However, Akt was not sufficient by itself to induce cytokine promoter and NF-κB reporters in Jurkat T cells, since signals from other pathways, in particular phorbol ester, the pleiotropic PKCθ activator, were shown to be required (9), implicating a functional Akt-PKCθ connection. PKCθ has been implicated as the prime candidate for PKC function (6), including Akt cooperation (13) in T cells; however, the biochemical basis has not been resolved. Here we addressed the detailed relationship between PKCθ and PI3K/Akt in TCR/CD28-mediated signal transduction. Our observations indicate the Akt/PKCθ cooperation as a critical process in TCR/CD28-induced signaling. Consistently, plasma membrane targeting of both PKCθ and Akt (e.g. by recombinant NH2-terminal myristoylation motifs) is sufficient to bypass TCR/CD28 ligation in order to start the IKKβ/IκBα/NF-κB-signaling cascade. The results provide evidence for a model of a direct cross-talk between PKCθ and Akt, downstream of TCR/CD3 and CD28 co-receptor, respectively, in the critical NF-κB signaling pathway.

**EXPERIMENTAL PROCEDURES**

Reagents and Plasmids—MG132, LY294002, and G6850 were purchased from Alexis, Lausen, Switzerland. [γ-32P]ATP was purchased from PerkinElmer Life Sciences, and PDBu and ionomycin were from...
PKCζ Akt1 Cross-talk

**Table I**

| PKCζ, -PKCζ-Myr hybrid, 5-ANP-Myr |
|-----------------------------------|
| 5-PKCζ, 5'-PKCζ-Myr hybrid, 5-ANP-Myr, 5-ANP-Myr |

*ANP, anchor primer, used in combination with the appropriate hybrid primer.

PKCζ Is Recruited and Catalytically Activated by TCR/CD3 Cross-linking—Initially, the distinct role(s) of TCR/CD3 and/or CD28 in engagement of endogenous PKCζ in Jurkat as well as peripheral T cells were investigated. As a first result, ligation of TCR/CD3 was shown to be sufficient to result in maximal plasma membrane recruitment of PKCζ in Jurkat T cells (using both IgG as well as IgM-agonistic antibody clones coupled to beads). CD28 co-cross-linking did not significantly enhance TCR/CD3-induced PKCζ membrane translocation (Fig. 1), even after recombinant CD28 overexpression (not shown). However, and in part consistent with a previous report (17), soluble anti-CD3 antibodies proved less effective in inducing PKCζ plasma membrane recruitment (not shown).

Next, and more importantly, PKCζ in situ activity was monitored, employing anti-phospho-(p)PKCζ immunoblotting of endogenous PKCζ immunoprecipitates derived from whole cell extracts. The PKCζ autophosphorylation-specific antibody used and characterized in this study selectively recognized PKCζ in its active state. Phorbol ester stimulation induced a marked immunoreactivity of endogenous PKCζ in isolated human PBMCs (Fig. 2A). Consistently, phorbol ester induced rapid immunoreactivity of highly purified recombinant enzyme preparations in *in vitro* autophosphorylation assays (Fig. 2B). This activation-induced phospho-status of PKCζ was shown to be dependent on the catalytic activity of PKCζ; only immunoprecipitates of transiently overexpressed and phorbol ester activated wild-type (wt) but not kinase-dead mutant PKCζ(K409R) enzyme were recognized by this phosphospecific PKCζ antibody (Fig. 2C).

RESULTS AND DISCUSSION

PKCζ is recruited and catalytically activated by TCR/CD3 cross-linking. Initial results showed that ligation of TCR/CD3 was sufficient to recruit PKCζ to the plasma membrane (Fig. 1). However, co-cross-linking with CD28 did not significantly enhance PKCζ membrane translocation. Subsequent studies indicated that soluble anti-CD3 antibodies were less effective in inducing PKCζ plasma membrane recruitment compared to recombinant CD28 overexpression.

Next, PKCζ in situ activity was monitored using anti-phospho-(p)PKCζ immunoblotting of endogenous PKCζ immunoprecipitates derived from whole cell extracts. The PKCζ autophosphorylation-specific antibody used selectively recognized PKCζ in its active state. Phorbol ester stimulation induced an increased immunoreactivity of endogenous PKCζ in isolated human PBMCs (Fig. 2A). Consistently, phorbol ester induced rapid immunoreactivity of highly purified recombinant enzyme preparations in *in vitro* autophosphorylation assays (Fig. 2B). This activation-induced phospho-status of PKCζ was shown to be dependent on the catalytic activity of PKCζ; only immunoprecipitates of transiently overexpressed and phorbol ester activated wild-type (wt) but not kinase-dead mutant PKCζ(K409R) enzyme were recognized by this phosphospecific PKCζ antibody (Fig. 2C). Finally, the established CA mutant PKCζ(A148E) (14) exhibited a constitutive high level of phosphorylation, as detected by this anti-(p)PKCζ antibody, independent of any...
LY294002, a selective PI3K inhibitor, abrogated NF-κB/coding. In order to define the PH-containing signaling protein transactivation (Fig. 3A) as well as the established negative regulator of PI3K signaling (20), we next investigated potential functional interaction of PKCδ with PH-containing N-terminal co-receptor shown to be functionally required for maximal PI3K signal transduction. Additionally, PI3K is an established major signaling molecule downstream of the CD28 (21), the biological relevance of this inhibition is confirmed by the finding that a DN-Akt also significantly reduced the activation-induced NF-κB signal (Fig. 3B).

Expression of combinations of CA mutant PKCδA148E and defined wild-type and mutant IKKβ proteins, the established downstream effector of PKCδ (7, 17, 18), demonstrated comparable results in parallel experiments (Fig. 3D). Overexpression of IKKβ wt enhanced the effect of PKCδ. Consistently, the DN mutants IKKβK/M and (as a positive control) PKCδK409R acting downstream of PI3K, Akt wt and Akt mutants have been employed to investigate the NF-κB signaling cascade(s) induced by PKCδ. As shown in Fig. 3C, kinase-active Akt overexpression enhanced the effect of PKCδ. In this respect, the Akt PH domain appears indispensable for PKCδ cooperation, since a PH deletion mutant of Akt completely failed to enhance PKCδ-mediated NF-κB induction (Fig. 3C). This may indicate the Akt PH domain is critical for the PKCδ interaction, similar to a reported Akt-PKCS interaction (24). Conversely, DN mutants of Akt inhibited PKCδA148E-induced NF-κB activity. The biological relevance of this inhibition is confirmed by the finding that a DN-Akt also significantly reduced the activation-induced NF-κB signal (Fig. 4B).
inhibited PKCδA148E action, respectively. An involvement of Rac1 GTPase function in the PKCδA148E-mediated NF-κB induction has also been found (Fig. 3B, and see Ref. 5). Combined, PKCδ action appeared to be functionally mediated via Akt and IKKδ induction, the latter also shown by IKKδ kinase complex assays (17, 18).

Additionally and to define further PKC subfamily involved in Akt-mediated NF-κB induction, Jurkat T cells were co-transfected with expression vectors encoding Akt as well as representative CA-PKC mutant isoforms, e.g. PKCα, -ε, -θ, and -δ. These experiments identify predominantly DMSO PKCδ but also at a reduced level PKCε (but not PKCα & -θ) as PKC isoenzymes capable to cooperate with Akt in Jurkat T cells (not shown). In this regard, a role of PKCε in NF-κB signal induction has been described previously (25).

**PKCδ and Akt1 Functions Are Both Required for Maximal NF-κB Transactivation**—Next, overexpression experiments of wt and DN mutants of PKCδ and Akt in phorbol ester/ionomycin-stimulated Jurkat T cells identified both PKCδ and Akt as predominant mediators of NF-κB activation. Overexpression of wt enzymes of PKCδ or Akt led to 4-fold increase of activation-induced NF-κB activity over that obtained in vector controls (Fig. 4A). Consistently, expression of kinase-dead PKCδ K409R or Akt triple mutant K179A,T308A,S473A, both shown to act in a dominant negative fashion in intact cells (9, 14), significantly reduced the activation-induced NF-κB activity (Fig. 4A).

Similarly, reduced effects were obtained under more physiological conditions, since expression of DN mutants of Akt and PKCδ were able to decrease the CD3/CD28-induced NF-κB signal. However, no complete inhibition could be achieved most likely due to multiple converging signals. Consistently, co-expression of both PKCδ wt and Akt wt did further enhance the CD3/CD28-induced NF-κB activity (Fig. 4B).

Complex Formation of PKCδ and Akt—As a next step, we investigated whether Akt is a potential downstream substrate of PKCδ. In *vivo* complex kinase assays showed that the phosphorylation status of neither PKCδ nor Akt was prominently affected by each other (Fig. 5A). PKC transphosphorylation-specific inhibitor G6850 (which does not affect PKCδ-auto-
Akt and PKC

Akt-wt and PKC

munoprecipitation of PKC

protein kinases. To assess this hypothesis, we performed co-

underlie the observed functional cooperation of these two pro-

was tempting to speculate that a physical interaction may

B

cells compared with the control (Fig. 5

immunostaining with the (p)PKC

H9258

Akt was immunoprecipitated with anti-HA tag antibody and analyzed

as in Fig. 2

D

). The immunoblots were stained for PKC\(^0\) and Akt, respectively. A

representative experiment is shown. C, interaction of endogenous PKC\(^0\)

with Akt. Jurkat T cells were transfected with pSRR-CD28 and HA-

tagged Akt-wt expression vectors, and 24 h posttransfection cells were

stimulated for 15 min at 37 °C with solid-phase IgM clones of TCR-

and/or CD28-specific antibodies or PDBu. Afterward, cell extracts were

immunoprecipitated (IP) with normal rabbit serum (Mock) or a poly-

clonal anti-PKC\(^0\) antibody. Immunoprecipitates were analyzed by im-

munoblotting with a monoclonal anti-Akt antibody (upper panel) and

subsequently with an anti-PKC\(^0\) antibody (middle panel). Independent

anti-HA tag immunostaining confirmed the specificity of the Akt pro-

tein (not shown). Additionally and to control for sufficient stimulation

conditions, PKC\(^0\) immunoprecipitates were subjected to immunoblot-

ning with the anti-(p)PKC\(^0\) antibody (bottom panel) as in Fig. 2D. Akt expression was

analyzed by immunoblotting (not shown). Similar results were repro-

duced in two independent experiments.

phosphorylation\(^2\) did not decrease (but rather increased) Akt

phosphorylation status, excluding PKC\(^0\) as a prominent pro-

tein kinase of Akt. More importantly, no increase of Akt-Ser\(^473\)

phosphorylation could be observed in PKC\(^0\) or endogenous

Akt was not modulated by Akt (both pre-

activated or not by PDK1 at Thr\(^308\)) (Fig. 5A). Co-expression of

neither Myr-Akt nor DN-Akt mutants in Jurkat T cells showed

any modulation of phosphorylation of Myr-PKC\(^0\) (Fig. 5C).

Consistently, phorbol ester-induced autophosphorylation of endo-

genous PKC\(^0\) protein was unaffected by DN-Akt expression (Fig.

5D).

Activation of PI3K frequently involves the PIP\(_3\)-mediated

recruitment of Akt to the plasma membrane, similar to the

TCR/CD3-induced translocation of PKC\(^0\) (see Fig. 1). Thus, it

was tempting to speculate that a physical interaction may

underlie the observed functional cooperation of these two protein

kinases. To assess this hypothesis, we performed co-

immunoprecipitation of PKC\(^0\) and Akt in vitro as well as in intact

cells. As a result, purified recombinant Akt (both preactivated or

not by PDK1 at Thr\(^308\)) was found to associate with purified

recombinant PKC\(^0\) in vitro indicating a direct physical PKC\(^0\)-

Akt interaction (Fig. 6A). Consistently, reverse co-immunopre-

cipitation confirmed this association (Fig. 6B); however, a mi-

nor nonspecific PKC\(^0\) fraction has been repeatedly found to

stick to the beads independently of immunoprecipitated Akt

(Fig. 6B, compare the 3rd lane to the 1st and 2nd lanes). In

Jurkat T cells the association of Akt with endogenous PKC\(^0\)

was found to be constitutive (Fig. 6C). Essentially no modula-

tion of this constitutive Akt/PKC\(^0\) interaction by TCR/CD28 or

PDBu stimulation was observed in reverse immunoprecipita-

tion results (not shown). Combined, these observations demon-

strate that PKC\(^0\) and Akt associate in preformed complexes in

vivo; however, enzymatic activities of neither Akt nor PKC\(^0\)

appear to be significantly modulated by each other. We there-

fore speculated that the observed PKC\(^0\)-Akt interaction may

specify cellular location and impose integration with other sig-

naling systems, e.g. local substrate availability as well as ex-

posure to allosteric activators.

Characterization of Membrane-targeted PKC\(^0\) Fusion Mutant,

Myr PKC\(^0\)—To examine further the role of plasma membrane

recruitment of PKC\(^0\) in the TCR/CD3 signal transduction

pathway, we prepared a constitutively membrane-bound

PKC\(^0\) derivative, Myr-PKC\(^0\), containing an NH\(_2\)-terminal my-
rystioylation signal (Fig. 7A). Similar rystioylation signal protein modifications have been made successfully for PKCα (26) and -isoenzymes (27). Overexpression in Jurkat T cells revealed substantial plasma membrane targeting but also accumulation in the detergent ns fraction of Myr-PKCγ shown by cellular fractionation (Fig. 7B) as well as immunofluorescence analysis in ectopic expression studies (not shown). In contrast, CA-PKCαA149E mutant was found to reside predominantly in the ns fraction (Fig. 7B). This subcellular location indicated its different nature of activation, as observed by its high transactivation capability (Fig. 7C). Additionally, accumulation of activated forms of PKCα in the detergent ns fractions may implicate a particular signaling function at this location.

Several signaling molecules, among them p56lck, known to bind to and phosphorylate PKCθ at tyrosine 90 are localized in this subdomains in intact T cells (28).

Functional studies of Myr-PKCθ resulted in significant stimulation the IL-2 signaling pathway (65-fold, Fig. 7C), as compared with PKCθ-wt, excluding a simple overexpression artifact. To control for non-PKCθ-specific rystioylation effect and/or decoy effect on the N-myristoyltransferase machinery, another Myr-PKCθ fusion mutant protein, Myr-ERK2 (fully characterized in Ref. 29), was used in our experimental setup. Myr-ERK2 (Fig. 7C) as well as the expressed catalytic subfragment of PKCθ (found to reside exclusively in the cytosolic fraction) had no effect on IL-2 signaling (not shown). PKCθCAAX, a COOH-terminal rarnesylation and palmitoylation signal fusion mutant, revealed substantial plasma membrane targeting but no transactivation of its downstream effectors. These results indicate a gene-specific Myr-PKCθ effect on its downstream targets and demonstrate Myr-PKCθ as a novel agonist-independent PKCθ mutant. Myr-PKCθ similar to the established CA mutant PKCθA148E (but not PKCθ-wt) exhibited high levels of basal phosphorylation, as detected by the anti-active(p)PKCθ antibody (Fig. 7D), confirming constitutive autophosphorylation.

However, and despite full in situ catalytic activity of PKCθ, as monitored by the anti-active(p)PKCθ result (Fig. 7D), Myr-PKCθ fusion mutant by itself was significantly less potent to transactivate (in combination with an ionophore) the IL-2 promoter than the established CA pseudosubstrate acidic exchange mutant PKCA148E (14) (Fig. 7C). This observation suggested to us that additional activation-dependent signal(s) are required to cooperate with Myr-PKCθ for maximal NF-κB signaling in these cells.

Membrane Targeting of PKCθ Exaggerates the TCR/CD28-Induced NF-κB Activation—Consistently with this hypothesis, stimulation by the TCR and/or CD28 in Myr-PKCθ (and much less PKCθ-wt)-transfected cells further enhanced the induction of the NF-κB reporter severalfold over the vector-transfected cells (Fig. 8). Given a near-maximal observed transcriptional NF-κB activity in just CD28 ligation-induced and Myr-PKCθ-expressing T cells, subcellular location of PKCθ to the plasma membrane appears to bypass the TCR/CD3 stimulation requirement for NF-κB transactivation. Although it is evident.
that TCR/CD3 stimulation is sufficient to recruit and activate PKCθ (see Fig. 1), the role of CD28 co-stimulation in the NF-κB induction remains undefined. One likely explanation is that expression of Myr-PKCθ mutants mimic in part the TCR/CD3 signal leading to NF-κB activation and that CD28 ligation induces a distinct signaling pathway able to functionally cooperate with PKCθ. In this regard, CD28 ligation has been reported to induce Akt (via PI3K action) in T lymphocytes (12, 13). Consistently, induction of NF-κB by expression of the established CA mutant PKCθA148E was enhanced by CD28 but not TCR/CD3 ligation (see Refs. 13 and 18 and data not shown).

Membrane Targeting of Both PKCθ and Akt Leads to a Synergistic Transactivation of the IKKβ1/2-xB/NF-κB Signaling Cascade—Along this hypothesis, we employed our constitutively membrane-targeted Myr-PKCθ mutant in combinations with Akt, Vav1, PKD1, or emt/itk. Consistent with a crucial role of subcellular location, Myr-PKCθ dramatically synergized with Myr-Akt (but also at a reduced level with Akt-wt) to activate the NF-κB reporter (Fig. 9, A and B). In contrast, the Myr mutants of Akt and PKCθ had only very little activities by themselves, and no potentiation of Myr-PKCθ action was observed by co-expression of any other PH domain-containing signaling molecule used (Fig. 9C). Particularly, no change in TCR/CD3-induced translocation as well as activation-induced autophosphorylation of endogenous PKCθ has been observed by PTEN expression (Fig. 9D). Consequently, no major changes in activation loop phosphorylation of PKCθ by PDK-1 could be detected (see similar findings for PKCδ in Ref. 31). Along this line, phosphorylation status of Myr-PKCθ was found not to be affected by PTEN expression (not shown).

However, a strict dependence on high PIP3 levels (via endogenous PI3K activity) has been observed for Myr-PKCθ/Akt-wt-mediated induction of the NF-κB reporter (Fig. 9D), as already observed for CA-PKCθA148E function (Fig. 3, A and B). Presumably this is through PTEN-mediated reduction of PIP3 levels and therefore inactivation of Akt wt in PTEN-expressing Jurkat T cells. Consistently, synergistic cooperation of membrane-targeted mutants Myr-PKCθ/Myr-Akt was affected to a much lower degree by PTEN expression (Fig. 9D). The Myr-Akt mutant has been shown to be activated mostly independent of PI3K function (32). The still observed partial (37%) inhibition effect is most likely due to a Myr-Akt fusion mutant pool, not effect is most likely due to a Myr-Akt fusion mutant pool, not

FIG. 10. Myr-PKCθ/Myr-Akt-mediated NF-κB induction involves IKKβ. Jurkat T cells were transfected with NF-κB-Luc reporter and Myr-PKCθ/Myr-Akt (A) in combinations with IKKβ-wt, DN mutants IKKβK/W, or Rac11671 respectively, or alternatively (B), 24 h posttransfection cells were split and incubated in the absence (DMSO buffer control) or presence of 2.5 μM MG132 and 50 nM Go6983, respectively, for an additional 16 h. DN mutants, as well as the pharmacological inhibitors used, did not affect PKCθ or Akt expression or transfection efficiency (data not shown). Normalized luciferase activity was quantified. Data are expressed as the means ± S.E. (n = 6). C, the expression level of the transfected IKKβ and Rac was assessed by immunoblotting.
PKCθ/Akt1 Cross-talk

and was inhibited by the proteasome inhibitor MG132 (which blocks IκB degradation, Fig. 10B). Consistently, TCR/CD28 signal transduction (as well as CA PKCθA149E function) was shown to activate the transcription factor NF-κB via IKKβ-mediated phosphorylation and subsequent degradation of IκB by the proteasome/ubiquitin pathway (7, 15, 17, 18).

Additionally, the PKCθ/Akt cooperation in NF-κB induction was dependent on the enzymatic activity of PKCθ, indicated by PKC inhibitor Go6980-mediated functional abrogation (Fig. 10B). Consistently, no synergy of Myr-Akt with the ‘kinase-dead’ double mutant PKCθA148E-K409R, DN-mutant PKCθK409R, as well as catalytic or regulatory subfragments of PKCθ has been found (not shown). Together with the significant decrease of phorbol ester/ionomycin- and TCR/CD28-mediated induction of both PKC activation. This is consistent with the hypothesis that recruit and reveal functional cross-talk between PKC in the TCR/CD28 signal transduction, which involves NF-

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