It is well established that members of the protein kinase C (PKC) family seem to have important roles in T cells. Focusing on the physiological and non-redundant PKC functions established in primary mouse T cells via germ-line gene-targeting approaches, our current knowledge defines two particularly critical PKC gene products, PKCδ and PKCθ, as the "flavor of PKC" in T cells that appear to have a positive role in signaling pathways that are necessary for full antigen receptor-mediated T cell activation ex vivo and T cell-mediated immunity in vivo. Consistently, in spite of the current dogma that PKCδ inhibition might be sufficient to achieve complete immunosuppressive effects, more recent results have indicated that the pharmacological inhibition of PKCδ, and additionally, at least PKCs, appears to be needed to provide a successful approach for the prevention of allograft rejection and treatment of autoimmune diseases.

**Keywords**: T cell regulation, protein kinases, PKC isotypes, immune disease therapy

**INTRODUCTION**

Members of the protein kinase C (PKC) family belong to the serine/threonine protein kinase subfamily, which plays an important role in the regulation of a variety of cell functions (Figure 2). The PKC family was originally discovered by Nishizuka and colleagues in 1977 (Takai et al., 1977) and consists of nine isotypes that are expressed in a wide range of cell types and tissues (Figure 1). The reasons for the heterogeneity of PKC isotypes are not yet fully understood. T lymphocytes, for example, express up to eight different species of PKC isotypes (Table 1), which makes it difficult to determine the specific cellular functions of these individual enzymes. The expression of more than a single PKC isotype in a given cell could suggest functional redundancy and/or specialization. Table 1 summarizes the overall lymphoid expression patterns and T cell phenotypes of knockout T cells and the different PKC isotypes encoded in the human genome.

**ROLE OF PKCθ IN IMMUNE CELL BIOLOGY**

The main function of mature T cells is to recognize and respond to foreign antigens. This process involves the activation, adhesion, and differentiation of the resting cell into a效应 lymphoblast that actively secretes immunoregulatory lymphokines or displays targeted cytotoxicity, ultimately leading to the recruitment of other cell types and initiation of an effective immune response. T cell activation is triggered by the ability of the T cell receptor (TCR) to recognize a peptide antigen, which is bound to major histocompatibility complex class I (MHC-I) or class II (MHC-II). T cells then begin to divide and differentiate on the basis of the processed antigen. The effector cell CD4+ T helper cell subset (including Th1, Th2, and Th17 cells) performs effector functions that are necessary to clear the pathogen. Th1 CD4+ T cells produce IFN-γ and IL-2 and promote cell-mediated immunity. Th2 CD4+ T cells produce IL-4, IL-5, IL-6, IL-10, and IL-13 and lead to the activation of the humoral immune system. Th17 CD4+ T cells produce IL-17, IL-21, and IL-22 and play roles in the defense against extracellular bacteria and fungi.

**INVOLVEMENT OF PKCθ IN THE IMMUNOLOGICAL SYNAPSE**

After cell–cell contact between a T cell and an APC, this contact is stabilized during the initiation of an immune response by interaction of the β2-integrin LFA-1 with its counterligand ICAM-1 (Mazerolles et al., 1988; Dustin and Springer, 1989; Penninger and Crabtree, 1999). LFA-1 avidity is controlled by inside-out signaling via the control of integrin conformation and surface distribution (Lub et al., 1995; Carman and Springer, 2003; Dustin et al., 2004). One important inside-out signaling molecule that controls cell adhesion is the small GTPase Rap1 (Kata gi et al., 2002; Shimonaka et al., 2003). Rap1A-deficient T cells show impaired LFA-1 clustering and adhesion after CD3 stimulation (Duchniwicz et al., 2006). Letschka et al. (2008) found a role of a PKCθ/RapGEF2 complex in regulating LFA-1 avidity in T cells. These authors showed that after T cell activation, PKCθ phosphorylates RapGEF2 at Ser960, which regulates Rap1 activation and LFA-1 adhesiveness to ICAM-1. In agreement, this study showed that in OT-II TCR-transgenic CD4+ T cells, LFA-1 clustering after antigen activation was impaired in PKCθ-deficient CD4+ T cells (Letschka et al., 2008). According to their study, PKCθ seems to positively regulate the adhesive capacity of T lymphocytes.

When a stable contact between a T cell and an APC is formed, the T cell co-stimulatory receptor CD28 is activated by binding to its cell ligands CD80 or CD86. Subsequently, the immunological synapse is generated at the contact area between the T cell and the APC (Rao et al., 1999). Part of the immunological synapse is the supramolecular activation complex (SMAC), which is characterized by different signaling proteins, such as LCK (SRC family tyrosine kinase), LFA-1 (lymphocyte function-associated...
antigen 1), and CD45 (Freiberg et al., 2002). Effective T cell stimulation is characterized by the recruitment of PKCθ to the SMAC (Schafer et al., 2004), at which it is phosphorylated by LCK at Tyr-90 (Liu et al., 2000). A physical interaction of PKCθ with the cytoplasmic tail of CD28 has been shown to be essential in this recruitment mechanism (Kong et al., 2011). Subsequently, PKCθ is phosphorylated at different sites (Bauer et al., 2001; Bi et al., 2001; Liu et al., 2002; Freeley et al., 2005; Lee et al., 2005) and autophosphorylated at Thr-219 (Thuille et al., 2005). Recently, Chuang et al. (2011) identified the MAP4K3 GCK-like kinase (GLK) as a kinase that directly phosphorylates PKCθ at Thr-538 which is essential to activation of NF-κB in T cells. Phosphorylation is important to retain PKCθ in the immunological synapse, in which one of its functions seems to be the regulation of the immunological synapse itself. Through the live imaging of components of the immunological synapse, the synapse has been shown to be dynamic in wild-type mice but more stable in PKCθ-knockout mice, which influences the strength, duration and location of signals (Dustin, 2008).

RECRUITMENT AND ACTIVATION OF SIGNALING MOLECULES

Another important role of PKCθ is to recruit and activate signaling molecules, such as phospholipase C (PLC), IL2-inducible T cell kinase (ITK), TRC, phospholipase Cγ1 (PLCγ1), and SPAK (a MAP4K that ultimately activates AP1) to the immunological synapse. PKCθ was identified to play a critical role in the NF-κB and Ca2+/NFAT pathways to activate the IL-2 promoter. Antigen binding to the TCR leads to an increase in intracellular Ca2+, which activates calcineurin. Calcineurin dephosphorylates NFAT and leads to its nuclear import. Subsequently, NFAT forms complexes with the AP-1 protein transcription factor family and regulates the expression of IL-2 by binding to its promoter. PKCθ-knockout T cells were first described by Sun et al. (2000). They generated PKCθ-knockout mice by replacing the exon encoding the ATP-binding site of the kinase domain with the neomycin resistance gene. In their study they found strongly reduced proliferation of PKCθ−/− CD3+/CD28 T lymphocytes accompanied by a reduced secretion of IL-2. Suitably they could show that TCR-initiated NF-κB activation was absent from PKCθ−/− CD3+/CD28 T lymphocytes but was normal in thymocytes indicating that PKCθ is essential for TCR-mediated T cell activation (Sun et al., 2000).

Pfeifhofer et al. (2003) generated a conditional PKCθ-knockout mouse by using Cre-mediated recombination where the complete coding sequences of exons 3 and 4 are deleted, followed by a frame shift mutation between exons 2 and 5. Additionally to the results Sun et al. (2000) observed, they saw that a deficiency of PKCθ abrogates NFAT transactivation after CD3/CD28 stimulation. In addition, decreased intracellular Ca2+ flux was observed (Pfeifhofer et al., 2003).

To induce and maintain the complete IL-2-producing capacity of a T cell after TCR stimulation and activation of CD28, the RING (really interesting new gene)-selective functions in signaling pathways, necessary for full T cell activation, differentiation and robust immune responses in vivo (for details see text). The dashed line depicts PKC functions which were characterized primarily via overexpression/knockdown studies in immortalized cell lines, while a validation in a more physiological system is pending.
**Table 1 | Lymphoid expression pattern and immune cell phenotypes of PKC isotype knockout mice.**

| Gene loci | Tissue expression | Knockout mouse immune phenotype | Reference |
|-----------|-------------------|--------------------------------|-----------|
| **Conventional PKCs** | | | |
| α | Ubiquitous, high in T cells | Reduced proliferation, reduced IFNγ production, defective IgG switching | Pfeifhofer et al. (2006) |
| β | Ubiquitous, high in B cells | Neutrophil-, B-, mast cell defect | Leitges et al. (1996), Nechushtan et al. (2000) |
| γ | Brain | ND | |
| **Novel PKCs** | | | |
| δ | Ubiquitous, high in T cells | Enhanced IL-2 secretion, enhanced proliferation, proapoptotic | Gruber et al. (2005), Lutu-Nicoladoni et al. (2005) |
| ε | Ubiquitous, high in T cells | Macrophage defect, defective bacterial clearance, influence on the nervous system | Castritto et al. (2004), Kumar et al. (2002) |
| η | Ubiquitous, high in T cells | Impairment of epithelial regeneration in wound healing, increased susceptibility to tumor formation in skin carcinogenesis, defective homeostatic proliferation | Chida et al. (2003), Fu et al. (2011) |
| θ | T cells, platelets, monocytes | Reduced proliferation, reduced IL-2 production, abrogated AP-1, NF-kB, and NFAT transactivation, impaired EAE development, impaired Th2 immunity against N. brasiliensis | Sun et al. (2000), Pfeifhofer et al. (2003), Marland et al. (2004), Salek-Ardakani et al. (2004, 2005) |
| **Atypical PKCs** | | | |
| ζ | Ubiquitous | Impaired Th2 cytokine secretion response | Martin et al. (2005) |
| η | Ubiquitous | Lethal phenotype | |

**IN VIVO IMMUNE RESPONSES**

During T cell development, thymocytes undergo a twofold selection process. During positive selection, CD4+CD8+ double-positive thymocytes bearing TCRs with low or moderate affinity to MHC/antigen complexes expressed on epithelial cells receive a survival signal. During negative selection, the high-affinity interaction of TCRs with self-MHC/self-peptide complexes selects the thymocytes for apoptosis. Selected thymocytes downregulate CD4 or CD8 and leave the thymus as fully mature lymphocytes. To address the question of whether PKCθ is involved in positive selection, Morley et al. (2008) analyzed MHCI-restricted TCR-transgenic and non-transgenic PKCθ-knockout mice. In both mouse models, they found a severe defect in thymocyte positive selection (Morley et al., 2008). In agreement with these results, Gruber et al. (2010) also found a crucial role for PKCθ in the positive selection of thymocytes in a pathway leading to the activation of ERK, NFAT, and NF-κB by analyzing MHCI-restricted TCR-transgenic and non-transgenic PKCθ-knockout mice. When a naive CD4+ T cell is activated, it differentiates into the effector subsets T11, T22, or T17. An imbalance of this differentiation leads to autoimmunity and hypersensitivity. Several studies showed that PKCθ is important in the regulation of the T11/T22-mediated immune response (Marland et al., 2004; Salek-Ardakani et al., 2004, 2005; Tan et al., 2006). After infection with *Nippostrongylus brasiliensis*, T22 cell immune responses were severely impaired in PKCθ−/− mice. Consistent with these results, another in vivo study showed that PKCθ appears to be involved in lung inflammation responses, which are controlled by Th2 cells (Marland et al., 2004; Salek-Ardakani et al., 2004). PKCθ−/− mice develop drastically reduced pulmonary hypersensitivity responses to inhaled allergens, such as lung inflammation, eosinophil infiltration, and immunoglobulin E production.

To address the question of whether PKCθ is involved in protection against bacterial infections, Nkowiec-Buszkiewicz et al. (2008) infected mice with *Listeria monocytogenes* (LM) and found that PKCθ is responsible for normal LM-specific T cell responses. Fauconnier et al. (2011) studied the role of PKCθ after the infection of mice with *Plasmodium falciparum*. They found that PKCθ-deficient mice are resistant to the development of cerebral malaria, and the recruitment and activation of CD8+ T cells in the brains of the resistant mice were reduced. To study the function of PKCθ in a chronic persisting infection model, Nishanth et al. (2010) infected mice with *Toxoplasma gondii*. PKCθ-deficient mice suffered from encephalitis and showed insufficient parasite control. T.gondii-specific CD4+ and CD8+ T cells were significantly reduced in the spleens and brains of infected PKCθ-deficient mice, indicating that PKCθ is important for intracerebral parasite control (Nishanth et al., 2010). Ten et al. (2006) and Salek-Ardakani et al. (2004, 2005) showed that PKCθ is also important for full development of experimental autoimmune encephalomyelitis (EAE), a multiple sclerosis-like autoimmune disease that is T11/T17 dependent. PKCθ−/− mice failed to develop EAE after injection with myelin oligodendrocyte
glycoprotein (MOG). In addition, T1-17 cells produced less IL-17 and failed to infiltrate the CNS.

Recently, Koorn et al. (2012) showed that PKCδ−/− mice had lower levels of Stat3, a transcription factor required for T1-17 differentiation, whereas the activation of Stat4 and Stat6, which are important for T1 and T1-17 differentiation was normal. Using a luciferase reporter gene driven by the Stat3 promoter they showed that PKCδ stimulates Stat3 transcription via the NF-κB and AP-1 pathway, resulting in the stimulation of T1-17 differentiation (Koorn et al., 2012).

In striking contrast, PKCθ−/− mice showed normal T1 responses after infection with Leishmania major (Marland et al., 2004), suggesting a lineage-specific function of PKCθ. Garaude et al. (2008) found an impaired anti-leukemic response in PKCδ-deficient mice. These authors induced leukemia with Moloney-murine leukemia virus and found a higher disease incidence earlier in PKCδ−/− mice.

Additionally, the intravenous injection of EL4 cells induced tumors in PKCδ−/− mice. The inflammation processes by affecting NF-κB, inflammation processes, and tumor progression. Different studies have revealed a role for PKCδ in the initiation, progression, and maintenance of inflammatory processes by affecting NF-κB transactivation (Sato et al., 2004; Hsieh et al., 2007).

Additionally, a pro-apoptotic role for PKCδ has been described in T cells. The subcellular localization of PKCδ in human T cells during apoptotic induction by cytokine deprivation and Fas ligation and during the prevention of apoptosis by IFNγ addition was analyzed by Scheel-Toellner et al. (1999). The addition of INFγ to T cells in a pro-apoptotic environment led to a rapid translocation of PKCδ from the nucleus and inhibited the caspase-3-mediated proteolytic activation of PKCδ (Scheel-Toellner et al., 1999).

An essential role for PKCδ in the apoptotic induction of mouse thymocytes was addressed in a study by Lutz-Nicoladoni et al. (2005). Thymocytes from a large panel of PKCδ-knockout mice were forced to undergo apoptosis in vitro via treatment with different apoptotic inducers (PDBu, dexamethasone, FasL, staurosporine, or etoposide), and the selective involvement of PKCδ-deficient primary mouse double-positive thymocytes were protected from apoptotic induction, indicating a clear pro-apoptotic role of PKCδ (Lutz-Nicoladoni et al., 2005). Garaude et al. (2008a) found a strongly reduced number of Treg cells in PKCδ-knockout mice, but these cells were as potent as wild-type Treg cells in inhibiting effector T cell activation, indicating that PKCδ was not required for Treg cell-mediated inhibitory functions. However, Zanin-Zhorov et al. (2011) found that PKCδ was sequestered away from the Treg immunological synapse with confocal imaging, and using a cotrans mouse model and a poorly described PKCδ inhibitor, they postulated a PKCδ-mediated negative feedback loop that enhances the activity of human Treg cells. A very recent publication by Ma et al. (2012) suggested that the differentiation of Treg cells is inhibited by PKCδ-mediated signals via the AKT-Foxo1/3A pathway.

ROLE OF OTHER PKCs IN IMMUNE CELL BIOLOGY

PKCθ

PKCθ is an isozyme belonging to a novel subclass of the serine/threonine PKC family and is expressed in most tissues and cell types. The kinase catalytic activity of PKCθ is mainly affected by trans- and autophosphorylation at conserved Ser/Thr sites in the catalytic domain (activation loop, turn motif, and hydrophobic motif), by tyrosine phosphorylation (by Src family kinases in the context of oxidative stress and DNA damage), Lu et al., 2007; Lomonaco et al., 2008) and by caspase-mediated proteolysis (during apoptosis, Kikkawa et al., 2002). Generally, upon stimulation, PKCθ translocates from the cytosol to nucleus to membrane/cytoskeletal compartments, enabling the phosphorylation of many target proteins and leading to the activation of several signal transduction pathways. It has also been shown that PKCθ can shuttle to mitochondria (Li et al., 1999; Majumder et al., 2001). PKCθ negatively affects a wide variety of cellular functions by inhibiting cellular growth and proliferation and promoting cell death, but it has also been shown to contribute to mitogenesis (Watanabe et al., 1992; Nakagawa et al., 2005; Santiago-Walker et al., 2005), migration (Jackson et al., 2005), and tumor progression. Different studies have revealed a role for PKCθ in the initiation, progression, and maintenance of inflammatory processes by affecting NF-κB transactivation (Sato et al., 2004; Hsieh et al., 2007).

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An involvement of PKCθ in lytic granule exocytosis of CD8+ CTLs (cytotoxic T lymphocytes) was shown by Ma et al. (2007, 2008). The combined use of pharmacological inhibitors and mice with targeted gene deletions allowed these authors to demonstrate that PKCθ is selectively required for lytic granule movement in response to TCR engagement on CD8+ CTLs but is dispensable for activation, cytokine production, and the expression of cytolytic molecules in response to TCR stimulation. In a follow-up study, the authors showed via a time-lapse analysis of living CD8+ CTLs that PKCθ localizes to secretory lysosomes and accumulates at the immunological synapse during target killing (Ma et al., 2007, 2008).

A correlation between impaired PKCθ activation/phosphorylation and the development of idiopathic and hydralazine-induced lupus was postulated by Gorelik et al. (2007). PMA-stimulated CD8+ T cells from patients with lupus showed an impaired PKCθ activity state compared with CD8+ T cells from healthy donors. This defect was responsible for decreased ERK signaling and led
An association of PKCδ with CD3ε in homozygous disruption of the PKCδ isoform (Hii et al., 2003). This is correlated with an activation defect of MAPK pathways in early AD patients, whereas the same treatment induced two distinct [(p)PKCδ] and [(p)PKCζ] T cell subpopulations in severe AD patients (Mascia et al., 2009).

**PKCε**

PKCε was first discovered among the novel PKC isotypes and is expressed at high levels in neuronal, hormonal, and immune cells. Essential roles for PKCε have been established in numerous cellular functions, including proliferation, differentiation, gene expression, muscle contraction, transport, tumorigenesis, enercy, and, in addition, in the classical activation by auto- and trans-phosphorylation on conserved sites in the catalytic domain. PKCε is activated by several different second messengers, including diacylglycerol (DAG), phosphatidylinositol-3,4,5-trisphosphate, and fatty acids. PKCε is targeted to specific cellular compartments depending on the interaction of second messengers with its C1 domain (DAG and triglycerenic acids evoke a plasma membrane and/or cytoskeleton translocation, whereas arachidonic and linoleic acids lead to recruitment to Golgi networks) and via crosstalk with adapter proteins (i.e., Rack1 and β2-Cop). An association of PKCε (via its actin-binding motif) with actin filaments in response to phosphatidylserine-independent stimulation has been reported (Akiwa, 2002).

In T cells, numerous studies have directly shown a positive role of PKCε in the regulation of NF-κB and NFAT/CAP pathways leading to IL-2 upregulation; the activation-dependent translocation of PKCε from the cytosol to the membrane compartment in TCR/CDD3+ or PMA-stimulated human PBIs has been reported previously (Keanan et al., 1997). The neutralization of PKCε in this cell type via the introduction of antagonistic antibodies led to a downregulation of IL-2 synthesis (Staud et al., 1998). Jurkat T cells expressing a constitutively active PKCε mutant showed increased NF-κB and NFAT/CAP transactivation (Genet et al., 1995). An inhibitory effect of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in the plasma membrane translocation of PKCε (and PKCζ), NF-κB nuclear translocation, and IL-2 transcription in PMA-stimulated Jurkat T cells has been described (Denis et al., 2005). A pivotal role for PKCε in thymus-mediated ERK1/2 activation in Jurkat cells has been shown by Maunon et al. (2001). The poor ability of neonatal T cells to produce lymphokines was linked to a lower PKCε level in the plasma membrane of PKCε-deficient cells (Hils et al., 2000). Interestingly, Glusker et al. (2005) reported that mice carrying a homozygous disruption of the PKCε locus showed an altered T cell development and maturation; in addition, mature primary CD4+ T cells isolated from PKCε−/− mice showed normal proliferation, IL-2 secretion responses, and NF-κB transactivation upon CD3/CD28 stimulation or allogeneic MHC presentation, suggesting that PKCε loss of function is compensated for by other members of the PKCε family. In contrast to the described redundant function of PKCζ in mouse T cell proliferation, a role of the PKCε isoform in the regulation of human CD4+ T cell proliferation and sensitivity to TGFβ1 has been shown by Mirandola et al. (2011). PKCε silencing by siRNA led to decreased IL-2 receptor chain expression and proliferation and reduced NF-κB1 and NF-κB2 gene expression upon CD3/CD28 stimulation, whereas the inhibitory effects of TGFβ1 were potentiated by PKCζ downregulation. In addition, a possible connection between increased PKCε expression levels in CD4+ T cells from Hashimoto thyroiditis patients and the molecular pathophysiology of this autoimmune disease was postulated (Mirandola et al., 2011).

Some studies have identified an anti-apoptotic role for PKCε. Jurkat T cells were rescued from Fas-mediated apoptosis by PKCε via the p90Rsk-dependent phosphorylation and inactivation of BAD (Bertolotto et al., 2000). The basis for the deletion of autoactive thymocytes during negative selection was previously addressed (Simon et al., 2000), a lack of the constitutive expression of PKCε in antigen-stimulated CD4+CD8+ thymocytes (in comparison to mature T cells) leading to an inhibition of NF-κB activity and increased cell death was postulated as a possible cause. A positive involvement of PKCε in the recovery of downregulated sphingosine-1-phosphate receptor 1 (S1PR1) in primary mouse CD4+ T cells was investigated (Graier et al., 2005) in PKCε-null mice and with PKCε-selective inhibitors. Quann et al. (2011) established a new redundant role for PKCζ in T cell polarity; the photocarcinization of TCR induced a rapid accumulation of both PKCε isoforms in a broader domain of the plasma membrane, in which they were required to promote the recruitment of PKCζ to the center of the immunological synapse and subsequent microtubule-organizing center (MTOC) reorientation.

**PKCζ**

PKCζ is a calcium- and diacylglycerol-independent serine/threonine protein kinase that binds to the atypical subfamily of PKC isoforms and displays strong homology (more than 70%) to PKCζ. It is ubiquitously expressed but is more highly expressed in the lung, brain, and testis. PKCζ contains a PR1 domain in the N-terminus that recognizes OPCA (OP/RPC/PC/AID) motifs of other proteins, such as the scaffold proteins PAR-6 and ZIP/p62 and the kinase MEK5. PKCζ activity is regulated by PDK-1 transphosphorylation of the catalytic domain activation loop, autophosphorylation, and important lipid components, such as phosphatidylinositols, phosphatidic acid, arachidonic acid, PIP3, and ceramide. Prostate apoptosis response-4 (Par-4) and partitioning defective gene-3 (PAR-3) have been reported to inhibit PKCζ activity through a specific protein–protein interaction. PKCζ has been shown to be involved in the regulation of several critical pathways for cell survival, proliferation, differentiation, and cell polarity, thereby affecting the NF-κB and MAPK pathways. A special role in modulating translation via the p70S6 kinase signaling cascade has also been described by numerous studies (Hirai and Chida, 2003). Recently, a link between PKCζ activity and...
A role for PKCζ in the biological processes of adhesion and cell motility has been described by several studies. The mechanism of the CD44-triggered regulation of LFA-1-mediated adhesion was investigated (Trucy et al., 2006). CD4 binding increased the activity of both PDK1 and PKCζ, and both kinases were necessary for the downregulation of LFA-1-dependent adhesion in the A201-CD44+ T cell line in a P3K-dependent manner. Real et al. (2007) showed that PKCζ and PDK1 were both required for T cell motility and the ability to scan DCs downstream of chemokine receptors. PKCζ is classified into the novel PKC subfamily and shows a high sequence similarity to PKCδ. It was originally isolated from a cDNA library of mouse skin in 1990 (Osada et al., 1990) and is localized on human chromosome 14 (Quan and Fisher, 1999) and mouse chromosome 12 (Chida et al., 1998). It is predominantly expressed in squamous epithelia including skin, tongue, esophagus, and trachea (Koizumi et al., 1993), but at high levels also in T and B cells (Mischak et al., 1991). In addition to phosphatidylinositol and diacylglycerol, PKCζ can be specifically activated by cholesterol sulfate (Ikura et al., 1994). An involvement in keratinocyte cell growth, terminal differentiation, and cell cycle arrest has been reported by several studies: PKCζ was shown to associate with and to activate Fyn, leading to keratinocyte growth arrest and differentiation (Cabodi et al., 2000); a PKCζ-induced terminal differentiation through a transcriptional activation of Tgase1 and involucrin was described by Ueda et al. (1996) and Efimova and Eckert (2000). In addition, PKCζ has been shown to induce G1 arrest in keratinocytes via an inhibition of cyclin-dependent kinase 2 activity (Kashwagi et al., 2000). An important role in the regulation of cell division and cell death during early B cell development was postulated by the work from Morrow et al. (1999).

The different lipid raft localization patterns of PKCζ, PKCη, and PKCθ in cisplatin-induced apoptotic Jurkat T cells was investigated by Solstad et al. (2000). A selective upregulation of PKCζ in these microdomains upon apoptosis induction was revealed, whereas the levels of PKCζ and PKCθ were significantly reduced. Recently, Fu et al. (2011) found a pivotal role of PKCζ in T cell activation and homeostatic proliferation. Comparing the phenotypes of PKCζ+/-, PKCζ-/-, and mice with a targeted disruption of both PKC isoforms, they were able to show that both isoforms share some redundancy in T cell biology. Both isoforms are recruited to the immunological synapse upon TCR stimulation and double-knockout mice showed a more severe defect in positive selection. Additionally, they found specific non-redundant functions as in self-antigen-dependent homeostatic proliferation. Using a live imaging approach a TCR-induced recruitment of GFP fusion proteins of PKCζ and PKCζ to the plasma membrane was also described by Quann et al. (2011). The timely well coordinated localized enrichment of these two isoforms served as a prerequisite for the subsequent translocation of PKζ to the center of the immunological synapse, necessary for the regulation of T cell polarity and T cell effector functions.

**PKCθ**

The alternative splicing forms PKCθI and PKCθII are members of the calcium-activated, phospholipid- and DAG-dependent classical or conventional PKC subfamily. Numerous studies have shown their role in various cellular processes, such as the regulation of B cell development and activation/proliferation, oxidative stress-induced apoptosis, androgen receptor-dependent transcription regulation, insulin signaling, and endothelial cell proliferation. In B cells, a signaling link between PKCθ and BTK has been described. PKCθ can downregulate BTK function through the direct phosphorylation of BTK at Ser-180, inhibiting its membrane translocation and subsequent activation (Kang et al., 2001). A key...
role for PKCα in BCR-induced NF-κB activation has been shown (Sommer et al., 2005), the direct phosphorylation of CARMA1 at three serines within its linker region induced its translocation into lipid rafts, the recruitment of BCL10/Ma1 and the subsequent activation of signaling molecules downstream of the CBM complex. Furthermore, PKCβ seems to play an important, even dual role in insulin signaling pathways: in muscle cells, PKCβ mediates insulin-dependent DNA synthesis through the RAF1-MAPK/ERK signaling cascade downstream of insulin receptor substrate 1 (IRS1), and in adipocytes, it negatively regulates glucose transport by inhibiting the translocation of the glucose transporters GLUT1 and GLUT4 (Formisano et al., 2000; Bosch et al., 2003; Perrini et al., 2004).

A selective impact of PKCδ on T cell migration has been shown by several studies (Volkov et al., 1998, 2001). LFA-1-triggered T cell locomotion led to the specific recruitment of PKCδ and PKCθ to the MTÖC and microtubules. A PKCδ-deficient T cell line was unable to either crawl or develop a polarized microtubule array upon integrin cross-linking, whereas the ability to adhere and form actin-based pseudopodia remained unaffected. The reconstitution of PKCδ(1) in non-motile PKCδ-deficient T cells restored their locomotory behavior in response to an LFA-1 signal.

The possible involvement of PKCα in IL-2 gene transcription and/or IL-2 protein secretion upon TCR/CD28-induced T cell activation has been addressed by several studies (Long et al., 2001; Alfaro et al., 2003; Perrini et al., 2004). In 2010, a re-investigation of IL-2 expression in PKCδ-deficient T cells showed that this isoform plays a specific role affecting also CD69 surface levels and IL-8 production. LFA-1 deletion revealed a predominant role in the collaborative action of PKCδ and PKCθ in BCR-induced NF-κB activation (Pfeifhofer et al., 2006). Gruber et al. (2009b) generated PKCθ−/− mice and found that PKCθ−/− double-knockout mice fail to develop experimental allergic encephalomyelitis (EAE) and display drastically reduced lung inflammation after the induction of allergic asthma and airway reactivity in TMx mice. The PKCδ−/− mice, however, seemed to be responsible for the induction of endoeytosis of non-engaged TCRs that recycle to the contact zone between the T cell and the APC. PKCδ, however, seemed to be responsible for inducing the endoeytosis of directly triggered TCRs at the contact zone. Furthermore, a study showed the involvement of PKCα in allergic processes (Ohi et al., 2004).

Our laboratory identified PKCs as a physiological and non-redundant PKC isotype in signaling pathways that are necessary for T cell-dependent IFNγ production and IgG2a/2b antibody responses using PKCα−/− knockout mice (Pfeifhofer et al., 2006). PKCα−/− mice develop a severe autoimmune inflammatory disease in the CNS and peripheral tissues, suggesting that PKCα by itself is an attractive monotherapy for modulation of the immune response. While this published evidence validates PKCα inhibition being essential, more recent results have indicated that additional PKC isotypes are involved in critical T cell signaling pathways. Because PKCα and PKCθ are both highly expressed in T cells (GNF SymAtlas) and have isotype-selective functions in T cells (Sun et al., 2000; Pfeifhofer et al., 2003, 2006), whether PKCα and PKCθ also exert overlapping functions has also been investigated. Gruber et al. (2009b) generated PKCα−/− × PKCθ−/− double-knockout mice and found that the NFAT pathway plays a predominant role in the collaborative action of PKCθ and PKCα. The NFAT kinase GSKβ is hyper-reactive in PKCα−/− × PKCθ−/− double-knockout CD4+ T cells. Subsequently, these authors found reduced nuclear translocation and DNA binding of NFAT. In an in vivo study, PKCα−/− × PKCθ−/− double-knockout T cells showed strongly reduced IL-2 cytokine secretion after injection of an anti-CD3 monoclonal antibody. Additionally, the mice showed an impaired allograft response, leading to significantly prolonged allograft survival in heart transplantation experiments (Gruber et al., 2009b).
To obtain complete immunosuppressive effects, the inhibition of more than PKCθ appears to be needed, and the pharmacologic inhibition of multiple PKC isoforms may provide a successful approach to avoid T cell effector functions that are relevant for diseases such as psoriasis, atopic dermatitis, and allergies, as well as other indications, including asthma, rheumatoid arthritis, multiple sclerosis, and transplant rejections.

Sottrastaurin (AEB071) is an immunosuppressive drug that inhibits multiple classical and novel members of the PKC family, resulting in decreased T lymphocyte activation (Evrënou et al., 2009). In primary human and mouse T cells, AEB071 abrogated IL-2 secretion and CD25 expression, which are markers of early T cell activation. CD3/CD28-induced T cell proliferation, and LFA-1-mediated T cell cell adhesion were potentely inhibited, and although previous PKC inhibitors, the apoptosis of murine T cell blasts was not enhanced (Evrënou et al., 2009). These mechanistic studies on Nε-vδB and NεAT transduction factor transactivation additionally suggest that AEB071 and Ca²⁺ have a complementary effect, resulting in the combined inhibition of IL-2 secretion. Additionally, other results suggest that AEB071 but not Ca²⁺ inhibits the adhesion capacities of T lymphocytes.

Skvara et al. (2008) performed a clinical study with patients suffering from psoriasis in which the patients received single and multiple oral doses of AEB071. They found a strong reduction in the clinical severity of psoriasis and a histological improvement in skin lesions, indicating that sottrastaurin may provide a new therapeutic option for psoriasis (Skvara et al., 2008). Even so, we cannot exclude additional PKC isoforms being involved in critical T cell signaling pathways. The effect of AEB071 on PKCθ, including other classical and novel PKC family members expressed in T cells, is the likely mechanism responsible for the strong AEB071 immunosuppressive activity.

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NEW CANDIDATE EFFECDOUR PATHWAYS MEDIATED BY PKC IN T CELLS

The challenge ahead for immunologists is the further elucidation of the molecular and cellular processes of PKCs and PKCθ that govern the development and function of T cells. PKC-mediated signaling in NFAT/AP-1 transactivation critically involves a pathway of the orphan nuclear receptor NR2F6. There is evidence that PKC-θ-induced signaling involves NR2F6 inactivation, presumably by stimulating the release of NF26 from DNA-binding sites. This inactivation facilitates NFAT/AP-1 binding to its enhancers in the IL-2 and IL-17A promoters. In agreement, PKCθ/− /− double-knockout T cells show almost no TCR/NFAT/AP-1 transactivation signaling (Graber et al., 2009). However, PKCδ and PKCθ might have an even broader role in regulating T cell functions than just acting downstream of T cell antigen receptors. Thus, despite the significant progress in assembling the PKC puzzle in T lymphocytes, defining downstream PKC substrates, including their effectors functions, triggered by this phosphorylation step remains to be investigated in physiological settings. From these investigations, innovative possibilities are likely to emerge for the manipulation of T cell pathways in treating immunological diseases by suppressing pathophysiologic immune responses or augmenting host-protective immunity.

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