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Editorial

Editorial: **Can PKCδ be a novel therapeutic target?**

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PKC is a family of multifunctional serine/threonine kinases, which are involved in the control of other proteins. So far, at least 10 PKC isoforms have been identified and can be subdivided into three groups: classical (α, β I, β II, and γ), novel (δ, ε, θ, and η), and atypical (ζ and ι/λ). Being important signaling transducers, PKCs are activated when second messengers bind to their regulatory domain, usually at the plasma membrane. The regulatory domain is recruited to the plasma membrane through calcium ions, phospholipids, and diacylglycerol, which release the catalytic domain of PKC to exert its function on targeted substrates [1]. On activation, PKC plays a central role in signal transduction and also participates in diverse biological and biochemical functions, such as glycogen metabolism, release of neurotransmitters, and protein transactivation. Moreover, the PKCδ isoform has received particular attention for being a promising target for new drugs. Why? There are several lines of evidence that PKCδ plays a crucial role in cell growth, migration, differentiation, and cell death, thus being involved in many human disorders, such as cancer, diabetes, and sepsis [1–5].

Several PKC isoforms have been associated with tumor progression. The mechanisms involved in PKC activation have been studied extensively and indicate that activation of PKC affects motility, invasion, and metastasis. Contradictory roles for PKCδ have also been reported, as it can activate and inhibit apoptotic pathways in different conditions and cell types that might affect tumor progression. Compared with control cells, a high expression of PKCδ has been demonstrated in human ductal, pancreatic, cancerous samples [2], which suggests that a genetic or epigenetic alteration in PKC contributes to pancreas tumor progression. Consequently, the clarification of the pathways involved is necessary for a better understanding of the function of this molecule in cancer.

In diabetes, a multifactorial disorder, the importance of PKCδ has also been highlighted. PKCδ activation by hyperglycemia causes vascular cell apoptosis and diabetic retinopathy. It was demonstrated that hyperglycemia triggers PKCδ activation and recruitment of Src homology-2 domain-containing phosphatase-1, which leads to dephosphorylation of PDGFRβ, reducing the downstream signaling [3]. The PKCδ signaling pathway may be exploited for therapeutic purposes, as many diabetic patients suffer from vascular complications associated to hyperglycemia. In immune-privileged sites, a better understanding of the PKCδ pathway might also contribute to preventing patients from disease progression, as inhibition of this pathway attenuates the blood-retinal barrier breakdown, which is the basis of diabetic retinopathy pathophysiology [4]. Development of therapeutic drugs targeting PKCδ is a provocative challenge, as it can act through direct or indirect pathways to regulate the inflammatory response, cancer, and diabetes.

The mechanisms described by Geraldes et al. [3] might be a good explanation as to what happens during a SIRS, which is triggered by LPS from Gram-negative bacteria and may target many organs, leading the patient to death. Lungs are particularly affected by SIRS, and alveolar macrophages provide a second wave of mediators/cytokines that amplify SIRS and the mortality associated to this condition. Binding of LPS to TLRs triggers a complex sequence of events leading to increased expression of PKCδ, specific genes through NF-κB and the release of a plethora of mediators, such as TNF-α, NO and PGE_2 in experiments conducted in vivo [5] and in vitro using alveolar macrophages [6, 7].

In previous studies, we have shown that there is a reduction of the number of leukocytes that migrate to the lung in response to LPS stimulation in diabetic rats when compared with control rats [8, 9]. In addition, we have demonstrated that diabetic rats showed a significant reduction in the phosphorylation of lung PKCδ after LPS challenge compared with the control group [5]. LPS also induced leukocyte transmigration and changes in permeability of the airway epithelium, at least in part, via PKCδ. Therefore, the reduction of the leukocyte transmigration in diabetic rats can be explained partially as a result of

Abbreviations: PDGF=platelet-derived growth factor, PDGFRβ=PDGF receptor β, PGE_2=prostaglandin E_2, PKC=protein kinase C, SIRS=systemic inflammatory response syndrome

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a failure of activation of the PKCδ pathway. As a consequence, therapeutic drugs targeting PKCδ by direct or indirect way may also regulate the SIRS.

Neutrophils play an important role in the host defense against bacterial infections, but if not regulated properly, they might contribute to severe inflammation inducing tissue damage. During the development of SIRS, proinflammatory cytokines, such as TNF-α, modulated neutrophil function and activated a proinflammatory cascade that culminated with neutrophil apoptosis. Enhanced neutrophil survival at the site of inflammation promoted increased bacterial activity and potentially exacerbated acute inflammatory damage as a result of an overload of reactive oxygen radicals on-site. The function of the PKCδ is also important in human inflammation, as TNF, which is implicated in the suppression of neutrophil apoptosis during sepsis, is regulated by PKCδ, inducing TNF-mediated, anti-apoptotic signaling [10].

This ability of PKCδ regulating the signaling mediators and controlling TNF-induced oxygen radical production [11] may be the key factor to control tissue damage at the site of inflammation. In their original paper, Kilpatrick et al. [12] have extended this observation providing important insight into the molecular mechanisms involved in the pathogenesis of lung injury associated to sepsis. Their hypothesis is that PKCδ may restore sepsis-induced lung immune responsiveness, and they have clearly shown that inhibition of the PKCδ pathway on the inflammatory site leads to reduction of cell infiltration, disruption of lung architecture, and pulmonary edema, using an intra-abdominal sepsis model (cecal ligation and double puncture in rat). However, that still leaves the question: can PKCδ be a novel therapeutic target? You will probably find this answer in the paper from Kilpatrick et al. [12] in the *Journal Leukocyte Biology*.

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KEY WORDS:
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