Pulmonary hyperplasia and the two sides of PKCζ

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Online publish-ahead-of-print 8 April 2008

The editorial refers to ‘Hypoxia exposure induces the emergence of fibroblasts lacking replication repressor signals of PKCζ in the pulmonary artery adventitia’ by M. Das et al.,* pp. 440–448, this issue.

Protein kinase C (PKC) was initially identified by Nishizuka and coworkers1 as a nucleotide-independent, Ca2+-dependent serine kinase. Molecular cloning identified at least 11 isoforms of PKC that were further divided into subfamilies based on sequence homology and mode of stimulation. The classical PKCs (α, βI, βII, and γ) are diacylglycerol (DAG) and calcium-dependent enzymes, whereas the novel PKCs (δ, ε, η, and ι) require DAG, but not calcium, for activation. The atypical PKCs (ζ, η/λ) are not responsive to activation by DAG or calcium, but are activated by other lipid-derived second messengers. PKCs contain N-terminal regulatory and C-terminal catalytic domains separated by a flexible hinge region. In the absence of activating cofactors, the catalytic domain is subject to autoinhibition by the regulatory domain that is mediated, in part, by a pseudosubstrate sequence motif resembling the consensus sequence for phosphorylation by PKC.2 PKCs in general are involved in multiple intracellular mechanisms, and although they belong to one family they might contribute to opposing effects by activating intracellularly various pathways.

In cardiovascular diseases, PKCs play a prominent role in promoting pathophysiological effects. PKC α, β, ε, ζ, and δ have been shown to be involved in proatherosclerotic effects in vascular smooth muscle cells (VSMCs), macrophages, and endothelial cells. PKCζ mediates the induction of NADPH oxidase by transforming growth factor-α in endothelial cells.3 Interestingly, PKCα seems to mediate inhibitory effects on the superoxide generation by endothelial NADPH oxidase, which is an essential element for the development of endothelial dysfunction.4

In cardiac fibrosis and heart failure, the role of PKC α, β, ε, ζ, and δ has been investigated intensively. PKCζ promotes growth factor effects on matrix remodelling,5 increases CTGF and collagen deposition, and mediates hypertrophic signalling, whereas PKCδ partially opposes these effects.6 Cardiac fibroblast proliferation is induced via PKCζ activation by transforming growth factor-β and is negatively regulated by PKCζ.7 This essential mechanism, the inhibitory control on the proliferation of fibroblasts by PKCζ, seems to be a key mechanism in the development of pulmonary hypertension and pulmonary remodelling in patients with acute respiratory distress syndrome.

In the present issue of Cardiovascular Research, Das et al.8 present findings that demonstrate that hypoxia changes the role of PKCζ from a negative regulator (replicant repressor) in adventitial pulmonary fibroblast to a stimulator of fibroblast proliferation (replication). The authors explain this phenomenon with the hypothesis that chronic hypoxia leads to a switch of phenotype of adventitial fibroblasts to a proliferative phenotype that lacks the replicant repressor effect of PKCζ.

Such a phenomenon is clearly not new, but it is a relevant phenomenon in cardiovascular and pulmonary diseases. In the vascular wall, the classical contractile phenotype of VSMCs switches to the secretory type and changes its cellular program to a proinflammatory character, leading to vascular inflammation and formation of vulnerable plaques. Therefore, it appears very likely that the proliferative adventitial fibroblast is a result of a disease-related (hypoxia) phenotype switch. The authors provide further insights in their study which characterize this phenomenon. They demonstrate different phosphorylation profiles of PKCζ in chronic hypoxic fibroblast populations compared with normal fibroblasts. They demonstrate intranuclear localization of extracellular signal-regulated kinase (ERK) and PKCζ in hypoxic fibroblasts as molecular events leading to proliferation. Godeny and Sayski9 have demonstrated that angiotensin II promotes proliferation in VSMCs by a similar mechanism. A heterotrimeric G-protein/PKCζ complex mediates the translocation of ERK1/2 into the nucleus after stimulation with angiotensin II. Das et al.8 describe a similar mechanism in the chronic hypoxic fibroblast population. It would be interesting to know whether there is an autocrine activator of this mechanism in the hypoxic proliferative population of fibroblasts. Activation by another PKC isoform could also play a role in this concept. Recently, it has been shown that the novel PKCδ functionally interacts with PKCζ and PKCζδ, which serve as direct downstream targets in the signalling pathway leading to activation of T-lymphocytes.10

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From a clinical viewpoint, pulmonary hyperplasia is a serious and deleterious pathophysiological event in neonatal and critical care medicine that leads to severe pulmonary hypertension and acute respiratory distress syndrome. Here Das et al. present new and exciting data that suggest a disease-related phenotype switch of pulmonary fibroblasts under the control of PKCζ leading to the detrimental hyperplasia in the pulmonary vasculature. These data present pulmonary PKCζ as a potential target for new therapeutic interventional strategies to prevent pulmonary hypertension, a road which has to be taken.

References


