Protein kinase C delta: a master regulator of apoptosis in neointimal thickening?

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This editorial refers to ‘Protein kinase C delta mediates arterial injury responses through regulation of vascular smooth muscle cell apoptosis‘ by D. Yamanouchi et al., pp. 434–443, this issue.

Smooth muscle cell (SMC)-driven neointimal hyperplasia is a key mechanism that reduces the long-term benefit of vascular interventions such as stenting, balloon angioplasty, and by-pass grafting. Furthermore, neointimal hyperplasia contributes significantly to the progression of atherosclerotic lesions. In response to arterial injury, neointimal hyperplasia develops rapidly—within a couple of months—as opposed to atherosclerotic lesions, which progress over decades. In general, the contribution of SMC to neointimal thickening can be attributed to increased SMC migration, proliferation, reduced apoptosis, and increased extracellular matrix accumulation. In addition, the recruitment of vascular progenitor cells and constrictive remodelling contribute to lesion formation and luminal narrowing. All of these mechanisms hold promise for the development of therapeutic interventions, and an impressive body of work has identified numerous potential targets. Unfortunately, many of these interventions were effective in rodent models but failed in human disease. However, in the recent past extensive clinical experience has been collected using drug-eluting stents (DES) for local delivery of antiproliferative drugs. Although highly efficient in inhibiting stent restenosis, sirolimus- and paclitaxel-eluting stents reduce endothelial re-growth and require long-term dual anti-platelet therapy. Therefore, new strategies that efficiently inhibit restenosis may still be of clinical interest if they are superior to current DES with respect to thrombotic complications and general safety.

Protein kinase C delta (PKCδ) belongs to the subfamily of novel PKC isoforms and is widely expressed in mammalian cells, including cancer cells, leucocytes, and SMC. The PKC family of serine–threonine kinases is activated by Gq-coupled seven transmembrane receptors and plays an integral role in signalling. Furthermore, activation of PKCδ occurs in response to hypoxia and oxidative and mechanical stress. Functionally, PKCδ is involved in the fine tuning of cellular phenotypes, including apoptosis, in a variety of biological systems. PKCδ-induced apoptosis requires cleavage of PKCδ by caspase 3 and release of the constitutively active catalytic domain (δCF) that then accumulates in the nucleus. δCF has a variety of nuclear targets, including the recently defined CCAAT enhancer-binding protein α. Furthermore, recent evidence points towards a dual role of PKCδ in regulating cell death because acute hypoxia activates PKCδ and its downstream targets JNK-1 and beclin-1, resulting in increased autophagy and cell survival. In contrast, sustained hypoxia induces apoptosis due to PKCδ activation and caspase 3-mediated cleavage of PKCδ. Taken together, these results indicate that PKCδ is an important regulator of apoptosis in a broad variety of different cell types.

Yamanouchi et al. elegantly studied the role of PKCδ in rodent models of neointimal hyperplasia. The expression of PKCδ and the caspase 3-mediated processing into δCF was increased during neointimal hyperplasia at 3 and 7 days after balloononing when SMC proliferation is still high. Therefore, PKCδ might represent an endogenous negative regulator of neointimal hyperplasia. This hypothesis was experimentally supported by the use of adenoviral overexpression in rat carotid arteries after balloononing and by the use of PKCδ-deficient mice, revealing that PKCδ indeed inhibits neointimal hyperplasia and that it is associated with SMC apoptosis in vivo. Furthermore, in vitro overexpression and knock-out of PKCδ confirmed the role of PKCδ in apoptosis of SMC. The fact that the inhibitory effect of PKCδ on vascular lesions was observed in different models such as rat balloon injury, carotid ligation in mice and in murine vein graft atherosclerosis is indicative of a robust effect on SMC in different types of vascular lesions. Furthermore, in human atherosclerotic plaques, apoptotic SMC showed high levels of PKCδ. These findings in vascular SMC are in line with the pro-apoptotic function of PKCδ reported in cancer cells and suggest that PKCδ may indeed be an endogenous master regulator of apoptosis in vascular SMC.

Selective activators of PKCδ are available and have been shown to inhibit cancer cells, mainly due to activation of PKCδ. Prototypic isoform-specific activators of PKCδ such as the 1,4-benzothiazepine derivative, JTV519, are also available but have not yet been used in experimental models of atherosclerosis or restenosis. Instead, both beneficial and detrimental effects of PKCδ on ischaemia/reperfusion were suggested using JTV519 and overexpression of the peptide PKCδ inhibitor, deltaV1-1. JVT519 reduces ischaemia/reperfusion.
injury in rat myocardium, and overexpression of deltaV1-1 also improves microvascular perfusion of infarcted myocardium. Furthermore, studies on rat microcerebrocirculation suggested an unfavourable role of PKCδ in the regulation of microcirculation. Therefore, it must be taken into account that PKCδ may be a regulator of microcirculation and microvascular permeability independent of its effect on vascular SMC apoptosis.

The work by Yamanouchi et al. raises the question whether PKCδ-dependent apoptosis of SMC could be translated into novel therapeutic strategies. One option might be the pharmacological activation of PKCδ to inhibit neointimal hyperplasia during atherosclerosis and/or restenosis. However, in the context of atherosclerosis it must be considered that vital SMC producing extracellular matrix are critical for plaque stability. Moreover, it was shown recently that SMC apoptosis even accelerates atherosclerosis in mice and that apoptosis indeed destabilizes atherosclerotic lesions. In addition, apoptosis in atherosclerotic plaques provides membrane vesicles that nucleate hydroxyapatite formation and thus plaque calcification. Therefore, it is unlikely that activation of SMC apoptosis by PKCδ activation will be useful in the treatment atherosclerosis. With the clinical experience on hand from paclitaxel- and sirolimus-eluting stents, the key question regarding restenosis may be whether PKCδ activation would affect endothelial re-growth and apoptosis. Although not as extensively studied as in other cell types, endothelial apoptosis also appears to be enhanced by PKCδ-dependent mechanisms. Therefore, additional work on the role of PKCδ in apoptosis of macrovascular endothelial cells and endothelial re-growth in vivo is required to assess the therapeutic potential of local PKCδ activation to limit neointimal hyperplasia.

References


