PTEN-uating Restenosis

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Within the last few years, the lipid phosphatase PTEN has gained increasing attention.\(^1\) Initially described as a tumor suppressor gene, the function of PTEN meanwhile ranges from the regulation of the immune system to the recently established important function in neuronal growth.\(^1,2\) On a cellular level, PTEN interferes with cell proliferation, survival, and growth. These effects are not restricted to a certain cell type or species but have been demonstrated from *Drosophila* to humans and in various cell types including cardiomyocytes.\(^2-4\) Consistent with a crucial role for PTEN in the regulation of cell fate, the complete deficiency of PTEN leads to embryonic lethality in mice.\(^5,6\) On a molecular level, PTEN dephosphorylates phosphatidylinositol-(3,4,5) trisphosphate [PtdIns (3,4,5)P\(_3\)], which is formed by the phosphatidylinositol-3-kinase (PI3K).\(^4\) Thereby, PTEN antagonizes the diverse downstream signaling effector pathways activated by PI3K-derived phospholipids (Figure).

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Now, in this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, the article of Huang and Kontos\(^7\) adds a new twist to the multifactorial roles of PTEN. The results of this study suggest that PTEN may comprise a new bullet against restenosis. Restenosis is the most important limitation of balloon angioplasty or stent placement and occurs in 20% to 40% of patients within the first few months after successful intervention.\(^8\) The development of restenosis is mainly due to reactivation of the normally quiescent smooth muscle cells, which are proliferating and migrating, resulting in neointimal hyperplasia in response to the injury of the vessel wall induced by the intervention.\(^8\) Although the potency of PTEN in vivo remains to be established, overexpression of PTEN was shown to inhibit the key players in restenosis, smooth muscle cells. Thereby, PTEN inhibits smooth muscle cell proliferation and migration and, concomitantly, increases apoptosis induction. PTEN acts upstream of a variety of important proliferative signaling cascades (Figure). The dephosphorylation of phospholipids by PTEN prevents activation of the phosphoinositide-dependent kinases (PDKs), which phosphorylate and activate the protein kinase B/Akt and the p70\(^66\) kinase. Furthermore, PTEN blocks the phospholipid-binding to the pleckstrin homology domain within Akt, which is essential for Akt activation. The inhibition of Akt activation leads to the consequent modulation of multiple downstream effector pathways.\(^9,10\) Most of the Akt substrates, which are inhibited by Akt, such as forkhead transcription factors or GSK-3, are involved in regulation of proliferation and apoptosis. Forkhead transcription factors induce the expression of the cell cycle inhibitor p27 as well as the pro-apoptotic proteins Bim or the Fas ligand.\(^11\) Moreover, GSK-3 seems to play an important role in vascular remodeling by regulating $\beta$-catenin and cyclin D1 stability.\(^12\) Finally, Akt was recently shown to phosphorylate and, thereby, inhibit the antiproliferative activity of p21.\(^13\) In addition to the antiproliferative and pro-apoptotic effects of PTEN, smooth muscle cell migration is also blocked by PTEN overexpression.\(^7\) The molecular mechanism underlying this inhibitory effect is less clear, but may involve a reduction of focal adhesion kinase expression. However, this could also be a secondary phenomenon, given that apoptosis induction is associated with proteolytic cleavage of focal adhesion kinase.\(^14\) An involvement of the Akt pathway on Rac should also be considered. At least in endothelial cells, Akt-dependent phosphorylation of the G-protein coupled–receptor EDG-1 is indispensable for Rac activation and endothelial cell chemotaxis.\(^15\)

Interestingly, PTEN also interferes with the target of rapamycin (TOR), which is currently one of the most promising therapeutic targets for treatment of restenosis.\(^16\) Initial clinical studies demonstrate that inhibition of TOR by rapamycin-releasing stents dramatically reduces restenosis (RAVEL-study).\(^16\) Akt is known to phosphorylate and, thereby, activate the kinase TOR.\(^17,18\) Thus, PTEN-induced Akt inactivation may prevent TOR phosphorylation and activation. Downstream of TOR, the p70\(^66\) kinase is also regulated by PDK1, a kinase which depends on PTEN-sensitive phospholipids. In addition, another downstream target of TOR, 4E-BP1, can be phosphorylated by Akt.\(^18\) Although it is not yet clear whether this model can be directly translated to smooth muscle cells, one may easily imagine that PTEN also blocks several rapamycin-sensitive pathways.

Taken together, a broad spectrum of cellular signaling cascades and smooth muscle cell functions are targeted by PTEN. Such a wide therapeutic range, which targets as many of the biological processes contributing to the development of restenosis, may indeed turn out to be an advantage for PTEN overexpression as an anti-restenosis strategy. However, further studies are required to establish the potency of PTEN overexpression in vivo. As such, the work by Huang and Kontos marks the beginning of an exciting question.

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Schematic illustration of the molecular signaling pathways influenced by PTEN: potential role in regulation of smooth muscle cell proliferation, survival, and apoptosis. PTEN dephosphorylates the PtdIns(3,4,5)P3, and thereby prevents activation of downstream effector pathways including the phosphoinositide-dependent kinases (PDK).

References

