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An Unexpected Molecule Linking Vascular Inflammation to the Actin Cytoskeleton

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Endothelial dysfunction, as defined by a decreased bioavailability of NO, is one of the earliest steps in the development of atherosclerosis. The resulting vascular inflammation including accumulation of lipid-laden macrophages hallmarks the pathology underlying the major clinical complications of cardiovascular disease. Many of the key players in these inflammatory events have been identified and validated in vivo, with a clear focus on the endothelial adhesion molecules like VCAM-1, the macrophage lipid handling machinery and inflammatory mediators like various chemokines that attract a variety of leukocytes to the atherosclerotic lesion. In the current issue of Circulation Research, Romeo et al identify a quite unexpected protein to play a pivotal role in these processes. Mice with a partial deletion of profilin-1 (Pfn1), an actin binding molecule that is involved in the dynamics of the actin cytoskeleton (Figure), are shown to be substantially protected against atherosclerosis. This is the second example for a prominent role of an actin binding molecule in cardiovascular disease, given the recent excitement regarding the potential implication for regenerative medicine of thymosin beta-4 (Figure 1), because of its action on preventing ischemic damage to myocardium and inducing cardiac neovascularization.

Romeo et al show that, when placed on an atherogenic diet for 2 months, Pfn1+/− Ldlr−/− mice exhibit remarkably decreased initial lesion sizes at atherosclerosis-prone sites in both the descending aorta, and the aortic arch and brachiocephalic artery. Consistent with current understanding, these early lesions indeed coincide with sites of disturbed flow profiles. They next go on to convincingly display several mechanistic insights into the causes of this protective effect of diminished profilin-1 levels. Endothelial NO production is preserved in the Pfn1+/− Ldlr−/− mice under dietary conditions that would normally severely comprise its production, and the accumulation of monocytes is partially prevented by a decreased expression of VCAM-1. In addition, the macrophages are less able to load lipids because of a partial inhibition of CD36-driven endocytosis of oxidized LDL. As before, profilin-1 is shown to be induced at these vascular sites in both the Pfn1+/− and Pfn1+/− mice, albeit to a much decreased level in the latter. What is causing this inhibitory effect on the earliest stages of atherogenesis? At a molecular signaling level, blunted inflammatory responses are ascribed to an attenuated activation of the p38 MAPK-ATF-2 axis, whereas effects on nuclear factor kappa B or c-Jun N-terminal kinase activity seem absent. The latter finding is consistent with recent findings on the specific localization of active phospho-ATF-2 in endothelium overlying early atherosclerotic lesions (and its absence in nonaffected endothelium) and the documented link of p38 MAPK-driven inflammatory gene expression to proatherogenic flow profiles. The concomitant prominent role of ATF-2 in the expression of proinflammatory gene expression in endothelium was shown to be related to the absence of the shear-induced transcription factor KLF2, a factor that, like shear itself, has an enormous impact on the architecture of the actin cytoskeleton.

Collectively, the findings by Romeo et al clearly set the stage for a prominent role of the actin cytoskeleton in modulating many unexpected aspects of the atherosclerosis process. Still, although a number of molecular mediators are identified, the intriguing question remains how these effects are produced by an actin-binding molecule. The authors suggest that these effects might be linked to a more promiscuous binding behavior of profilin-1 to nonactin molecules through its well known proline-rich peptide binding domain. Unfortunately, most of the circumstantial evidence for such elusive binding partners is extrapolated from the properties of its brain-specific homologue profilin-2, whereas profilin-1 seems much more restricted in its affinity for actin in vivo. Can subtle changes in actin cytoskeleton dynamics through an altered level of profilin-1 explain the observed effects in vivo? Despite 3 decades of work unraveling the biochemistry of actin fiber dynamics and the role of profilin therein, a link to cellular signaling, let alone in vivo roles in (patho-)physiology and disease remain obscure. Unfortunately, the effect of partial profilin-1 deficiency on the architecture and dynamics of the in vivo actin cytoskeleton has not been documented in the present study by Romeo et al. A plethora of potential links to atherosclerosis seem at hand. Disturbed hemodynamics at atherosclerosis prone areas of the vasculature have been linked to both endothelial dysfunction and effects on the cytoskeleton. Indeed, the actin network itself has been proposed to be the most plausible mechanosensor, directly linking mechanical forces to signal transduction via integrin stimulation. Stress fibers are modulated by altered shear forces and they themselves have been shown to alter the localization of important inflammatory members of the MAPK signaling network.

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The pivotal role of profilin-1 in actin dynamics and its cardiovascular effects. Profilin-1 greatly increases the rate of actin polymerization by both binding actin-ADP to catalyze nucleotide exchange to yield actin-ATP and by acting as the substrate of the processive actin-polymerising enzyme Formin, which adds actin-ATP to the barbed ends of (newly) formed actin fibers, with a concerted release of profilin. In addition, in the absence of growing actin fibers, profilin sequesters actin-ATP in the cytoplasm to prevent spontaneous, uncatalysed polymerization allowing the cell to maintain a high concentration of actin-ATP, ready to be incorporated when a new actin fiber is nucleated. In mammalian cells, a large portion of actin-ATP is transferred from profilin to thymosin-beta4, where it is prevented from both spontaneous and from formin-catalyzed incorporation into actin-fibers, because the actin-thymosin dimer cannot act as a substrate for formin.13–15

In conclusion, the article by Romeo et al4 has now provided the first in vivo evidence for a prominent effector role of profilin-1 in cardiovascular disease and has linked the actin cytoskeleton and its dynamics directly to vascular inflammation. This sets the stage for examining in much more detail the close molecular links between the actin cytoskeleton and vascular inflammation as such detailed knowledge will be crucial for finding a practical medical application of these findings. This in view of the essential role of profilin-1 in both embryogenesis and all cell division processes in adult life, as evidenced by the embryonic lethality of the full Pfn1−/− knockout attributable to defective cytokinesis.24 One pivotal issue being the regulation of the Pfn1 gene, and how this connects to the observed increase in vascular expression in response to an atherogenic diet.4,7 This will provide potential innovative handles to more subtly and specifically influence these processes in a way that would be beneficial for patients suffering from atherosclerosis and its complications.

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Disclosures

None.

References


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