Editorial Commentary

New Targets and Opportunities at the Level of the Endothelium

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For a single layer of cells \( \approx 1 \mu \text{m} \) in thickness, the vascular endothelium displays an increasingly impressive array of tricks. In small arteries, complex pathways transmit vasodilatory signals to the vascular smooth muscle layer opposing the tonic force of myogenic constriction and thus regulate blood pressure. In larger arteries, viability of the endothelium prevents atherosclerosis at sites of turbulence. Also, although not yet proven, it seems likely that endothelial health contributes to the maintenance of large vessel elasticity. As such, given the crucial role played by the endothelium in cardiovascular health, 2 recent publications from Yue et al\(^1\) at the University of Illinois are particularly exciting. Their latest study\(^1\) shows that, in cultured human umbilical vein endothelial cells, the phospholipid binding protein apolipoprotein E (ApoE) reverses the inhibitory effect of caveolin 1 on endothelial NO synthase. ApoE was derived from an exudate taken from a cultured macrophage colony. The interaction between ApoE and caveolin 1 underlying the functional effects on endothelial NO synthase was elucidated in 2011 when Yue et al\(^2\) showed that ApoE colocalized with caveolin 1 at the plasma membrane of adipocytes. The implication of the work of Yue et al\(^1,2\) is that, in vivo, local macrophage production of ApoE may increase endothelial NO bioavailability and, thus, enhance vasodilation (in small arteries). NO release is a major component of small artery vasodilation and contributes \( \approx 20\% \) to \( \approx 30\% \) of the maximal response to acetylcholine on preconstricted arteries. More importantly, however, human studies have consistently demonstrated that it is the NO component of the endothelium-dependent dilation that is damaged in conditions such as diabetes mellitus\(^3\) or obesity.\(^4\) The capacity to modulate NO bioavailability from the endothelium is, therefore, a very attractive therapeutic opportunity. A further consideration is that macrophages influence blood vessel function not only from the luminal surface but also from perivascular sites, such as adipose tissue.\(^5\) As such, one can easily envisage how this new pathway could potentially have major ramifications for control of vascular tone.

The challenge now is to translate this novel finding from human umbilical vein endothelial cells into whole artery studies of vasodilation. This may not be as simple as it sounds. Although commercially available cultured cells are increasingly used in biomedical research, one must remember that there are major differences between cultured cells and their native counterparts. In a study of the transcriptome of both blood and lymphatic endothelial cells, there were profound changes to gene expression between cultured and ex vivo cells that encompassed almost all of the major endothelial functions (adhesion, migration, cytoskeleton, and signaling).\(^6\) Another consideration is that vascular endothelial cells also display a large degree of heterogeneity depending on their anatomical location. This heterogeneity between different in vivo sites is lost after multiple passage cultures.\(^7\) From a functional perspective, vascular endothelial cells behave differently when in contact with the smooth muscle cells compared with their function when studied alone. An example of this is the flow-mediated activation of mammalian target of rapamycin signaling in endothelial cells. Mammalian target of rapamycin is a target for the drug sirolimus, which is used in drug eluting stents to prevent restenosis. However, when endothelial cells are cocultured with vascular smooth muscle cells, flow-mediated activation of mammalian target of rapamycin signaling in the endothelial cell is blunted.\(^8\) Studies such as these are reminders that processes in single cell culture models will not always translate directly into native systems.

It is very clear that a large part of endothelial cell function is attributed to the in vivo architecture and the relation and proximity of endothelial cells to their immediate neighbors. In small arteries, this is best exemplified by the presence of myoendothelial projections. These are tendril-like structures that extend through the internal elastic lamina onto the surface of vascular smooth muscle cells (Figure). Localized calcium release from the endoplasmic reticulum within the myoendothelial projections, known as calcium pulsars, activates...
small and intermediate conductance calcium sensitive potassium channels on the endothelial cell plasma membrane. Subsequent potassium exit from the endothelial cell causes hyperpolarization and vasodilation. Thus, structure determines function.

In summary, the article by Yue et al hints at exciting possibilities to improve endothelial function in patients with diseases common to clinical practice. Much work on native vessels is now needed to validate these findings.

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References
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