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HYPERTENSION

Mechanosensation by PIEZO1 in blood pressure control

The sensing of fluid shear stress and subsequent relaxation of vascular smooth muscle is a regulatory process that controls arterial vasodilation and blood pressure; however, the flow-sensing mechanism that leads to the release of vasoactive mediators such as nitric oxide (NO) is unclear. New research has identified the endothelial mechanosensitive cation channel, PIEZO1, as a key regulator of flow-induced ATP release and subsequent activation of downstream signalling pathways with effects on vascular tone and blood pressure.

To investigate the effect of PIEZO1 on endothelial responses to fluid shear stress *in vitro*, Stefan Offermanns and colleagues first assessed the effect of small interfering RNA-mediated knockdown of PIEZO1 on shear-stress-induced endothelial responses in cultured human umbilical arterial endothelial cells. Knockdown of PIEZO1 inhibited shear-stress-induced increases in intracellular Ca^{2+}, endothelial NOS (eNOS) activity, and ATP release. Administration of a specific activator of PIEZO1, Yoda1, mimicked the effects of fluid shear stress on endothelial cells, increasing intracellular calcium levels, AKT and eNOS phosphorylation, and ATP release. These effects were attenuated by knockdown of PIEZO1 or by blocking G_q/G_{11}-mediated purinergic $P2Y_2$ signalling, suggesting that $P2Y_2$ and G_q/G_{11}, which are known to mediate phosphorylation and activation of AKT and eNOS, are downstream of PIEZO1 in flow-induced endothelial signalling.

To assess the effects of PIEZO1 on vascular tone and blood pressure, the researchers generated inducible endothelium-specific PIEZO1-knockout mice. These mice had arterial hypertension with impaired eNOS activity and demonstrated impaired vasodilation in response to flow or to intravascular administration of Yoda1, supporting a central regulatory role for endothelial PIEZO1-mediated signalling in controlling endothelial NO formation, vascular tone, and arterial blood pressure *in vivo*.

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> “[PIEZO1-knockout] mice had arterial hypertension with impaired eNOS activity”

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