S52-2 Blood flow sensing mechanism via calcium signaling in vascular endothelial cells

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The structure and function of blood vessels adapt to environmental changes, for example, physical development and exercise. This phenomenon is based on the ability of endothelial cells (ECs) to sense and respond to blood flow. ECs are in direct contact with blood flow and exposed to shear stress. A number of recent studies have revealed that ECs recognize changes in shear stress and transmit signals to the interior of the cell, which leads to cell responses that involve changes in cell morphology, cell function, and gene expression. Cultured human pulmonary artery ECs (HPAECs) showed Ca^{2+} influx via an ATP-operated cation channel, P2X4, in response to shear stress. We recently found that shear-induced activation of P2X4 requires endogenously released ATP, and that shear stress induced HPAECs to release ATP, which was mediated by cell-surface ATP synthase located in caveolae. To gain insight into its significance, we generated a *P2X4*-deficient mouse. *P2X4*$^{-/-}$ mice do not exhibit normal EC responses to flow, such as Ca^{2+} influx and subsequent production of NO, a potent vasodilator. Additionally, vessel dilation induced by acute increases in blood flow is markedly suppressed in *P2X4*$^{-/-}$ mice. Furthermore, *P2X4*$^{-/-}$ mice have higher blood pressure than wild-type mice. Moreover, no adaptive vascular remodeling is observed in the *P2X4*$^{-/-}$ mice. Thus, P2X4-mediated shear stress mechanotransduction plays an important role in the vascular homeostasis, including the control of blood pressure and vascular remodeling.