Mechanosensitive Ion Channel Protein Piezo1 in Vascular Biology

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Mechanotransduction of shear-stress has a key role in cardiovascular physiology and pathophysiology. But the mechanisms by which physical forces regulate endothelial cells to determine the complexities of vascular structure and function are enigmatic. Studies of sensory neurons have suggested Piezo proteins as subunits of Ca^{2+}-permeable non-selective cationic channels for detection of noxious mechanical impact. Here we show Piezo1 (Fam38a) channels as sensors of frictional force (shear stress) and determinants of vascular structure in both development and adult physiology. Global or endothelial-specific disruption of mouse *Piezo1* profoundly disturbed the developing vasculature and was embryonic lethal within days of the heart beating. Haploinsufficiency was not lethal but endothelial abnormality was detected in mature vessels. The importance of Piezo1 channels as sensors of blood flow was shown by Piezo1 dependence of shear-stress-evoked ionic current and calcium influx in endothelial cells and the ability of exogenous Piezo1 to confer sensitivity to shear stress on otherwise resistant cells. Downstream of this calcium influx there was protease activation and spatial reorganization of endothelial cells to the polarity of the applied force. Our data suggest that Piezo1 channels function as pivotal integrators in vascular biology.