Piezo1 mechano-sensor in vascular physiology and disease

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In mammals the sensing of blood flow is pivotal for embryonic vascular maturation and adult physiology and disease. How this sensing occurs has been surprisingly difficult to decipher. We have revealed how calcium-permeable non-selective cationic channels formed by Piezo1 proteins assemble to act as sensors of blood flow and determinants of vascular structure in murine development and adult physiology (Li *et al.*, 2014). The developmental role was found to be so strong that constitutive deletion in the endothelium was embryonic lethal. Conditional deletion techniques have been necessary for detailed studies in the adult where we found that endothelial Piezo1 was not essential for life but necessary for determining blood pressure during whole body physical exercise (Rode *et al.*, 2017). We suggested the idea that it behaves as an exercise sensor (Beech & Xiao, 2018). In both embryo and adult studies we found compelling evidence for endothelial Piezo1 channels as direct sensors of force, yet exactly how they enable sensing of this force – and thus blood flow - remains unclear. Intriguingly, Piezo1 channels present a dichotomy for the endothelium in conferring both vasodilator and vasoconstrictor capabilities, the relative importance of which may depend on context (Rode *et al.*, 2017; Evans *et al.*, 2018). Small-molecule activation of Piezo1 channels has been discovered in the form of Yoda1 and our studies have started to show the tight chemical requirements for this pharmacological effect, yet there was sufficient flexibility for us to discovery a competitive antagonist of Yoda1 which we refer to as Dooku1 (Evans *et al.*, 2018). Disease-causing mutations in human PIEZO1 have been linked to Generalized Lymphatic Dysplasia, suggesting importance in human endothelium. Our studies of tissues from patients are also suggesting relevance to human physiology and disease (Morley *et al.*, 2018). While there might be potential for novel therapeutics targeted to Piezo1 channels it will be necessary to take account of the broad roles of Piezo1 in a variety of cell and tissue types (Beech & Xiao, 2018).

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