Mechanobiology in Epithelial 3D Tissue Constructs

ME3T LECTURES

GRK 2415

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PIEZO1 force sensor in cardiovascular health and physical exercise

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Seminarraum B1.72
DWI – Leibniz-Institut für Interaktive Materialien
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Abstract: The two PIEZOs, PIEZO1 and PIEZO2, were first reported in 2010. These proteins form trimeric ion channels with little resemblance to other ion channels. A striking feature is their exquisite, robust and apparently specific sensitivity to activation by a range of mechanical forces. There is widespread agreement that they are bona fide direct sensors of force. We identified the importance in cardiovascular biology, first showing PIEZO1's activation by physiological force and its roles in embryonic vascular maturation and the sensing of fluid shear stress as generated by blood flow. This and subsequent work firmly established PIEZO1's role in endothelial biology and showed its ability to integrate force with vascular architecture. By generating conditional genetic deletion in the adult mouse to avoid embryonic lethality we found that endothelial PIEZO1 is required for elevated blood pressure of whole body physical activity, necessary for capillary density in skeletal muscle and critical in physical exercise performance. Such functions require continuous activity of PIEZO1 and so it was perplexing how this could be possible when over-expression studies reveal powerful intrinsic inactivation gates in PIEZOs. However, we showed that native PIEZO1 channels of endothelial cells are non-inactivating. We discovered the mechanism by which the inactivation gate is disabled, unexpectedly through relationship of PIEZO1 to sphingomyelinase SMPD3 and the membrane lipid ceramide. We went on to show slow gating also in red blood cells (RBCs) with implications for understanding hereditary anaemia. We showed that PIEZO1 is important for mechanical sensitivity of calcium-regulated proteases (calpain and ADAM10), nitric oxide production via NOS3, cell interaction via NOTCH1, inflammation and fibrosis via p38, interleukin-6 and tenascin c and cell apoptosis via thrombospondin-2. Through medicinal chemistry studies of Yoda1 (a small-molecule agonist of PIEZO1) we found a Yoda1 antagonist (Dooku1) and new PIEZO1 agonists including one we named Yoda2 with improved reliability, efficacy, potency and physico-chemical properties. To understand the full-length mouse and human channels, their dynamics and responses to force, we performed molecular dynamics simulations in model endothelial and RBC membranes. These models predict complex structural rearrangements and lipid interactions, some of which are now validated by laboratory techniques. In conclusion: PIEZO1 forms an exceptionally sensitive mechanical detector mechanism that responds rapidly to forces such as shear stress. It is important in endothelium, cardiovascular biology generally and physical exercise responses.