Sensing pressure with ion channels

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Stretch-activated ion channels

Bilayer model
- $K^+$ selective channels
- $Ca^{2+}$ permeable non-selective channels
- Bilayer tension

Tether model
- Tether
- Extracellular matrix
- Tether

Indirect gating
- Mechanosensitive protein
- Cytoskeleton

Which molecules?
- Gating model?
- Physiological role?
- Associated pathologies?
Autosomal dominant polycystic kidney disease

The most frequent monogenic disease 1/1000

Cysts in the kidney from every nephron segment

Responsible for 4-10% of patients on dialysis

Extrarenal manifestations:

Cysts in the liver and pancreas

Hypertension

Valvular defects

Intracranial aneurysms
The polycystin receptor-ion channel complex PC1/PC2
Polycystins and cellular signaling

Cardiovascular expression of polycystins

Pkd1

Arterial blood flow and pressure
What are polycystins doing in arterial smooth muscle cells?

Are they involved in pressure sensing?
Embryonic lethality in *Pkd1* -/- mice

Lethal at E13.3-E14.5


Cardiovascular, skeletal and renal defects
Oedema, localized hemorrhages and increased vascular permeability

Smooth muscle specific knock-out of *Pkd1*
SM22 Cre x *Pkd1* lox/lox
Viable
Pkd1 knock-out decreases SAC activity
Increase in intraluminal pressure

VSMC membrane stretch

SACs opening

Cell depolarization

Opening of CaV

Calcium influx

Contraction
Isobaric arteriography
*Pkd1* knock-out impairs the myogenic tone.
PC2 overexpression inhibits SAC activity
Rescue of *Pkd1* deficient myocytes by knocking down *Pkd2*
The actin binding protein Filamin-A interacts with PC2

Filamin A cross-links actin filaments: gelation and mechanoprotection
Filamin A requirement for SAC inhibition by PC2

![Bar graph showing the comparison of SAC inhibition between Filamin A +/- and Mock/PC2 conditions. The x-axis represents the genotypes (Filamin A +/-, M2 cells), and the y-axis represents the current (I) in pA. The graph indicates a significant difference (*** for Filamin A +/-, NS for M2 cells).]
The actin binding protein Filamin-A: an integrator of cell mechanics and signalling

FLNA loss-of-function mutations cause periventricular heterotopia (PH) with abnormally migrated neurons present near the lateral ventricle.

PH is an X-chromosome-linked, male lethal disease in which affected females have seizures.

PH patients display patent ductus arteriosus, mitral valve prolapse and arterial fragility with a propensity for premature stroke.

Similar cardiovascular phenotype in PH and ADPKD patients.

In the mouse, FLNA knock out is embryonic lethal with severe cardiac structural defects and widespread vascular patterning.

Similar cardiovascular phenotype in Pkd1, Pkd2 and FLNA knock out mice.
Polycystins: mechanotransduction and calcium homeostasis

flow → primary cilium

PC2

PC1

Ca²⁺

renal epithelial cells
endothelial cells

Polycystin-1 and -2 dosage regulates pressure sensing

PC₁/PC₂

SACs

stretch

FLNA

F actin

Piezo1 and Piezo2 are essential components of distinct mechanically activated cation channels

24 to 36 predicted transmembrane domains

mock COS-7 transfected cells

Coste et al., 2010 Science, 330, 55-60
Conclusions

- The polycystin-1 and -2 dosage tunes arterial pressure sensing
- PC-2 is a negative regulator of SACs
- PC-2 inhibits SACs through the actin cytoskeleton
- Filamin-A links PC2 to the actin cytoskeleton and is required for SACs inhibition
- Piezo1 is a candidate for the arterial SAC