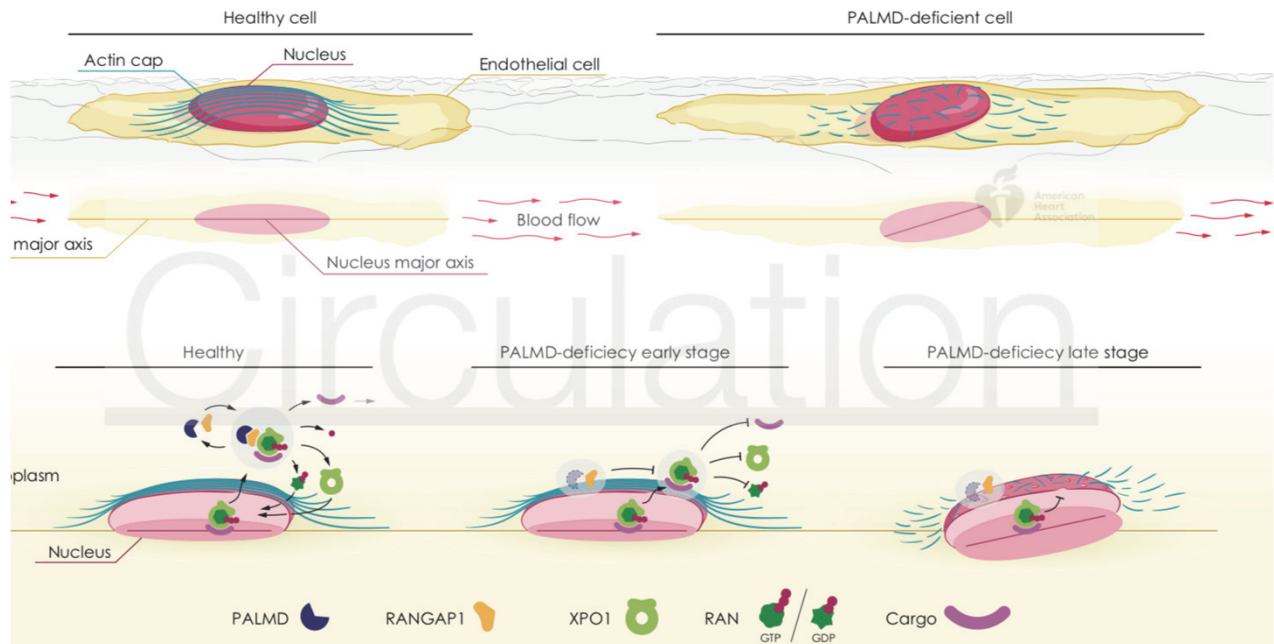


### Palmdelphin Regulates Nuclear Resilience to Mechanical Stress in the Endothelium.

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#### Key findings:

1. Palmdelphin (PALMD) mediates the development and progression of calcific aortic valve stenosis (CAVS).
2. The regulatory role of PALMD is on display in siRNA-treated EC cultures, in genetically mutated mice, and samples stemming from human aortic valve tissue specimens.
3. RAN GTPase activating protein1 (RANGAP1) is identified as a direct interaction partner of PALMD in ECs. Targeting of this PALMD/RANGAP1 axis changes RANGAP1's (and XPO1's) subcellular localization, which in consequence results in failure of nuclear actin cap formation and flow regulated axis alignment. This triggers nuclear arrest of p53 and p21, which augments actin-dependent resilience in the nucleus.
4. Overall PALMD reduction is identified as a novel key mediator in the calcification and loss of function in aortic valve disease.
5. The finding is of clinical relevance, as PALMD is prominently expressed in ECs of aortic valves, while the identification of the PALMD SNP rs7543130 can be linked with endothelial dysfunction and CAVS. Here, the study provides strong evidence that endothelial dysfunction is of crucial importance at the onset of CAVS.