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Piezo1-Mediated Ca^{2+} Activities Regulate Brain Vascular Pathfinding during Development

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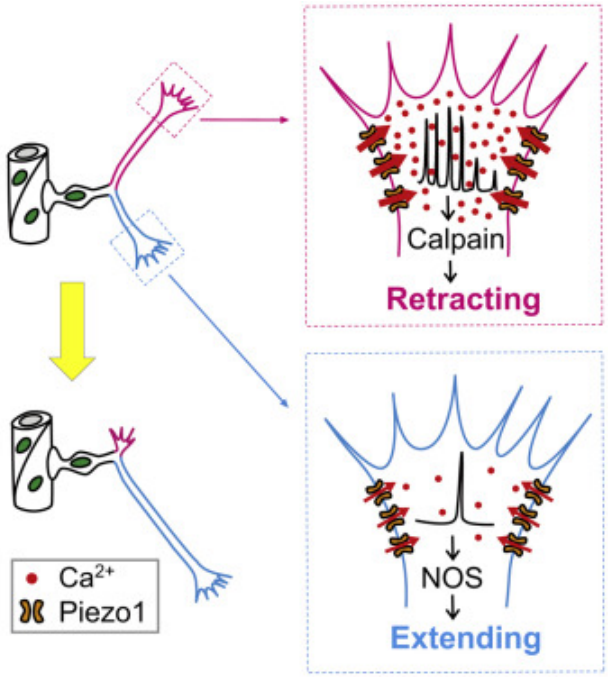
Highlights

- Brain endothelial tip cells (ETCs) show local Ca^{2+} transients at primary branches
- High- and low-frequency Ca^{2+} transients distinctly regulate ETC branch dynamics
- Mechanosensitive Piezo1 channels mediate local Ca^{2+} transients of ETC branches

Summary

During development, endothelial tip cells (ETCs) located at the leading edge of growing vascular plexus guide angiogenic sprouts to target vessels, and thus, ETC pathfinding is fundamental for vascular pattern formation in organs, including the brain. However, mechanisms of ETC pathfinding remain largely unknown. Here, we report that Piezo1-mediated Ca^{2+} activities at primary branches of ETCs regulate branch dynamics to accomplish ETC pathfinding during zebrafish brain vascular development. ETC branches display spontaneous local Ca^{2+} transients, and high- and low-frequency Ca^{2+} transients cause branch retraction through calpain and branch extension through nitric oxide synthase, respectively. These Ca^{2+} transients are mainly mediated by Ca^{2+}-permeable Piezo1 channels, which can be activated by mechanical force, and mutating *piezo1* largely impairs ETC pathfinding and brain vascular patterning. These findings reveal that Piezo1 and downstream Ca^{2+} signaling act as molecular bases for ETC pathfinding and highlight a novel function of Piezo1 and Ca^{2+} in vascular development.

Graphical Abstract



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Piezo1 • Ca2+ activity • brain vessel • endothelial tip cell • pathfinding • zebrafish • nitric oxide synthase • calpain • mechanical force • vascular development