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Perivascular Retinal Neurons Direct 3D Vascular Lattice Formation

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The vasculature of the central nervous system is a 3D lattice composed of laminar vascular beds interconnected by penetrating vessels. The mechanisms controlling 3D lattice network formation remain largely unknown. Combining viral labeling, genetic marking, and single-cell profiling in the mouse retina, we discovered a perivascular neuronal subset, annotated as Fam19a4/Nts-positive retinal ganglion cells (Fam19a4/Nts-RGCs), directly contacting the vasculature with perisomatic endfeet. Developmental ablation of Fam19a4/Nts-RGCs led to disoriented growth of penetrating vessels near the ganglion cell layer (GCL), leading to a disorganized 3D vascular lattice. We identified enriched PIEZO2 expression in Fam19a4/Nts-RGCs. Piezo2 loss from all retinal neurons or Fam19a4/Nts-RGCs abolished the direct neurovascular contacts and phenocopied the Fam19a4/Nts-RGC ablation deficits. The defective vascular structure led to reduced capillary perfusion and sensitized the retina to ischemic insults. Furthermore, we uncovered a Piezo2-dependent perivascular granule cell subset for cerebellar vascular patterning, indicating neuronal Piezo2-dependent 3D vascular patterning in the brain.