

BDR SEMINAR (Kobe & online hybrid)

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Tuesday, March 31, 2026

14:00-15:00

1F Auditorium, DB Building C, Kobe / Broadcast online via Zoom
Zoom meeting URL will be announced on the event day by e-mail.

※This seminar is open only to BDR members.

Zebrafish Dissect Vascular Disease

Summary

Rasa1 negatively regulates Ras signaling, and its mutation in humans causes pre- and postnatal vascular malformations (VMs) affecting both blood and lymphatic vessels. However, the embryonic origin and progression of these defects remain poorly understood. To define the earliest pathogenic events in lymphatic system, we generated *rasa1a*-deficient zebrafish using CRISPR, including a frameshift mutation and a floxed allele for cell-specific knockout. On a *rasa1b* mutant background, *rasa1* double-knockout embryos developed lymphedema with valve defect and arrested circulation by 4 days post-fertilization (dpf). Strikingly, loss of *rasa1* caused precocious trunk lymphatic vessel formation at 3 dpf in an endothelial cell-autonomous manner. Pharmacological inhibition of Vegfr3/Flt4 or MEK/ERK signaling rescued this phenotype. Using a mosaic knockout strategy, we found that *rasa1*-deficient endothelial cells in the posterior cardinal vein preferentially contributed to lymphatic vessels. Single-cell RNA sequencing revealed transcriptional changes largely confined to venous endothelial cells, including increased ER stress, RhoA upregulation, and ectopic expression of the lymphatic determinant *prox1a*. RhoA inhibition prevented excessive lymphatic growth. Time-lapse imaging demonstrated that wild-type lymphovenous progenitors generate asymmetric daughter fates (venous and lymphatic endothelial cells), whereas *rasa1*-deficient progenitors consistently produced two lymphatic endothelial cells, explaining the expansion of lymphatic endothelium. Together, these findings identify *rasa1* as a key regulator of early lymphovenous fate decisions and signaling thresholds that restrict lymphatic vessel growth, providing mechanistic insight into vascular malformation pathogenesis. Ongoing studies are investigating VMs in the brain vasculature to assess the presence of arteriovenous malformations.