Artery/Vein Plasticity After Vessel Injury

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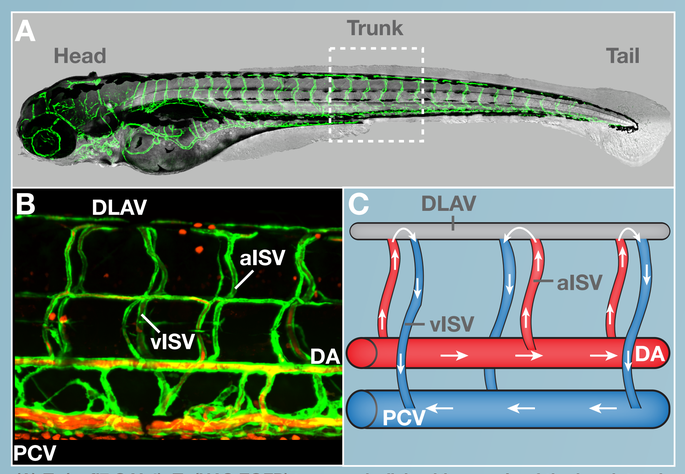
Introduction

- Blood circulation must be carefully balanced between arteries and veins.
- Disruption to balanced flow can lead to severe consequences such as reduced blood flow (ischemia) or rupture of the vessel wall (hemorrhage).
- Zebrafish are an ideal model organism to study vascular damage and re-patterning: optically clear, genetically and experimentally accessible, conserved vascular anatomy.

Zebrafish Vascular Anatomy



(A) *Tg(egfl7:GAL4)*, *Tg(UAS:EGFP)* transgenic fish with vessels of the head, trunk, and tail in green. (B) A close up of the trunk area in (*Tg(kdrl:EGFP), Tg(gata:dsRed)*) transgenic zebrafish shows the major vessels within that region including the dorsal longitudinal anastomotic vessel (DLAV), dorsal aorta (DA), intersegmental arteries (aISV) and veins (vISV), and the posterior cardinal vein (PCV). Blood vessels are green and blood cells are red. (C) Schematic of the major trunk vessels shows the direction of blood flow through each vessel with anterior to the left and posterior to the right.

ISV Assembly During Development

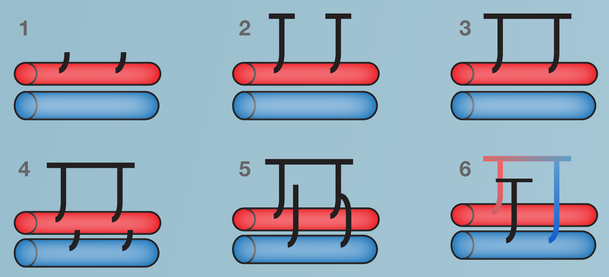
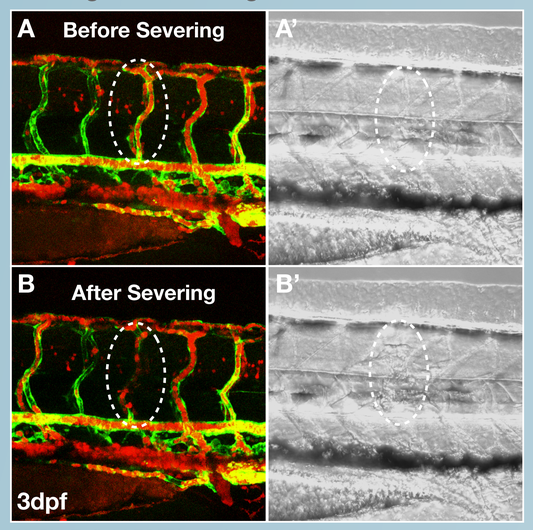


Image adapted from Isogai *et al*, Development 2003.

1) Primary sprouts emerge from the DA
2) Sprouts grow dorsally and branch caudally and rostrally
3) Branches connect to form the DLAV
4) Secondary sprouts emerge from the PCV
5) Some secondary sprouts connect to primary sprouts and others do not,
6) Primary sprouts connected to secondary sprout segments became vISVs (blue) and those still connected to the DA remain aISVs (red).

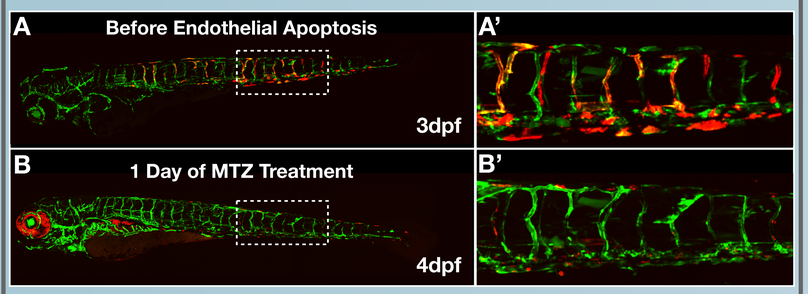
Vascular injury can be induced *in vivo* through different means

1. Vessel Severing: Multi-photon laser ablation can be used to sever blood vessels. Targeting individual endothelial cells ensures minimal surrounding tissue damage.



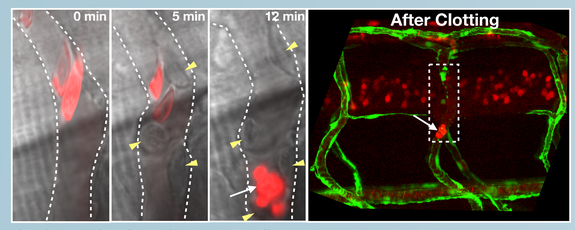
(A-B) *Tg(kdrl:EGFP), Tg(gata:dsRed)* transgenic fish with blood vessels in green and blood cells in red. Dotted oval shows area before injury (A-A') and after injury (B-B'). Fluorescent and DIC images are shown.

2. Endothelial Apoptosis: Treatment with metronidazole (MTZ) in fish mosaically expressing nitroreductase (NTR) in endothelial cells triggers apoptosis in those vessels.



(A-B) *Tg(egfl7:GAL4), Tg(UAS:EGFP)* transgenic fish whose blood vessels are fluorescently labeled in green express a *Tol2(UAS:epNTR-TagRFP)* construct in red.

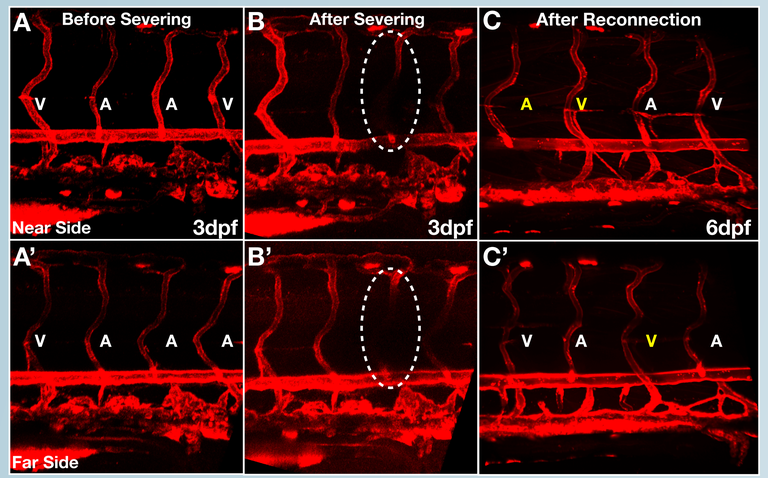
3. Vessel Clotting: Exposure to a 561nm light after injection of the photosensitizer Rose Bengal into the blood stream can cause clotting.



(*Tg(kdrl:eGFP), Tg(gata:dsRed)*) transgenic zebrafish are depicted. Yellow arrowheads show damaged cells collapsing into the ISV. White arrow shows initiation of blood clot.

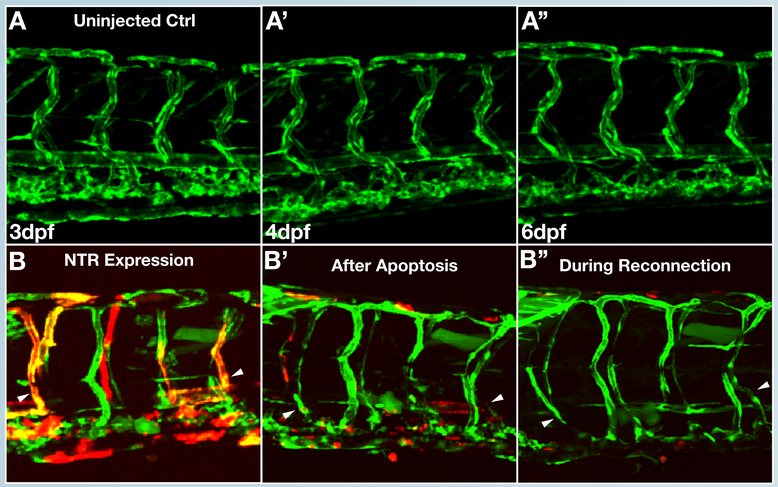
Vessel patterning can change after vessel injury

Severed vessels reconnect after injury but vessel patterning of ablated vessels and their neighbors can be altered.



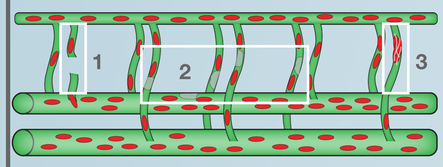
(A-C) *kdrl:mCherry-Caax* transgenic fish have vessels shown in red. Dotted oval shows severed vessels. V and A labels depict veins or arteries respectively. Yellow labels indicate vessels that have switched identity after injury.

Endothelial apoptosis drives new vessel formation but can lead to changes in vein and artery ISV patterning.



Tg(egfl7:GAL4), Tg(UAS:EGFP) transgenic fish exposed to MTZ either without NTR (A-A") or with NTR (B-B"). Vessels that were once arterial are seen regrowing from the PCV to become veins (white arrowheads) (B"). Without injury ISVs maintain they venous and arterial identity. Vessels are shown in green and NTR expressing cells are shown in red.

Conclusions and Future Directions



- Vascular injury can be induced by (1) vessel severing, (2) endothelial apoptosis, or (3) vessel clotting .
- Vessel regrowth can lead to changes in arterial/venous patterning.
- Future studies will determine if developmental processes are utilized to regrow and re-pattern ISVs after injury.

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