Investigating endothelial cell behavior during vascular regeneration at single-cell resolution in zebrafish

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Abstract:

Endothelial damage is directly associated with various cardiovascular diseases, including stroke and ischemic heart disease, the two leading causes of death globally. Previous studies showed that vascular regeneration involves a subset of regenerating endothelial cells (ECs) with distinct proliferative ability and molecular signature. However, the specific molecular mechanisms driving vascular regeneration remain elusive.

Here, we establish and characterize a zebrafish vascular regeneration model by utilizing nitroreductase-mediated EC ablation at embryonic and larval stages. By following the regenerating ECs during regeneration using state-of-the-art high-resolution time-lapse imaging, we observed that certain ECs are more proliferative, sprout better, and reconnect with the neighboring ECs. These data suggest a heterogeneous response to tissue damage by some EC subpopulations, which possess a higher capacity of repopulating the vasculature. To delineate this heterogeneity, we performed single-cell RNA-sequencing after EC ablation and recovered 6051 cells with 8 major cell types from the larval caudal region. We further analyzed 1929 ECs and found two sub-clusters displaying a higher proliferative capacity. One of these proliferative EC sub-clusters expresses genes involved in Notch signaling, leading us to hypothesize that it is involved in vascular repair. We now aim to unravel the molecular and cellular features of these proliferative EC sub-clusters by performing cell-specific manipulations *in vivo*. Overall, our findings can help us gain a better understanding of the gene programs critical for vascular repair and regeneration, which may have therapeutic implications.