AB042. Pericytes on microvessels lead to vascular dysfunction during retinal ischemia

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Background: Pericytes are contractile cells that wrap along the walls of capillaries. In the brain, pericytes play a crucial role in the regulation of capillary diameter and vascular blood flow in response to metabolic demand. During ischemia, it has been suggested that pericytes may constrict capillaries, and that pericytes remain constricted after reperfusion thus resulting in impaired blood flow.

Methods: Here, we used a mouse model of retinal ischemia based on ligation of the central retinal artery to characterize the role of pericytes on capillary constriction. Ischemia was induced in transgenic mice carrying the NG2 promoter driving red fluorescent protein expression to selectively visualize pericytes (line NG2:DsRed).Changes in retinal capillary diameter at 1 hr after ischemia were measured *ex vivo* in whole-mounted retinas from ischemic and control eyes (n=4–6/group) using a stereological approach. Vessels and pericytes were three-dimensionally reconstructed using IMARIS (Bitplane). Furthermore, we used a novel and minimally invasive two-photon microscopy approach that allowed live imaging of microvasculature changes in the retina.

Results: Our data show a generalized reduction in capillary diameter in ischemic retinas relative to sham-operated controls in all vascular plexus (ischemia: 4.7±0.2 µm, control: 5.2±0.2 µm, student's *t*-test, P<0.001). Analysis of the number of capillary constrictions at pericyte locations, visualized in NG2:DsRed mice, demonstrated a substantial increase in ischemic retinas relative to the physiological capillary diameter reductions observed in controls (ischemia: 1,038±277 constrictions at pericyte locations, control: 60±36 constrictions at pericyte locations, student's *t*-test, P<0.01). Live imaging using two-photon microscopy confirmed robust capillary constriction at the level of pericytes on retinal capillaries during ischemia (n=6–8/group).

Conclusions: Collectively, our data demonstrate that ischemia promotes rapid pericyte constriction on retinal capillaries causing major microvascular dysfunction in this tissue. To identify the molecular mechanisms underlying the pathological response of pericytes during ischemia, we are currently carrying out experiments in mice and zebrafish to modulate signaling pathways involved in calcium dynamics leading to contractility in these cells.

Keywords: Ischemia; pericyte; blood flow regulation; *in vivo* two-photon microscopy

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