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Microglia Associate with the Vasculature and Pericytes in the Healthy and Inflamed Brain

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Microglia contribute to homeostatic brain functions including structural plasticity, synaptic plasticity, neurite formation, myelination and vasculogenesis. They are also the resident immune cells of the brain. A proportion of microglia have been found to reside near capillaries (capillary-associated microglia (CAM) and may play a role in blood vessel flow indirectly through pericytes. Pericytes are contractile cells located on capillaries that maintain brain health through the regulation of both cerebral blood flow (CBF) and the blood-brain barrier (BBB). We hypothesised that in the healthy brain, microglia and pericytes often associate with each other, which may mediate specific vascular functions, and that this association may be altered during an inflammatory event. We implanted cranial windows in 3-month-old NG2-DsRed x CX3CR1-GFP mice (n=6), which enables the visualisation of DsRed positive pericytes and GFP positive microglia. We used *in vivo* two-photon microscopy, in conjunction with isoflurane anaesthetic, to visualise pericytes, the vasculature and microglia over 28 days in the healthy brain (Figure 1). We classified microglia residing adjacent to capillaries as CAM (Figure 1Bi) and microglia residing adjacent to pericytes as pericyte-associated-microglia (PEM; Figure Bii). The labelling of the vasculature with FITC-dextran, administered via the tail vein prior to imaging, enabled mapping of the vascular tree and allowed capillary diameter to be assessed. Mapping of the vascular tree highlighted that pericytes, CAM and PEM were found at all levels of the capillary tree and were not preferentially located on a specific capillary order. Capillary vessel width was found to be increased beneath CAM, and pericytes with or without an associated PEM. Of 32 PEMs identified at day 0, only 45% remained at day 28, but the total number of PEMs at each timepoint did not significantly change, suggesting that these PEM-pericyte interactions are dynamic. 24 hours following the administration of the immune stimulant lipopolysaccharide (LPS, 3mg/kg), via intraperitoneal injection, reactive microglia were observed clustering around the vasculature, with the number of PEM significantly increased. These findings suggest that microglia associate with pericytes to maintain normal physiological processes and that during inflammation microglia migrate to pericytes, potentially to change CBF and BBB permeability. Therefore, the association between microglia and pericytes may regulate brain vasculature function and maintenance in health and disease.

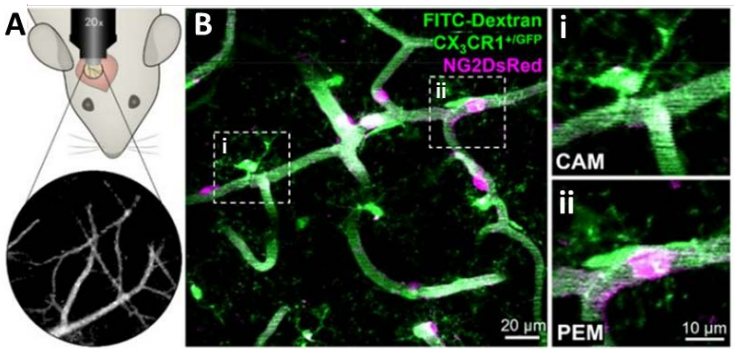

Figure 1 - Microglia directly associate with capillaries and pericytes. (A) Schematic of cranial window location in NG2DsRed x CX3CR1+/GFP mice with blood vessels used as landmarks. (B) Representative 30µm thick projection image of NG2-DsRed positive pericytes (magenta), CX3CR1-GFP positive microglia (green) and FITC-dextran positive vessel lumen (green) in layers II/III of the somatosensory cortex of adult NG2-DsRed x CX3CR1-GFP mice imaged using *in vivo* two-photon microscopy. Dashed boxes highlighting a (i) CAM and (ii) PEM are magnified in panels to the right