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The role of pericytes in the regulation of brain blood flow and their dysfunction in dementia

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The brain is an energy-intensive organ requiring a constant supply of nutrients to remain functional. The neurovascular unit (NVU), a grouping of cells that maintains cerebrovascular function, regulates this energy supply through a complex intercellular signalling network. At the heart of the NVU are cells called pericytes, which reside along the extensive network of capillaries throughout the brain. Pericytes have many functions including driving angiogenesis, providing vascular maintenance and stability, regulating the trafficking of immune cells into the brain, and maintaining the blood-brain barrier (BBB)[1]. Pericytes have processes that enwrap capillaries, allowing them to modulate capillary blood flow, by constricting or dilating the underlying vessel in response to cues from the surrounding environment. Human brain pericytes express a number of proteins involved in cell contractility, such as alpha-smooth muscle actin. Furthermore, our *in vitro* experiments have illustrated that pericytes can contract or relax in response to a number of vasoactive mediators. Using *in vivo* two-photon microscopy (under isoflurane inhalation anaesthesia, 5% induction 2% maintenance carried in oxygen) through cranial windows in transgenic mice with fluorescent pericytes (*NG2-DsRed*), we have revealed that under basal conditions capillary width is increased at pericyte soma. This suggests that pericytes can actively relax blood vessels to maintain flow.

A growing body of literature implicates pericytes in the pathogenesis of various neurodegenerative diseases. For example, it has been reported in Alzheimer's disease (AD) that extensive pericyte loss may contribute to degenerating brain health[2]. In our work, we observed an increase in pericyte number in the superior frontal gyrus of human post-mortem AD cases, suggesting that pericyte loss may not be a pathological feature of human AD. Using a mouse model of amyloidosis (*APP/PS1*), we also observed an increase in pericyte and vessel density at 3 months of age, prior to the formation of amyloid plaques, above that observed in age-matched wild type mice. In subsequent *in vitro* experiments, we have found that monomeric amyloid can stimulate pericyte proliferation, while fibrillar amyloid causes pericyte death. Since pericytes can phagocytose amyloid, the proliferation of pericytes may represent an effort by pericytes to take up and clear amyloid, to prevent amyloid aggregation. Microglia are also capable of phagocytosing amyloid, and we have found that there is a reduced number of microglia adjacent to both pericytes and the vasculature in the human AD brain. Given that microglia are also important for vascular function, this loss of pericyte-associated microglia could contribute to vascular dysfunction and pathogenesis. Our findings suggest that pericytes may play distinct roles throughout the progression of AD and may represent an attractive target to maintain vascular function, prevent the accumulation of amyloid and subsequent neurodegeneration in AD.

1. Brown LS, Foster CG, Courtney JM, King NE, Howells DW, Sutherland BA. (2019) Pericytes and Neurovascular Function in the Healthy and Diseased Brain. *Front Cell Neurosci.* **13:**282.
2. Sengillo JD, Winkler EA, Walker CT, Sullivan JS, Johnson M, Zlokovic BV. (2013) Deficiency in mural vascular cells coincides with blood-brain barrier disruption in Alzheimer's disease. *Brain Pathol.* **23:**303-10.