Abstract: 630

Ablation of pericytes impedes motor function, induces blood-brain barrier leakage, and stimulates glial cell activation.

Jake M. Cashion[1], Lachlan S. Brown[1], Gary P. Morris[1], Jo-Maree Courtney[1], Loic Auderset[2], Kalina Makowiecki[2], Carlie L. Cullen[2], Kaylene M. Young[2], Brad A. Sutherland[1]

[1]Tasmanian School of Medicine, College of Health and Medicine, University of Tasmania, Hobart, Australia [2]Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia

The brain has an exceedingly high energy demand but low energy storage capacity, and so it requires a constant blood supply to meet its energy needs. It is at capillaries where oxygen, nutrient and waste exchange occurs between the circulating blood and the brain parenchyma. Therefore, capillary blood flow regulation is critical to support brain function. Pericytes are contractile cells that envelop capillaries, allowing them to actively modulate capillary diameter to regulate blood flow. Pericytes are also important for the formation of new blood vessels, maintaining the blood-brain barrier and regulating neuroinflammation. Pericyte dysfunction and loss has been observed in neurodegenerative diseases such as stroke, Alzheimer's disease, and multiple sclerosis, suggesting they may play an important role in disease progression. Despite these observations, pericytes remain poorly understood.

Here, we developed a genetically-induced model of pericyte ablation by delivering tamoxifen by oral gavage to *PDGFRβ-CreER^{T2} :: Rosa26-DTA* transgenic mice (Figure 1). Seven days later, these mice have impaired motor function, as shown by bean walk and open field tests. Histological analyses confirmed significant pericyte loss from the brain and increased blood-brain barrier permeability, however, the vascular endothelium and basement membrane integrity remained largely intact. Larger vessels and their vascular smooth muscle cells also remained unaltered. Pericyte loss was accompanied by extensive glial cell activation with large microglia clusters forming around capillaries as well as increased astrocytic activation. These data provide evidence that *PDGFRβ-CreER^{T2} :: Rosa26-DTA* mice are an effective model of inducible pericyte depletion in the brain. Our results highlight the importance of pericytes for brain health and identifies mechanisms by which pericyte loss contributes to neurological disease pathophysiology.

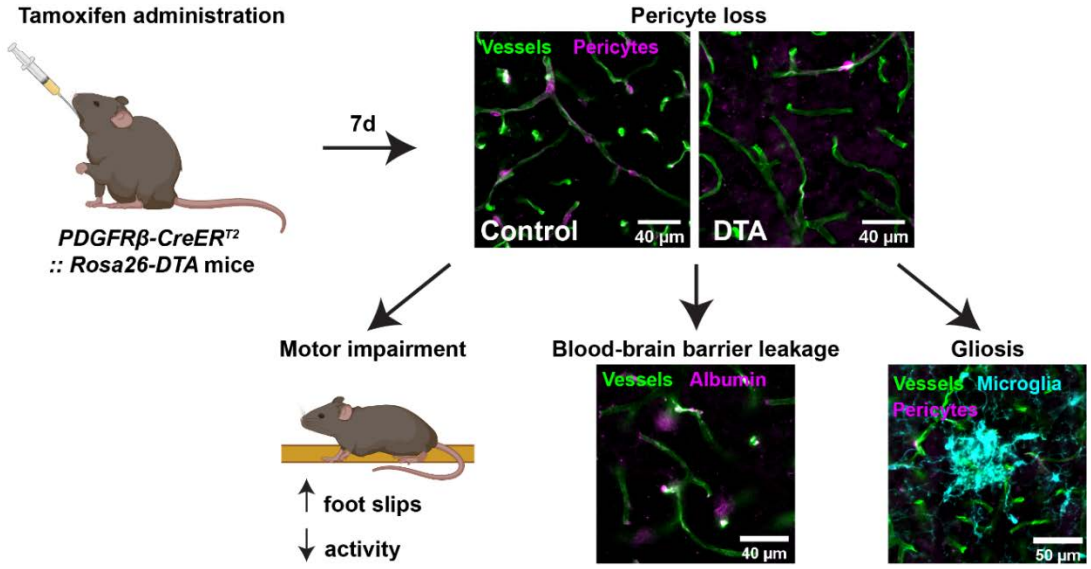

Figure 1. Tamoxifen administration via oral gavage to *PDGFRβ-CreER^{T2} :: Rosa26-DTA* mice induces pericyte loss, impaired motor function, blood-brain barrier leakage and glial cell activation. DTA = diphtheria toxin fragment A.