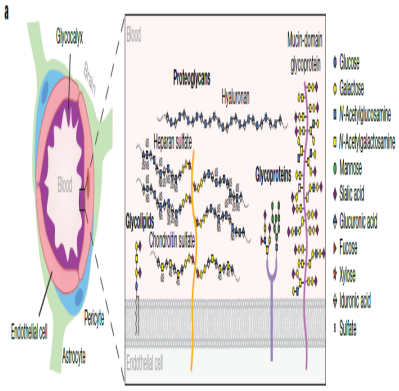

Glycocalyx dysregulation impairs bloodâ??brain barrier in ageing and disease

Description

The bloodâ??brain barrier (BBB) is highly specialized to protect the brain from harmful circulating factors in the blood and maintain brain homeostasis. The brain endothelial glycocalyx layer, a carbohydrate-rich meshwork composed primarily of proteoglycans, glycoproteins and glycolipids that coats the BBB lumen, is a key structural component of the BBB. This layer forms the first interface between the blood and brain vasculature, yet little is known about its composition and roles in supporting BBB function in homeostatic and diseased states. The authors find that the brain endothelial glycocalyx is highly dysregulated during ageing and neurodegenerative disease. They identify significant perturbation in an underexplored class of densely O-glycosylated proteins known as mucin-domain glycoproteins. The authors demonstrate that ageing- and disease-associated aberrations in brain endothelial mucin-domain glycoproteins lead to dysregulated BBB function and, in severe cases, brain haemorrhaging in mice. The results suggest that BBB function can be improved, neuroinflammation reduced, and cognitive deficits reduced in aged mice by restoring core 1 mucin type O glycans to the brain endothelium using adeno-associated viruses. Cumulatively, these findings provide a detailed compositional and structural mapping of the ageing brain endothelial glycocalyx layer and reveal important consequences of ageing- and disease-associated glycocalyx dysregulation on BBB integrity and brain health.

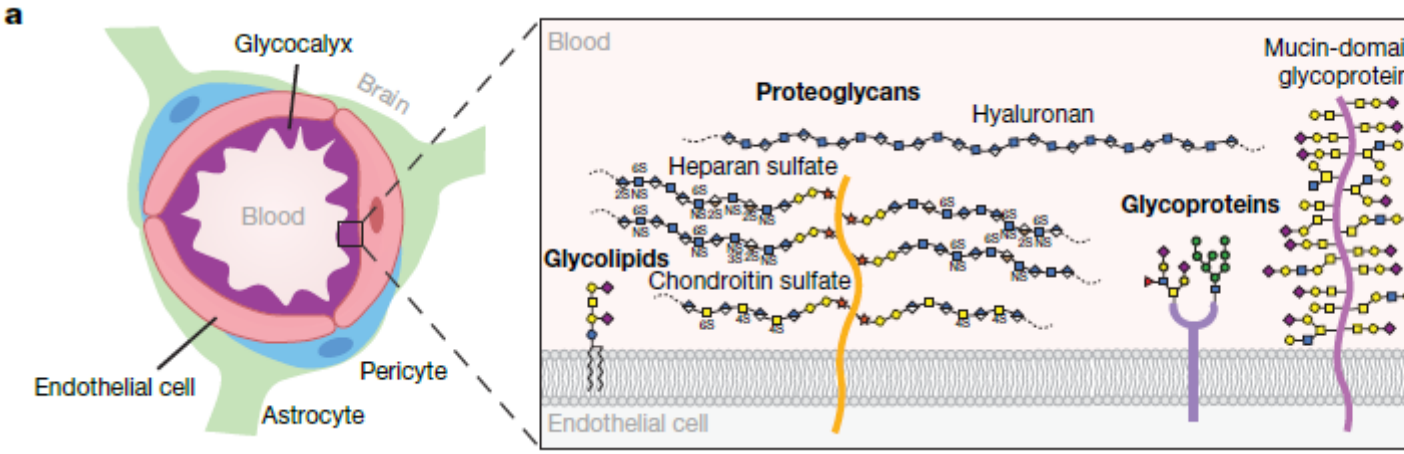

Diagram of the bloodâ??brain barrier and brain endothelial glycocalyx layer

Category

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