Impairment of glymphatic pathway function in the aging brain

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The ‘Glymphatic’ Pathway

Paravascular CSF-ISF exchange is a feature of the sleeping brain

Para-arterial CSF influx driven by arterial pulsatility

Key role of astrocytes
• Perivascular AQP4
• Regulation of extracellular volume

Is glymphatic pathway function compromised in the aging brain?

Strittmatter J Clin Invest 2013
Paravascular influx is impaired in the aging brain

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Paravascular influx is impaired in the aging brain
Interstitial solute clearance is impaired in the aging brain

What is the mechanism for impaired para-vascular clearance in the aging brain?
Astrocytes are positioned as gatekeepers to the paravascular spaces.
Aquaporin-4
A perivascular astrocytic water channel
Aqp4 gene deletion reduces CSF influx into the brain parenchyma

CSF Tracers
Ovalbumin-ALEXA647 (45kD)

Intracisternal Injection
(Subarachnoid Space)

Wild Type
AQP4KO

Ex Vivo Imaging
OA-647
DAPI

t = 30min

Loss of perivascular AQP4 polarization in the aging mouse brain
AQP4 polarization is lost in the aging human cortex
Regional patterns of AQP4 localization in the aging human brain.
AQP4 is mis-localized in the aging human brain and in patients with AD. However, patterns of localization are more complex than in rodents.
Paravascular clearance of interstitial solutes
- A feature of the sleeping (and anesthetized) brain
- Key participant in amyloid β clearance
- Driven by arterial pulsation
- Astrocytes are key facilitators (AQP4 and cell volume)

AQP4 localization and glymphatic pathway function are impaired in pathophysiological states
- Aging (slowed amyloid β clearance)
- Traumatic brain injury (slowed tau clearance)
- Diffuse ischemic injury

It seems likely that this contributes to onset and development of pathology in several neurodegenerative states (AD, CTE, others).
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