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IMMUNITY

CSF: a key player in brain's immunity

Pulous, F.E., Cruz-Hernández, J.C. et al. *Nat. Neurosci.* **25**, 567–576 (2022)

Cerebrospinal fluid (CSF) is a plasma-like fluid surrounding the central nervous system (CNS) that contributes to waste removal and provides nutrients and a protective environment to the brain. CSF is produced by the choroid plexus, circulates through the ventricles and the subarachnoid space ultimately to be absorbed into venous blood and lymphatics. A new study reports that the CSF can also exit through skull channels into the skull bone marrow, a new route that might contribute to immune surveillance.

The CNS is separated from the body's immune system by the blood-brain barrier (BBB), which, under steady state, limits the crosstalk between the CNS local immune cells and the peripheral leukocytes. However, previous work showed that under pathological conditions, immune cells can bypass the BBB to reach the brain. "Our lab discovered a network of channels that connect the skull bone marrow to the outer layers of membranes that cover the brain, called meninges. During neuroinflammation, skull marrow releases immune cells that migrate through these channels to reach the brain", explains Fadi Pulous, the first author of the study.

However, how the brain communicates with the skull to induce an immune response remained unanswered. Speculating that perhaps CSF could flow through these channels to turn on the immune response in the skull, Pulous and colleagues tracked CSF flow in the mouse brain by injecting fluorescent tracers in cisterna magna and performed ex vivo and in vivo imaging. The investigators found that CSF can travel along the perivascular spaces of dural blood vessels and transit into marrow cavities via skull channels. Using additional fluorescent labelling and skull-specific bone marrow transplantation experiments, the team also showed that in mice with bacterial meningitis, bacteria can use this CSF outflow to enter the marrow and incite the release of immune cells as a response to inflammation and induce cranial emergency hematopoiesis. "We found that bacterial meningitis can be sensed by stem cells that are in the skull marrow to instigate this immune cascade", comments Pulous.

Given that CSF outflow to the skull might contribute to immunity surveillance, these findings may extend to other inflammation-related brain disorders, including dementia and Alzheimer's disease. "Understanding what types of "messages" immune cells in the skull marrow are reading from the brain may allow us, one day, to modulate the immune system to improve brain function in these diseases", concludes Pulous.

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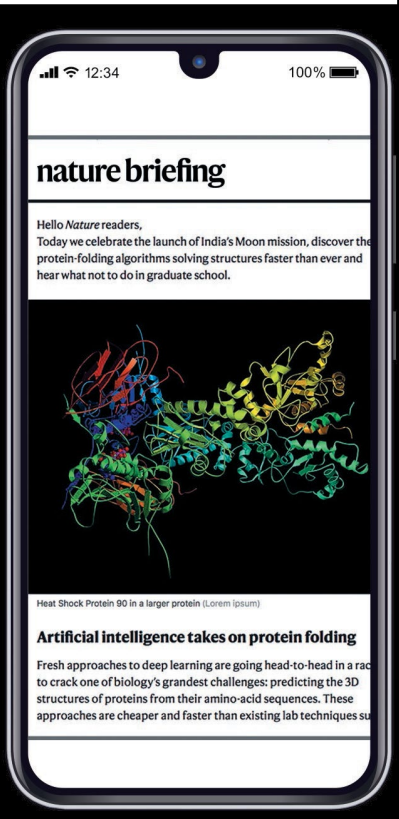

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