Lymph and lymphatic vessels

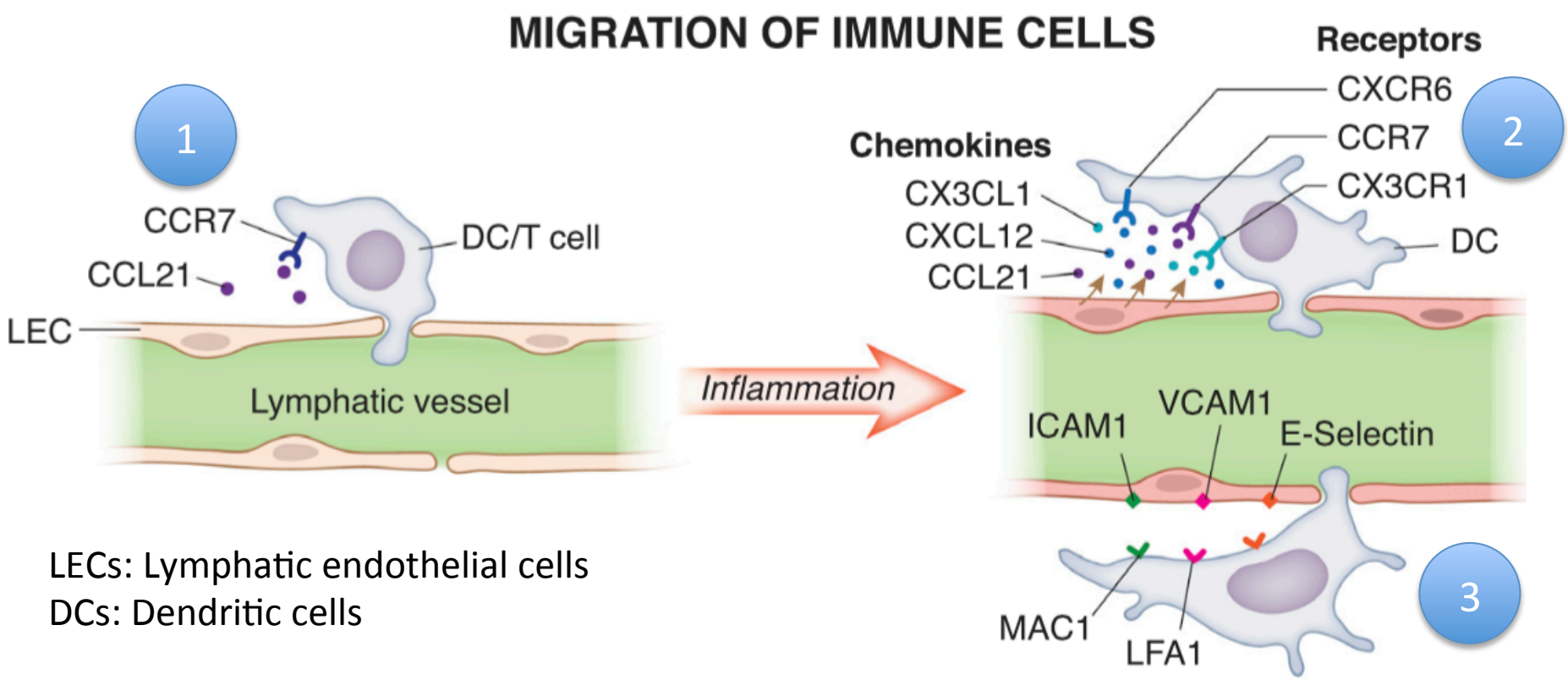
- **Lymph**: the extracellular fluid produced continuously by filtration from the blood

- **Three types of lymphatic vessels (**or **lymphatics)**
  1. Initial lymphatics (or lymphatics capillaries)
  2. Collecting vessels (afferent and efferent): Transport lymph through lymph nodes
  3. Ducts (thoracic ducts and right lymphatic duct): Return lymph to blood circulation

The roles of lymphatic system

- Major role in maintaining interstitial fluid (ISF) balance
- Prime player in regulating immune responses and immune surveillance of tissues

Modulation of immune cell migration and function by LECs

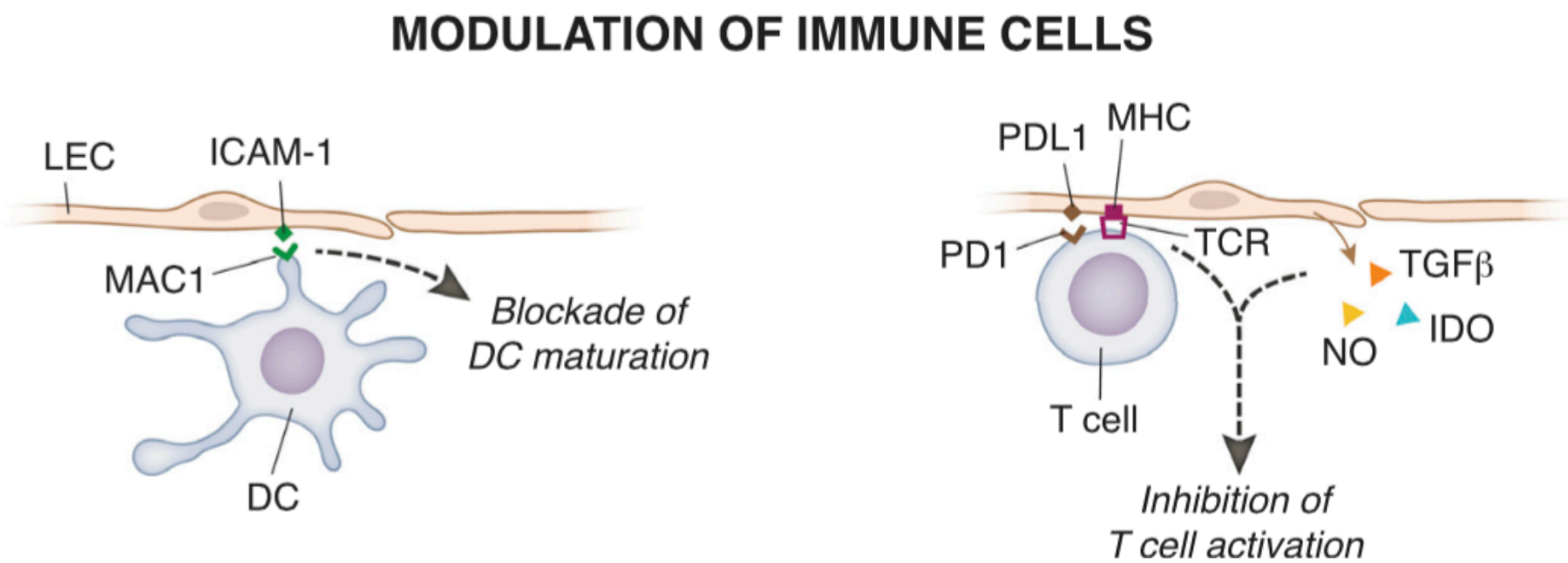


LECs: Lymphatic endothelial cells
DCs: Dendritic cells

1. Promote the entry of DCs and T cells into the lymphatic vasculature
2. Upon an inflammatory stimulus, facilitate their migration through the lymphatic vasculature
3. Promote adhesion and entry of the immune cells into the lymphatic vasculature

Louveau *et al*. (2016) Neuron 91: 957-73

Modulation of immune cell migration and function by LECs

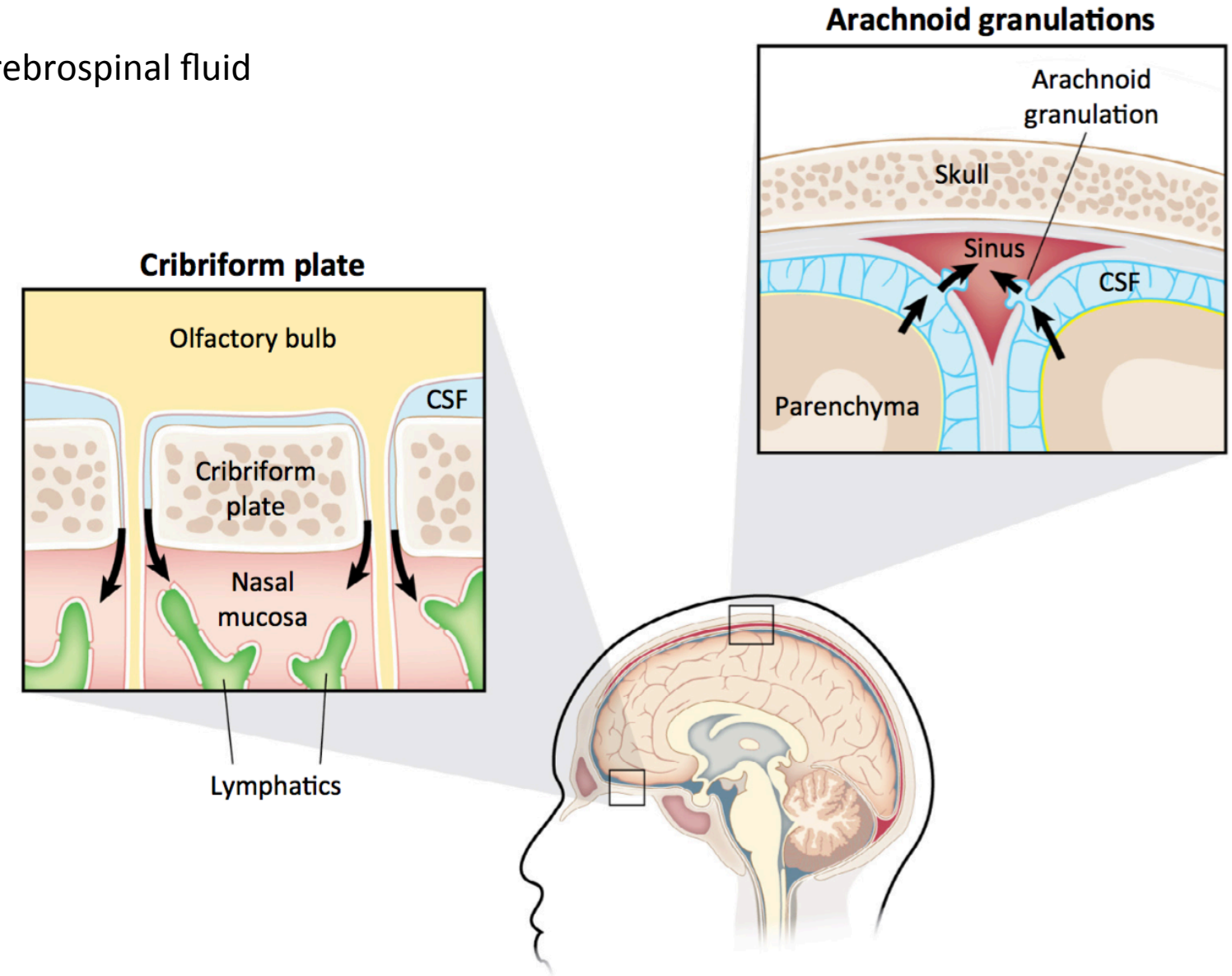


In the lymph nodes:
inhibit the maturation of DCs and the activation of T cells

Louveau *et al*. (2016) Neuron 91: 957-73

Paths of CSF drainage

CSF: Cerebrospinal fluid



Louveau *et al*. (2015) Trends in immunology 36: 569-77

Paths of CSF drainage

- The CSF, flowing between the arachnoid and the pia mater of the meninges, can drain into the bloodstream through the arachnoid granulations located along the superior sagittal sinus and the transverse sinuses

- The CSF reach the lymphatic vasculature of the nasal mucosa by crossing the cribriform plate, localized under the olfactory bulbs, along the olfactory nerves

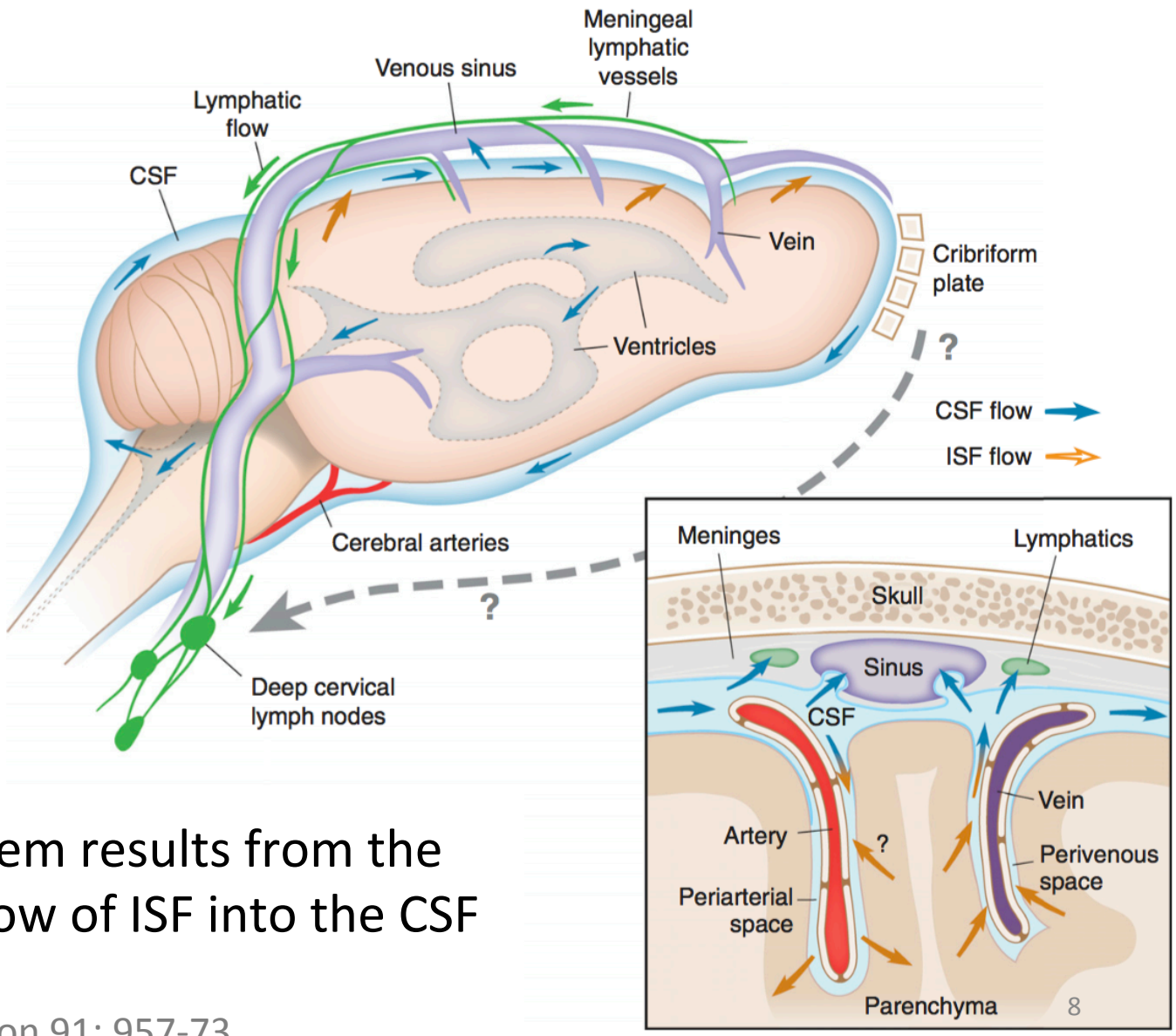
Louveau *et al*. (2015) Trends in immunology 36: 569-77

Drainage from the CNS

In addition to blood, the CNS contains CSF and ISF

1. The glymphatic system: ISF and macromolecules
2. The meningeal lymphatic system: macromolecules and immune Cells
3. pathway was via the cribriform plate into the lymphatic system of the nasal mucosa and then to the deep cervical lymph nodes

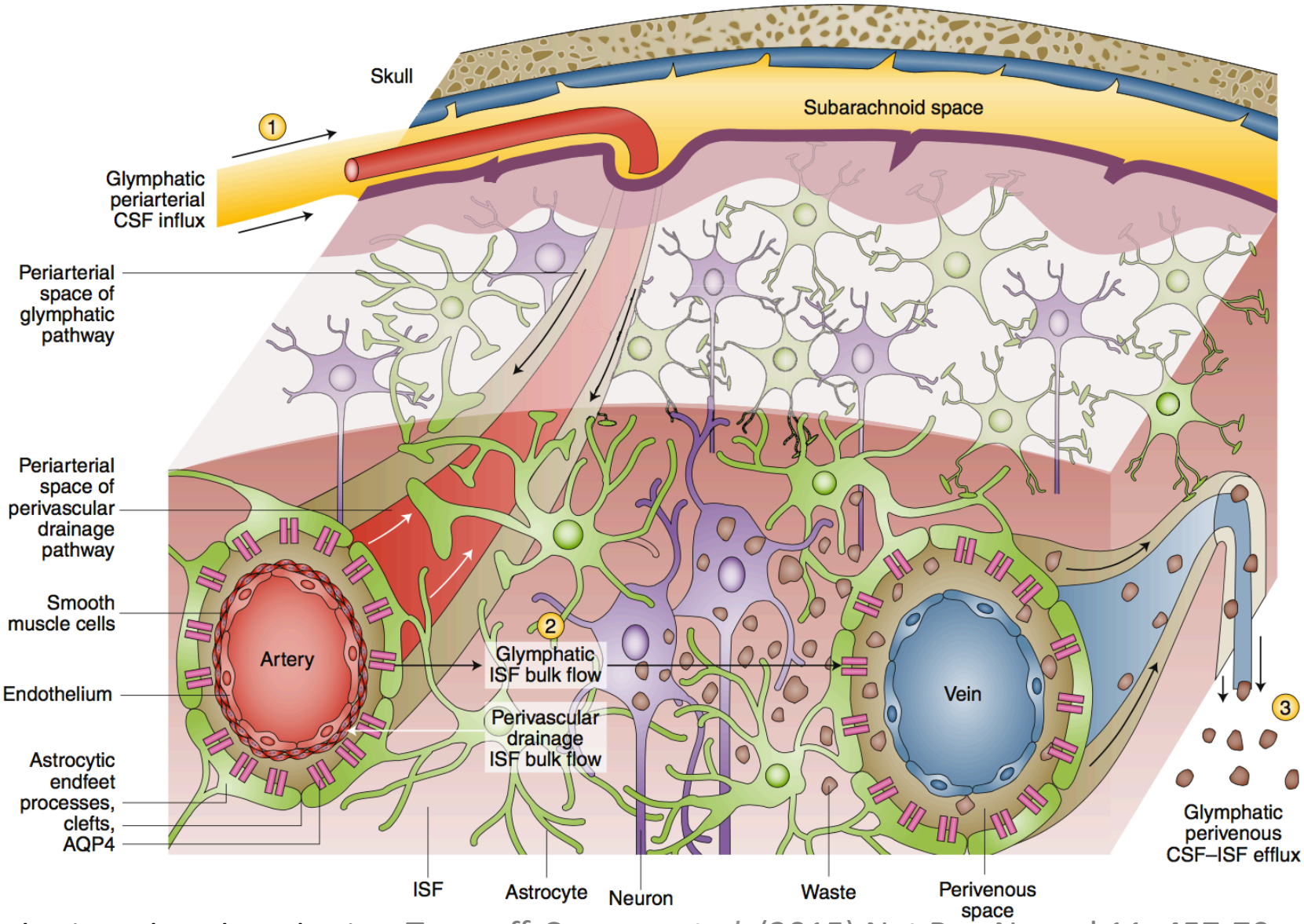
Pathways of fluid circulation and drainage in the brain



The glymphatic system results from the paravascular bulk flow of ISF into the CSF

Louveau *et al*. (2016) Neuron 91: 957-73

Perivascular clearance comprises perivascular drainage and glymphatic pathways



Glymphatic = glia + lymphatic

Tarasoff-Conway *et al.* (2015) Nat Rev Neurol 11: 457-70

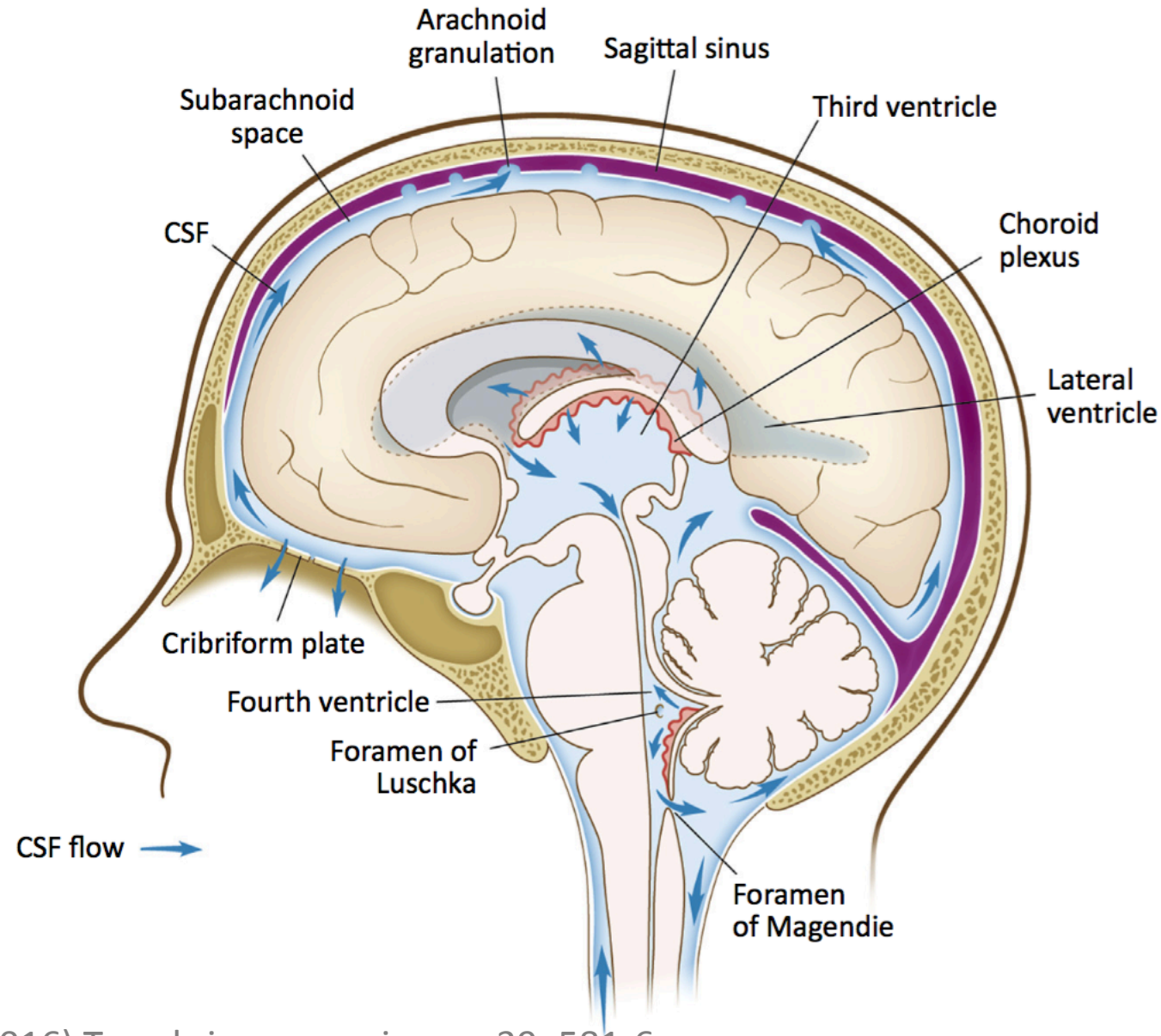
Perivascular clearance comprises perivascular drainage and glymphatic pathways

- The **perivascular drainage pathway** moves waste into the periarterial space[1] and towards the subarachnoid space in the direction opposite to blood flow
- The **glymphatic pathway** clears waste from the ISF through the brain parenchyma, and comprises three functional components
  - ✓ **CSF influx**, unidirectionally with blood flow, **into the periarterial space**[2], where the water component of CSF crosses astrocytic AQP4 channels to enter the brain parenchyma
    - ➢ CSF solutes can be cleared with astroglial transporters or channels, or can pass through the astrocytic endfeet clefts
  - ✓ **CSF–ISF exchange** within the brain parenchyma
  - ✓ **CSF–ISF movement into the perivenous space** of deep-draining veins
    - ➢ Effluxed waste can then recirculate with the CSF, or eventually be absorbed into the lymphatic system

[1]Periarterial space: located along smooth muscle cells and the capillary basement membrane
[2]Periarterial space: between the basement membrane of smooth muscle cells and pia mater

Tarasoff-Conway *et al.* (2015) Nat Rev Neurol 11: 457-70

Production and circulation of CSF within the CNS



Raper *et al*.(2016) Trends in neurosciences 39: 581-6

Production and circulation of CSF within the CNS

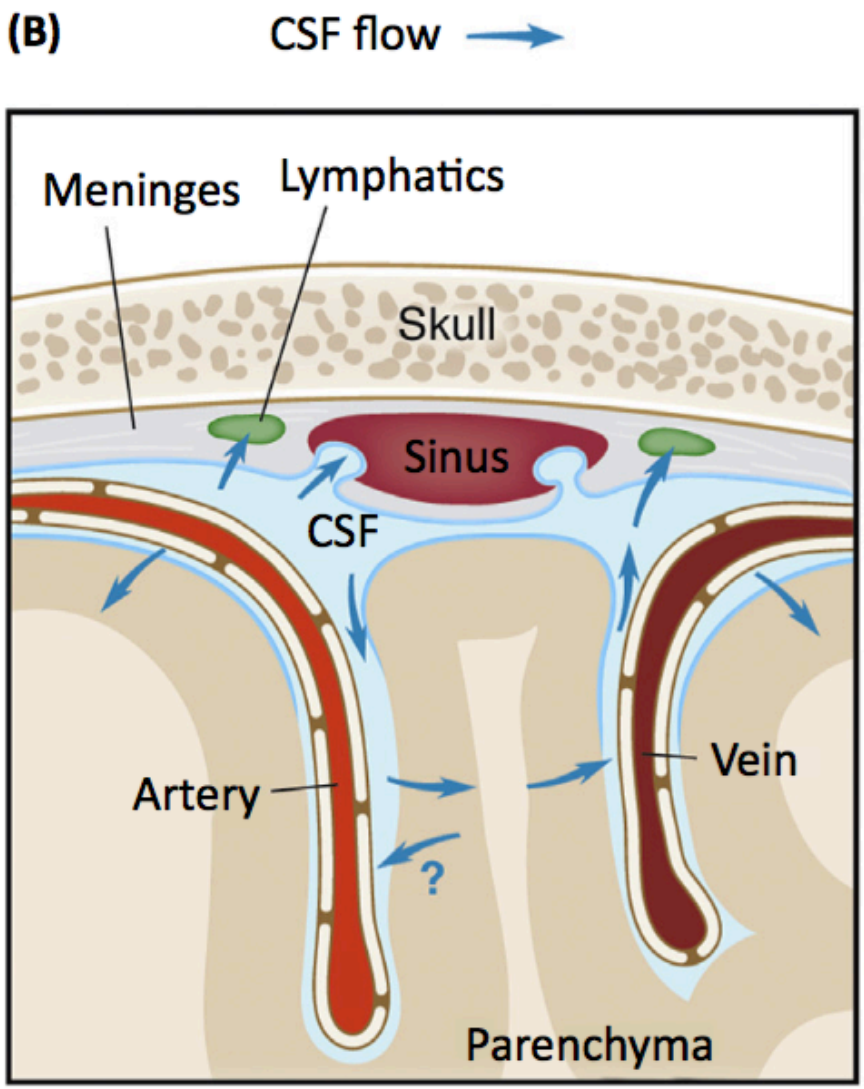
- CSF is produced by the choroid plexus of the lateral and fourth ventricles, and flows from the third ventricle to the fourth ventricle through the cerebral aqueduct

- After circulating over the hemispheres, CSF absorption into the superior sagittal sinus, transverse sinus, and sigmoid sinuses is via arachnoid granulations, as well as efflux from the CNS along the olfactory nerves through the cribriform plate

Raper *et al*.(2016) Trends in neurosciences 39: 581-6

Production and circulation of CSF within the CNS

- CSF–ISF flow from and to the subarachnoid space
- CSF can diffuse in and out of the brain parenchyma along the perivascular space



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Conclusions

- Lymphatic vasculature drains interstitial fluids, which contain the tissue's waste products, and ensures immune surveillance of the tissues, allowing immune cell recirculation

- In the meninges of a lymphatic network that drains the CNS calls into question classic models for the drainage of macromolecules and immune cells from the CNS

- In the context of neurological disorders, the presence of a lymphatic system draining the CNS potentially offers a new player and a new avenue for therapy

Louveau *et al*. (2016) Neuron 91: 957-73