Introduction to Immunology of the Brain

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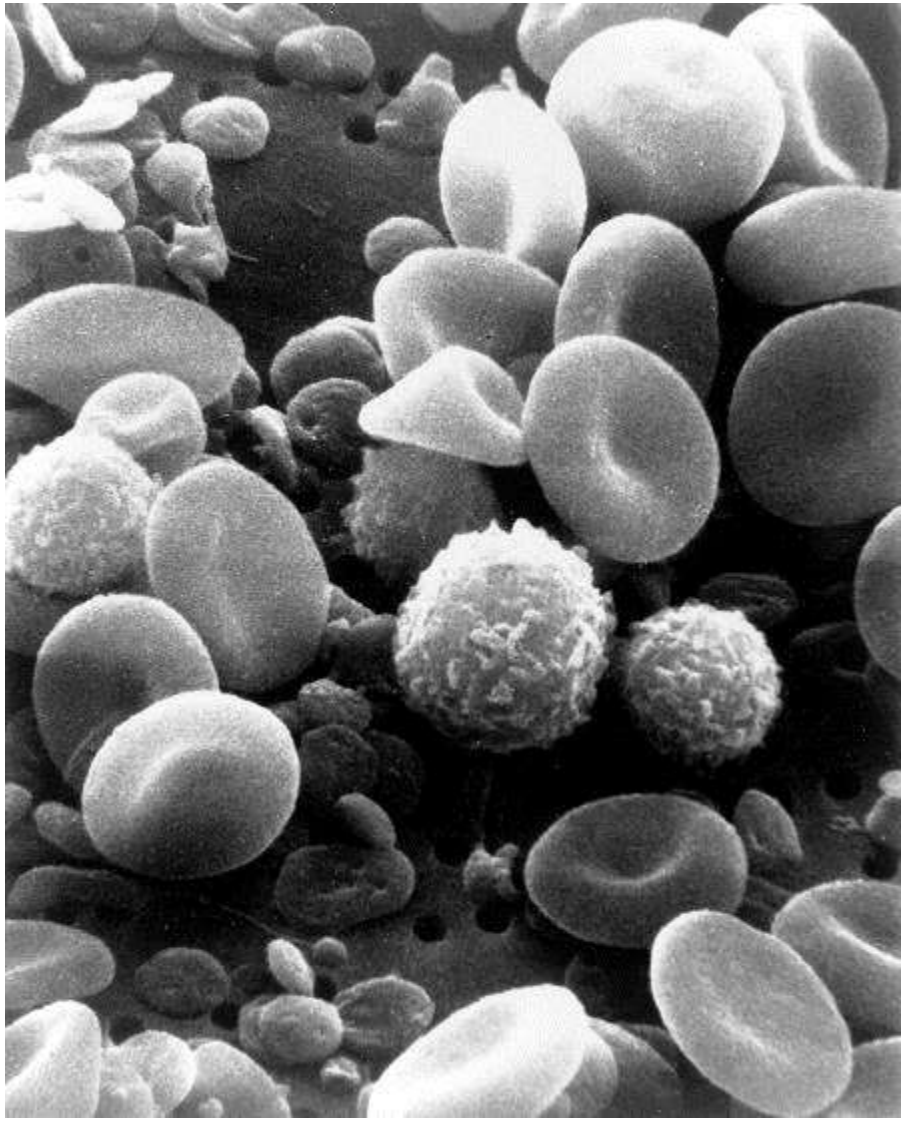
Outline

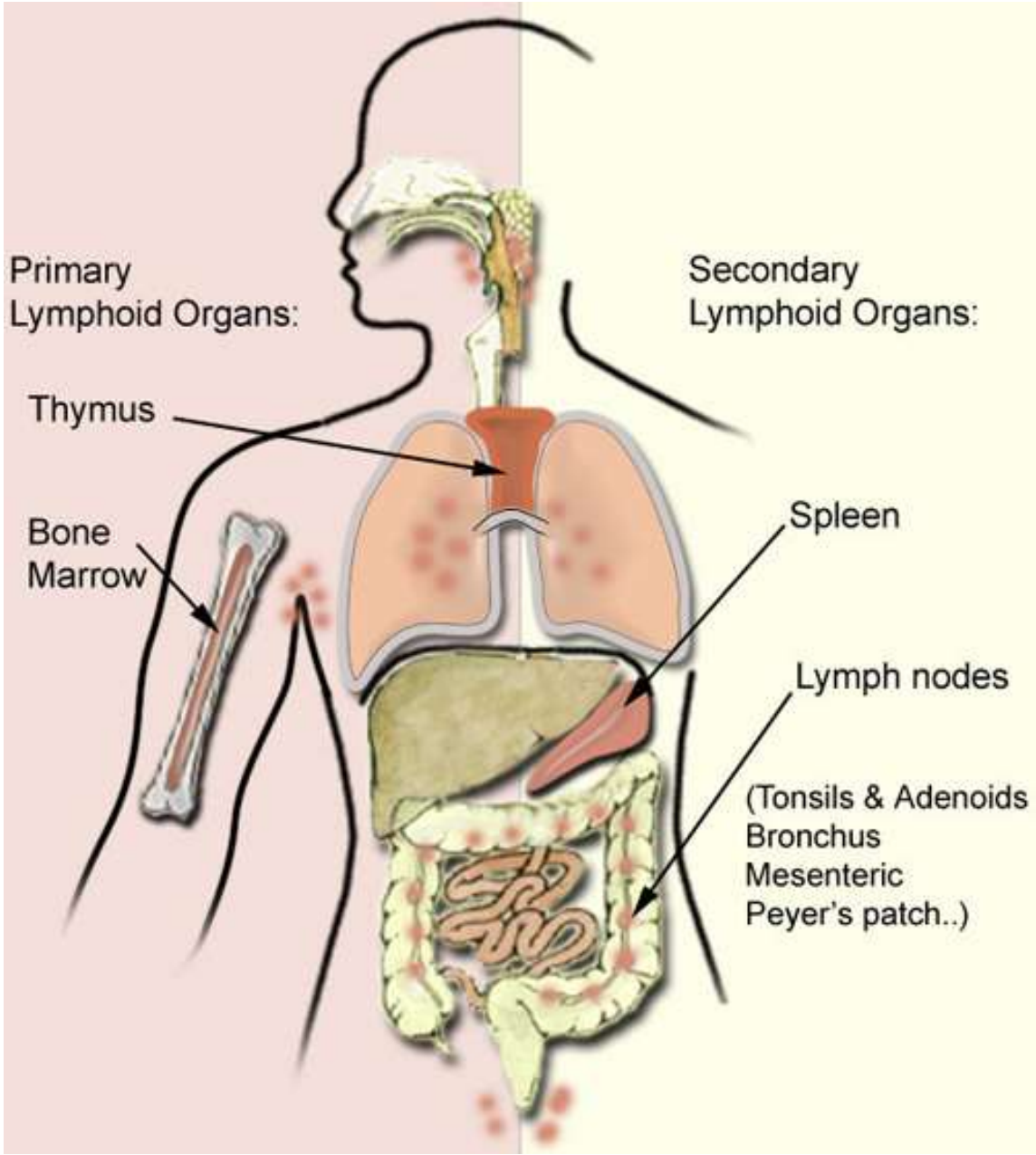
- Immune system basics
- Innate immune system in the brain
- Peripheral immune cell trafficking into the brain
- Neuro-immune integration

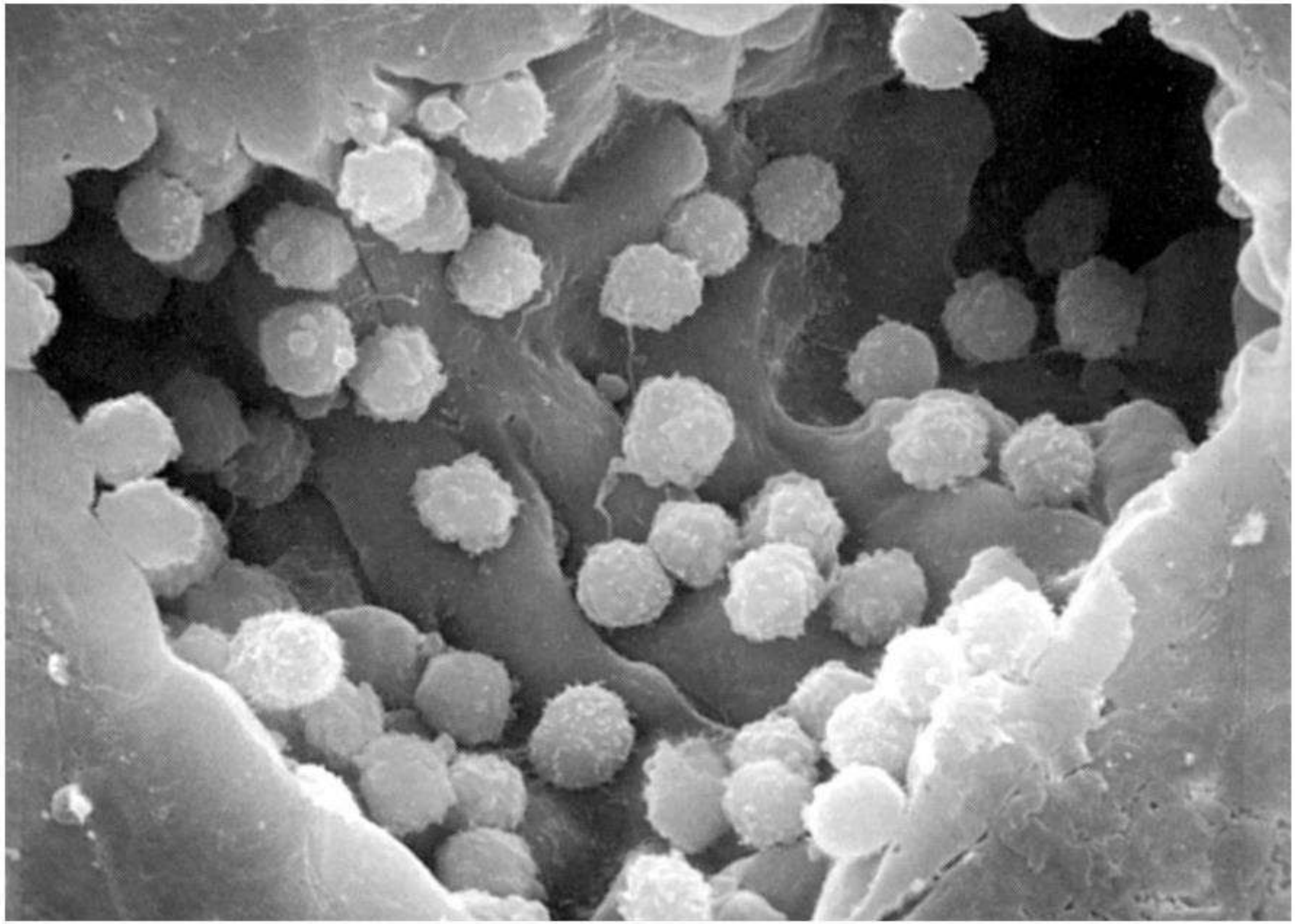
White blood cells

- Messengers and effectors of immune responses
- Purpose is to seek out and defend against pathogens
- Circulate in the blood and can enter organs, including the brain
- Stored in immune organs like the spleen and lymph nodes



Immune Organs





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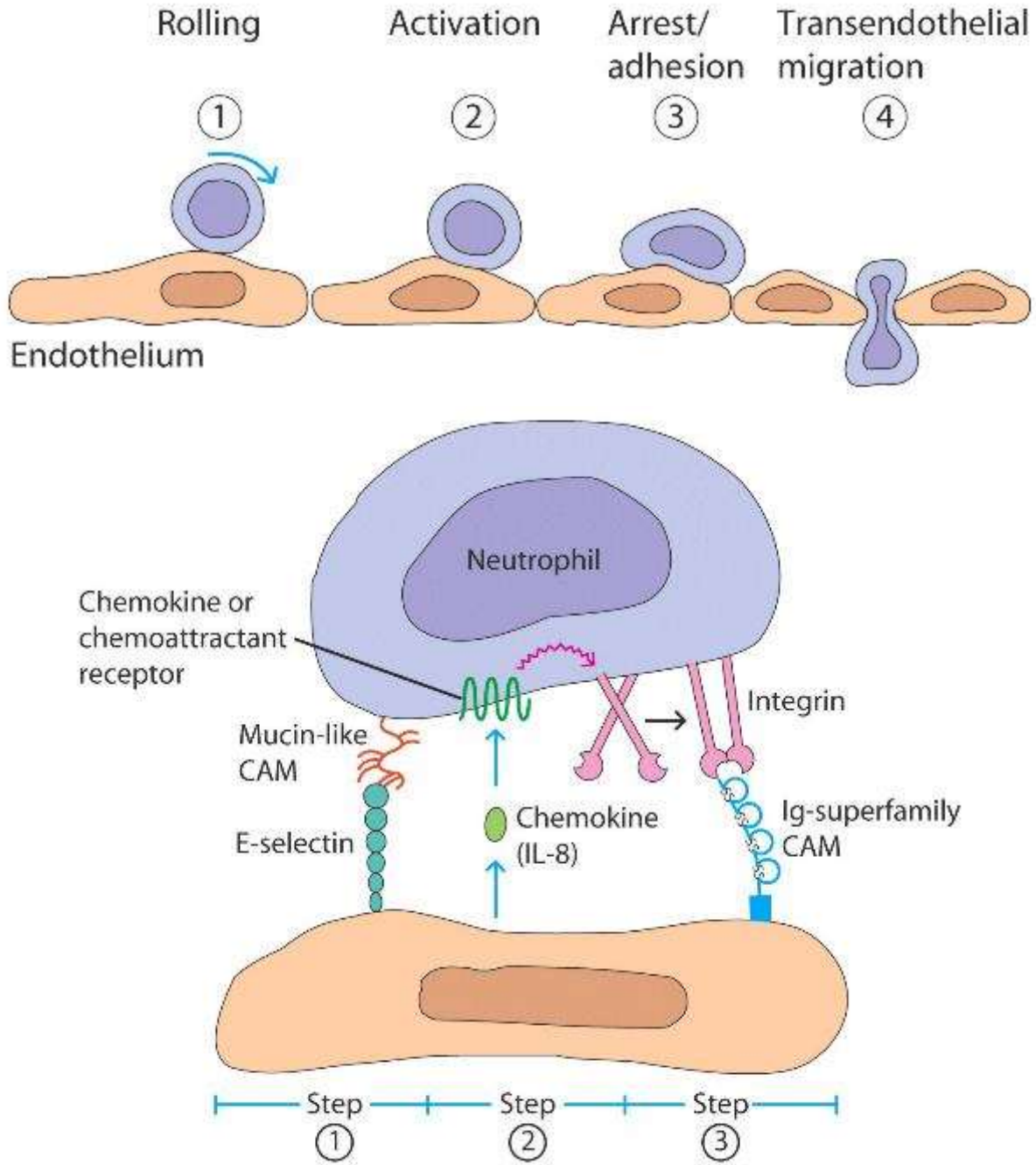
Rolling
Activation
Arrest/
adhesion
Transendothelial
migration
1
2
3
4
Endothelium
Neutrophil
Chemokine or
chemoattractant
receptor
Integrin
Mucin-like
CAM
E-selectin
Chemokine
(IL-8)
Ig-superfamily
CAM
Step
1
Step
2
Step
3

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The lymphatic system

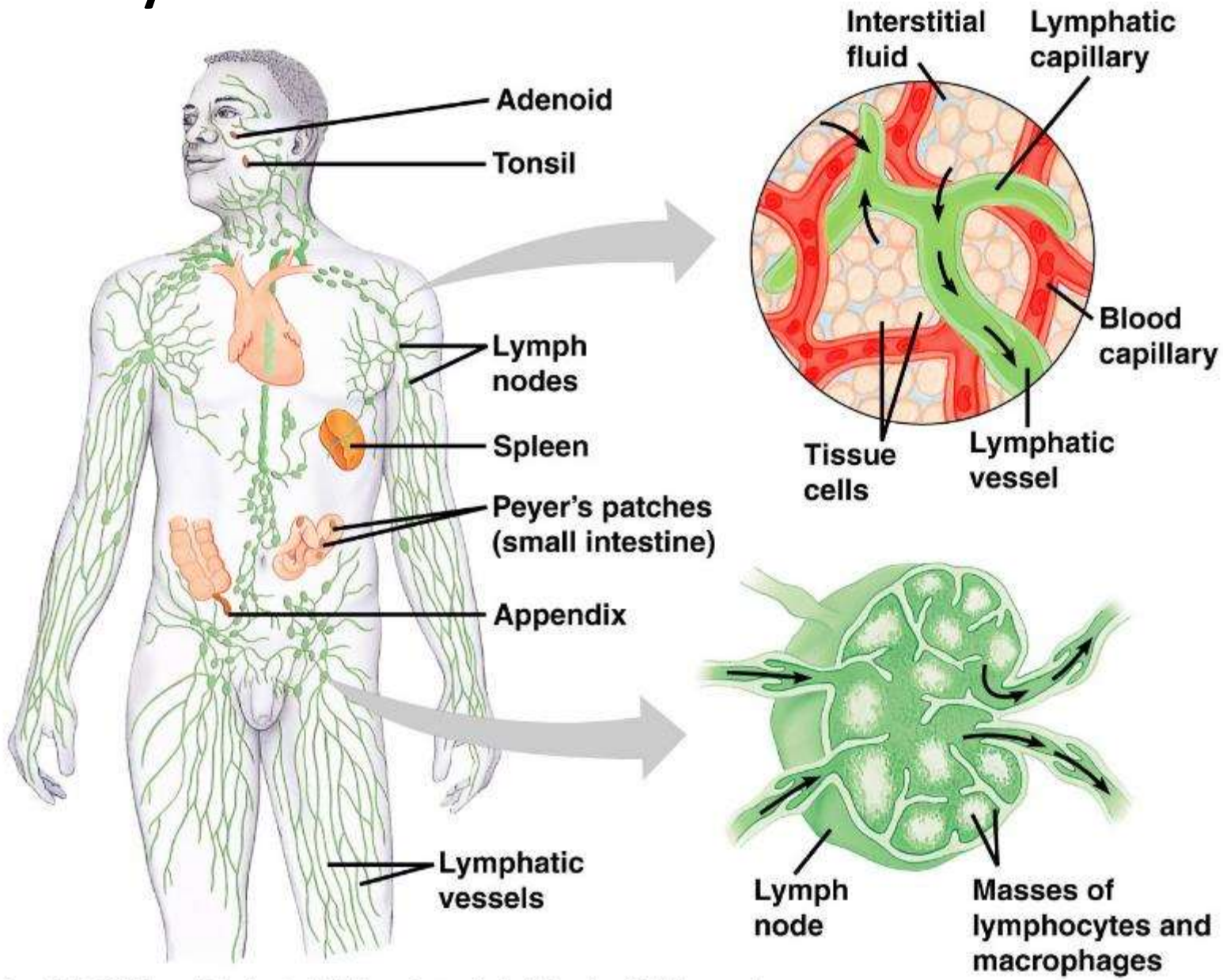

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TABLE 1-3 Comparison of adaptive and innate immunity

	Innate	Adaptive
Response time	Hours	Days
Specificity	Limited and fixed	Highly diverse, improves during the course of immune response
Response to repeat infection	Identical to primary response	Much more rapid than primary response

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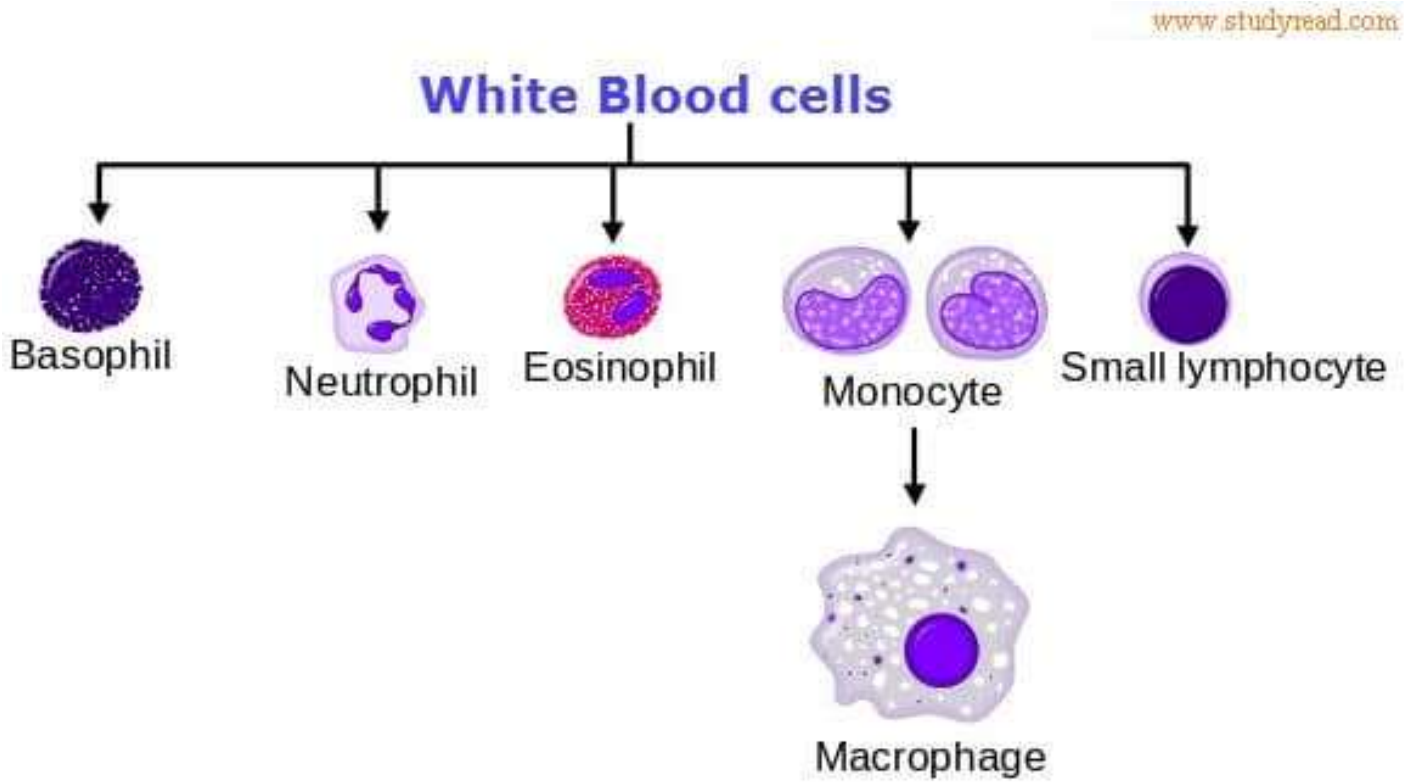
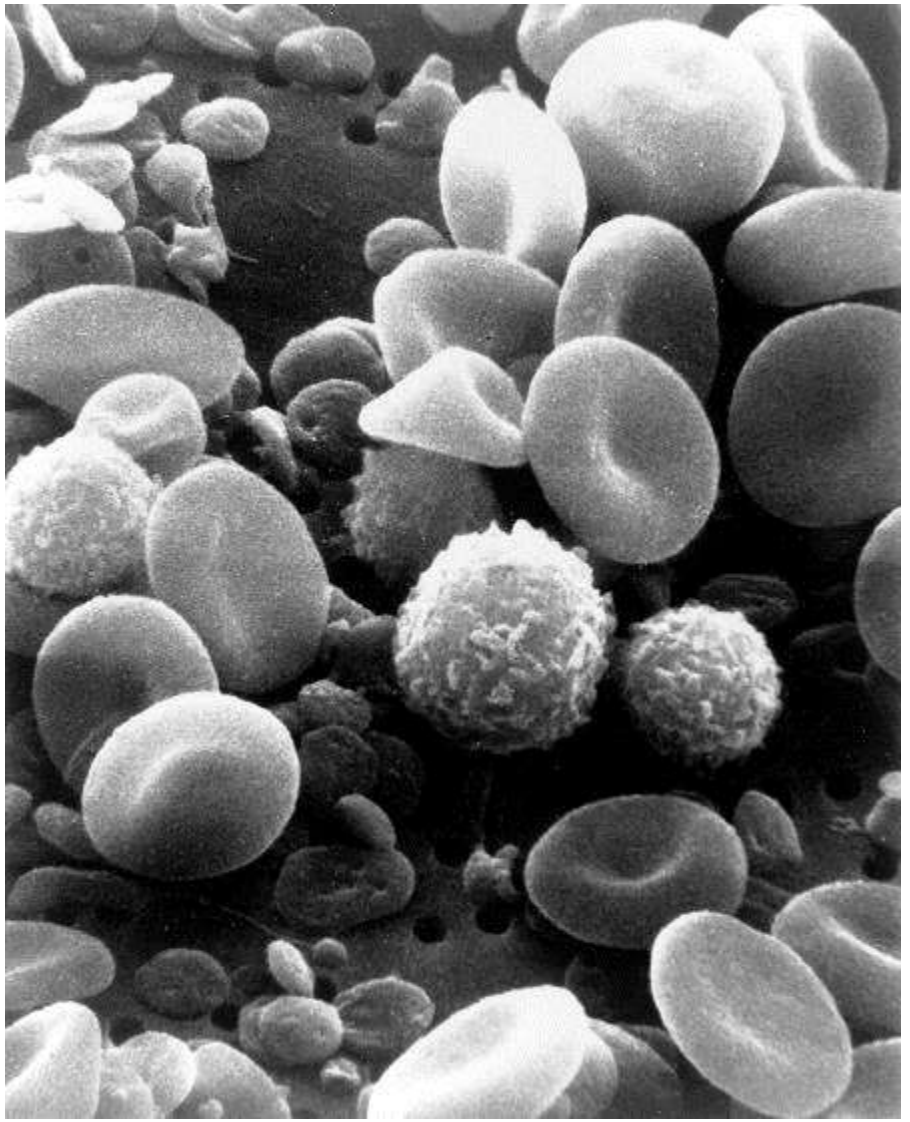
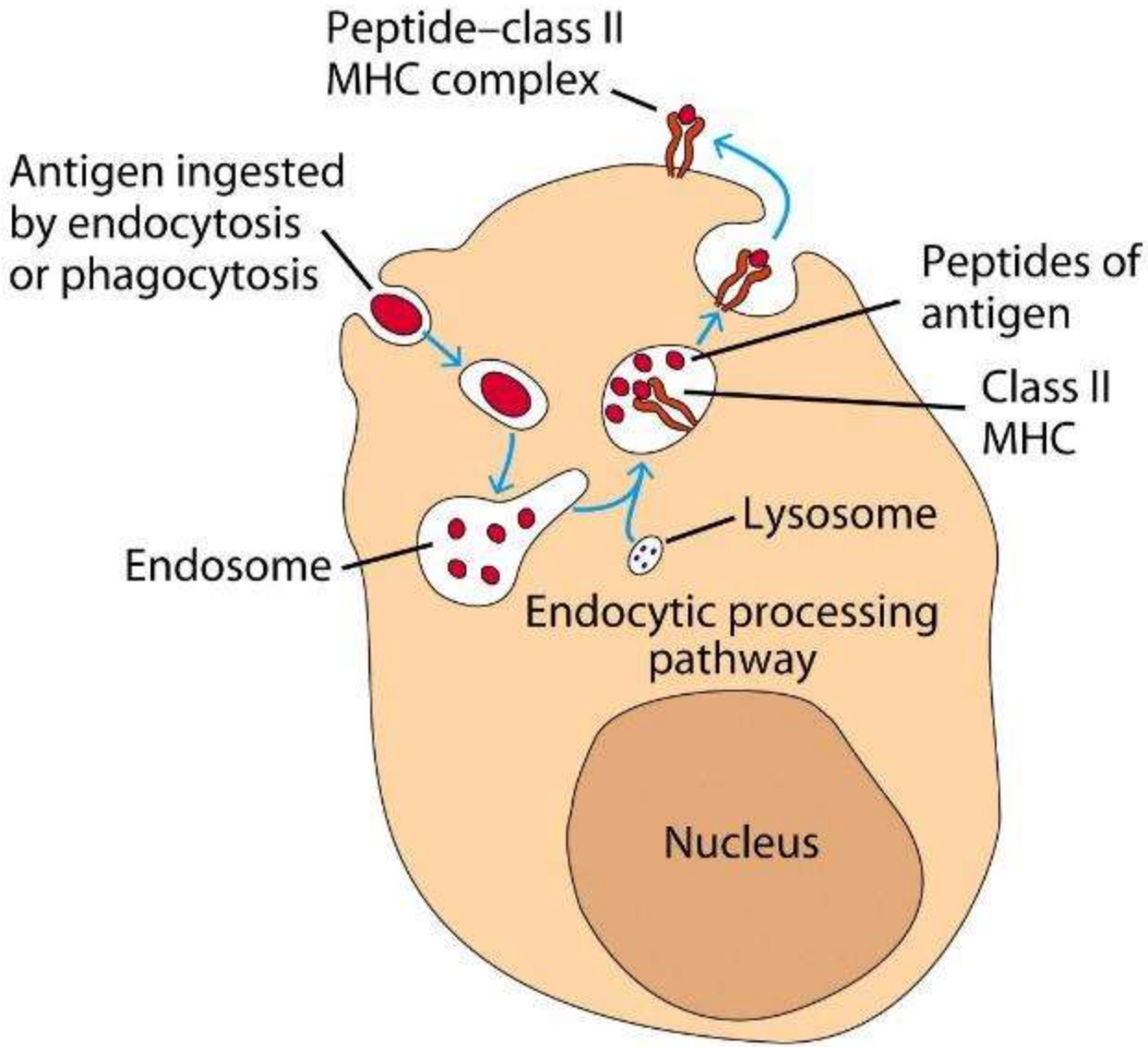
White blood cells





Innate: Antigen-presenting cells, e.g. macrophages



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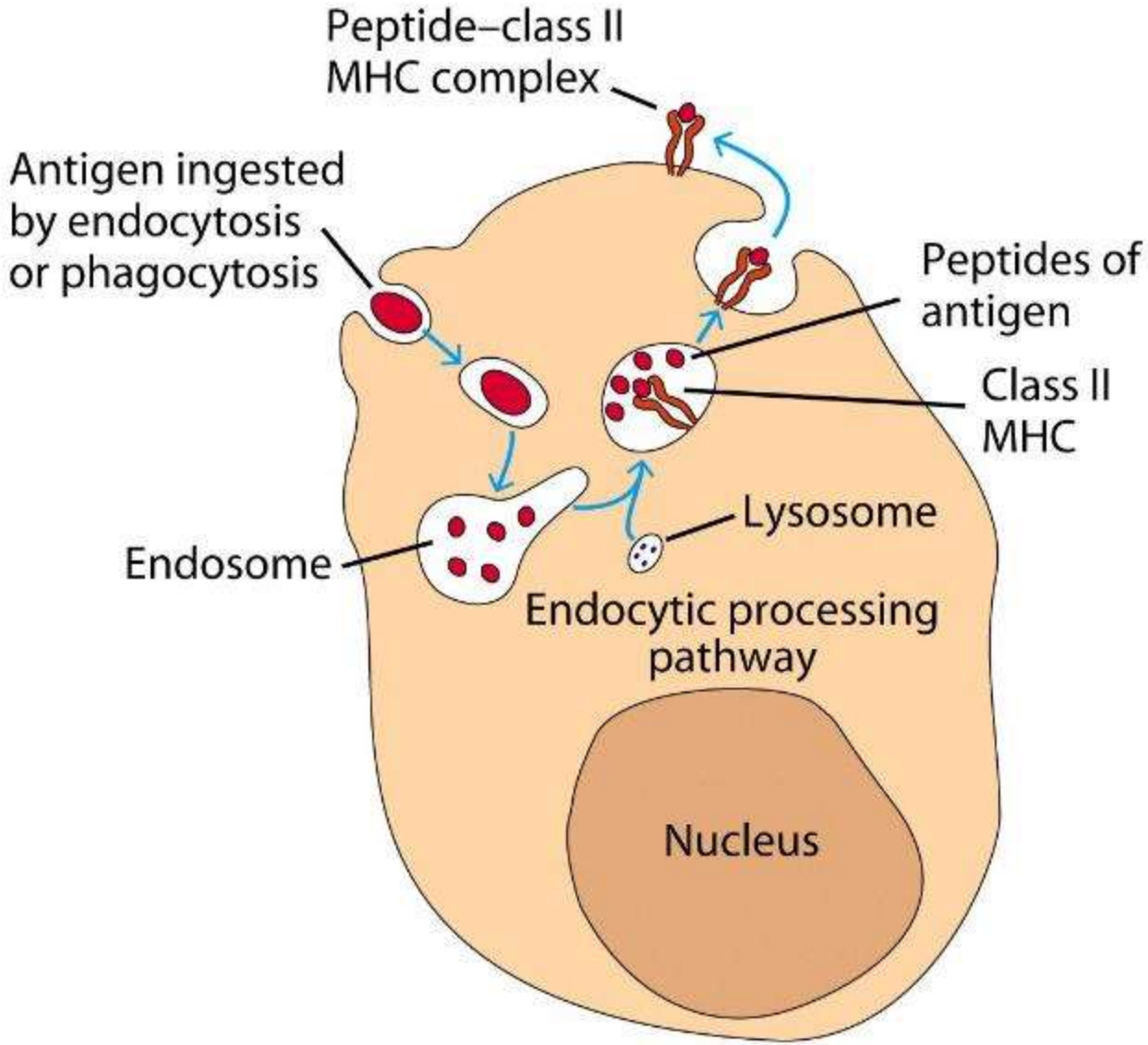
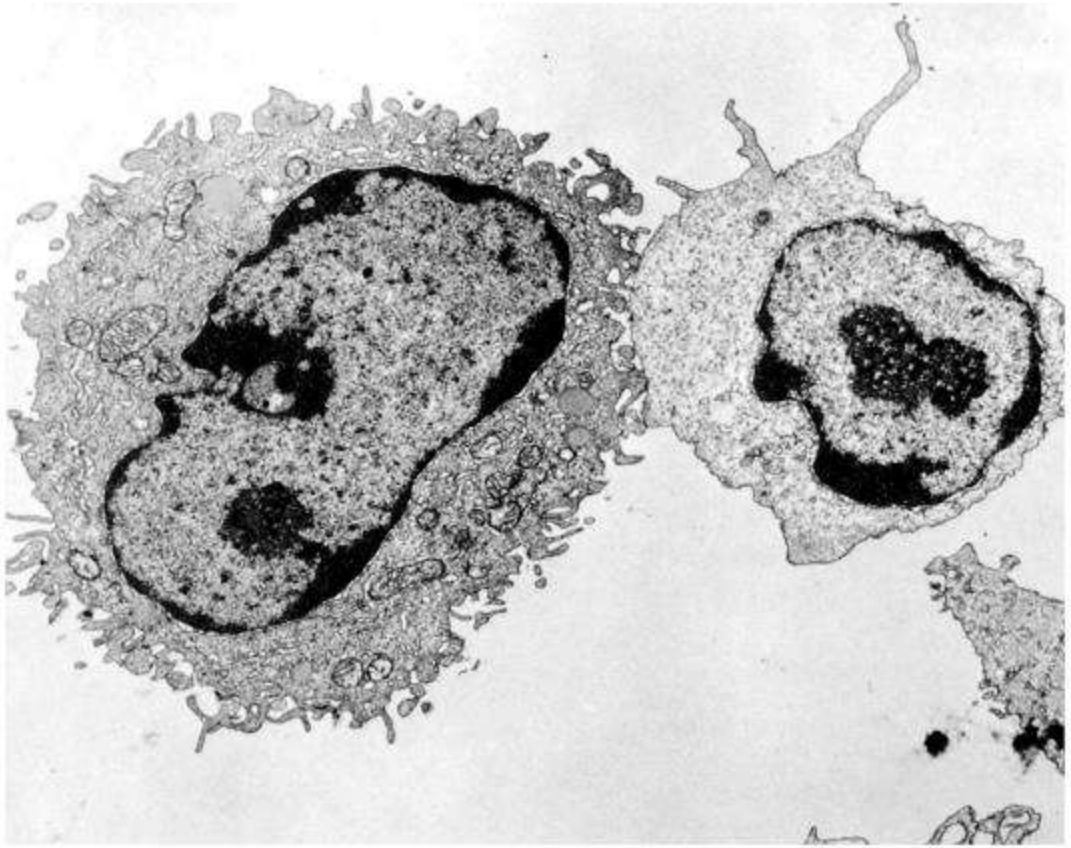
Innate: Antigen-presenting cells: microglia, monocytes





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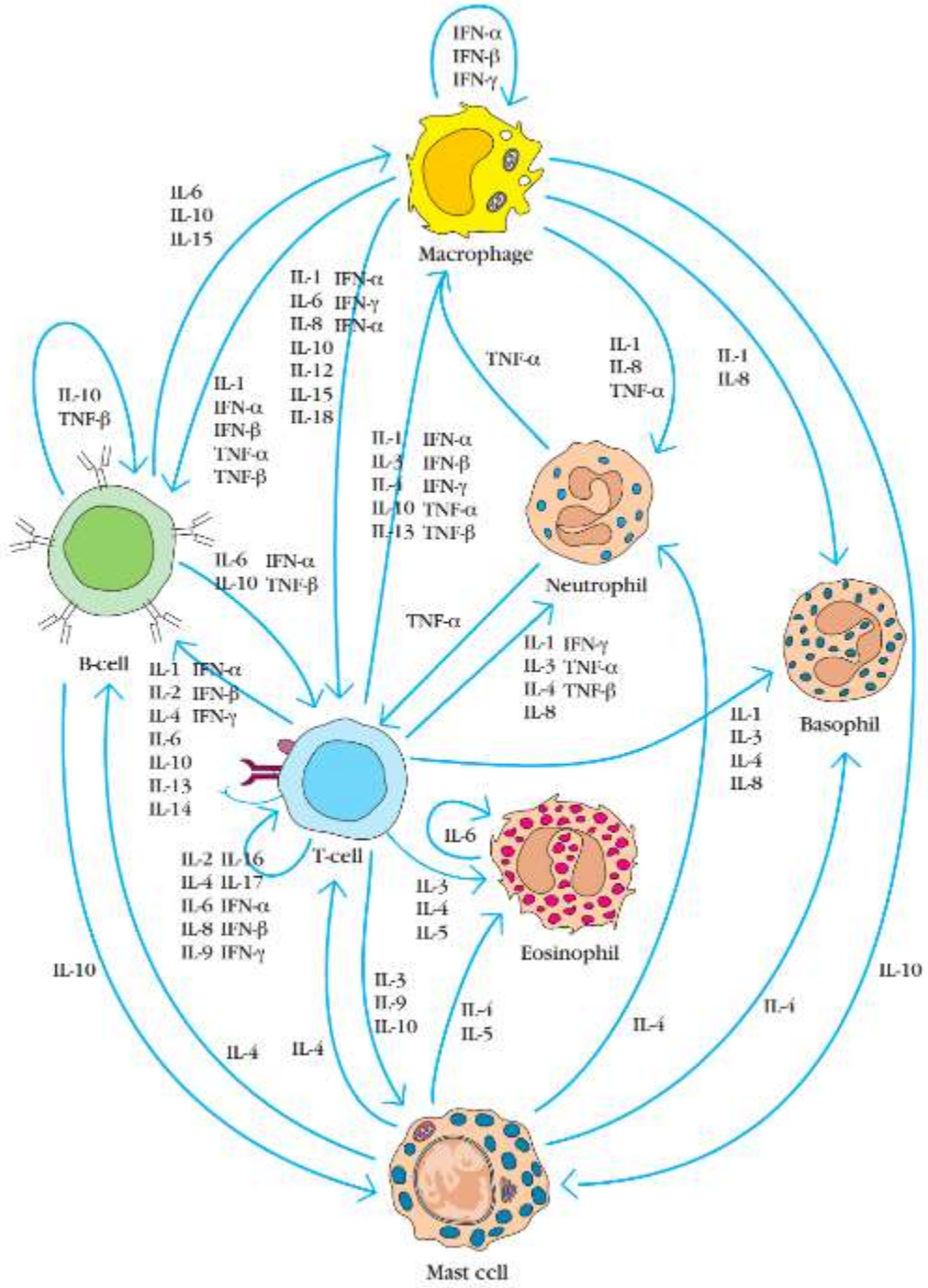
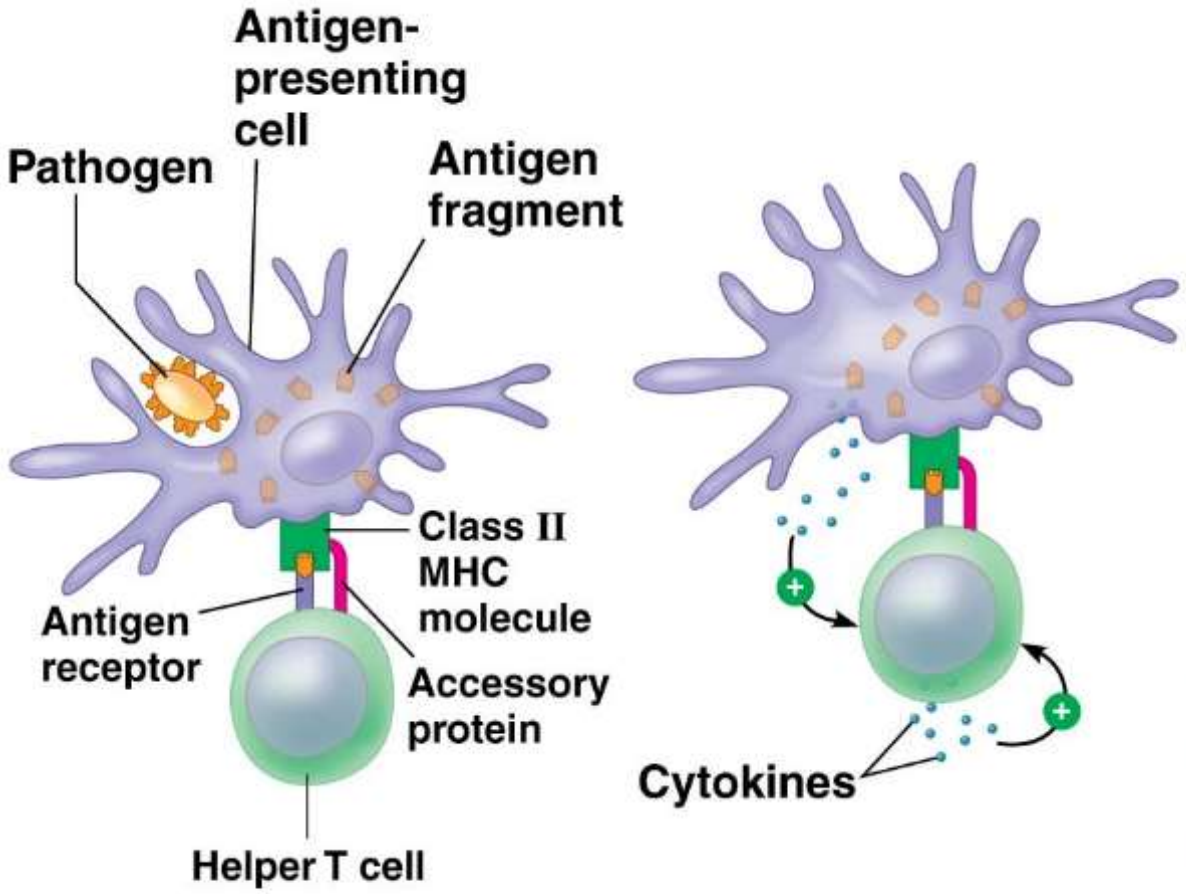
White blood cells signal each other via cytokines and chemokines

- Typically paracrine but can be endocrine
- Effects are pleiotropic
- Sometimes antagonistic or synergistic depending on context



Kuby Immunology, 7th Edition 2013

Class II MHC molecules present antigens to helper T cells and bind to CD4 on the helper T cell membrane. When bound to MHC II, the helper T cells proliferate.



The cytokines released can polarize helper T cells and other immune cells in the area:

- Th1 cells -> increased response
- Th2 cells -> tolerance/ less response
- Associated with M1/M2 macrophages
- Th17 cells -> autoimmunity

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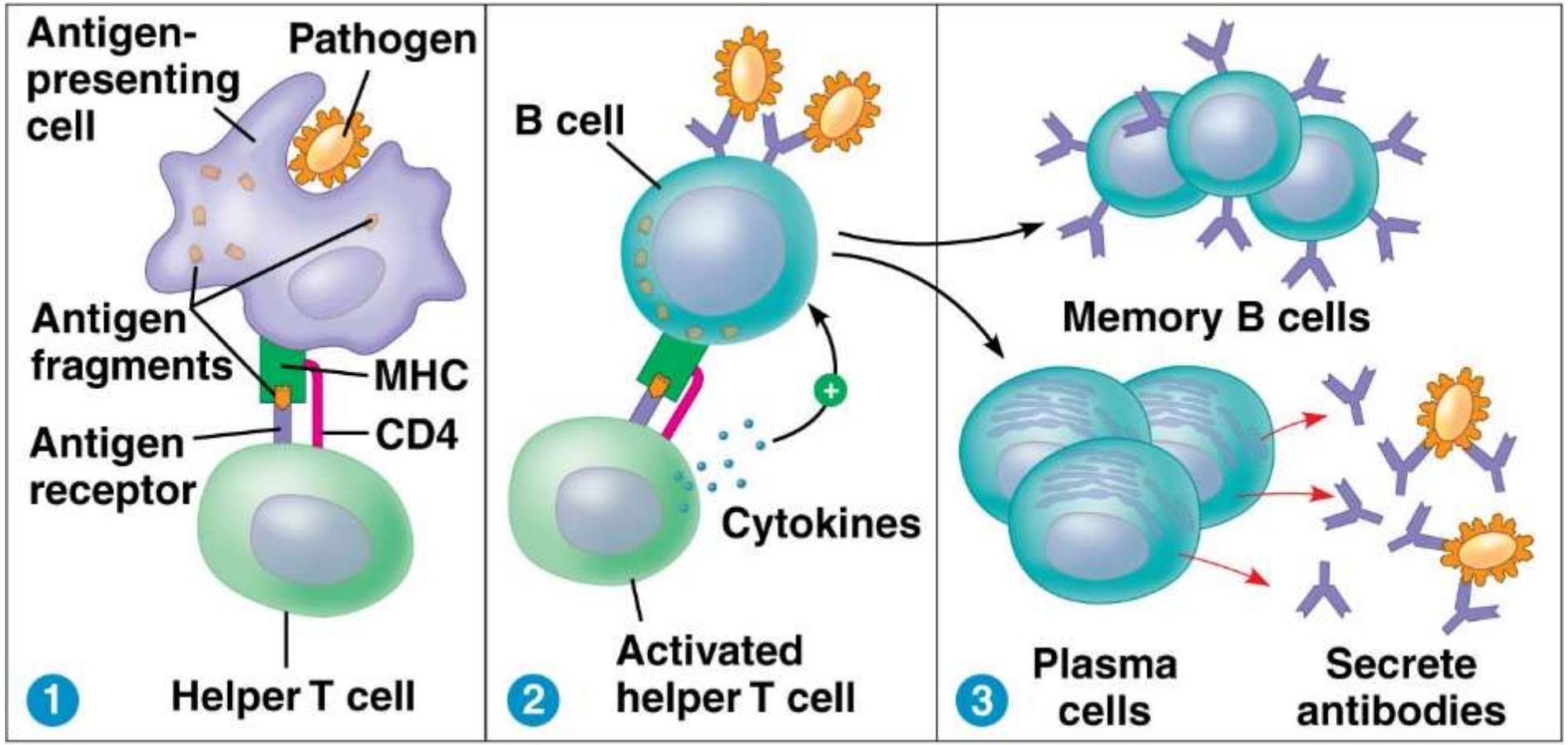
Helper T cells and free floating antigens stimulate B cells to proliferate to make antibody-secreting plasma cells & memory cells. B cells present antigens on class II MHCs to make even more B cells!



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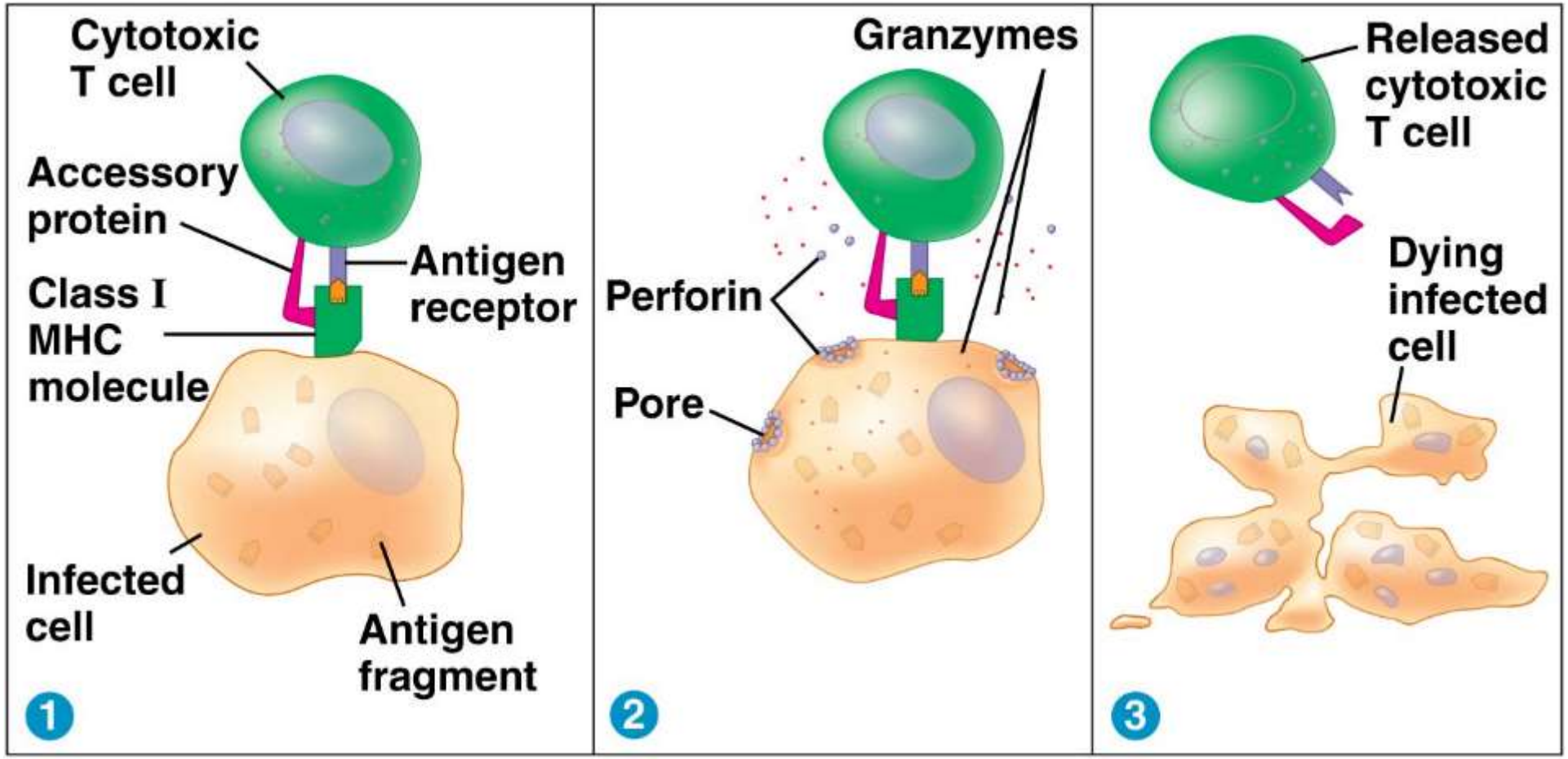
Cell-Mediated Response--When cytotoxic T cells are activated, they kill infected cells. CD8 (on the membrane of cytotoxic T cells) binds to Class I MHCs. When it recognizes a foreign antigen, it kills the cell by releasing perforin and granzymes which initiate apoptosis.



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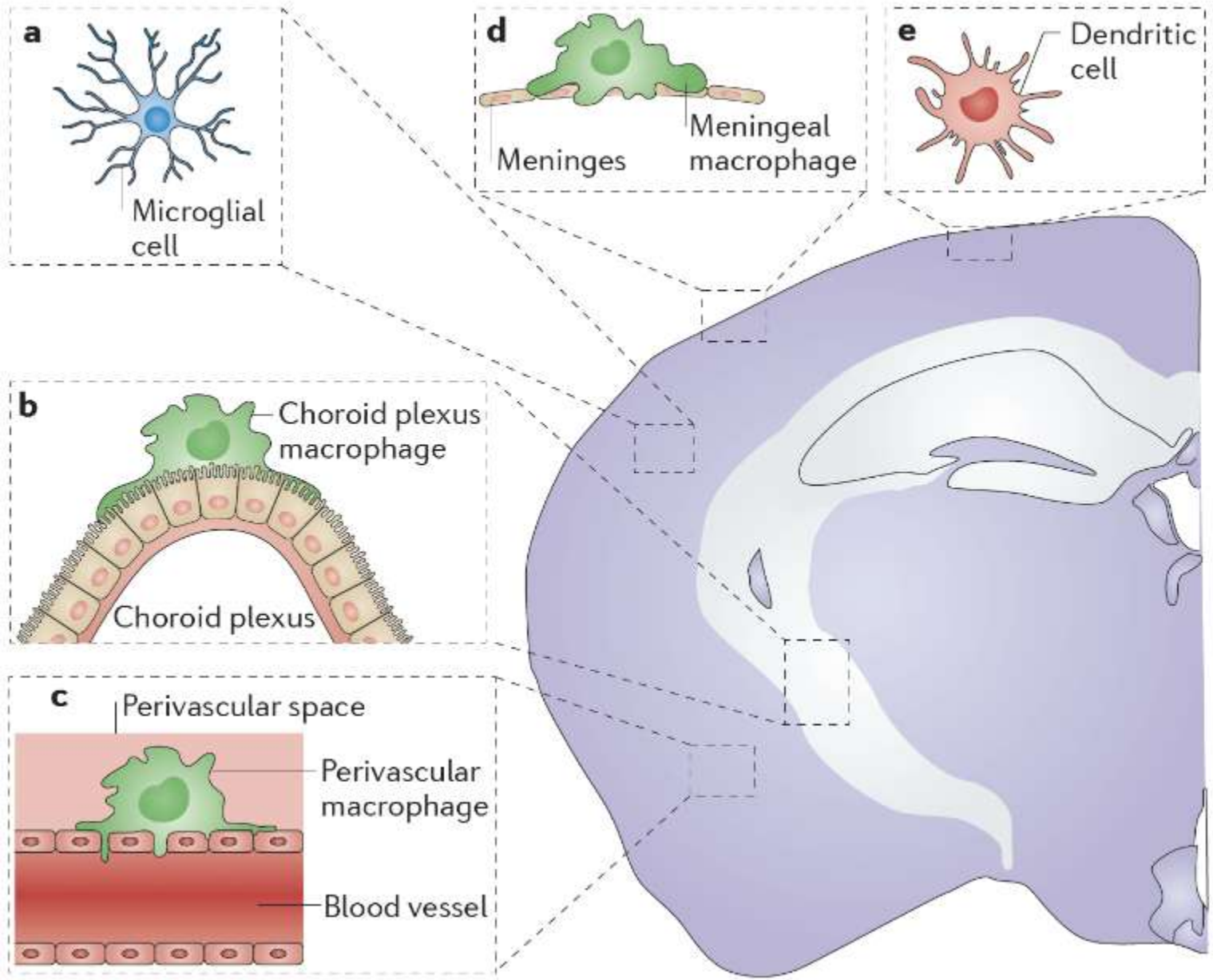
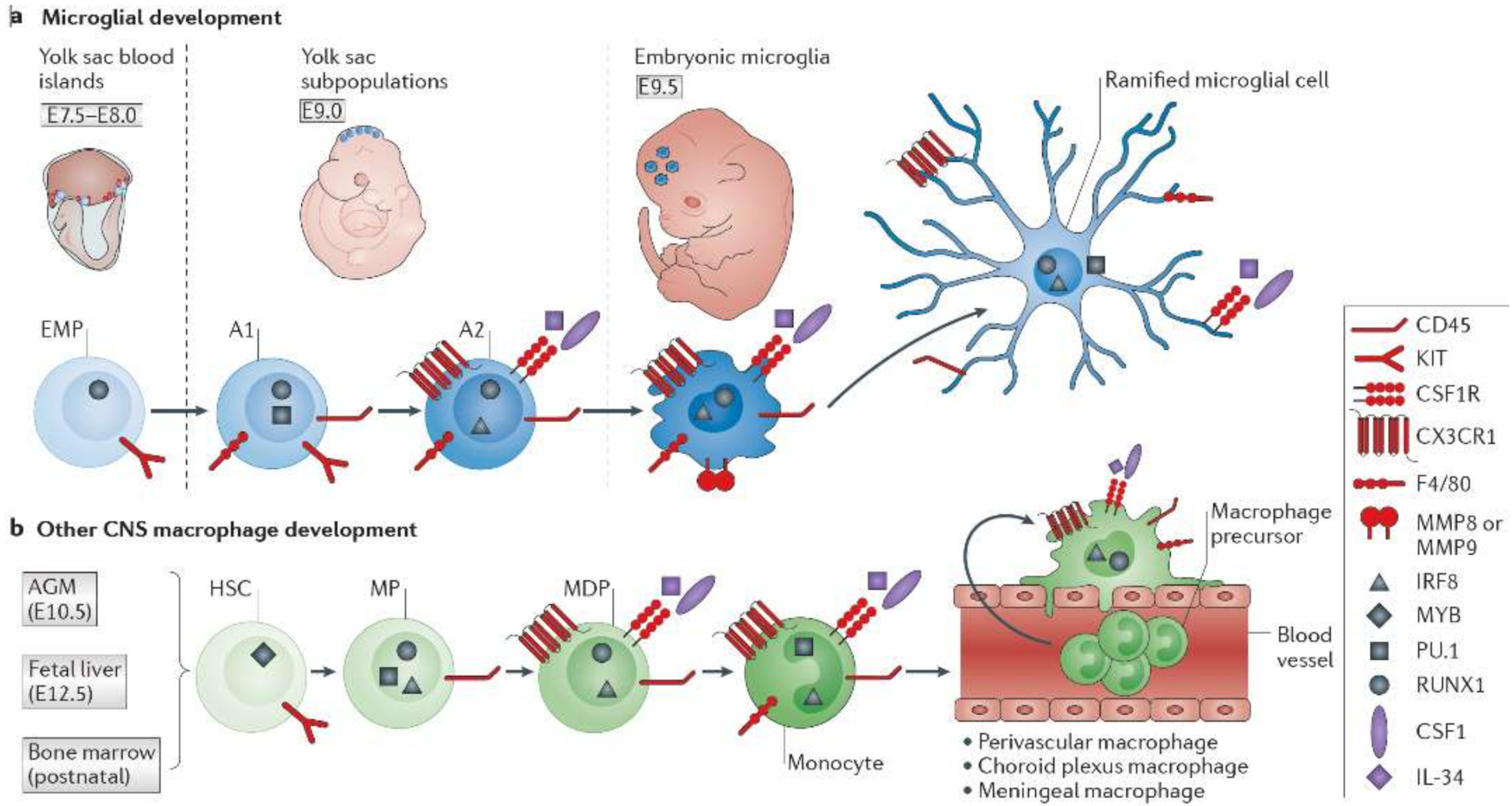
Multiple myeloid cell types in the brain



Prinz & Priller, 2014 Nature Neuroscience Reviews

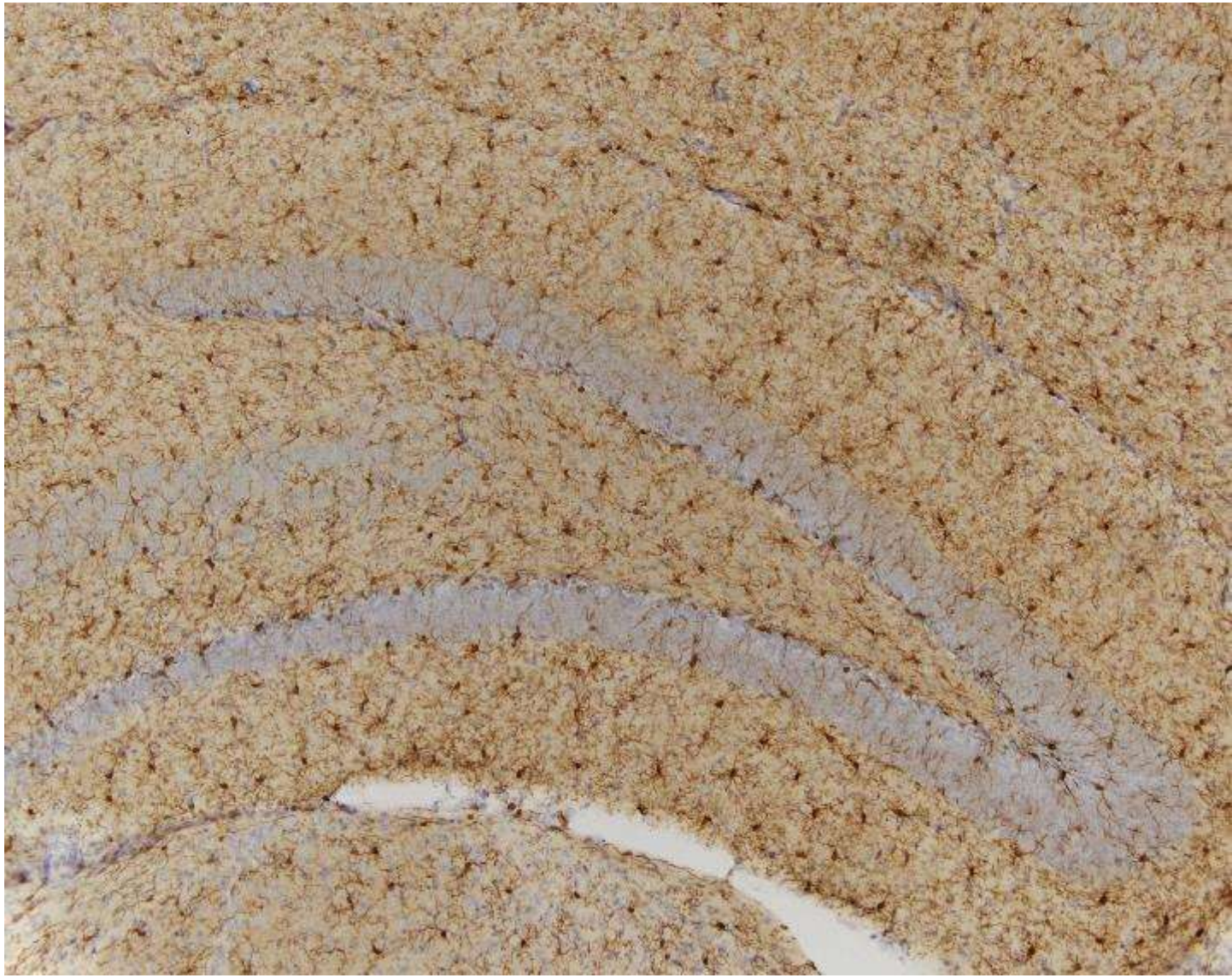
Development of brain myeloid cells



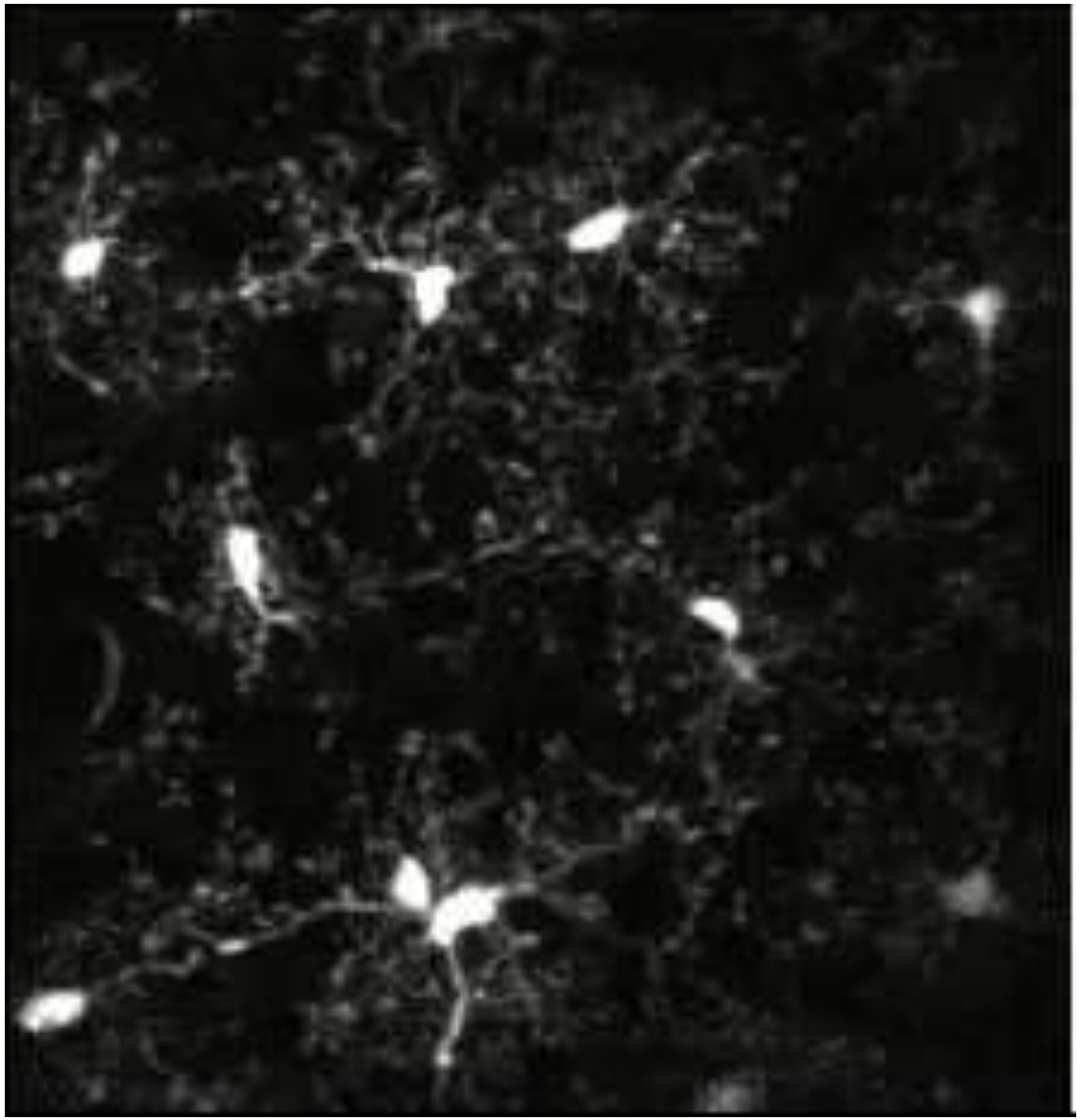
Prinz & Priller, 2014 Nature Neuroscience Reviews

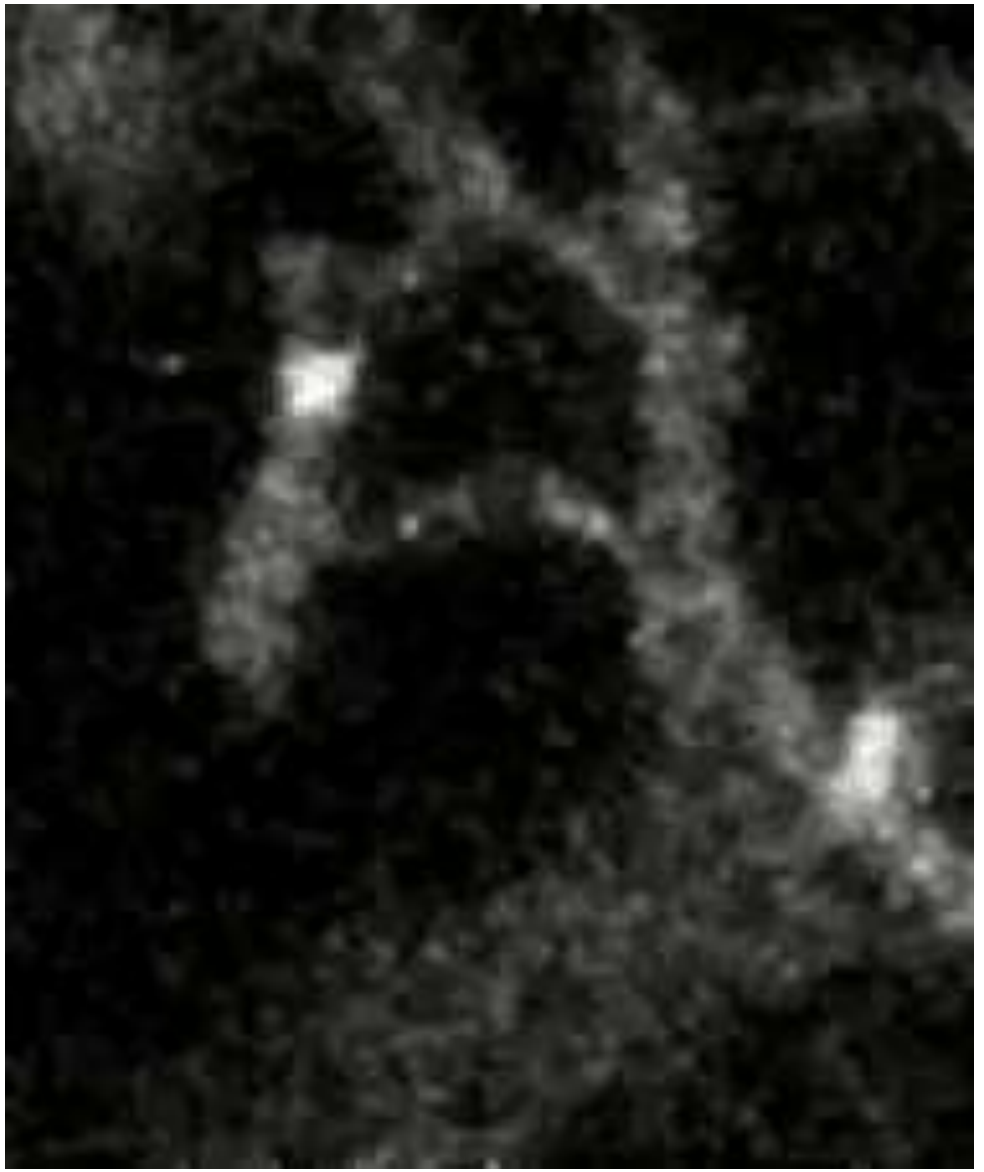
Innate - microglia

- Brain resident macrophages
- 10% of all brain cells
- Respond to ATP/purinergic signaling - ?respond to neuronal activity
- Required to phagocytose complement-tagged synapses during development
- They are alive!

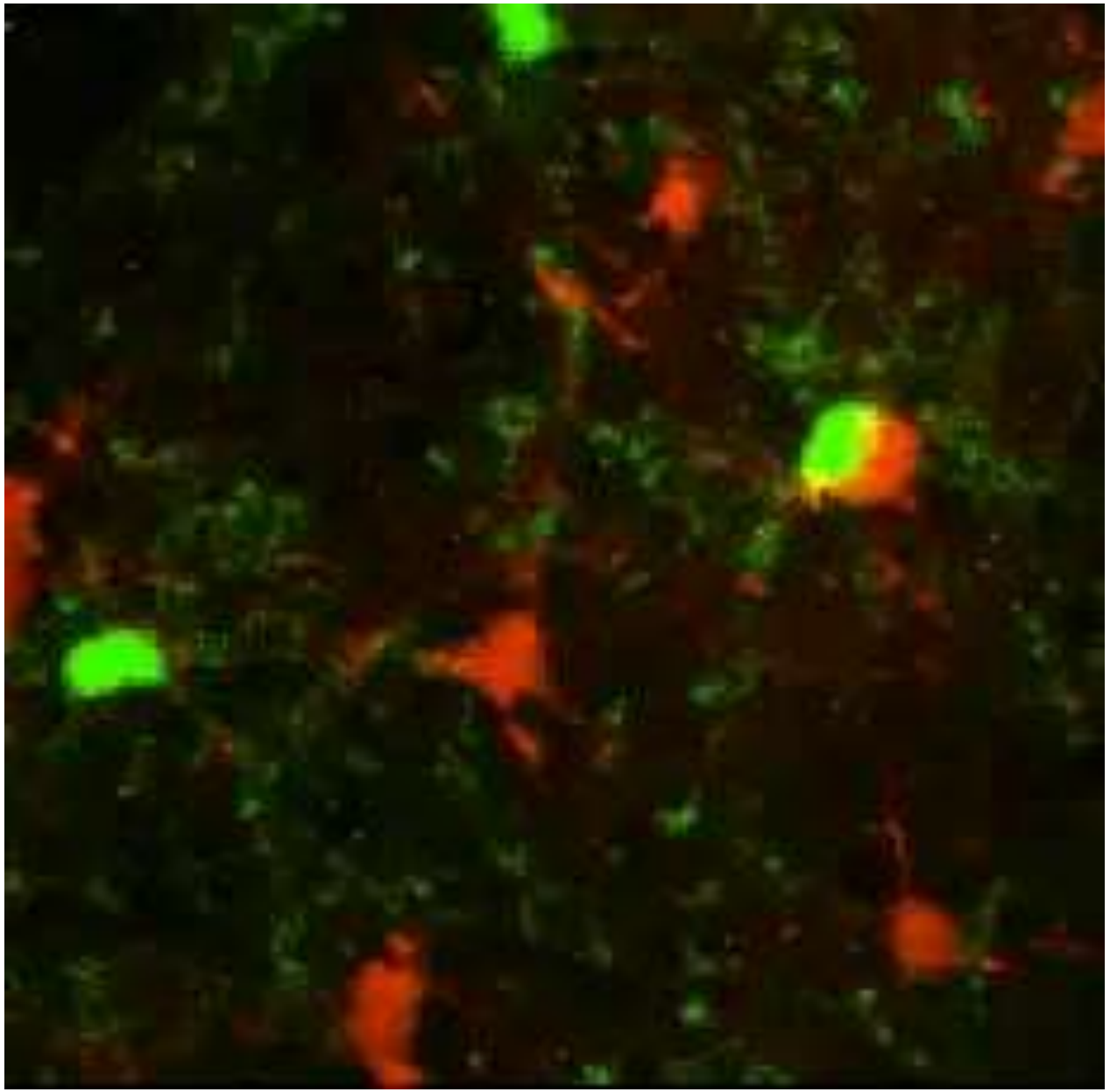


Iba1-immunostained mouse hippocampus with cresyl violet counterstain





Nimmerjahn et al,
Science, 2005.

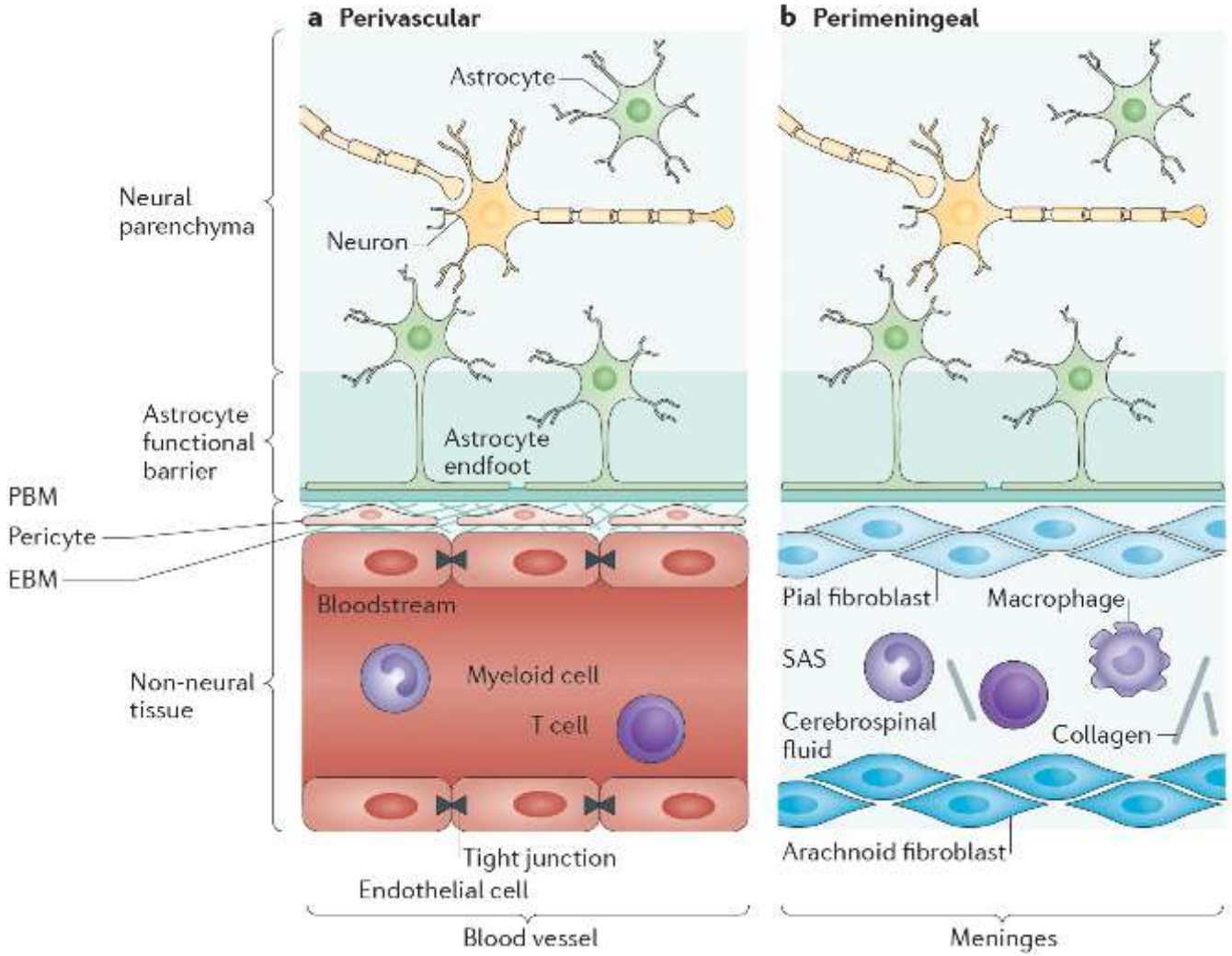


Microglia are injury-responsive

Microglia
Astrocytes
Laser

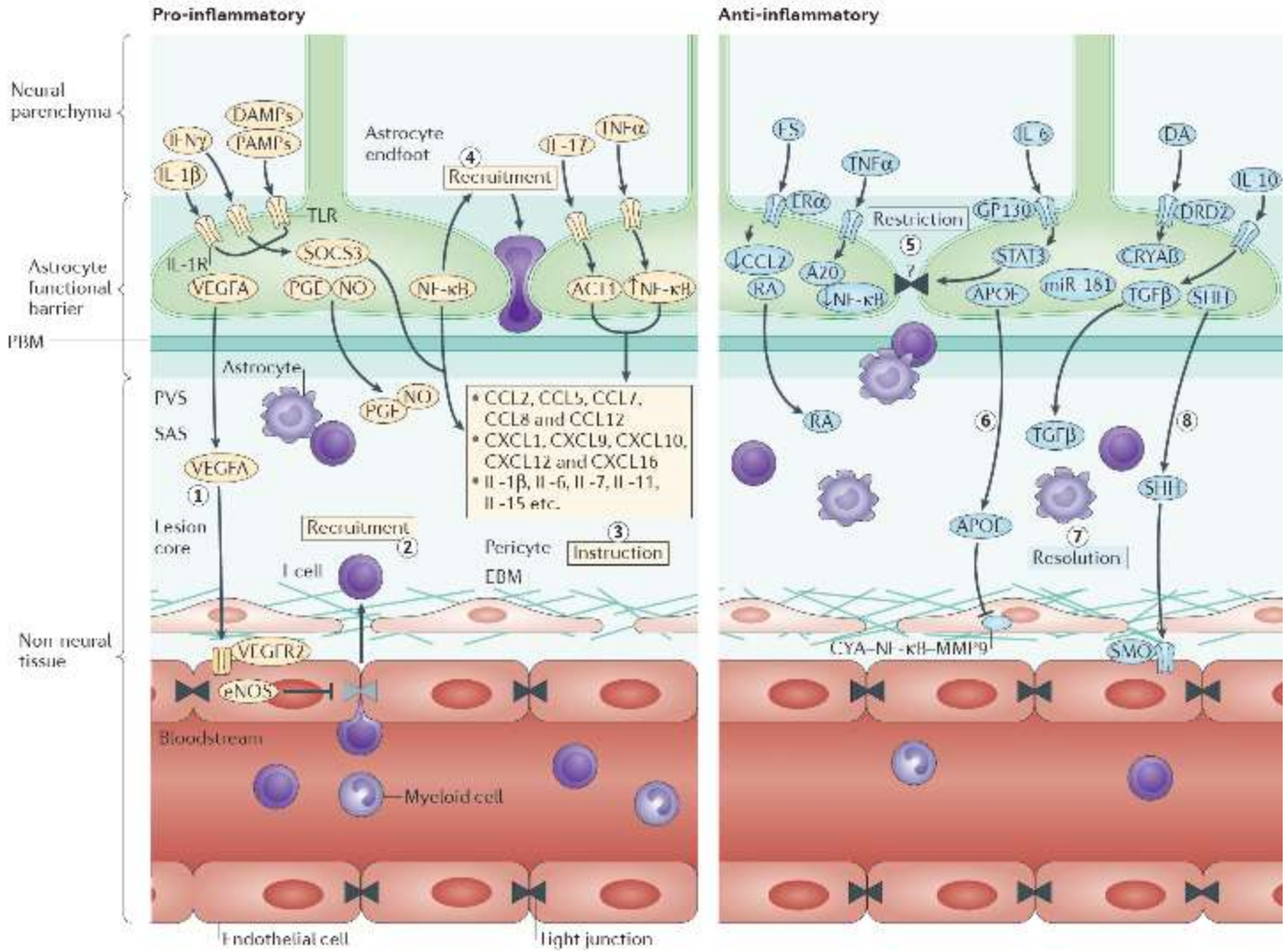
Nimmerjahn et al,
Science, 2005.

Astrocytes also regulate immune responses: Physical barrier



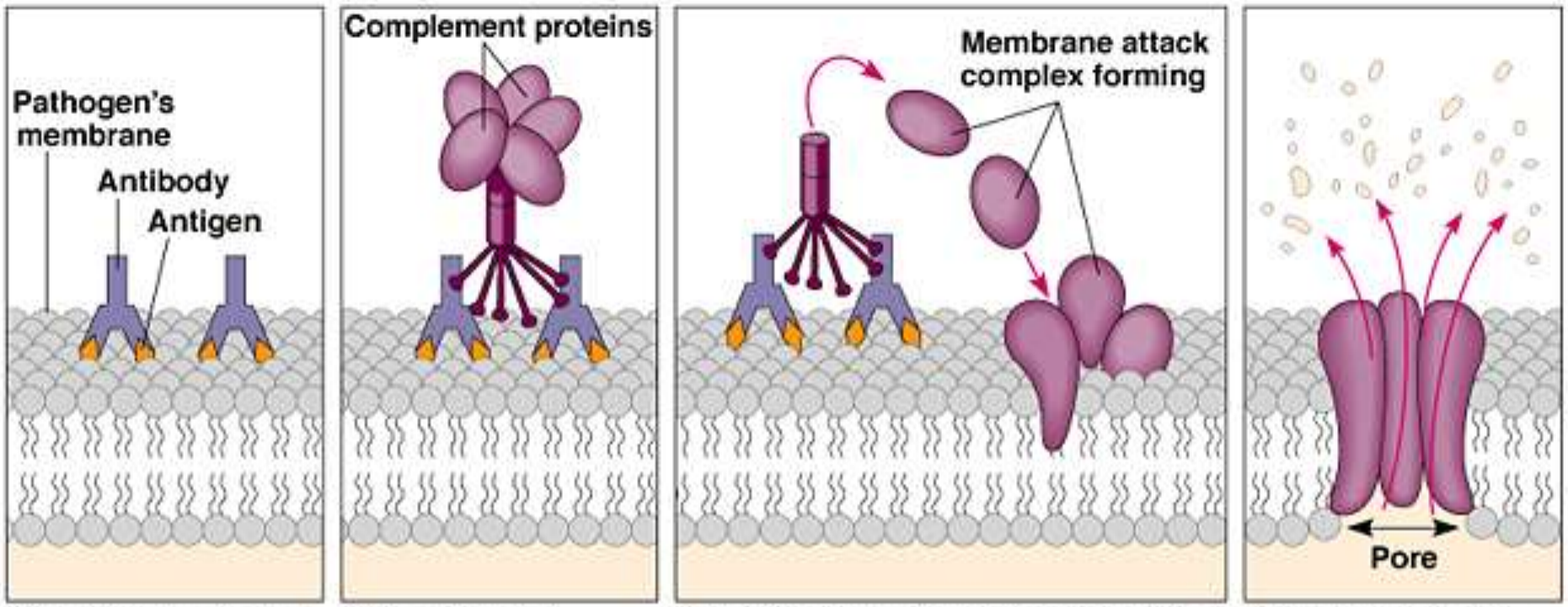
Sofroniew, 2015 Nat Neurosci Rev

Astrocytes also regulate immune responses: Chemical barrier/regulation



Sofroniew, 2015 Nat Neurosci Rev

• Complement system—30 proteins interact in a series of steps that results in lysis of invaders



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Complement in the Normal and Injured CNS

Normal CNS

- all complement factors are synthesized by microglia, astroctyes, or neurons
- various complement receptors are expressed on glia and neurons
- Tags synapses for destruction by microglia

Injured CNS

- complement expression increases with age and injury
- Increased complement is associated with neurodegeneration
- Membrane attack complex is detected on neurons in excitotoxic and nerve lesion models, stroke, and neurodegenerative diseases

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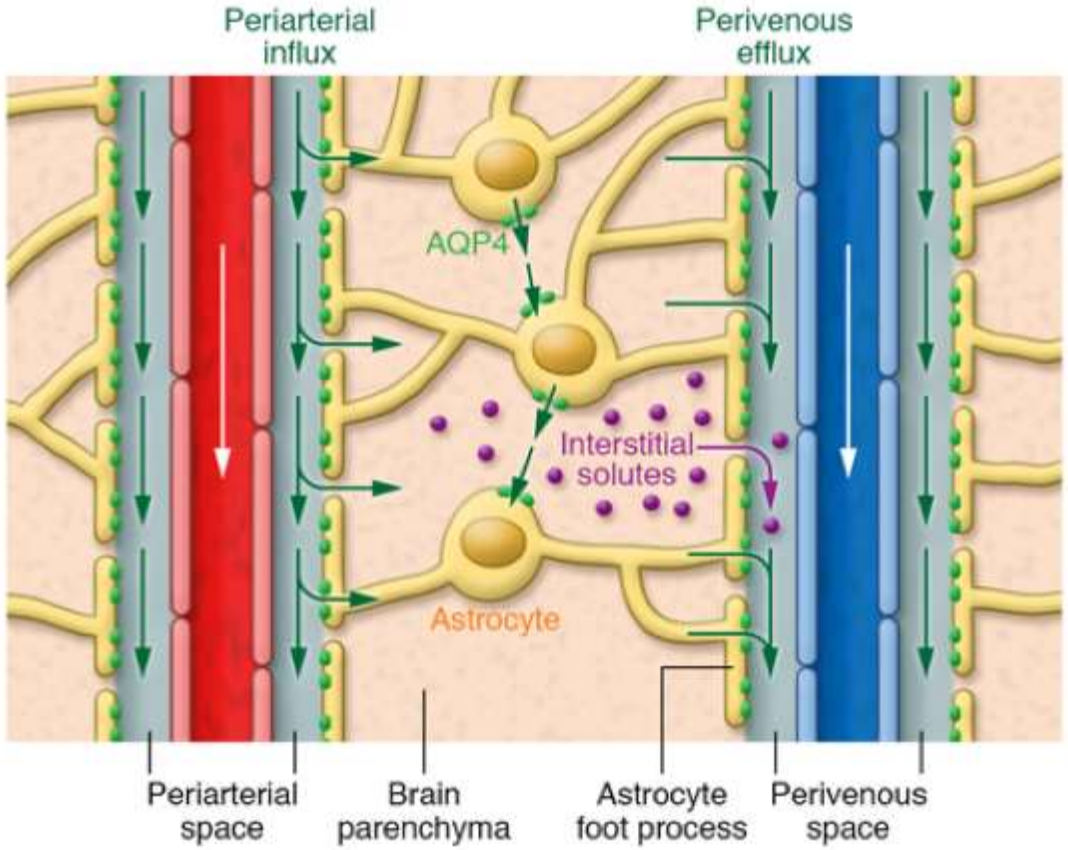
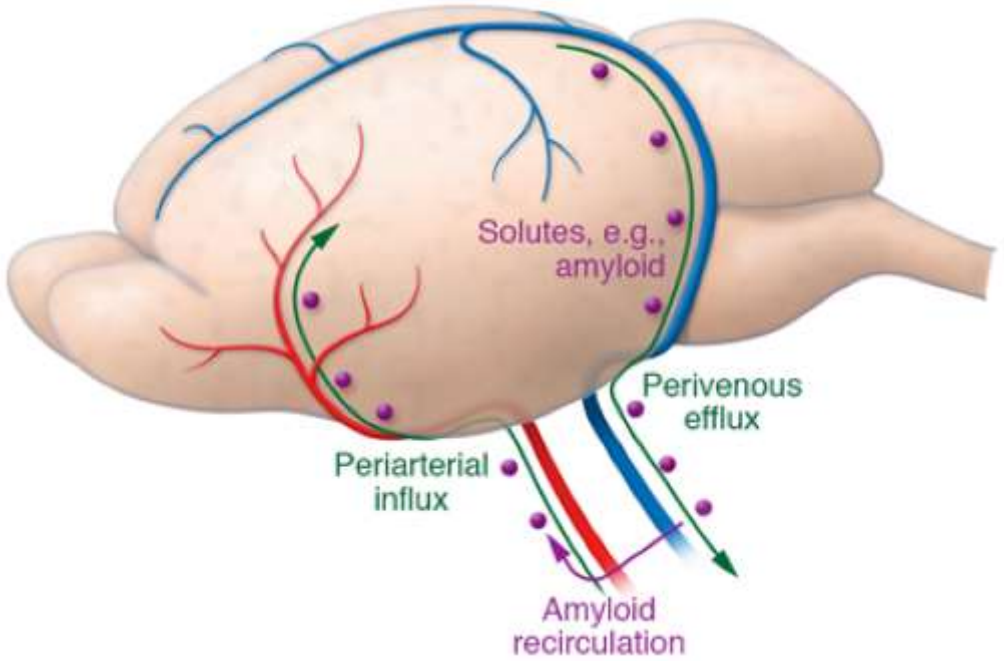
CNS “immune privilege”

- Term coined after experiments on skin transplantation into brain
  - Rejection takes longer
  - Except if the rejection response is already established in the body
- But we now know that
  - the brain is patrolled regularly by T and B lymphocytes
  - there are CNS lymphatics

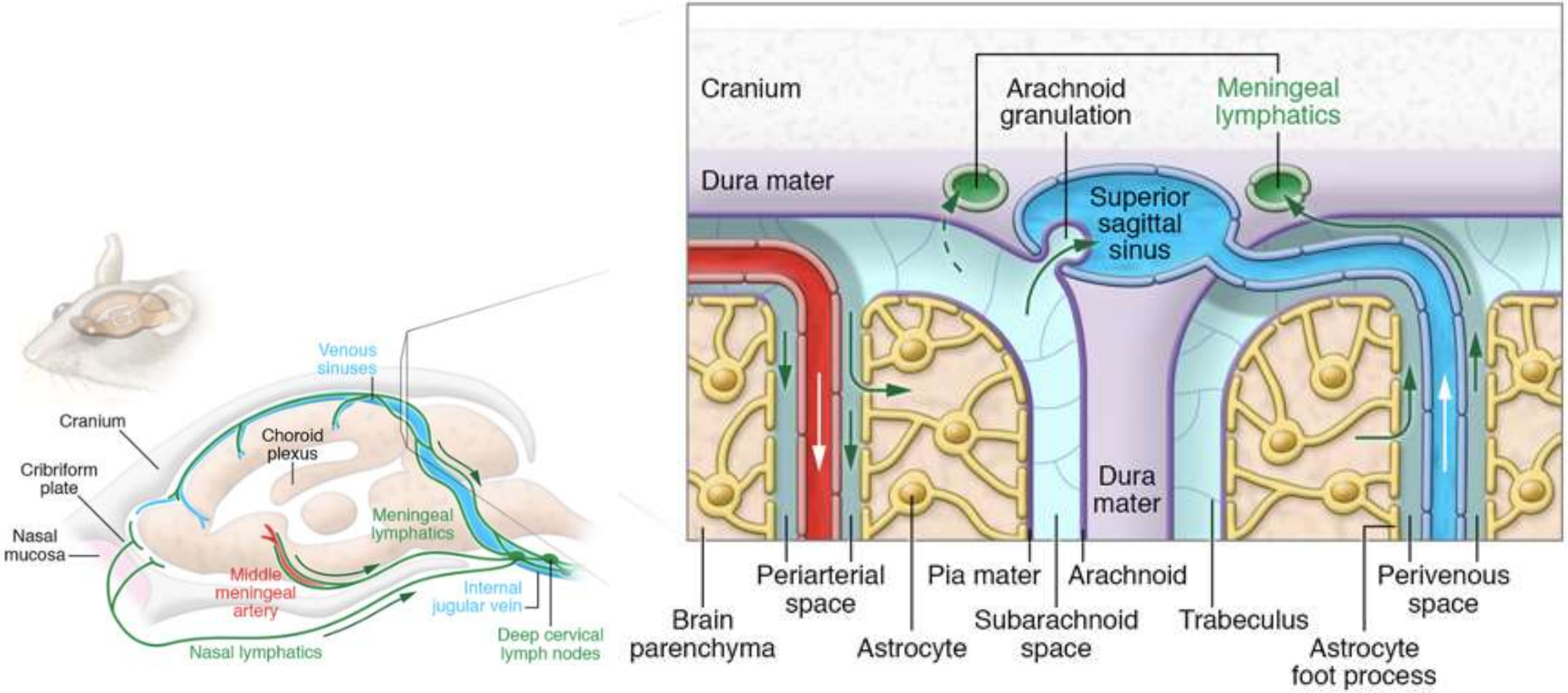
The glymphatic system





Louveau et al, 2017, JCI 127(9):3210-3219

Brain lymphatic system



Louveau et al, 2017, JCI 127(9):3210-3219

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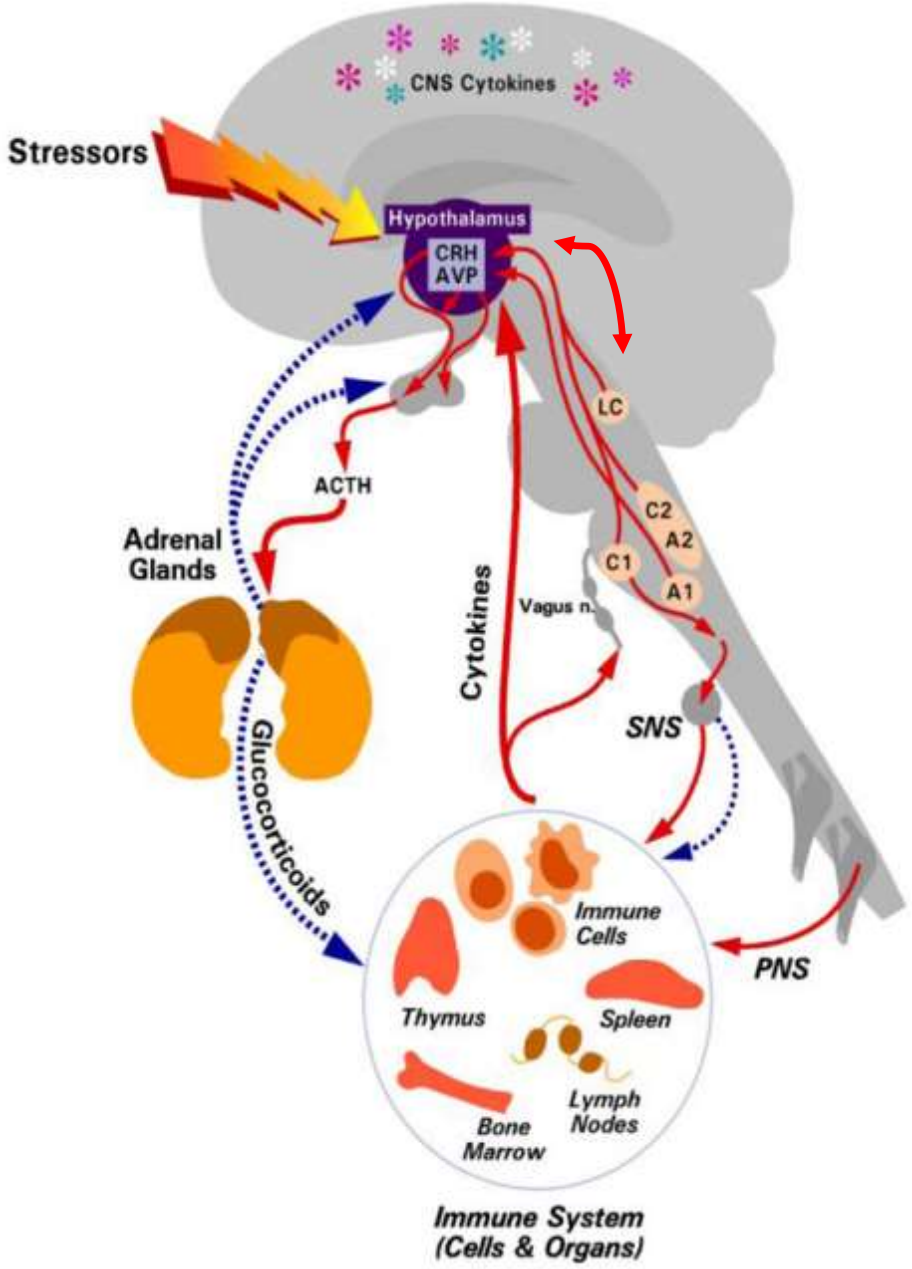
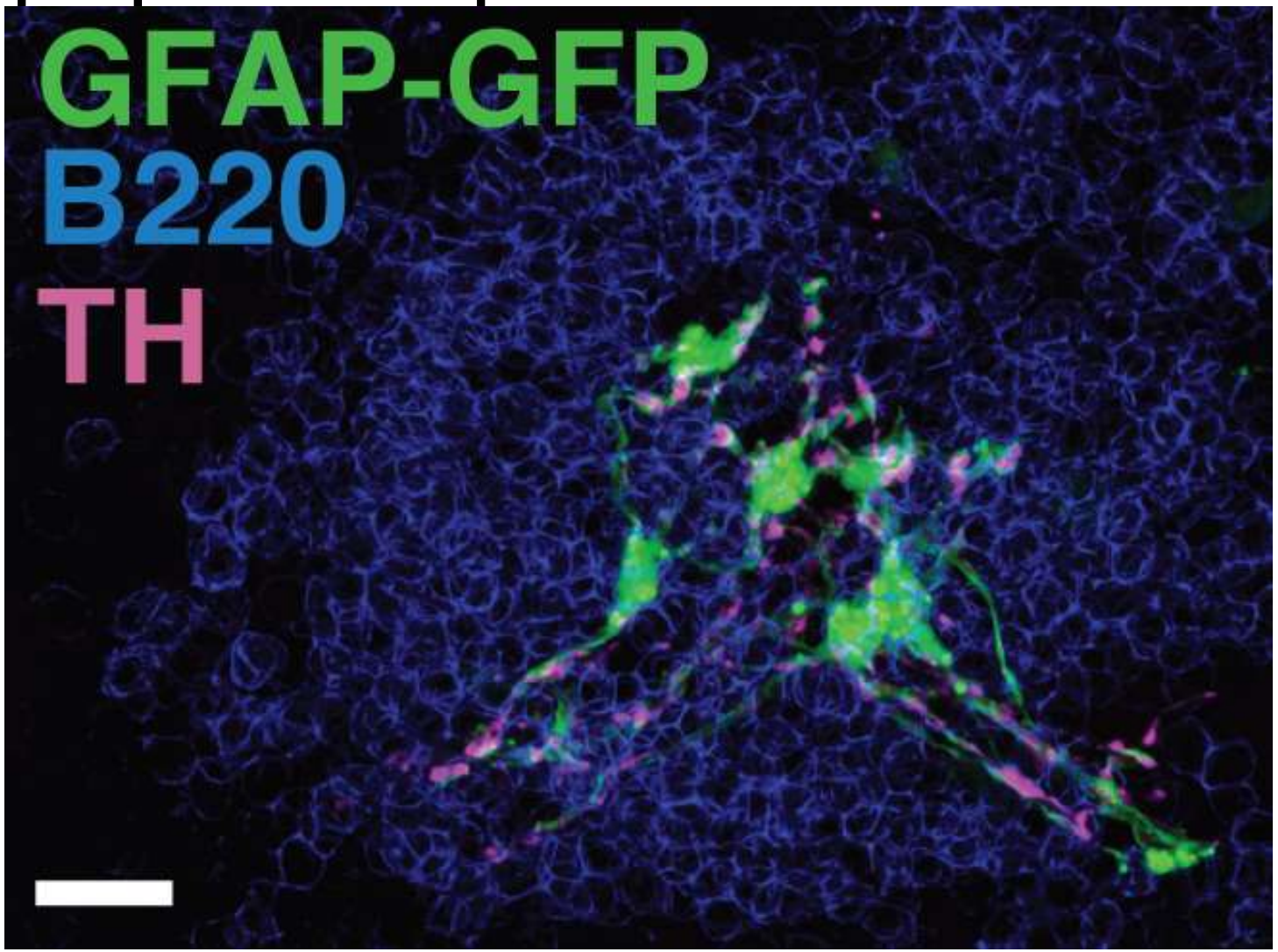
Sympathetic Pathways / Stress responses

- There is bi-directional interaction between the locus coeruleus and the hypothalamus

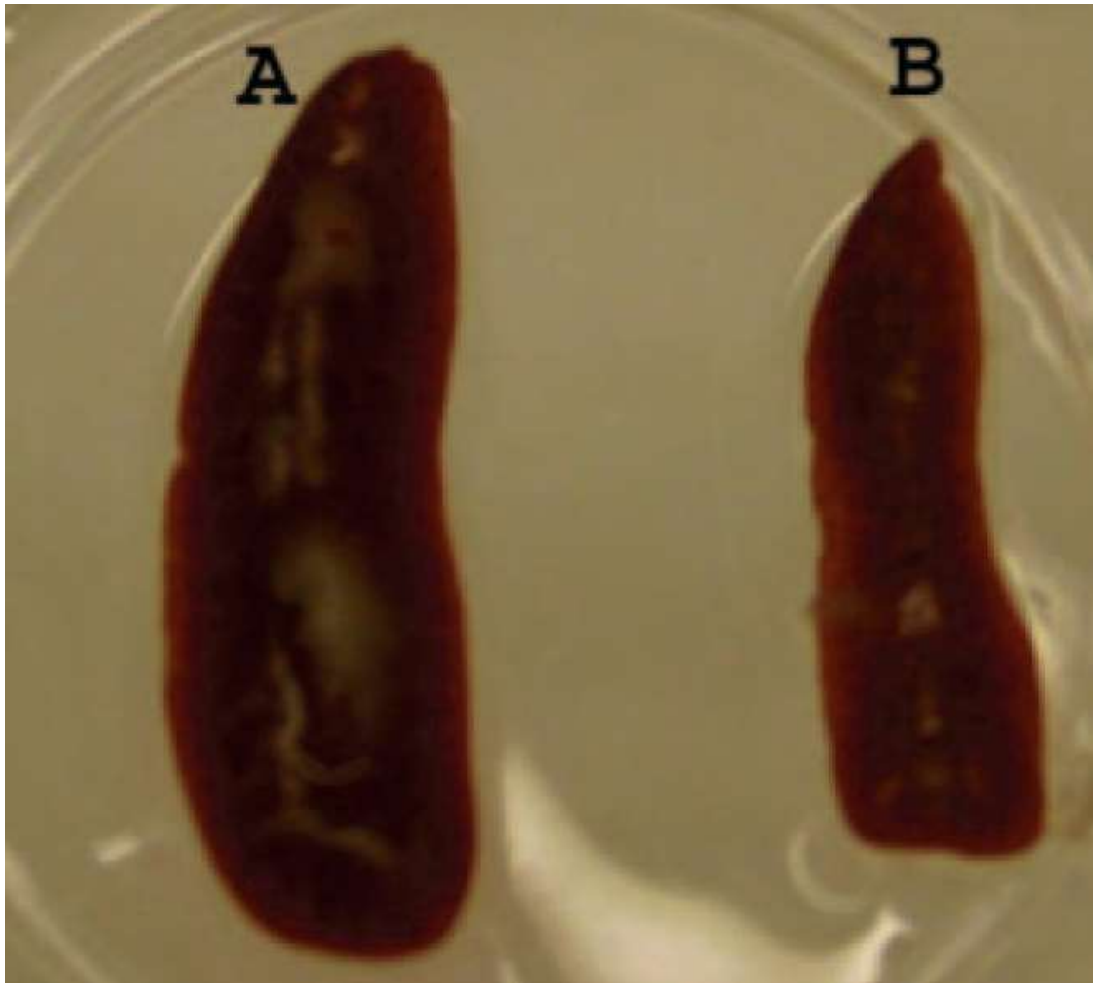
- Central sympathetic activation is required for glucocorticoid release as well as epinephrine release by the adrenal glands



Spleen glia and sympathetic nerves in a B cell follicle in white pulp of the spleen

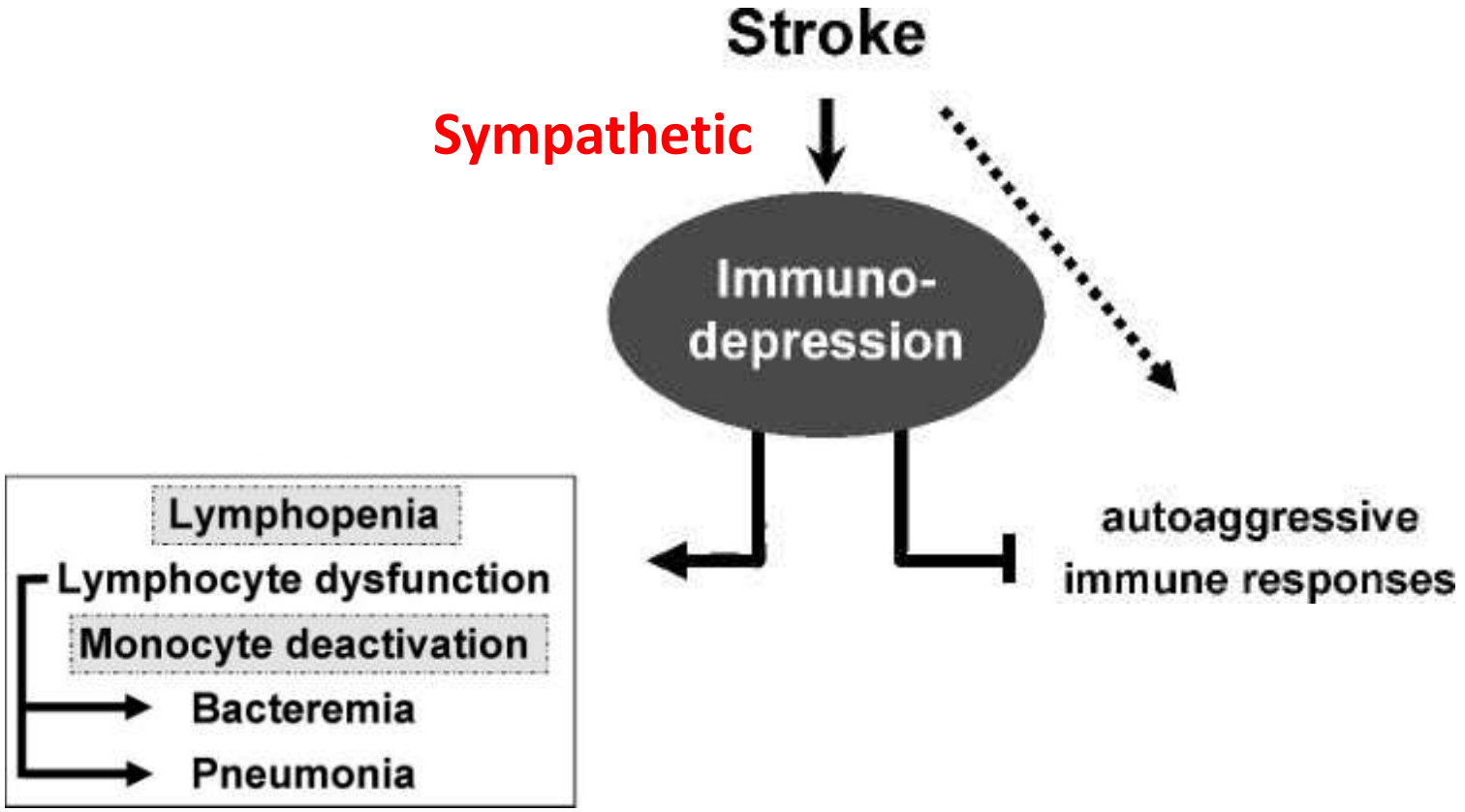


Splenic atrophy 4d after stroke



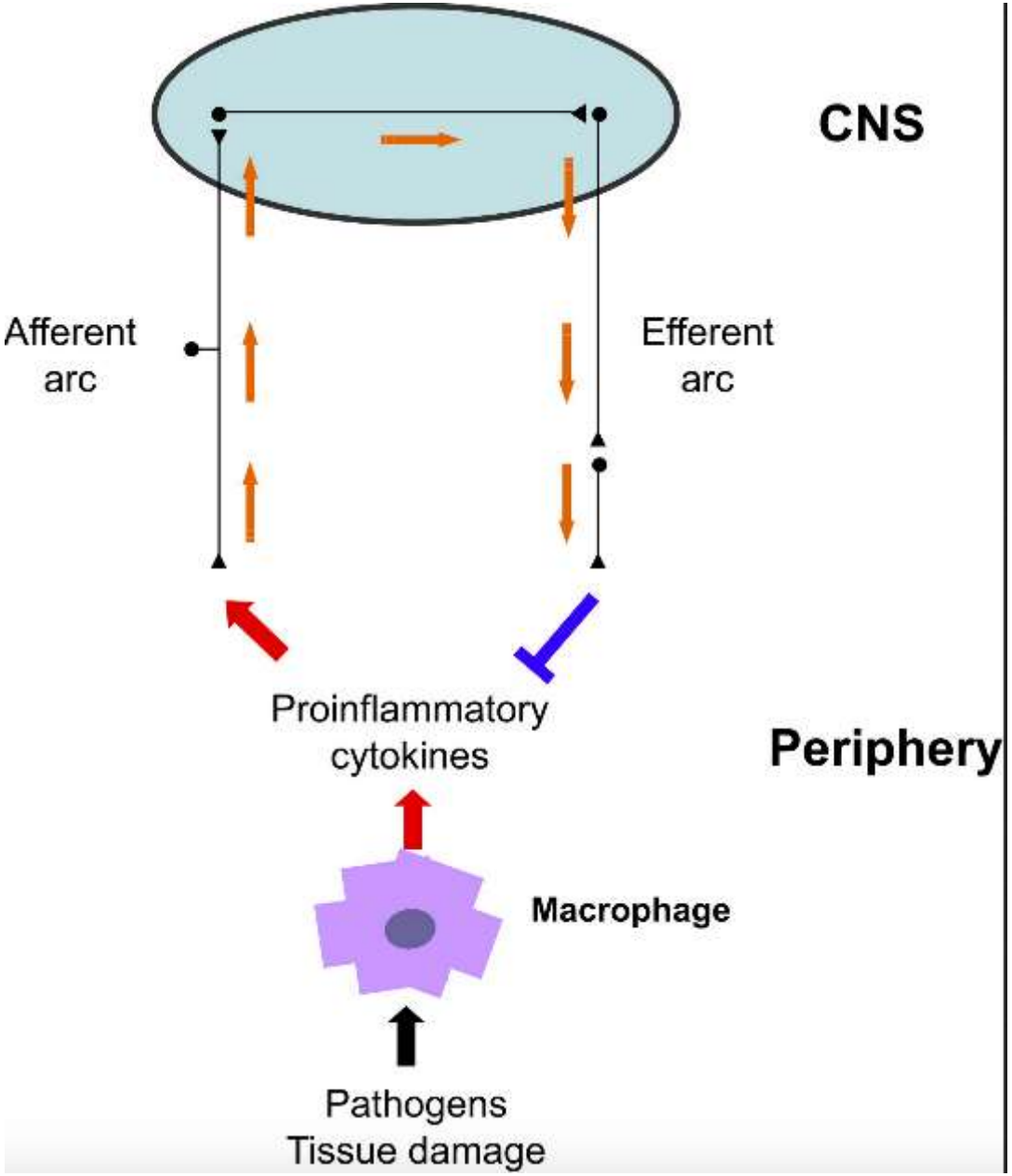
Offner, 2006. J Immunol 176:6523.

Stroke-induced Immunodepression



Dirnagl et al, Stroke. 2007;38[part 2]:770- 773

There is also a cholinergic/ parasympathetic immunosuppression reflex



Rosas-Ballina & Tracey, Neuron 2009

The secretome of the immune system is part of normal biology in the brain

- Immune molecules haven’t always “read the textbook”
- Neurons make most chemokines and cytokines, and can express their receptors
- Cytokines have been implicated in maintaining or diminishing synaptic strength
- Chemokines guide axonal sprouting during development and probably during disease
- Neurogenesis is modulated by neuroinflammation
- Chemokines are implicated in sensory neuron function and chronic pain
- MHC class I on neurons is important for brain development, synaptic strength, and perhaps targeting them for immune destruction

Any questions?