Key Concepts in Neuroimmunology, a dialogue between Philosophers and Scientists

Which cells are the immune cells of the brain?

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MICROGLIA: THE BRAIN INNATE IMMUNE SYSTEM

THE CNS: A SITE OF LIMITED IMMUNE SURVEILLANCE

MICROGLIA: THE RESIDENT IMMUNE CELLS OF THE BRAIN

(Ransohoff, 2016)
The Discovery of Microglial Cells

- First called “microglia” around 1920
- Based on Nissl staining

1. Microglia enter the brain during **early development**.
2. These invading cells have amoeboid morphology and are of mesodermal origin.
3. They use vessels and white matter tracts as guiding structures for migration and enter all brain regions.
4. They transform into a **branched, ramified morphological** phenotype in the more mature brain (known today as the resting microglia).
5. In the mature brain, they are found almost **evenly dispersed** throughout the central nervous system and display little variation.
6. Each cell seems to occupy a **defined territory**.
7. After a **pathological event**, these cells undergo a transformation.
8. Transformed cells acquire amoeboid morphology similar to the one observed early in development.
9. These cells have the capacity to **migrate, proliferate and phagocytose**.

**Still valid today**
CNS IMMUNE REGULATION: THE CLASSICAL VIEW

(Hanisch and Kettenmann, Nature Neuroscience, 2007)
THE YIN AND YANG OF MICROGLIAL ACTIVATION

PHENOTYPIC PLASTICITY
OF MICROGLIA

EACH PATHOLOGICAL SITUATION IS ASSOCIATED TO A
UNIQUE PHENOTYPIC SHIFT

(Perry et al., Nature Reviews Neurology, 2010)
MICROGLIA IS NOT JUST AN IMMUNE CELL
MICROGLIA ENTERS THE BRAIN VERY EARLY DURING DEVELOPMENT

(Ginhoux et al., Frontiers in Cellular Neuroscience, 2013)
MICROGLIA IS INVOLVED IN CNS DEVELOPMENT

(Frost and Schafer, Trends in Cell Biology, 2016)
MICROGLIA: FAR FROM BEING « DORMANT SOLDIER »

Resting Microglial Cells Are Highly Dynamic Surveillants of Brain Parenchyma in Vivo

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(Nimmerjahn et al., Science, 2005)
MICROGLIA MAKES CONTACTS WITH NEURONS

(Wake et al., Journal of Neuroscience, 2009; Kettenmann et al., 2012)
MICROGLIA NEVER WALKS ALONE
THE BRAIN IMMUNE SYSTEM
ANATOMY MATTERS

(Engelhardt et al., Nature Immunology, 2016)
CNS-ASSOCIATED LEUKOCYTE DIVERSITY IN THE STEADY-STATE

(Mrdjen et al., Immunity 2018)
CNS-ASSOCIATED LEUKOCYTE DIVERSITY IN THE STEADY-STATE

(Mrdjen et al., Immunity 2018)
BORDER-ASSOCIATED MACROPHAGES (BAM)

√ 4 SUBSETS OF BAMS.

(Mrdjen et al., Immunity 2018)

√ DIFFERENT LOCATIONS WITHIN THE CNS
DENDRITIC CELLS

(Mrdjen et al., Immunity 2018)
LEUKOCYTES TURNOVER

(Mrdjen et al., Immunity 2018)
AGING CAUSES AN ALTERED CNS IMMUNE LANDSCAPE...

(Mrdjen et al., Immunity 2018)
... AND A SUBSET OF REACTIVE MICR OGLIA EMERGES

(Mrdjen et al., Immunity 2018)
AUTOIMMUNE NEUROINFLAMMATION
EAE MODEL

Steady state CNS leukocytes

Peak EAE CNS leukocytes

Cell type
1. Microglia
2. BAMs
3. Neutrophils
4. Ly6C\textsuperscript{hi} monocytes
5. MDCs
6. Ly6C\textsuperscript{low} monocytes
7. cDCs
8. pDCs
9. B cells
10. T cells
11. NK T cells
12. NK cells
13. ILCs
14. Eosinophils
15. Mast cells

(Mrdjen et al., Immunity 2018)
CONCLUSION

THE CNS IMMUNE SYSTEM: NEW CONCEPT

NEUROINFLAMMATION

STATE 1

STATE 2

STATE 3
CONCLUSION
THE CNS IMMUNE SYSTEM: NEW CONCEPT

✓ What is the Brain Immune System?

✓ What is its role? Steady-state, Pathology?

✓ How do leukocytes coordinate their response in the CNS

✓ What is the role of microglia under immune activation?

✓ Interaction with peripheral immune system?

✓ Is there a frontier between peripheral and central immune systems? Role of that frontier in immune response
Thank you for your attention