MACROPHAGES

# Microglial cell origins

There is much debate as to the origin of microglial cells (the resident macrophages of the central nervous system (CNS)). It has been proposed that haematopoietic progenitor cells are recruited from the blood and differentiate in the CNS in waves during the embryonic and perinatal stages of development (a process termed definitive haematopoiesis). Ginhoux *et al.* now show that microglial cells derive from primitive myeloid progenitors, which arise in the yolk sac before embryonic day 8 (E8.0). They also demonstrate that microglial cells are maintained independently of definitive haematopoiesis.

Initial data from congenic bone marrow chimeric mice and from parabiotic mice (which are surgically joined and have a common blood circulation) suggested that postnatal microglial cells are maintained in the CNS independently of circulating monocytes. Instead, they seem to be maintained by tissue-resident radio-resistant precursor cells.

To further understand the origin of microglial cells during development, the authors used mice in which a marker for early myeloid progenitors and microglial cells, $CX_3C$-chemokine receptor 1 ($CX_3CR1$), was linked to green fluorescent protein. They found that $CX_3CR1^+$ (macrophage/microglial) cells were first detected at E9.5 and that microglial cells were found in the cephalic mesenchyme and the neuroepithelium at E10.5.

The authors next carried out lineage tracing studies in knock-in mice in which embryonic cells that were induced to express a specific gene on different days of gestation could be indelibly marked and traced. Until E8.0, the expression of this gene is restricted to primitive haematopoietic progenitors. The authors found that 'marked' myeloid progenitors that arise before E7.5 (primitive haematopoietic cells) contribute significantly to the adult microglial cell population and have little potential to develop into blood leukocytes. Functional blood vessels were required for the migration of microglial cell progenitors from the yolk sac to the brain rudiment between E8.5 and E9.5. Furthermore, the induction of this gene after E8.5 did not give rise to marked microglial cells in the adult brain, whereas the number of marked leukocytes was greatly increased, indicating that definitive haematopoiesis makes a minimal contribution to adult microglial cell development.

So, primitive myeloid precursors give rise to adult microglial cells in the CNS and are maintained with minimal contribution from circulating monocytes in the steady state, indicating that microglial cells are an ontogenically distinct population in the mononuclear phagocyte system.

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**ORIGINAL RESEARCH PAPER** Ginhoux, F. *et al.* Fate mapping analysis reveals that adult microglia derive from primitive macrophages. *Science* **330**, 841–845 (2010)