Microglia: origin and function

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• Highly motile cells within the CNS with macrophage features
• Rapidly activated upon changes of the brain homeostasis
"Primary microgliopathies": diseases induced primarily by microglia (mutations in CFS1-R in HDLS, etc.), evtl. MECP2 in Rett, TREM2 in FTD, CD33 in AD, TNFR, IRF-8 in MS etc.

"Secondary microgliopathies": microglia as disease enhancing cells in neurodegeneration (AD, PD etc.), inflammation (MS) and psychiatric disorders (autism) etc.

What is the origin of microglia?
Possible origin of microglia (& tissue macrophages)

Embryonic

Primitive myelopoiesis

Blood island

Yolk sac stem cell

Erythromyeloid precursor

Embryonic/Postnatal (bone marrow)

Definitive myelopoiesis

Placenta

Hematopoietic stem cell

Myeloid precursor

F4/80\textsuperscript{hi} cells

F4/80\textsuperscript{lo} cells

Monocyte

Microglia

F4/80\textsuperscript{lo} cells

Possible origin of microglia (& tissue macrophages) [Prinz & Priller, 2014]

Myb-dependent and independent tissue macrophages in the body

Brain

Pu.1\textsuperscript{++}

Primitive hematopoiesis

Yolk sac

Definitive hematopoiesis

Fetal liver

→ most tissue macrophages are derived from both primitive and definitive hematopoiesis
→ c-myb ko mice lack definitive hematopoiesis
→ microglia are present in normal numbers in c-myb ko mice

Schulz et al., Science, 2012
**Microglia progenitors can be targeted starting from E8.5 in utero**

Schulz et al., Science, 2012

**Origin of microglia & tissue macrophages**

Are YS macrophages microglia progenitors?  
→ There are no macrophages in the E7.25-8.5 YS!  

Prinz & Priller, 2014
What is the microglia progenitor in the yolk sac?

Thanks to: Katrin
**Tool to trace myeloid cell fate**

![Image of Cx3cr1^en^, E9.75](image)

**Characterization of yolk sac progenitors**

![Graphical representation of cell fate characterization](image)

Kierdorf et al., Nat Neurosci, 2013
**c-kit+ YS progenitors have myeloid potential**

Differentiation on methylcellulose

- **A**
  - dpc 8.0
  - CD45+ maternal hemat. cells
  - FACS sorting

- **B**
  - dpc 9.9
  - A1 progenitors
  - FACS sorting
  - A2 progenitors

→ *c-kit+ YS cells at 8.0 dpc have erythromyeloid potential = EMP*

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**Yolk sac progenitors (EMPs) can differentiate into microglia on organotypic hippocampal slice cultures**

- **A**
  - dpc 8.0
  - CD45+ Maternal hemat. cells
  - FACS sorting

→ *EMPs give rise to CX3CR1^GFP+ microglia = microglia progenitor!!*

*Kierdorf et al., Nat Neurosci, 2013*
Dynamic gene regulation during microglial development

Analysis of transcription factors

Kierdorf et al., Nat Neurosci, 2013
**IRF8 is required for normal microglia development**

Kierdorf et al., Nat Neurosci, 2013

**IRF8 deficiency leads to reduced A2 cells**

Kierdorf et al., Nat Neurosci, 2013
Increased apoptotic A1 cells in the absence of IRF8

Kierdorf et al., Nat Neurosci, 2013

Microglial development

→ Microglia development depends on Irf-8 (and PU.1, CSF-1R and ligands)

→ Microglia are independent on c-myb, Klf4, Batf4, Id2
Is it possible to target microglia specifically?

Yes we can…

Thanks to: Peter & Tobi
and Jung lab!
Previous tools to target microglia in vivo: the LysM Cre line

Goldmann, Wieghofer et al., Nat Neurosci, 2013

Previous tools to target microglia in vivo: the CD11c Cre line

Goldmann, Wieghofer et al., Nat Neurosci, 2013
**A new tool to target myeloid cells in the body: the CX3CR1 Cre line**

A

B

C

D

E

Ly6Ch[T] monocytes
Ly6Ch[T] monocytes
Granulocytes
CD11b+ T cells
CD4 T cells
B220 B cells
MHCII+ NK cells

**A new tool to target microglia only: the CX3CR1 ERT2 Cre line**

A

B

C

D

E

Ly6Ch[T] monocytes
Ly6Ch[T] monocytes
Granulocytes
CD11b+ T cells
CD4 T cells
B220 B cells
MHCII+ NK cells

Goldmann, Wieghofer et al., Nat Neurosci, 2013
Different turn over/half live of microglia versis monocytes revealed by CX3CR1 ERT2 Cre

Tak1 is master regulator of cell activation

Ajibade et al., 2013
Normal microglia homeostasis in the absence of Tak1

Goldmann, Wieghofer et al., Nat Neurosci, 2013

Tak1 dependent pathways are induced during CNS inflammation (EAE)

Goldmann, Wieghofer et al., Nat Neurosci, 2013
**Microglia-restricted absence of TAK1 abolishes inflammation in a mouse model of multiple sclerosis**

- **NestinCre-Tak1fl/fl**
  (KO in neurons, oligodendro- & astrocytes)

- **CX3CR1CreER-Tak1fl/fl**
  (KO in microglia)

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**Reduced CNS damage and immune suppression in CX3CR1CreER:Tak1fl/fl mice**

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Goldmann, Wieghofer et al., Nat Neurosci, 2013
Microglia-specific Tak1 controls activation of p65

![Image](image_url)

Goldmann, Wieghofer et al., Nat Neurosci, 2013

Summary

- Microglia have a distinct origin from the yolk sac (Kierdorf, Nat Neurosci, 2013): EMP migrate into the brain at day E 9.5 in mouse
- Microglia share yolk sac origin with other tissue macrophages (Schulz, Science, 2012)
- Microglia can be targeted by using CX3CR1 ERT2 Cre in mouse (Goldmann, Nat Neurosci, 2013): monocytes in blood are short living, microglia long living
- TGF-β activated kinase (TAK)1 is induced during CNS autoimmunity (Goldmann, Nat Neurosci, 2013)
- Microglial TAK1 induces CNS inflammation, demyelination, axonal damage (target) via Nf-kB, JNK, ERK1/2 (Goldmann, Nat Neurosci, 2013)
Become a member of the team: Neuropathology in Freiburg!

Bone marrow
HSC → GMP → Ly-6c<sup>hi</sup> monocyte → Ly-6c<sup>lo</sup> monocyte

Katrin Kierdorf:
Nat Neurosci, 16(2):273-80.

Akki Mildner:
Nat Neurosci, 10(12):1544-53.

Angie Dann:

Tobi Goldmann & Peter Wieghofer:

Biber Lab, Freiburg
Geissmann Lab, London
Hanisch Lab, Göttingen
Jung Lab, Rehovot
Priller Lab, Berlin
Rosenbauer Lab, Münster
Waisman Lab, Mainz

...and many more.