CNS Barriers and Immune Responses in Mouse CNS TB

Zsuzsa Fabry & Matyas Sandor
University of Wisconsin-Madison
WI, USA
Basic Question: What are the mechanisms that govern CNS TB?

• Question 1: What is the mechanism of *Mtb* dissemination into the CNS?
• Question 2: What are the CNS and systemic host responses to CNS TB?
Hypothesis: Infected CD11c\textsuperscript{high} cells traffic from granulomas and might contribute to dissemination to the CNS

Schreiber et. al 2011 JCI, Harding et. al 2015 Sci Rep
DCs produce MMP2 and 9 and DC transmigration through BBB is inhibited by MMP inhibitors (TJ proteins are substrate for MMPs)

Zozulya A.
Mtb infection of CD11c\textsuperscript{high} cells leads to their decreased mobility (and chemokine receptor expression)

Fruzsina Walter and Trey Gilpin, AAI presented abstract 2017

35 mm glass bottom dish

Plugs

RPMI Cells

2 mm migration field of view

20 mm coverglass, No. 1.5 (0.16-0.19 mm thickness)

Non-inf. DC

Inf. DC

Accumulated distance (unit)

Velocity (units)

Fruzsina Walter and Trey Gilpin, AAI presented abstract 2017
BMDC transmigrate through brain microvessel endothelium by a MIP1α and MMP dependent manner. DC produced MMP 2 and 9 reorganize occludin and decrease electrical resistance. MMP blockers decrease DC migration (Zozulya A et al 2007 JI).

In an in vitro blood brain barrier model infected BMDC has limited capacity to migrate through
Infected CD11c^{high} cells cross the Blood Brain Barrier (BBB) at sites of cellular aggregates formed with P25 PBMCs.
CD11c\textsuperscript{high} cell invasion and foci formation in the choroid plexus

Bar: top row: 0.5 mm, bottom row: 100 µm.

Fruzsina Walter and Trey Gilpin, AAI presented abstract May 2017
Basic Question: What are the mechanisms that govern CNS TB?

- **Question 1:** What is the mechanism of *Mtb* dissemination into the CNS?
  - CD11c expressing dendritic cells might contribute to *Mtb* entry into the CNS.
  - Infected DCs induce inflammatory foci formation that correlates with dissemination.
  - Meninges and choroid plexus are potential portals.
Basic Question: What are the mechanisms that govern CNS TB?

• Question 2: What are the CNS and systemic host responses to CNS TB?
*Mtb* Infection is Controlled in the CNS

Hernandez, G. Manuscript in submission AJP 2017
Granuloma formation in the brain following IC *Mtb* inoculation

Hernandez, G. Manuscript in submission AJP 2017
CD11c<sub>high</sub> Dendritic Cells Infiltrate into the CNS Following IC *Mtb* Infection

Hernandez, G. Manuscript in submission AJP 2017
IC *Mtb* leads to robust infiltration of IFNγ-producing T lymphocytes

- Post IC infection there is an IFNγ dominant T cell response in the CNS
- Most are in granulomatous lesions
- P25 transgenic T cells are seen directly interacting with eYFP+ cells in the CNS

Hernandez, G. Manuscript in submission AJP 2017
Specific anti-bacterial T cell expansion is induced earlier by IC *Mtb* compared to lung infection.
IFNγ-producing T lymphocytes and CD11c cells most likely access the CNS via the choroid plexus.
CNS *Mtb* infection induces microglia and astrocyte activation in the brain.

*Myobacterium Tuberculosis* (*Mtb*) induction microglia and astrocyte activation in the brain.

- C1q?
- TNFα?
- IL1α?

**Neurotoxin**?

**Neuronal Death**?

**Reactive Astrocytes**

- A1?
- Factor B?
CNS *Mtb* infection induces complement production in the brain

Aisha Mergaert, unpublished data
CNS *Mtb* infection increases Blood Brain Barrier (BBB) “leakage” in the brain

Naïve | 1 Week | 3 Weeks | 7 Weeks

Aisha Mergaert, unpublished data
Basic Question: What are the mechanisms that govern CNS TB?

Question 2: What are the CNS and peripheral host responses to CNS TB?

- Gliosis (astrocytes and microglia)
- Complement activation
- Vascular leakage (IgG staining)
- Robust T cell priming and infiltration via choroid plexus (mostly)
- Inflammatory myeloid cell accumulation
- Strong and early protection

School of Medicine and Public Health
UNIVERSITY OF WISCONSIN-MADISON
Conclusions: What are the mechanisms that govern CNS TB?

- Infected dendritic cell-induced cellular aggregation promotes bacterial dissemination into the brain.
- Protective immunity against CNS TB is dominated by IFN-γ producing Th1 cells – entry though choroid plexus.
- Bacteria-specific T cell responses are earlier compared to the lung.
What can we learn from murine CNS TB models that could contribute to clinical CNS TB treatment?

- Inhibition of infected DC migration across the BBB might contribute to therapies: MMP blockers? Others pathways for interrupting migration?
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