Maturation of iBALT can be mediated by vaccination and serve as backdoor for T cells to the *Mycobacterium tuberculosis* (Mtb) infected lung

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The TB granuloma contain or are associated with iBALTs

- Granulomas contain or are associated to tertiary lymphoid structures (TLS) called iBALT that develop in the lung during Mtb infection (Mice, NHP, Man)

- iBALTs associated with good TB control in animal models

- Different maturation states
  - Loose lymphoid follicles ⇒ HEV+iBALTs

- IL-17-producing subsets implicated in formation

Kauffman et al., 2017

Immunization with CAF01 leads to significant protection and less pathology.
s.c. immunization with CAF01 drives Th1/Th17 and promotes/matures iBALT

TF+ve E6 Tetramer specific CD4 T cells

% IFN-γ +  -  +  -
IL-17 +  -  +  -

0.006

% of E6-tet+iv- neg

Lung cells

Wk8

H107/CAF01

Saline

CD38

GL7

GC Pre-GC

# iv-ve B220+IgD- cells

10^3

10^4

10^5

IgD- B cells

Lung

HEV (F1; all sLex)

HEV (MECA-79; PNADs (sulfo-sLex))

Saline

CD4

Immunized

Week 4 p.i.

Week 9 p.i.
Can HEV+iBALT serve as an direct route into the TB granuloma?

"Conventional route"

Migration into lung interstitium
- Partly CXCR3 dependent
- Likely dependent on the cumulative effect of multiple chemokine receptors

Hoft. et al., 2019
Woodworth et al., 2017
Sallin et al., 2017

"Backdoor"

However, access to the granuloma core is a major impediment for control of Mtb

Gern et al., 2021
Kauffman et al., 2017
Srivastava 2013
CAN iBALT BE A BACKDOOR TO THE GRANULOMA?

- T cells
- 'Marked' T cells
- Dye
- Transfer
- Infected + Immunized with H107/CAF01
- Wk 6 infected recipients
- T cell homing/Microscopy
- Analysis

Leukocyte extravasation

+ HEV blocking
Preliminary data suggests a role for HEV-mediated entry to the Mtb infected lung

Lymph node entry of T cells from peripheral blood occurs exclusively through HEV-mediated interactions

- iBALT promoting vaccines can facilitate entry through HEV
- Ongoing studies to reveal positioning of cells
CONCLUSIONS

- The Th1/Th17 inducing vaccine H107/CAF01 promotes the development of fully mature iBALT in infected mice.
  - In comparison to unimmunized mice, immunized mice display highly organized iBALTs with clear formation of high endothelial venules (HEVs), aggregated T cell zones as well as increased infiltration of activated B cells.

- Blocking HEV-mediated entry with a-CD62L Abs reveal a potential role for HEV-mediated entry in vaccine modalities, where mature HEV+iBALTs are formed.

- Suggests that iBALT promoting vaccines can open a backdoor of T cell entry to the lung that potentially could improve intralesiononal positioning.

- Studies are ongoing to address this aspect.
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