New insights into lung resident immunity to *Mycobacterium tuberculosis*

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13th June 2023; Recognition and Control of Mtb infected Cells: From Basics to the Clinic
Overview of the immune response to Mtb

Inhaled Bacterium

Mtb

Lungs

Innate Immunity

Neutrophil

Macrophage

Irritated cell

Adaptive Immunity

Dendritic cell

Granuloma formation

Trafficking to Lymph Node $\approx$8-12 Days

Lymph Node

Lymphatics and Bloodstream

Effector T cells (Pro-inflammatory, Cytotoxic & Regulatory)

Memory T cells (Effector & Central)

T Cell Priming

Trafficking from Lymph Node $\approx$14-17 Days

Marino S & Kirschner DE, Computation (Basel) 2017
Classical paradigm of host lung immune response to Mtb

- TNF-α, IL-1β, IL-12, IL-18
- IFN-γ

Stimulation of IFN-γ producing cells
Initiation of adaptive immunity
Granuloma formation & containment of Mtb

Mtb

APC - Alveolar macrophage
- Dendritic cell

T-cell (CD4+/CD8+)
NK-cell

Adapted from Rook & Zumla Nat Rev Immunol 2005
Delayed onset of adaptive immunity following Mtb infection

Progression of Mtb infection in all animal models follows the same basic pattern: Rapid expansion followed by immune-controlled “stasis”.

Time course and distribution of Mtb by lung cell subsets

M. tuberculosis infection triggers recruitment of interstitial macrophages to the infected lung

Environmental pressures active within the phagocyte.

Nutritional shift
Production of ROIs
Production of RNIs
Acidification of the phagosome
Acquisition of lysosomal hydrolases, i.e.
proteinases
lipases
glucosidases
nucleotidases

Alveolar phagocytes are critical in early immune responses to Mtb
Current paradigm of macrophage control of Mtb

**Controller Cells**
- Th1 activated macrophages
- Product of IFN-g exposure
- Good at controlling Mtb *in vitro* and *in vivo* (in mice)
- Efficacy revealed in loss of function studies (KO mice)
- Vaccine efficacy assessed by immune correlates of Th1

**Permissive Cells**
- M2 macrophages or another cell type?
- Exposure to IL-10/IL-4 or TGF-b?
- Permissive for bacterial expansion *in vitro* and *in vivo*?
- We have minimal data on bacterial permissiveness as an immune function
- We also need bacterial correlates of permissiveness +/- immune correlates.
Using HIV infection to understand immunity to *M. tuberculosis* in the human lung
HIV infection increases the risk of developing TB disease

Cumulative hazard estimate of pulmonary TB incidence, by HIV status among South African gold miners (Pre-ART)

Sonnenberg et al., *J Infect Dis* 2005

Cumulative hazard estimate of pulmonary TB incidence, by HIV status among South African gold miners (Pre-ART)

Sonnenberg et al., *J Infect Dis* 2005

TB incidence rates during 8 years of follow-up of an ART cohort in South Africa: comparison with rates in the community

Gupta et al., *PLoS One* 2012
Potential mechanisms for increased risk of TB disease in HIV-infected people

HIV infection of alveolar CD4+ T-cells: Loss of immune surveillance

Alveolar macrophages (AMs) co-infected with HIV & Mtb: Impaired phagocyte function & loss of immune recognition

Alveolar macrophages co-infected with HIV & Mtb: Increased permissiveness for Mtb

Altered airway immune microenvironment
HIV-associated impairment and ART-mediated recovery of alveolar pathogen-specific immune responses

**Influenza**

<table>
<thead>
<tr>
<th>Group</th>
<th>Proportion of cytokine-secreting CD4 T cells</th>
<th>p-value</th>
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<tbody>
<tr>
<td>HIV- ART naive</td>
<td></td>
<td>0.001</td>
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<tr>
<td>HIV+ ART naive</td>
<td></td>
<td>0.04</td>
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<tr>
<td>HIV+ ART &lt;4 years</td>
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<td>0.73</td>
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<tr>
<td>HIV+ ART &gt;=4 years</td>
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<td>0.91</td>
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**M. tuberculosis**

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<tr>
<td>HIV- ART naive</td>
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<tr>
<td>HIV+ ART naive</td>
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Delayed and incomplete recovery of *M. tuberculosis*-specific CD4+ T cell numbers and function in HIV-infected adults on long term ART

Jambo et al., Am J Respir Crit Care Med 2014
HIV-associated impairment of airway innate effector cells

A. Alveolar macrophage (AM) proteolytic function

B. Frequency of airway MAIT cells

Impaired AM phagosome function pre-ART and delayed recovery on ART. HIV-associated depletion of MAIT cells in the airway targets the resident population.

Jambo KC et al., Am J Respir Crit Care Med 2014

Mvaya L et al., Frontiers Immunol 2019
Single cell analysis of alveolar macrophages reveals heterogeneity

(A) Umap plots showing unbiased clustering of AMs in mice and humans. (B) Gene expression values for the marker genes (Top2a and Mki67) of the AM_4 population indicative of cell replication (C) Gene expression values for (Cd63 and Fcer1g) of the AM_1 population. (D) Gene expression values for Zeb2, as well as the percentage of mitochondrial reads of the AM_2 population indicative of OXPHOS metabolism.

Pisu et al., J Exp Med 2021
Growth of Mtb *in vivo* segregates with host macrophage metabolism and ontogeny

Model 1. Re-Programming

- In the M1/M2 Re-Programming model Mtb growth is regulated by cytokine environment.

Model 2. Pre-Programming

- In the Pre-Programming model macrophage metabolism and ontogeny regulate Mtb growth.
Concluding remarks

1. Immunity to *M. tuberculosis* is complex.

2. Altered lung immune environment may promote/enhance growth & survival of Mtb in permissive AMs and progression to active TB.

3. Exploiting HIV-mediated lung immune impairment may unravel what constitutes protective immunity to TB in humans.

4. Modulation of epigenetic programming of tissue resident macrophage lineages by new TB vaccines/drugs could be a novel strategy to impact Mtb infection, control and persistence in humans.