Protective Antigen Specificity of B cells in TB

Jacqueline M. Achkar, MD, MSc, FIDSA
Professor
Departments of Medicine (Div. of Infectious Diseases), Microbiology & Immunology
Albert Einstein College of Medicine
What are the important antigenic targets for B cells?

- Passive transfer studies in mice (mostly murine IgG mAbs)
  - AM/LAM
  - PstS1 (Ag 38)
  - HSPX (α-crystatin, 16 kDa; IgA)
  - HBHA
  - MPT83

- Murine serum transfer from vaccine studies
  - AM/LAM, Ag 85

Reviewed in Achkar & Casadevall, CHM 2013
Enhanced control of *Mycobacterium tuberculosis* extrapulmonary dissemination in mice by an arabinomannan-protein conjugate vaccine


Prados-Rosales et al., *PLoS Pathog* 2017
## Human defense mechanisms in *Mtb* exposure & infection

**Inflammation & Mtb burden**

![Diagram showing lung sections with various infection states](image)

<table>
<thead>
<tr>
<th>Host Defense Mechanisms</th>
<th>Colonization &amp; Early Clearance</th>
<th>Non-traditional LTBI/Resisters</th>
<th>Traditional LTBI</th>
<th>At Risk for Reactivation</th>
<th>Progressor/Incipient TB</th>
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<tbody>
<tr>
<td>Mechanical</td>
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<tr>
<td>Cilia/Defensins</td>
<td>+?</td>
<td>?</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Innate Immunity</td>
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<td>Recruited Macrophages</td>
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<td>+/-</td>
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<td>x?</td>
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<tr>
<td>Neutrophils</td>
<td>-</td>
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<td>?</td>
<td>+/-</td>
<td>x</td>
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<tr>
<td>Adaptive Immunity</td>
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<tr>
<td>T cells</td>
<td>-</td>
<td>-/+</td>
<td>++</td>
<td>+</td>
<td>x</td>
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<tr>
<td>B cells/Abs</td>
<td>-</td>
<td>-/+</td>
<td>+</td>
<td>?</td>
<td>x?</td>
</tr>
</tbody>
</table>

*X = failure and/or imbalance and/or pro-inflammatory dominance*

Boom, Schaible & Achkar, JCI 2021
A Functional Role for Antibodies in Tuberculosis

Lu et al., Cell 2016


Lu et al, Cell 2016
Latently and uninfected healthcare workers exposed to TB make protective antibodies against *Mycobacterium tuberculosis*

Hao Li*, Xing-xing Wang*, Bin Wang*, Lei Fu*, Guan Liu*, Yu Lu*, Min Cao*, Hairong Huang*,1, and Babak Javid*,1

20 mg serum IgG i.p. 5 hrs prior to 100-200 CFU aerosolized Mtb

Li *et al.*, PNAS 2017
Mycobacterial Surface Polysaccharide AM & LAM

Jackson *Cold Spring Harb*, 2014
Capsular glycan recognition provides antibody-mediated immunity against tuberculosis

Tingting Chen, …, Todd L. Lowary, Jacqueline M. Achkar

12 ug AM-specific serum IgG i.p.
Prior to Mtb infection of B6 mice
Association of AM oligosaccharide recognition with IgG function against Mtb infection

Chen et al., J Clin Investigation 2020
Binding to glycan epitopes affects functions of anti-AM mAbs against *Mtb*
Human antibodies targeting a Mycobacterium transporter protein mediate protection against tuberculosis

Watson et al., Nat Commun 2021
Potential protective roles of antibodies and B cells in the lung during initial *Mtb* exposure and LTBI
IV BCG induced higher titers of IgG and IgA against \textit{Mtb} whole cell lysate in BALF and plasma than other vaccination routes.

Presence of plasma IgM to LAM, PstS1, and Apa and BALF IgA, IgG, and IgM to LAM and PstS1 correlated with reduced \textit{Mtb} burden
Mtb antigen-unbiased approach to investigate antibody correlates of protection against TB in cynomolous macaques

LTBI (n = 35)  TB (n = 21)

Pre-infection  Early infection (2 – 3 months)  Late infection (5 – 6 months)

IgM  IgG & IgA

Data processing with normalization & Filtering for reactive Mtb glycans and proteins

Analysis with identification of Mtb glycans and proteins associated with LTBI outcome

Ishida et al, in revision
Pre-existing mucosal airway and systemic IgA responses to specific AM motifs correlate with control of *Mtb* infection

Ishida et al, in revision
Lu et al., *Nature Rev Immunol* 2018
Major remaining gaps of knowledge

- Most critical B cell antigens/epitopes
- Antigen expression on infected cells
- Interactions with other immune arms and mechanisms of protection
- B cells vs antibody effects
- Mucosal vs systemic antibody responses and their likely different mechanism of protection
- Role of isotypes at different stages of *Mtb* infection
- Natural vs vaccine induced immunity
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