Update TB immunology

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Disclosure of speaker’s interests

No conflicts of interest
TB infection stages

Mtb exposure → infection

- about 5% will develop active TB disease
- about 95% will remain latent TB infection (LTBI)

Cured TB

BCG vaccination

vaccine
Mtb infection and disease

BCG vaccination

Mtb exposure → ??% → infection → ~95% → LTBI

~5% → active TB disease
Immune responses activated by *Mtb*

- **Adaptive immune responses**, mostly (CD4) T-cells (IFN-γ⁺ or multifunctional T-cells)
- Protection against other childhood infections, activation of innate immunity?

- **T-cell immunity to Mtb**

- **~95%** LTBI
- **~5%** active TB disease

- **Adaptive immune responses**, IFN-γ, multifunctional T-cells, B-cells, antibodies
- **NK cells**
Detection of *Mtb* infection

- Mtb exposure
- *Mtb* infection
- *Mtb* not detectable in LTBI individuals
- Rely on detection of host immunity to *Mtb* (antigens) to determine infection state
- We love IFN-γ

**Tuberculin skin test**
**Quantiferon TB Gold**
**T-spot TB**
**IFN-γ**
TB induced immunity

Screening of Th1 immune responses in individuals with a positive TST in a low endemic country (2007-2013), 2 year follow up

QFT-Gold in tube ~24 hrs stimulation

6 day PBMC stimulation assay

Mtb specific memory responses detected in majority of individuals using prolonged stimulation
Memory immunity

A. all individuals

B. no treatment

C. LTBI treatment

<table>
<thead>
<tr>
<th></th>
<th>Contact investigation N=196</th>
<th>Immigrant screening N=48</th>
<th>Screening for other indications a N=251</th>
<th>Total N=495</th>
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<tbody>
<tr>
<td>QFT- TST-</td>
<td>15 (8%)</td>
<td>4 (8%)</td>
<td>26 (10%)</td>
<td>45 (9%)</td>
</tr>
<tr>
<td>QFT- TST+</td>
<td>106 (54%)</td>
<td>10 (21%)</td>
<td>173 (69%)</td>
<td>289 (58%)</td>
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<td>QFT+ TST-</td>
<td>2 (1%)</td>
<td>1 (2%)</td>
<td>1 (0.4%)</td>
<td>4 (0.8%)</td>
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<tr>
<td>QFT+ TST+</td>
<td>68 (35%)**</td>
<td>26 (54%)**</td>
<td>40 (16%)</td>
<td>134 (27%)</td>
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<tr>
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<td>5 (3%)</td>
<td>7 (15%)</td>
<td>11 (4%)</td>
<td>23 (5%)</td>
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<tr>
<td>LSTEC- TST-</td>
<td>9 (4%)</td>
<td>2 (4%)</td>
<td>18 (7%)</td>
<td>29 (6%)</td>
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<tr>
<td>LSTEC- TST+</td>
<td>70 (36%)</td>
<td>11 (23%)</td>
<td>109 (43%)</td>
<td>190 (38%)</td>
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<tr>
<td>LSTEC+ TST-</td>
<td>8 (4%)</td>
<td>3 (6%)</td>
<td>5 (2%)</td>
<td>16 (3%)</td>
</tr>
<tr>
<td><strong>LSTEC+ TST+</strong></td>
<td>77 (39%)</td>
<td>21 (44%)*</td>
<td>79 (31%)</td>
<td>177 (36%)</td>
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<tr>
<td>Missing</td>
<td>32 (16%)</td>
<td>11 (23%)</td>
<td>40 (16%)</td>
<td>83 (17%)</td>
</tr>
</tbody>
</table>

Recent contact not associated with high EC recognition

de Paus et al
Tuberculosis (2017), 106:62-72
Borderline QFT results mostly reflected MTB-specific responses rather than random assay variability:

1. QFT results below the cut-off occurred in three-fold excess over the number expected based on random assay variability

2. Patients with borderline results were similar to those with positive results with regard to all other available evidence of TB infection rather than to the negative QFT group

> Apply different cut-off depending on the risk of TB, analogous to the graded cut-off for the interpretation of the TST at 5, 10 or 15 mm depending on setting and immune status?
Most borderline QFT reflect true infection

Unexpected high frequency of QFT results between 0.15-0.35

Most individuals with borderline QFT have positive TST or T-SPOT

> Most borderline QFT results truly reflect Mtb infection

Uzorka et al
Tuberculosis (2018), 111: 102-108
Immunosuppression in QFT borderline patient

The Netherlands, low risk setting

Migration from Morocco to the Netherlands


Exposure
Visited her aunt with sputum smear-positive TB

April May June July Aug Sept Oct Nov Dec Jan Feb March April May


Screening
TST: 10 mm (was overlooked)
QFT: TB1 0.11 IU·mL⁻¹
TB2 0.22 IU·mL⁻¹
Chest radiography not performed

Clinical work-up
QFT: TB1 5.37 IU·mL⁻¹
TB2 5.55 IU·mL⁻¹
Chest radiography: hilar lymphadenopathy and diffuse nodular pattern

Microbiology
Sputum: auramine⁺;
*M. tuberculosis* complex PCR⁺;
*M. tuberculosis* culture⁺

Gastric lavage: *M. tuberculosis*
complex PCR⁺;
*M. tuberculosis* culture⁺

Urine: auramine⁺ PCR⁻

CSF: auramine⁻; *M. tuberculosis*
complex PCR⁻

Diagnosis: miliary TB

Dec 14 2017

Feb 12 2018

hilar lymphadenopathy and a diffuse nodular pattern,
suspicious of miliary TB

Uzorka et al
Eur Respir J (2018), 52 (2): pii 1800913
Mtbc exposure: infection vs clearance

Resistance to infection vs early (innate) clearance

Mtbc exposure

??%

infection

??%

Resistance/ clearance

Tuberculin skin test

Quantiferon TB Gold

T-spot TB

IFN-γ
Mtb exposure: alternative markers of infection?

Ugandan HHC of TB patients: exposed but persistently negative in TST and/or QFT > resistors?

Resistors have antibodies against Mtb, including against ESAT-6/CFP10

Antibodies have class-switched > suggests long-term antigen exposure

Antibodies have same functional profile as in LTBI
Resistors have Mtb specific T-cell responses

Resistors have T-cells that recognized Mtb antigens, including ESAT-6/ CFP-10

T-cells become activated and produce multiple cytokines, but not IFNg in response to ESAT-6/ CFP-10

>> Antigen specific T-cells in resistors
Early clearance possibly prevented switch to IFNγ producing cells?
Early Mtb clearance in persistently negative HHC?

- Indonesian household contacts of TB cases, IGRA baseline and 14 weeks post recruitment
- Persistently IGRA-negative contacts:
  - Resolving innate cellular response from 2 to 14 weeks in but not converters
  - More proinflammatory cytokines following heterologous stimulation with *E. coli* and *S. pneumoniae*.

- Early clearance of *M. tuberculosis* is associated with enhanced heterologous innate immune responses similar to those activated during induction of trained immunity

Verall, J Infect Dis, 2019, doi: 10.1093/infdis/jiz147
Unbiased approaches: Analyse immune system as a whole rather than isolated components

- Whole blood transcriptome studies
- Functional assays to assess the capacity to eliminate mycobacteria >

**Mycobacterial Growth Inhibition Assay (MGIA)**

Hoft et al, J Infect Dis. 2002;186(10):1448-57
Tanner et al, Vaccine. 2016;34(39):4656-4665
Lack of control during latency

BCG vaccination  | Mtb exposure  | infection  | LTBI  | active TB disease

Lack of control observed in (long-term) LTBI, despite presence of strong adaptive immune responses and control of the infection in vivo

Joosten, J Clin Invest, 2018, 128(5): 1837-1851
Strong control in most individuals after recent exposure to patient with active TB
Not all individuals are ‘infected’ (TST/ QFN)

Joosten, J Clin Invest, 2018, 128(5): 1837-1851
Strongest BCG control upon recent exposure

BCG vaccination | Mtb exposure | infection | LTBI | active TB disease

Δ median: 1.07 < 0.0001

Highest control of BCG outgrowth observed in recently exposed individuals
Adaptive responses and control of mycobacterial growth

Antigen specific responses do not correlate with control of BCG outgrowth

Joosten, J Clin Invest, 2018, 128(5): 1837-1851
Monocytes correlate with control upon recent exposure

- BCG vaccination
- Mtb exposure
- Infection
- LTBI
- Active TB disease

**BCG growth control is associated with a non-classical monocyte population**

Joosten, J Clin Invest, 2018, 128(5): 1837-1851
Non classical monocytes derived CXCL10 mediates growth control

CXCL10 is produced by non-classical monocytes mostly in exposed individuals
CXCR3 receptor blockade reversed mycobacterial growth control
T-cells are required to mediated growth control

Joosten, J Clin Invest, 2018, 128(5): 1837-1851
Immune responses activated by Mtb

Mtb exposure

Trained innate immunity
Functional control of mycobacterial outgrowth

Mtb infection

Resistance/clearance

LTBI

Borderline QFT responses may indicate Mtb infection

~95%

~5%

active TB disease

‘Resistors’ to QFT conversion can have T-cells and Abs reactive with Mtb, but lack IFN-γ producing T-cells

Early Mtb clearance does not always result in activation of T-cell immunity

BCG vaccination
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