Trained immunity and vaccination: mechanisms and new insights

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Radboudumc
Coverage highest in families with TB

Reduction was in infancy, but TB deaths occur later

This made little sense

“One could evidently be tempted to find an explanation for this much lower mortality among vaccinated children in the idea that BCG provokes a non-specific immunity...”

Carl Naeslund 1932
Long-term epigenetic reprogramming in myeloid cells

Naive macrophage
- Stimulation
- Histone
  - Low gene expression
  - Absent H3K4me3

Activated macrophage
- Resting
- Active gene expression
  - Active H3K4me3

"Trained" macrophage
- Quiescent
- Restimulation
  - Low gene expression
  - H3K4me1
  - High gene expression
  - Enhanced H3K4me3

Resting

Infection

Resting

Re-infection
Long-term epigenetic reprogramming in myeloid cells

- Low gene expression
  - Absent H3K4me3
- Active gene expression
  - Active H3K4me3
  - H3K4me1
  - High H3K4me3

PAMPs
- β-Glucan
- Peptidoglycan
- BCG

Naive myeloid cell
- Activated myeloid cell
- Quiescent myeloid cell
- Activated myeloid cell

Promoter
Immune gene

mRNA
Trained immunity: mechanisms

Trained immunity: from bone marrow to local defenses

BCG vaccination, macrophage activation and TB control

\[ \text{Median: } 1.07 \quad P < 0.0001 \]

- Controls
- BCG
- Recently exposed
- LTBI
- TB

CI of median
1 log reduction

No control
Intermediate
Good control

Joosten et al, JCI 2018
BCG vaccination, macrophage activation and TB control

D

\%
\% CD14_{dim}

<0.0001

Controls  BCG  Recently exposed  LTBI  TB

E

log CFU

0.1120

% CD14^{bright}

F

log CFU

<0.0001

% CD14^{dim}

Joosten et al, JCI 2018
BCG vaccination, TB infection and cytokine production

### Fold change

| Chemokine receptors: | IFN-γ | TNF-α | IL-1β | IL-4 | IL-6 | IL-10 | IL-16 | GM-CSF | CCL23 | CCL24 | CCL26 | CCL17 | CCL22 | CCL20 | CCL21 | CCL19 | CCL25 | CCL27 | CCL13 | CCL2 | CCL3 | CCL14 | CCR1 | CCR2 | CCR3 | CCR4 | CCR5 | CCR6 | CCR7 | CCR8 | CCR9 | CCR10 | CCR1, 4, 5 | CCR2, 4, 5 | CCR3, 5 | CCR4, 5 | CCR5, 6 |
|----------------------|------|-------|-------|------|------|-------|-------|--------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Trained immunity by BCG vaccination | SA | CA | Mtb | LPS |
| 1-1.5 | | | | |
| 3-4.5 | | | | |
| >4.5 | | | | |

### Subcohort:

<table>
<thead>
<tr>
<th>TB infection cohorts</th>
<th>BCG recently exp.</th>
<th>LTBI</th>
<th>TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-1.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-4.5</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&gt;4.5</td>
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</tbody>
</table>
BCG vaccination and protection against TB infection

Home visits
IC 465
HC 2090

Eligible participants
IC 464
HC 1620

Included
IC 462
HC 1347

Baseline
IGRA negative 490

Baseline
IGRA positive 780

14-week
IGRA negative 317

14-week
IGRA positive 116

Ineligible HC 470
Previously had TB 197
Spends <5 hours with the case 50
Under 5 years of age 206
Other 17

HC did not consent 273

IGRA indeterminate 17
Active TB 28
Unevaluated symptoms of TB 32

IGRA Indeterminate 11
Active TB 1
Unevaluated symptoms of TB 2
Lost to follow-up 43
Table 5. Assessment of Risk Factors for Interferon-γ Release Assay Conversion in Household Contacts Who Were IGRA Negative at Baseline (n = 432)

<table>
<thead>
<tr>
<th>Contact Characteristic</th>
<th>IGRA Persistently Negative (n = 317)</th>
<th>IGRA Converter (n = 115)</th>
<th>RR (95% CI)</th>
<th>P Value</th>
<th>ARR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age scaled</td>
<td>27.9 (12.1–39.8)</td>
<td>22.8 (14.6–35.7)</td>
<td>0.99 (.90–1.08)</td>
<td>.8</td>
<td>0.97 (.88–1.07)</td>
<td>.6</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>170 (54)</td>
<td>59 (51)</td>
<td>1.00 ref</td>
<td>1.00</td>
<td>ref</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>147 (46)</td>
<td>57 (49)</td>
<td>1.08 (.79–1.50)</td>
<td>.6</td>
<td>0.88 (.57–1.36)</td>
<td>.6</td>
</tr>
<tr>
<td>BCG vaccination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>41 (13)</td>
<td>30 (26)</td>
<td>1.00 ref</td>
<td>1.00</td>
<td>ref</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>276 (87)</td>
<td>86 (74)</td>
<td>0.56 (.40–.79)</td>
<td>.001</td>
<td>0.56 (.40–.77)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non smoker</td>
<td>241 (76)</td>
<td>78 (68)</td>
<td>1.00 ref</td>
<td>1.00</td>
<td>ref</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>76 (24)</td>
<td>37 (32)</td>
<td>1.34 (.97–1.85)</td>
<td>.07</td>
<td>1.47 (.96–2.26)</td>
<td>.08</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diabetes</td>
<td>292 (92)</td>
<td>103 (89)</td>
<td>1.00 ref</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Prediabetes</td>
<td>14 (4)</td>
<td>7 (6)</td>
<td>1.28 (.67–2.42)</td>
<td>.5</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11 (3)</td>
<td>6 (5)</td>
<td>1.35 (.69–2.65)</td>
<td>.4</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>13.8 (1.6)</td>
<td>14.2 (1.6)</td>
<td>1.11 (1.01–1.21)</td>
<td>.04</td>
<td>1.14 (1.01–1.30)</td>
<td>.04</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>41.2 (4.2)</td>
<td>42.0 (4.8)</td>
<td>1.03 (.99–1.08)</td>
<td>.1</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Neutrophils (1000/μL)</td>
<td>4.3 (1.6)</td>
<td>4.3 (1.6)</td>
<td>1.00 (.90–1.10)</td>
<td>.9</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Lymphocytes (1000/μL)</td>
<td>2.6 (0.7)</td>
<td>2.6 (0.8)</td>
<td>1.02 (.82–1.26)</td>
<td>.9</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Monocytes (1000/μL)</td>
<td>0.4 (0.2)</td>
<td>0.4 (0.2)</td>
<td>0.75 (.30–1.91)</td>
<td>.6</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Verrall et al, JID 2020
Early clearance and innate cytokine production
### TLR Agonists as Mediators of Trained Immunity: Mechanistic Insight and Immunotherapeutic Potential to Combat Infection

Allison M. Owen, Jessica B. Fults, Naeem K. Patil, Antonio Hernandez and Julia K. Bohannon

#### Table

<table>
<thead>
<tr>
<th>Route</th>
<th>Bacterial Species</th>
<th>Effect</th>
<th>Reference</th>
</tr>
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<tr>
<td>i.p.</td>
<td><em>P. aeruginosa</em> (topical inoculation of burn wound or i.p.)</td>
<td>↑ Bacterial clearance</td>
<td>Romero et al. (65)</td>
</tr>
<tr>
<td></td>
<td>Polymicrobial abdominal sepsis (CLP surgical model)</td>
<td>↓ Pro-inflammatory cytokines (plasma)</td>
<td>Bohannon et al. (67)</td>
</tr>
<tr>
<td>i.p.</td>
<td><em>P. aeruginosa</em> (topical inoculation of burn wound)</td>
<td>↑ Neutrophil mobilization &amp; recruitment to site of infection</td>
<td>Bohannon et al. (67)</td>
</tr>
<tr>
<td>i.p.</td>
<td><em>P. aeruginosa</em> (i.p.)</td>
<td>↑ Neutrophil &amp; macrophage recruitment</td>
<td>Fensterheim et al. (76)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ Pro-inflammatory cytokines (plasma)</td>
<td></td>
</tr>
<tr>
<td>i.v.</td>
<td><em>S. aureus</em> (i.v.)</td>
<td>↑ Bacterial clearance</td>
<td>Fensterheim et al. (63)</td>
</tr>
<tr>
<td></td>
<td><em>C. albicans</em> (i.v.)</td>
<td>↓ Pro-inflammatory cytokines (plasma)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ Organ injury (kidney)</td>
<td></td>
</tr>
</tbody>
</table>
M72/AS01 and TB protection

Proportion of Participants Free of TB Disease According to Case Definition 1

Hazard ratio by Cox regression model, 0.46 (90% CI, 0.25–0.86; 95% CI, 0.22–0.97)
P=0.04 by log-rank test

No. at Risk
M72/AS01\textsubscript{E} 1623 1618 1612 1607 1593 1584 1580 1576 1354 847 500 166 0
Placebo 1660 1648 1640 1630 1613 1594 1587 1584 1347 849 509 170 1
Beta-glucan-induced trained immunity and TB

A
RPMI/β-glucan  RPMI/Mtb
Wash out & rest  24hr  5 days  24hr

B
IL-6
Mtb restimulation

TNFα
Mtb restimulation

C

CFU H37Rv

Control  β-glucan

4 hr  day 3

Moorlag et al, Cell Reports 2020
Beta-glucan-induced trained immunity and TB

Moorlag et al, Cell Reports 2020
Future vaccine could combine induction of trained immunity and adaptive memory.
Thank you!

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