Trained immunity as a mechanism behind the wider applicability of BCG

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100 years of BCG:
- Significant reduction of in particular childhood TB
- But also reduced overall childhood mortality, larger than expected from reduction in TB
- BCG (re)vaccination resulted in reduced respiratory tract infections
- BCG may boost other vaccine responses
- Applied therapeutically against bladder cancer

>> Many effects seem unrelated to antigen specific responses induced by vaccination

>> Currently explored in prevention of SARS-CoV2
Heterologous protection by vaccination

BCG vaccination contributes to reduced ‘all cause’ childhood mortality

Guinee-Bissau, RCT
BCG scar infant: 41% lower mortality (4.5 and 36 months)
66% reduction if mother also BCG scar, 8% if mother had no BCG scar
> Maternal BCG priming important for effect of BCG vaccination on child survival.

Berendsen, J Pediatric Infect Dis Soc, 2019, doi10.1093
Infants, Melbourne, Australia; BCG within 10 days after birth
Serological analyses at 1 month post 6 and 12 month routine vaccination

Zimmerman, *Vaccine* 2019: Vol. 37, Issue 28, p3735
BCG protects against YF viremia

- BCG-induced changes correlated with protection against experimental virus infection
- Viremia reduction correlated with IL-1β upregulation, indicative of trained immunity
- SNPs in IL1B affect the induction of trained immunity by BCG
- Trained immunity did not alter adaptive response to YF

Arts, Cell Host Microbe, 2018, 23(1): 89-100
BCG activates non-specific immune responses

BCG revaccination (adolescents): reduced upper respiratory tract infections

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (N=329)</th>
<th>H4:IC31 (N=330)</th>
<th>BCG (N=330)</th>
<th>Total (N=989)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>95% CI</td>
<td>n (%)</td>
<td>95% CI</td>
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<tr>
<td><strong>Systemic AEs</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Headache</td>
<td>22 (7)</td>
<td>1 (&lt;1)</td>
<td>24 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>25 (8)</td>
<td>1 (&lt;1)</td>
<td>31 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17 (5)</td>
<td>1 (&lt;1)</td>
<td>16 (5)</td>
<td>0</td>
</tr>
</tbody>
</table>

p=0.0003 calculated by two by three Chi Square test

Nemes, NEJM, 2018, 379 (2): 138-149

de Bree, NEJM, 2018, 379 (20): 1969

BCG protects against other unrelated pathogens, vaccine responses are enhanced in BCG vaccinated individuals > state of immune activation, effects are wide > innate immune activation?
‘Innate memory’

Defense ready state:

• High glycolysis
• Increased cytokine release upon restimulation
• Enhanced effector responses

Training by microbial ligands or metabolic triggers (OxLDL) permits augmented response to heterologous encounters

Training results in epigenetic alterations: H3K4Me3, H3K27Ac mark loci with enhanced access and thereby increased responsiveness to secondary stimulation

Netea, Science, 2016,352(6284): aaf1098
Quintin, Curr Opin Immunology 2014, DOI:10.1016/j.coi.2014.02.006
BCG educates hematopoietic stem cells

- Access of BCG to the bone marrow expands HSCs and promotes myelopoiesis
- BCG educates HSCs to generate trained monocytes/macrophages
- BCG induces a unique epigenetic and transcriptomic signature in macrophages
- BCG-trained macrophages are highly protective against pulmonary M. tuberculosis infection
BCG Vaccination in humans elicits trained immunity

- Peripheral blood cells release more pro-inflammatory cytokines 3 months after BCG
- Myeloid transcription profile of human HSPCs
- Persistent (90 days) innate training of CD14⁺ monocytes
- Persistent epigenetic changes in peripheral monocytes

Cirovic, Cell Host Microbe, 2020, 28(2):322-334.e5
BM monocytes, LPS stim, 24 hrs

- Mucosal vaccination with BCG resulted in enhanced training in NHP compared to routine ID vaccination

>> different administration routes of BCG may induce innate training of myeloid (monocytic) populations, likely through reprogramming of BM progenitors

Early Mtb clearance related to trained immunity

- 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
  - More proinflammatory cytokines following heterologous stimulation with *Escherichia coli* and *Streptococcus pneumoniae*.

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

CV: IFN-γ release assay converters
PN: persistently negative contacts

Verall, J Infect Dis, 2019, doi: 10.1093/infdis/jiz147
Functional control of mycobacterial outgrowth

In vitro PBMC based mycobacterial killing assay (MGIA): assess capacity of PBMCs to control mycobacterial growth (here BCG)

> control of BCG outgrowth correlated with secretion of hallmark cytokines for trained immunity

Joosten, J Clin Invest, 2018, 128(5): 1837-1851
CXCL10-CXCR3 new player in trained immunity

- Trained immunity correlates with strong functional control of antimycobacterial immunity
- CXCL10-CXCR3 novel player in trained immunity

Joosten, J Clin Invest, 2018, 128(5): 1837-1851
Trained innate immunity is induced by BCG vaccination

Training is the result of alterations in HSPCs in the BM and persists (at least) for several months

Epigenetic changes that result in increased accessibility of specific loci (e.g., cytokine genes) are a hallmark of trained immunity

Trained monocytes produce increased levels of pro-inflammatory cytokines and have altered metabolic profiles

Functional control of mycobacterial outgrowth correlates with innate trained immunity

BCG can induce Trained Immunity which may affect the response to mycobacterial but also unrelated pathogens
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