Gut microbiota during crucial developmental periods modulates responses to BCG vaccination

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BCG vaccination

- Live-attenuated mycobacterial vaccine
- Usually given at birth to > 100 million infants annually
- Elicits robust Th1 responses in neonates
- Some evidence that BCG less efficacious geographically
  - Unknown mechanisms

Trunz, 2006
Microbiota and immune development

• Infant gut microbiota play a key role in immunity and metabolism
• Maternal microbiota strong determinant of infant microbiota, and consequent immune development
• Gut microbiota varies by geographical location
• Some evidence for gut microbiota association with vaccine immunogenicity

InFANT* Study

400 HIV-exposed uninfected (HEU)
250 HIV-unexposed (HU)

- Term, vaginal deliveries
- Negative HIV DNA PCR
- All breastfed

- Stool for microbiome studies
- Blood (vaccine immunogenicity, PBMC, HIV DNA PCR)
- BCG vaccination

*Innate Factors associated with Nursing Transmission
BCG-specific T cell responses

Net % Th1 cytokine+ CD4 cells

High responders

Low responders

Net % CD4 cells producing any cytokine

R=0.75
p<0.0001


Agano Kiravu, Anna Happel, Jerome Wendoh
Early life gut microbiota in high versus low BCG responders at week 7

Shannon index

Birth <W1 W4 W6 W7 W15 W36 M18

BCG

Axes 1 (24.3%) and 2 (11.7%)
Differentially abundant taxa in high vs low responders in iHEU

Do FMTs from high versus low responders of germ-free mice differentially influence immunity
FMTs from high vs low responder infants and inherent immunity in germfree mice

Ly6C

Ly6G

Neutrophils 37.2

Ly6C<sub>lo</sub> monocytes 30.3

Ly6C<sub>hi</sub> monocytes 15.1

Weight (g)

D11c1o

PBS LR HR

Donald Nyangahua
To investigate causal role in vaccine immunogenicity, we performed monoclonizations of germ free mice.
Live *B. longum subsp. infantis* induces higher TB10.4 specific T cells post BCG

Stain for TB10.4-specific T cells using tetramers

**B. thetaiotaomicron**

**B. longum (infantis)**

![Flow cytometry plots for TB10.4 and CD44 expression](image)

![Graph showing log CFU/g of feces vs. time](image)

Donald Nyangahu, Urdahl lab
B. longum subsp infantis and B. thetaiotaomicron differentially impact the memory CD4 transcriptome in BCG immunized mice

No differences in other cell subsets including innate cells
Stool metabolome signatures differ with *B. longum* vs. *B. theta* gavage.
Specific metabolites correlate with tetramer responses

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>r</th>
<th>P value</th>
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<tbody>
<tr>
<td>Xanthine</td>
<td>0.543</td>
<td>0.0009</td>
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<tr>
<td>Riboflavin</td>
<td>0.417</td>
<td>0.0142</td>
</tr>
<tr>
<td>Anthranilic Acid</td>
<td>-0.407</td>
<td>0.0169</td>
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<tr>
<td>Ethanolamine</td>
<td>0.398</td>
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<td>TMAO</td>
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<tr>
<td>G6P</td>
<td>0.370</td>
<td>0.0313</td>
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</table>

Riboflavin precursor to co-enzyme of xanthine oxidase. XO converts Xanthine to Uric acid, a potent inflammasome activator.

Metabolite of the IDO-KYN pathway of tryptophan metabolism, immune regulator, causes apoptosis of Th1 cells.
Summary: infant gut microbiota and vaccine immunogenicity

- Specific gut microbes influence CD4 T cellular immunogenicity of neonatal vaccines
- *Bifidobacterium longum* subsp. *infantis* has potential as a probiotic to improve Th1 responses in neonates (e.g. TB)
- Bifidobacterial metabolites could be further explored as prebiotics or adjuvants
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