Immune-endocrine Interactions in Type 2 Diabetes During Latent and Active TB

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The link between the immune and endocrine system

- Hormone receptors are expressed on immune cells
- Structural similarity between cytokine and hormone receptors
- Hormones are produced by cells of the immune system

ACTH is produced by lymphocytes and binding of CRH to lymphocytes stimulates ACTH production.
Hormones can affect immune function

Kleynhans et al. PlosOne 2011
Kleynhans et al. Infection and Immunity 2013
How can TB infection/disease affect the endocrine system?

Adapted from Glaser 2005 Nature Reviews Immunology
IFN$_\gamma$ secretion negatively correlates with serum cortisol concentrations in LTBI

$r = -0.4$

$p = 0.02$
Endocrine changes during active TB and TB treatment

Table 1: Characteristics of study groups.

<table>
<thead>
<tr>
<th></th>
<th>Cured (n = 27)</th>
<th>Failed (n = 10)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>35.0 ± 10.42</td>
<td>38.6 ± 11.9</td>
<td>0.44</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>14/13</td>
<td>5/5</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)*</td>
<td>18.1 ± 0.4</td>
<td>18.8 ± 0.7</td>
<td>0.33</td>
</tr>
<tr>
<td>CXR score*</td>
<td>57.6 ± 6.3</td>
<td>71.7 ± 11.3</td>
<td>0.31</td>
</tr>
</tbody>
</table>

*Results are shown as mean ± SD. F: female, M: male, BMI: body mass index, CXR: chest X-ray
Can chronic inflammation influence the HP axis?

Adapted from Glaser 2005 Nature Reviews Immunology
TB and Diabetes lead to changes in the GC system

- Tuberculosis
  - ↑ cortisol
  - ↑ transient hyperglycaemia
  - ↑ GRβ – GC resistance

- Type 2 diabetes
  - ↑ cortisol HPA (?)
  - ↑ cortisol periphery (11β-HSD1)
  - ↑ GRβ – GC resistance

- Obesity
  - ↑ HPA-axis (GC system)
ALERT Study (NIH-ROI)

Altered Endocrine Axis in Type 2 Diabetes and Risk for Tuberculosis

Chronic Inflammation: ↑ IL-6, IL-1β, TNFα, Leptin

DM2 → ↑ Insulin

Compromised Tc, MN, APC responses to Mtb

Reduced Mtb containment

HPA-axis activation

CRH

Pituitary

Other HP and downstream hormones? (HPT-axis (TSH, T4, T3), AgRP)

ACTH

Adrenal gland

Hypothalamus

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Gaps and Future Directions

- Interdisciplinary approach to fight the TB-T2DM co-epidemic
  - TB is more than an infectious lung disease
  - T2DM is a complex disorder
- New therapeutic opportunities, host directed therapies
  - DHEA derivatives
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