Immunology of leprosy - 2013

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Recent developments: unanswered questions

1. Immediate or innate immune responses shape the T cell response that controls *M. leprae* infection

2. Different types of T cells & different targets

3. Role of macrophage phenotype and signaling in the survival of *M. leprae* in lepromatous leprosy

*In general, observations are based on the extremes of leprosy phenotype rather than early in course of infection*
Active Tuberculosis is associated with gene expression signature: Type I interferon signaling & Neutrophils

Distinct whole blood gene transcription in active TB: IFNα/β signalling & increased neutrophils.
Inverse relation between IFN\(\alpha/\beta\) & IFN\(\gamma\) pathway gene expression in leprosy:
Lepromatous - IFN\(\alpha/\beta\) & IL-10:
Tuberculoid & RR- IFN\(\gamma\) & vit D dependent anti-microbial pathway

Tuberculoid (T-lep), self-healing
Lepromatous (L-lep), disseminated
Reversal reactions (RRs)

IFNβ & IFNαR1 mRNA expression in lepromatous leprosy & IFNγ mRNA expression in Tuberculosis leprosy
IL-10 expression increased in LL leprosy: IL-10 induced by IFNβ & *M. leprae* and inhibits macrophage response to IFNγ

*M. leprae* sonicate & IFN-β induce IL-10

IFN-γ induced killing of *M. leprae* blocked by IFN-β & IL-10

Model for IFN-β suppressing IFN-γ induced antimicrobial activity in leprosy

But IL-10 produced both from T cells & Macrophages:

Desvignes & Ernst, Cell Host Microbe 2013
Balance between pro- and anti-inflammatory responses to *M. leprae* in the skin: role keratinocytes

Model: Type 1 Reversal reactions in skin

Beta-defensins (hBD2, hBD3) - chemoattractant anti-microbial peptides
Produced by keratinocytes not macrophages: suppressed by prednisolone

Cogen AL et al PLOS Negl Trop Dis 2012, 6:1
Spectrum of immune responses in leprosy
Th1 T cells in tuberculoid and Th2 T cells in lepromatous leprosy

M. leprae-infected DCs

Tho → NFAT

Th1
IL-2, IFN-γ, TNF

Th2
IL-4, IL-5, IL-10

Tuberculoid leprosy

Lepromatous leprosy
More complex pattern of CD4 & other T cell responses in leprosy

CD8
HLA Class I-restricted cells
Present in leprosy lesions

Tho
IL-2

NFAT

CD1b-restricted DN CD4⁻ CD8⁻ T cells
Recognise LAM

Th1
IL-2, IFN-γ, TNF

Th2
IL-4, IL-5, IL-10

T17
IL-17,IL-22,TNF

Treg
IL-10, TGF-β
Express CTA-4
T regulatory T cells increased in lepromatous leprosy


A-E: Lepromatous leprosy: CD25, FoxP3 (A), Treg express IL-10 (C), CTLA4 (D) TGF-β (E), F: Tuberculoid leprosy, CD25, FoxP3.
Macrophage phenotype & control of *M. leprae*

Type 1 Macrophages: activated IFN-γ → anti-microbial
Type 2 Macrophages: IL-10 → permissive for *M. leprae*

Macrophage markers
- Galectin 3 – associated with IL-10 expression
- CD163 scavenger receptor 3 – associated with IL-10 & IDO expression
- IDO – indoleamine deoxygenase in Mφ & Schwann cells
Galectin-3 increased expression LL leprosy, but not TT/BT, leprosy lesions.

Addition of galectin-3 (Gal-3) to APC increases IL-10 and reduces IL-12 production in response to TLR2/1 stimulation & T cell activation

CD163 (Scavenger receptor) favours *M. leprae* survival & persistence by promoting anti-inflammatory pathways in lepromatous macrophages

IL-10 & IDO upregulated in LL leprosy

Moura et al, Eur J Immunology 2012, 42: 2925
Indoleamine 2, 3-dioxygenase & Tryptophan metabolism: Macrophage IDO upregulated by *M. tuberculosis* & IFN-γ

**IDO activation depletes Tryptophan: possible immunosuppressive**

- **Tryptophan** → **IDO** → **TDO** → **Formylkynurenine** → **Kynurenine** → **Kynurenine 3-hydroxylase** → **KYNURENINASE** → **3-Hydroxyanthralic acid** → **3-hydroxyanthralic acid oxidase** → **Amino-3 carboxymuconic Semialdehyde** → **Quinolinic Acid** → **Quinolinic phosphoribosyltransferase** → **Picolinic carboxylase** → **Aminomuconic semialdehyde** → **Picolinic Acid**

**Mtb & BCG induce macrophage expression of IDO**

A

<table>
<thead>
<tr>
<th>IFNγ [U/ml]</th>
<th>0</th>
<th>100</th>
<th>500</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>ctrl</em></td>
<td>0.15 ± 0.02</td>
<td>0.20 ± 0.03</td>
<td>0.25 ± 0.04</td>
</tr>
<tr>
<td><em>Mtb</em></td>
<td>0.05 ± 0.01</td>
<td>0.10 ± 0.02</td>
<td>0.15 ± 0.03</td>
</tr>
</tbody>
</table>

B

<table>
<thead>
<tr>
<th>BCG + IFNγ</th>
<th>0 h</th>
<th>24 h</th>
<th>48 h</th>
<th>72 h</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>medium</em></td>
<td>0.01 ± 0.001</td>
<td>0.02 ± 0.002</td>
<td>0.03 ± 0.003</td>
<td>0.04 ± 0.004</td>
</tr>
<tr>
<td><em>IFNγ</em></td>
<td>0.05 ± 0.005</td>
<td>0.07 ± 0.007</td>
<td>0.09 ± 0.009</td>
<td>0.11 ± 0.011</td>
</tr>
<tr>
<td><em>BCG</em></td>
<td>0.10 ± 0.010</td>
<td>0.12 ± 0.012</td>
<td>0.14 ± 0.014</td>
<td>0.16 ± 0.016</td>
</tr>
<tr>
<td><em>BCG + IFNγ</em></td>
<td>0.15 ± 0.015</td>
<td>0.17 ± 0.017</td>
<td>0.19 ± 0.019</td>
<td>0.21 ± 0.021</td>
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C

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<tr>
<td><em>medium</em></td>
<td>0.02 ± 0.002</td>
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<td>0.18 ± 0.018</td>
</tr>
<tr>
<td><em>BCG + IFNγ</em></td>
<td>0.18 ± 0.018</td>
<td>0.20 ± 0.020</td>
<td>0.22 ± 0.022</td>
<td>0.24 ± 0.024</td>
</tr>
</tbody>
</table>

**QA nontoxic to *Mtb*  PA toxic to *Mtb***

Scandurra et al, Tuberculosis, 2008
Indoleamine 2, 3-dioxygenase: expressed in macrophages & DC in lepromatous, but not in BT leprosy or reversal reactions

De Souza Sales et al, 2011 Clin Exp Immunol 165: 251-263,
Inverse relation of IDO metabolites and IFN-γ in sera of LL and BT/RR leprosy patients: possible role in immunosuppression

Differences in Macrophage & Schwann cell IDO responses
SC IDO, TDO & Kyureninase down-regulated by *M. leprae*

IDO activation depletes Tryptophan: possible immunosuppressive

- **Tryptophan**
  - IDO
  - TDO

- **Formylkynurenine**
  - Kynurenine
  - Kynurenine 3-hydroxylase

- **3-Hydroxylkynurenine**
  - **KYNURENINASE**

- **3-Hydroxyanthrolinic acid**
  - Aminomuconic semialdehyde
  - Picolinic carboxylase
  - Picolinic Acid

Quinolinate phosphoribosyltransferase

Frances Bradstock, unpublished

*M. leprae* infection of Schwann cell line ST88 downregulates IDO, TDO and Kynureninase

Arrays

RT-PCR

IFN-γ upregulates IDO in Schwann cells

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<tr>
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<tbody>
<tr>
<td>IDO</td>
<td>1400</td>
<td>1200</td>
</tr>
<tr>
<td>TDO</td>
<td>1000</td>
<td>800</td>
</tr>
<tr>
<td>KYNU</td>
<td>800</td>
<td>200</td>
</tr>
</tbody>
</table>

Frances Bradstock, unpublished
IFN-\(\gamma\), but not *M. leprae* infection, induces IDO in Schwann cells.

Macrophage and SC have different IDO responses to *M. leprae* infection, but IFN-\(\gamma\) induces IDO expression in both.
CD8$^+$ T cells recruited to reversal reaction lesions in HIV/leprosy patients: ? Possible role in pathogenesis

AL de Oliveira et al, 2013, Immunology 140:47-60,