Targeting checkpoint inhibitor-PD-1 for enhancing efficacy of therapeutic vaccines in tuberculosis

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Tuberculosis Patients

Chemotherapy Vs. Immune containment

Singh et al, PlosOne’ 2013

• Therapeutic Vaccines: Synergism
FoxP3+ Regulatory T Cells Suppress Effector T-Cell Function at Pathologic Site in Miliary Tuberculosis

Prabhat K. Sharma 1*, Pradip K. Saha 2*, Amar Singh 1, Surendra K. Sharma 2, Balaram Ghosh 3, and

Foxp3+ Regulatory T Cells among Tuberculosis Patients: Impact on Prognosis and Restoration of Antigen Specific IFN-γ Producing T Cells

Amar Singh 1, Aparajita Ballave Dey 2, Anant Mohan 2, Prabhat Kumar Sharma 1, Dipendra Kumar Mitra 1*

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Inhibiting the Programmed Death 1 Pathway Rescues Mycobacterium tuberculosis–Specific Interferon γ–Producing T Cells From Apoptosis in Patients With Pulmonary Tuberculosis

Amar Singh *, Anant Mohan, Aparajit B. Dey, Dipendra K. Mitra


Programmed death-1+ T cells inhibit effector T cells at the pathological site of miliary tuberculosis

A. Singh, * A. Mohan, * A. B. Dey and D. K. Mitra *
**Problem: Active suppression of T cell response in patients**

**On CD4+ FoxP-3+ cells**

- **P = 0.0001**
- **P = 0.00013**

**Media**  **Mt.b.**  **Mt.b. + α-PD-1**  **Mt.b. + α-PD (L1/2)**  **Mt.b. + α-PD (1+L1/2)**

- **1.67%**
- **4.14%**
- **8.49%**
- **7.26%**
- **9.7%**
Impact of PD-1 on Mtb. specific Teff cells is Pronounced in lungs of Miliary Tuberculosis

Loss of poly-functional T cell in TB patients

Dominant TNF-α+ Mycobacterium tuberculosis–specific CD4+ T cell responses discriminate between latent infection and active disease

Giuseppe Pantaleo et al., Nature Medicine, 2011

Latent TB (PPD+)
Active TB
Household Contacts (PPD-)

% Positive CD4 T cells

(N=15)
Preferential rescue of IFN-$\gamma$+ TNF-$\alpha$+ producers after PD-1 blocking.

**Media**

TB-148,M,1.003ECD4

- IFN-$\gamma$: 0.98%
- TNF-$\alpha$: 0.65%
- IFN-$\gamma$+TNF-$\alpha$+*: 0.49%

**Mt. Ag**

TB-148,Ag,S1.002ECD4

- IFN-$\gamma$: 2.05%
- TNF-$\alpha$: 1.07%
- IFN-$\gamma$+TNF-$\alpha$+*: 2.93%

**Mt. Ag + a-PD-1**

TB-148,Ag+aPD1,2.006ECD4

- IFN-$\gamma$: 4.29%
- TNF-$\alpha$: 4.08%
- IFN-$\gamma$+TNF-$\alpha$+*: 3.91%

N=5

*Graph showing % PD-1 expression with bars and error bars.*
Cytokine Milieu influences the fate of Mtb infected MDMs

TNF-α milieu promotes Necrosis whereas IFN-γ alone and in combination with TNF-α results in apoptotic death of M.t.b. infected MDMs

Recombinant TNF-α
- Early Apoptotic: 2%
- Late Apoptotic: 12%
- Necrotic: 86%

Recombinant IFN-γ
- Early Apoptotic: 8%
- Late Apoptotic: 30%
- Necrotic: 62%

Recombinant IFN-γ + TNF-α
- Early Apoptotic: 10%
- Late Apoptotic: 57%
- Necrotic: 33%

(N=3)

<table>
<thead>
<tr>
<th>Mtb (H37Rv)</th>
<th>+</th>
<th>+</th>
<th>+</th>
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</thead>
<tbody>
<tr>
<td>rIFN-γ</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>rTNF-α</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>rIFN-γ+rTNF-α</td>
<td>-</td>
<td>-</td>
<td>+</td>
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</table>
Tregs

αPD-1

Percentage Increase

IFN-γ + cells

TNF-α + cells

IFN-γ + TNF-α + cells

Necrosis of CD14+ cells

H37Rv

H37Rv + anti PD-1

α IFN-γ

α TNF-α

CFU/ml

Mtb (H37Rv)

α PD-1

(N=7)
Administration of anti-PD-1 reduces CFU burden in lungs and spleen of mice

Mt6 infected mice

Naïve

Isotype Control

α-PD1

ATT

ATT + α-PD1

40X
ID93 antigen along with α-PD-1 enhances the bacterial clearance in in vitro MDM model
The impact of cytokines on the efflux pumps of *M. tuberculosis*

<table>
<thead>
<tr>
<th>Gene</th>
<th>Efflux Pump</th>
<th>Drugs</th>
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<tbody>
<tr>
<td>RV1258</td>
<td>Major Facilitator Superfamily (MFS)</td>
<td>Rifampicin, Fluoroquinolones</td>
</tr>
<tr>
<td>Mmp17</td>
<td>Resistance-nodulation-division (RND) family</td>
<td>Isoniazid</td>
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Targeting dendritic cells to accelerate T-cell activation overcomes a bottleneck in tuberculosis vaccine efficacy

Kristin L. Griffiths¹, Mushtaq Ahmed¹, Shibali Das¹, Radha Gopal², William Horne², Terry D. Connell³, Kelly D. Moynihan⁴, Jay K. Kolls², Darrell J. Irvine⁵, Maxim N. Artyomov⁶, Javier Rangel-Moreno⁷ & Shabaana A. Khader¹

The development of a tuberculosis (TB) vaccine that induces sterilizing immunity to Mycobacterium tuberculosis infection has been elusive. Absence of sterilizing immunity induced by TB vaccines may be due to delayed activation of mucosal dendritic cells (DCs), and subsequent delay in antigen presentation and activation of vaccine-induced CD4⁺ T-cell responses. Here we show that pulmonary delivery of activated M. tuberculosis antigen-primed DCs into vaccinated mice, at the time of M. tuberculosis exposure, can overcome the delay in accumulation of vaccine-induced CD4⁺ T-cell responses. In addition, activating endogenous host CD103⁺ DCs and the CD40–CD40L pathway can similarly induce rapid accumulation of vaccine-induced lung CD4⁺ T-cell responses and limit early M. tuberculosis growth. Thus, our study provides proof of concept that targeting mucosal DCs can accelerate vaccine-induced T-cell responses on M. tuberculosis infection, and provide insights to overcome bottlenecks in TB vaccine efficacy.
**Biased Imagination**

- Inhibiting PD1
  - Rescues protective T cells
  - Synargism with chemotherapy
  - Better bacillary clearance
  - Prevention of relapse

- Likely to potentiate the effect of therapeutic vaccines

- May aid to therapeutic vaccination in MDR Tuberculosis
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