Host genotypes, inflammatory response and outcome of TBM Vietnam

Nguyen T.T. Thuong

Oxford University Clinical Research Unit
Ho Chi Minh City, Vietnam
Tuberculous Meningitis (TBM)

- Diagnosis remains difficult
- Delay in treatment associated with poor outcome
- Mortality of those treated (n=1700) is 23% in HIV-uninfected and 50% in HIV-infected.
- Common factors for mortality: HIV, severity, CSF lymphocyte count

<table>
<thead>
<tr>
<th>Factors for death (HIV uninfected)</th>
<th>HR</th>
<th>95%CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [per +10 years]</td>
<td>1.24</td>
<td>1.15 - 1.34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MRC Grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- MRC Grade I</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- MRC Grade II</td>
<td>1.36</td>
<td>0.87 - 2.13</td>
<td>0.17</td>
</tr>
<tr>
<td>- MRC Grade III</td>
<td>2.97</td>
<td>1.83 - 4.83</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous TB treatment : Yes</td>
<td>1.46</td>
<td>1.00 - 2.13</td>
<td>0.05</td>
</tr>
<tr>
<td>Focal neurological signs: Yes</td>
<td>1.80</td>
<td>1.22 - 2.64</td>
<td>0.003</td>
</tr>
<tr>
<td>CSF lymphocyte count [cells/ mm³]</td>
<td>0.88</td>
<td>0.82 - 0.94</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Meta-analysis, unpublished, OUCRU*
While we kill bacteria, should we also control the inflammatory response?
Anti-inflammatory dexamethasone reduces risk of death from TBM

Relative risk of death, 0.69
95% CI 0.52-0.92, p=0.011
LTA4H deficiency and excess both increase TB susceptibility
A human *LTA4H* promoter polymorphism regulates gene expression.

Cell 2012. 148(3):434-46
LTA4H rs17525495 Minor allele frequency

Geography of Genetic Variants Browser
Data from 1000 Genomes project
**LTA4H** genotype influences survival in TBM

Overall survival

Survival

Days after enrollment

LTA4H Genotype-Adjusted Survival

Survival

Days after enrollment

CT (HET)

TT (HIGH)

CC (LOW)

P=0.02

NEJM. 2004. 351:1741-1751

Cell 2012. 148(3):434-46
$LTA4H$ genotype influences treatment response

Overall response

Genotype-adjusted response

PLACEBO

CT (HET)

CC (LOW)

TT (HIGH)

DEXAMETHASONE

TT

CT

CC

P=0.005
Intensified anti-tuberculosis treatment did not improve outcome in TBM

- Randomised controlled trial
- All patients received adjunctive dexamethasone
- Data for death outcome with 9 months follow-up
Inflammatory response – Hypotheses

1. *LTA4H* genotype predicts survival of TBM patients receiving corticosteroids
2. *LTA4H* genotype influences inflammatory phenotype
   2.1 *LTA4H* genotype influences cytokine production
   2.2 *LTA4H* genotype determines bacterial load
   2.3 *LTA4H* genotype regulates Lipoxin A4 level
3. Hyper-inflammation is associated with death
4. HIV infection is associated with an attenuated CSF inflammatory response
H1: *LTA4H* genotype predicts survival of TBM patients receiving corticosteroids

- **All**
  - TT, death 19/89 (21.3%)
  - TC, death 91/356 (25.6%)
  - CC, death 101/341 (29.6%)
  - P = 0.13

- **HIV-uninfected**
  - TT, death 3/43 (6.98%)
  - TC, death 39/220 (17.7%)
  - CC, death 40/193 (20.7%)
  - P = 0.04

- **HIV-infected**
  - TT, death 16/46 (34.8%)
  - TC, death 52/136 (38.2%)
  - CC, death 61/178 (41.2%)
  - P = 0.41

*JID 2017. 215 (7): 1020-1028*
H2.1: *LTA4H* genotype influences cytokine production

**HIV uninfected**

**HIV infected**
Cytokine expression by $LTA4H$ genotype
Mycobacterial detection from CSF samples

P trend <0.0001 for both comparisons
H2.2: *LTA4H* genotype determines bacterial load
LTA4H genotype is associated with Lipoxin A4, cytokine response and bacterial load in HIV-uninfected individuals. *(CC+CT) vs TT*
H3: Hyper-inflammation is associated with death
H4: HIV infection is associated with an attenuated CSF inflammatory response

I = HIV infected
UI = HIV uninfected
Inflammatory response in HIV-infected patients

CD4 ≤150
CD4 >150
HIV negative
HIV negative
LTA4H Genotype

Immune response
LTA4H/CSF cytokines

Mtb load

Response to DEX

Outcome - Death

HIV-positive
Immune response

CD4 > 150
CD4 ≤ 150

Response to DEX: unclear, good
Outcome - Death: high, low
Mtb load: high, low
Immune response: low, high
HIV negative LTA4H Genotype: CC, CT, TT
We want to test the following hypotheses

In TBM HIV-uninfected:
Should adjunctive corticosteroid treatment be personalised according to $LTA4H$ genotype?

In TBM HIV-infected:
Do adjunctive corticosteroids improve outcome?
Host genetic markers for TBM outcome

• Deep-sequenced the whole gene region of the \textit{LTA4H} gene and 78 genes involved in inflammatory response in 1000 TBM cases and 1000 controls

• 486 potentially functional variants (stop, frameshift, missense) identified

• Analyses include case vs control and survival vs death for each variant
Host genetic markers for TBM outcome

- 3 protective and 6 risk alleles in case vs control
- 4 protective and 2 risk alleles in survival
- *LTA4H* T allele is confirmed as a protective allele for survival in treatment with dexamethasone OR=1.73, p=0.004
Acknowledgments

Collaborators:
Lalita Ramakrishnan
Mary-Claire King
David Tobin

OUCRU TB group