How Hepatitis B vaccine response and non-response can immunologically be explained

Pieter Meysman
25 April 2019
Hepatitis B vaccine

- Uses Hepatitis B surface antigen (HBsAg)
- 3- to 4-dose vaccination scheme
- 5%-10% non-responders
- Life-long protection

Ref: Leuridan et al. Infectious Diseases. 2011
Experimental overview

- Recruited 33 individuals with no prior Hepatitis B vaccination or disease history.

Ref: Bartholomeus et al. Vaccine. 2018
Response at day 60

42% non-responders after two doses

14 Non-responders
Ab titer < 10 mIU/ml

10 Low responders
10 < Ab titer < 100 mIU/ml

10 Strong responders
Ab titer > 100 mIU/ml
Progression of response

- Most of the non-responders at day 60 do increase later
RNA sequencing: PCA analysis

Largest source of variation is individual specific
RNA sequencing

How does the gene expression change in response to the vaccine?

Resulting differential expressed genes (DEGs):

<table>
<thead>
<tr>
<th>Dataset / #DEGs</th>
<th>Day 3 vs Day 0</th>
<th>Day 7 vs Day 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td>349</td>
<td>40</td>
</tr>
<tr>
<td>Non-responders</td>
<td>10</td>
<td>155</td>
</tr>
</tbody>
</table>

Many DEGs associated with the immune system
Responder vs Day 0

Protein–protein network

- T- and B-cell immunity included
  - None directly related to antibody production

Ref: Meysman et al. IEEE TCBB. 2016
Non-responder | Day 7 vs Day 0 | PP network

- Upregulation of T-cell mediated immunity, leukocyte activation and lymphocyte costimulation

Ref: Meysman et al. IEEE TCBB. 2016
RNA sequencing

How does the gene expression differ between responders and non-responders?

Resulting differential expressed genes (DEGs):

<table>
<thead>
<tr>
<th>Dataset / #DEGs</th>
<th>Day 0</th>
<th>Day 3</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders vs Non-responders on each time point</td>
<td>23</td>
<td>9</td>
<td>0</td>
</tr>
</tbody>
</table>

Biggest difference on day 0 (before the vaccination)
**Time point | Day 0 | Expression profile**
Granulin (GRN), cell growth regulator
CXCL5, cytokine
Role in inflammation and host immune defense
Granulin is secreted by granulocytes
Predictability of vaccine response

- Use of gene expression data before vaccination to predict long term response.

**Graphs:**

1. **Micro-array (n=174)**
   - 15 gene probes
   - AUC = 0.618

2. **RNAseq (n=33)**
   - 10 principal components
   - AUC = 0.662
   - Ref: Bartholomeus et al. Vaccine. 2018
Take home message

• Inter-variability of individuals

• Immune peak response: shift between responder and non-responders

• Day 0 differences

• The role of granulocytes and secretion of granulin

• Gene expression-based classifier not yet good enough for clinical practice
Acknowledgements

**Vaccinology and infectious diseases**
- Prof. Benson Ogunjimi
- Prof. Pierre Van Damme
- drs Marlies Boeren

**Next-generation sequencing**
- Prof. Geert Mortier
- Dr. Arvid Suls
- drs Esther Bartholomeus

**Biostatistics and Health economics**
- Prof. Niel Hens
- Prof. Phillipe Beutels
- drs Nina Keersmaekers

**Experimental Immunology**
- Prof. Viggo Van Tendeloo
- Prof. Evelien Smits
- drs George Elias

**Bioinformatics**
- Prof. Kris Laukens
- Dr. Pieter Meysman
- drs Nicolas De Neuter
- drs Sofie Gielis