BACTERIAL MENINGITIS

Basic Science review of Host-Pathogen interactions

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A brief introduction to bacterial meningitis

1. Bacterial meningitis is a serious health threat worldwide with a case fatality rates ranging from 10% to 50% and reaching 100% if left untreated.

2. *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Hemophilus influenzae*, Group B. *streptococcus* and *Listeria monocytogenes* account for 85% of meningitis cases in infants and adults.

3. Other bacteria that cause meningitis include *Escherichia coli* K1, *Salmonella*, *Klebsiella* spp., *Staphylococcus aureus*, and a zoonotic pathogen *Streptococcus suis*.

4. *Mycobacterium tuberculosis* (Mtb) also cause meningitis in 1% of all TB cases. Mtb-meningitis affects all age groups, but very common in young children and in people with untreated HIV-infection.

5. Despite treatment with effective antibiotics and required supportive care, 50% of survivors suffer neurological complications such as mental retardation, hearing loss, and learning deficits.
### Major steps and mechanisms involved in the pathogenesis of meningitis …..

<table>
<thead>
<tr>
<th></th>
<th>NM</th>
<th>SP</th>
<th>GBS</th>
<th>EC</th>
<th>Mtb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonization</td>
<td>Nasopharynx</td>
<td>Nasopharynx</td>
<td>Hematogenous Nasopharynx</td>
<td>Hematogenous Nasopharynx/GIT</td>
<td>Lung Hematogenous?</td>
</tr>
<tr>
<td>Colonizer</td>
<td>Common inhabitant</td>
<td>Common inhabitant</td>
<td>Colonizer of female genital tract</td>
<td>Colonizer of female genital tract</td>
<td>Inhalation</td>
</tr>
<tr>
<td>Capsule, Pili, Outer membrane proteins</td>
<td>Capsule, cell-wall proteins, cytolysin</td>
<td>Cell-wall anchored proteins, capsule, LTA, pili, cytolysin.</td>
<td>OmpA, Capsule, CNF-1,Fimbriae, IbeA</td>
<td>HABA</td>
<td></td>
</tr>
<tr>
<td>Survival in blood</td>
<td>Complement inhibition, PMN-killing</td>
<td>Complement inhibition</td>
<td>Complement Inhibition, intracellular survival</td>
<td>Compl. inhibition, PMN &amp; MΦ intracellular survival</td>
<td>Compl. Inhibition?, PMN &amp; MΦ intracellular survival</td>
</tr>
<tr>
<td>CNS entry</td>
<td>B-CSFB, Pili, Opa proteins</td>
<td>BBB, B-CSFB, P-choline pneumolysin</td>
<td>BBB, Pili, LTA, other adhesins</td>
<td>BBB Fimbriae, Omps, CNF-1</td>
<td>BBB Several genes are required for entry</td>
</tr>
</tbody>
</table>
NM interaction with epithelial cells of nasopharynx

Ref: Hill et al., Clinical Science (2010), 118, 540-564.
**E. coli K1 interaction with epithelial cells**

Figure B, reused from Burns et al., Pediatrics Research, 49, 30-37, 2001, (Copy Right permission obtained)

EC: Mittal et al., J. Biol. Chem. 286, 2183-93, 2011 and unpublished results

Figure B, reused from Burns et al., Pediatrics Research, 49, 30-37, 2001, (Copy Right permission obtained)
Syndecans are involved in Mtb attachment to lung epithelial cells

Figures reused from Zimmerman et al., Cellular Microbiology, 18, 1846-1856, 2016 (copyright permission obtained from Nature publications).
Complement evasion strategies of meningitis-causing bacteria

Neisseria meningitidis

**LOS**
- TLR4
  - MyD88-dependent
    - TNF, IL-1, MCP-1, MIP-3
  - MyD88-independent
    - IFN-β, NO, IFN-indu. protein 10

**NhhA**
- TLR4
  - MyD88-dependent
  - MyD88-independent
  - FL-LPS
    - Galactin-3
      - Increased adhesion to immune cells
      - Survival to establish bacteremia

- G-CSF, M-CSF, IL-6

**NO & TNF-α**
- HMGB-1
  - (organ damage in sepsis)
  - Apoptosis

E. coli K1 entry and survival mechanisms in macrophages

Mechanisms of Mtb entry and survival in macrophages

TLR2: LAM, LM, 38- and 19-kDa (LpqH) mycobacterial glycoproteins, PIM, triacylated (TLR2/TLR1), or di-acylated (TLR2/TLR6) lipoproteins, chaperon proteins

TLR4: Tetra-acylated LM, HSP65, 50S ribosomal protein

TLR9: CpG DNA

MR: Mannose (LAM and manLAM)

FcgR: Fc-gamma receptors

CR: Complement receptors

Autophagy is another mechanism by which macrophages recognize Mtb antigens on the cell surface.

Mechanisms of Mtb inhibition of phagosome maturation include:
1. Prevention of Rab5 recruitment
2. Deactivation of PI3K
3. Ndk (Mtb nucleoside diphosphate kinase) interact with Rac1 and blocks NOX2 assembly (mechanism is not clear).
4. Ndk also blocks the fusion of Rab7.

NM binding to and invasion of brain endothelial cells

Invasion mechanisms involved in *E. coli* K1 crossing of the BBB

This figure is generated based on the data from Prasadarao’s, Huang’s and Kim’s labs (partial).
Mtb invasion of brain endothelial cells

### Summary of overview of bacterial meningitis

<table>
<thead>
<tr>
<th>Infection stage</th>
<th>Bacterial pathogens</th>
<th>Mycobacterium tuberculosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Entry into the host</td>
<td>Asymptomatic colonizers of nasopharynx, female genital tract or GIT</td>
<td>Inhalation of droplets containing Mtb</td>
</tr>
<tr>
<td>2. Colonization</td>
<td>Mucosal epithelial cells</td>
<td>Lung epithelial cells</td>
</tr>
<tr>
<td>3. Complement evasion</td>
<td>Binding to C4bp or FH</td>
<td>Mechanism unclear (C4bp?)</td>
</tr>
<tr>
<td>4. Immune cell interaction</td>
<td>Binding to receptors to avoid killing by different immune cells by altering their function.</td>
<td>Prevents phagosome maturation</td>
</tr>
<tr>
<td>5. Interaction with the BBB</td>
<td>Several bacterial ligand-interactions with BMEC receptors. Cytoskeletal rearrangements required</td>
<td>Bacterial ligands and their cognitive receptors are not known. Cytoskeletal rearrangements required</td>
</tr>
</tbody>
</table>
THANK YOU FOR YOUR ATTENTION