An unusual presentation of a human TLR pathway deficiency: lessons
Helen Chapel
Prague 2004
Contents

• Case
• Clinical phenotypes
• TLRs and signalling pathways
• Defects
Case report - infections

Eldest of 3 siblings - non consanguinuous

• “septic pustules” at birth, IV antibiotics
• 3 yrs - abscess over scapula
• 3-6 years - more abscesses over shoulder, hip, knee, cheek
• 6 yrs - septic arthritis
• 7 yrs - four more abscesses
• 10 yrs - Meningitis & septicaemia
Case: Pathogens

Organisms

- Pseudomonas aeruginosa
- Staph. aureas
- Strep. pyogenes

All from separate sites at separate times

- Septic arthritis - Strep. Pneumoniae
- Meningitis/septicaemia - Shigella sonnei
Case: Shigella sonnei meningitis/septicaemia

- Outbreak in local water supply
- Only individual to be systemically unwell
- D & V for 5 days before becoming acutely unwell “septic shock”; in ITU
- Shigella sonnei cultured from stool, CSF, blood
CH in ITU
CH
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Progress with time

- **1974**: Born
- **1974 - 84**: 11 episodes of serious sepsis
- **1984**: Meningitis/ septicaemia
- **1984 - 94**: 3 episodes of sepsis: cellulitis, abscess, osteomyelitis
- **1994 - 00**: 2 abscesses, less severe
- **2000 - 04**: No infections
Acute phase - poor

- Neonatal abscess - Neutrophils $1.02 \times 10^9/l$
- Septic arthritis - no fever, ESR 7, WBC 7.6
- Abscess -15 mls pus, ESR 5, Neutrophils 3.1
- Meningitis/septicaemia - ESR 10, WBC 7.2
- Osteomyelitis (14yr) - Neutrophils 5.1, ESR 35, CRP 6 mg/l
- Cellulitis knee (16yr) - WBC 5.9, CRP 6, ESR 3
### Antibody tests

**Serum immunoglobulin concentrations:**

<table>
<thead>
<tr>
<th>Protein</th>
<th>Value</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG **</td>
<td>16.7</td>
<td>6.0 – 13.0 g/l</td>
</tr>
<tr>
<td>IgA</td>
<td>1.1</td>
<td>0.8 – 3.0 g/l</td>
</tr>
<tr>
<td>IgM</td>
<td>1.9</td>
<td>0.4 – 2.5 g/l</td>
</tr>
<tr>
<td>IgE</td>
<td>400</td>
<td>&lt;125 KU/l</td>
</tr>
</tbody>
</table>

**Antibodies to:**

- **tetanus,** 0.06 >0.01 IU/ml
- **diphtheria,** 0.18 ≥0.1 IU/ml
- **pneumococcal ags** >100 >50 U/ml
### Neutrophil tests

**Nitroblue tetrazolium dye test:**

<table>
<thead>
<tr>
<th></th>
<th>%</th>
<th>±%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medium only</td>
<td>2%</td>
<td>8.7</td>
</tr>
<tr>
<td>Phorbol myristate acid (PMA)</td>
<td>99%</td>
<td>99.2</td>
</tr>
<tr>
<td>Lipopolysaccharide (LPS)</td>
<td>7%</td>
<td>&gt;60%</td>
</tr>
</tbody>
</table>

**Chemotaxis to:**

<table>
<thead>
<tr>
<th></th>
<th>%</th>
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<tbody>
<tr>
<td>N-formaldehyde methionyl peptides (FMLP)</td>
<td>12%</td>
<td>15.7–22.4%</td>
</tr>
<tr>
<td>Casein</td>
<td>7.0%</td>
<td>8.4–14.4%</td>
</tr>
</tbody>
</table>
Tested for IL-6 production
Casanova’s lab - Horst von Bernuth

- Whole blood
- Stimulation IL1 / SAC/ LPS / poly I:C stimulation
- No pro-inflammatory cytokines [IL-6]
- PMA - normal
- TNF - normal IL-10 secretion
Impaired production of IL-6 in response to all the TLRs.
Impact of IRAK-4 deficiency

from Puel et al 2003

Microbes

TLRs

IL-1R

IL-1
IL-6
IL-12
IL-18
TNF-α

IRAK4

Phagocytes

Lymphocytes

Current Opinion in Immunology
IRAK-4 deficiency

- Homozygous *IRAK4* mutation
- Mutation 877 C to T leading to a premature stop Q 293 X in kinase domain
- ? amorphic - *IRAK4* mRNA /protein by Northern and Western blots - *in progress*
- ? recessive, heterozygous members - *being tested*
Thank you

Oxford:
• Patient
• Physicians:
  Christopher Conlon
  Martin Moncrieff
  Siraj Misbah
  Richard Moxon
  Simon Kroll
  David Issacs
• Oxford Immunology Laboratory

Paris:
• Jean-Laurent Casanova
• Anne Puel
• Horst von Bernuth
  Tatiana Lawrence
  Cheng-Lung Ku
  Estelle Chang
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TLR recognising viral proteins & related molecules

From Vaidya & Cheng 2003
TLR signalling in macrophages resulting in anti viral gene expression

from Vaidya & Cheng 2003

12/7/2006
Recognition by mammalian (mice) TLR- pathways

From Kopp & Medzhitov 2003
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Impaired IFN$\alpha$ production in response to the ligands of TLR7/8 (R848, 3M), TLR9 (CpG) and two viruses (HSV, VSV), but a normal response to TLR3 (polyI:C) compared with control.
Impaired or diminished production of IFNβ in response to all the TLRs and tested viruses.
Type I IFN induced MX1 gene expression: Normal to TLR3(polyI:C), TLR4(LPS) and HSV, but the response to TLR7/8 & TLR9 is abolished, the response to VZV is diminished.
Impaired TNFα production in response to all the TLRs tested
Relationship of surface receptors & NFkB from Puel et al 2003
From Puel et al 2003