Genomics of *Streptococcus pneumoniae* and *Streptococcus mitis*

Regine Hakenbeck

Department of Microbiology and Nano+Bio Center
University of Kaiserslautern
Colonizer of the Nasopharynx

- Meningitis
- Otitis
- Pneumonia
- Sinusitis
- Sepsis

patho-genomics

antibiotic resistance
The Transforming Principle

Oswald Theodore Avery  
(1877-1955)

The Transforming Principle

90 capsular types

rough (cps+)

colonies

smooth (Δcps)
Intra- and interspecies gene transfer

'Strategy bottleneck'

Mutation

Gene transfer

Spread of new clones
Streptococcus pneumoniae on blood agar plate
Genetic Evidence

of Gene Transfer of Virulence
The success of one major class of mosaic \textit{pbp2x} genes

\textbf{S. pneumoniae resistant}

\begin{itemize}
  \item CZ 14
  \item SP 6B
  \item Fi 6B
  \item F 6B
  \item TW 23F
  \item SA 19A
  \item SP 14
  \item TW 19F
  \item USA 23F
  \item SP 23F
  \item F 9V
  \item SV18
\end{itemize}

\textbf{S. mitis sensitive}

\begin{itemize}
  \item SV10
  \item M3
  \item 614
  \item B6
  \item 614
  \item B6
\end{itemize}

\textbf{S. mitis resistant}

\begin{itemize}
  \item 492
  \item 697
  \item 691
  \item 713
  \item 714
  \item 715
  \item 711
  \item 717
  \item 703
  \item 566
  \item 560
  \item Uo5
  \item 197
  \item 698
  \item 476
  \item 694
  \item 532
  \item 586
  \item 621
  \item 699
\end{itemize}
Penicillin resistance is mediated by highly diverse mosaic genes
Mosaic Genes - Mosaic Chromosomes?
Genomes

Streptococcus pneumoniae R6 2.04 Mb

Streptococcus pneumoniae TIGR 4 2.16 Mb

Pathogens

Streptococcus mitis B6 2.14 Mb

Commensals
Streptococcus pneumoniae
commensal
S. mitis
commensal
S. oralis
gene pool
virulence factors
Streptococcus pneumoniae
pathogen
antibiotic resistance determinants
Gene transfer
Genomic Comparison of *Streptococcus pneumoniae*

% difference

- between clones: 12
- within clones: 4

% different genes

TIGR specific clusters versus R6

Comparison of 20 *S. pneumoniae* strains (TIGR array)

- R6 clusters vs TIGR: 69 kb
- TIGR clusters vs alle anderen: 90 kb
- TIGR clusters vs R6: 157 kb

316 kb "floating material" in 20 *S. pneumoniae*

- pili
- bacteriocins
- cell surface proteins
- V-ATPase
- antibiotic resistance transporter

16 (partial) genomes: 1.550 kb core genome (Hiller et. al., 2007. J. Bacteriol.)
MLST analysis of Streptococcus sp.

S. pneumoniae

S. mitis

S. oralis

Chi et al., 2007. IJMM 279: 503-512
One *pbp2x* gene family in three 'species'

- **S. pneumoniae**
- **S. mitis**
- **S. oralis**
S. pseudopneumoniae
tree based on
ddl, gdh, rpoB, and sodA

S. mitis

S. pneumoniae

S. infantis

S. oralis

Kilian et al., PLoS ONE 3: July 2008
**Streptococcus mitis B6:**
A high level beta-lactam and multiple antibiotic resistant strain

In vitro antibiotic susceptibilities of *Streptococcus mitis* B6

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin G</td>
<td>&gt;32</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>&gt;32</td>
</tr>
<tr>
<td>Piperacillin</td>
<td>&gt;256</td>
</tr>
<tr>
<td>Cephalothin</td>
<td>&gt;256</td>
</tr>
<tr>
<td>Cefepime</td>
<td>&gt;32</td>
</tr>
<tr>
<td>Cepodoxime</td>
<td>&gt;256</td>
</tr>
<tr>
<td>Cefpirome</td>
<td>64</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>&gt;256</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>&gt;256</td>
</tr>
<tr>
<td>Imipenem</td>
<td>2.0</td>
</tr>
<tr>
<td>Meropenem</td>
<td>2</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>0.19</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>0.125</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>&gt;1024</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>&gt;256</td>
</tr>
<tr>
<td>RP59500</td>
<td>1.5</td>
</tr>
<tr>
<td>Sparfloxacin</td>
<td>0.75</td>
</tr>
<tr>
<td>Tetracyclin</td>
<td>r</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>s</td>
</tr>
</tbody>
</table>

Streptococcus mitis B6

163 kb in six clusters

- aminoglycoside resistance 25.4 kb
- ser-rich cell surface protein cluster 34.4 kb
- tet(M) cluster 27.3 kb
- prophage ΦB6 44.2 kb
- V-type ATPase 15.5 kb
- conserved / hypothetical 16.2 kb
Streptococcus pneumoniae virulence factors

Phase variation (blood versus mucosa)

CELL WALL POLYSACCHARIDES
- capsule
- peptidoglycan
- choline containing WTA, LTA

LPXTG
LXXC
lipoproteins

BACTERIOTINS

PROTEINS RELEASED UPON AUTOLYSIS
- pneumolysin
- autolysin

CBPs
cell wall associated proteins

SECRETED PROTEINS
- neuraminidase
- hyaluronidase
communication is evolution is communication is evolution is communication is evolution is communication is evolution is communication is evolution is communication is evolution is communication is evolution is communication is evolution is communication is evolution is communication is evolution is communication is evolution is communication is evolution is communication is evolution is communication is evolution is communication is evolution is communication is evolution is communication is evolution is communication is evolution is communication is evolution is communication is evolution is communication is evolution is communication is evolution is communication is evolution is communication is evolution is communication is evolution is communication is evolution is communication is evolution is communication is evolution is communication is evolution is communication is evolution is communication is evolution is communication is evolution is communication is evolution is 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