Virulence of the H1N1 2009 pandemic influenza virus

Prasert Auewarakul
Faculty of Medicine Siriraj Hospital
Mahidol University
The 2009 H1N1 pandemic is a mild virus?

It lacks most of the known genetic virulence determinants: HA cleavage site, PB1F2, NS1 PDZ domain, etc.

It induced low levels of proinflammatory cytokines from human cells in vitro.
The 2009 pandemic was a mild one.

- Is the 2009 H1N1 pandemic a mild virus?
- It lacks most of the known genetic virulence determinants: HA cleavage site, PB1F2, NS1 PDZ domain, etc.
- It induced low levels of proinflammatory cytokines from human cells in vitro.
But

- Severe cases have been more often observed than in seasonal outbreaks.

- Studies comparing pandemic and seasonal influenza in the same outbreak showed increased mortality in pandemic influenza.

- Severe cases showed clinical picture quite similar to those caused by H5N1 avian influenza.
H1N1 pandemic influenza virus is more pneumotropic than seasonal influenza viruses.
Sialic acid structure

$\text{SA}_\alpha^2,3\text{Gal or SA}_\alpha^2,6\text{Gal}$
Lung of a H1N1 pandemic flu patient with increased viral receptor

Normal lung

Lung of another H1N1 pandemic flu patient with normal level of viral receptor
Innate defenses against influenza

- Interferon and cytokines
- Soluble factors: e.g.
  - Surfactant proteins (SPA and SPD)
  - Scavenger receptor gp340
<table>
<thead>
<tr>
<th>Virus strain</th>
<th>Virus name</th>
<th>HI titer of pooled BAL (8+14+22)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BAL + normal saline</td>
<td>BAL+RD E</td>
</tr>
<tr>
<td>H1N1</td>
<td>Si-03/06</td>
<td>32</td>
</tr>
<tr>
<td>H3N2</td>
<td>Fujian</td>
<td>64</td>
</tr>
<tr>
<td>H1N1 2009</td>
<td>Non/102</td>
<td>32</td>
</tr>
</tbody>
</table>
BAL

- $\alpha$ and $\gamma$ inhibitors = sialic, e.g. gp340, SPA, serum $\alpha 2$ microglobulin
- $\beta$ inhibitors = lectins, e.g. SPD
- BAL seems to contain more $\alpha$ and $\gamma$?
- H1N1 2009 is less sensitively to SPD and serum, and BAL $\gamma$ inhibitor
- Determinant of this resistance?
- Effect on virulence?
- Variation? Risk groups?
Our data indicate that the main anti-viral activity in BAL was not contributed by SPD.

A recent report has showed that the H1N1 2009 pandemic influenza was less sensitive to SPD due to their lack of glycosylation on HA (Job, 2010).
Down-regulated

- development
- organismal process
- response to stimulus
- transcription regulator activity
- establishment of protein localization
- locomotion
- viral reproduction
- water transporter activity
- peroxiredoxin activity
- binding
- cellular process
- metabolic process
- catalytic activity
- localization
- multicellular developmental process
- cellular component organization
- communication
- cell cycle
- cell death
- vesicle-mediated transport
- cell motion
- cell activation
- response to retinoic acid
- response to chemical stimulus
- response to stress
- cellular response to stimulus
- behavior
SPD staining

Normal lung

H5N1-infected Lung with ARDS
Conclusions

- H1N1 2009 pandemic influenza virus is less susceptible to soluble innate antiviral factors in the lung.
- The reduced sensitivity may explain the enhanced virulence of this virus.
Acknowledgements

- My lab: Ornpreya Suptawiwat, Kanyarat Ruangrung, Alita Kongchanagul, Chompunuch Boonarkart
- Siriraj: Kittipong Maneechotesuwan, Mongkol Uiprasertkul, Pilaipan Puthavathana
- Biotec: Anan Jongkaewwattana
- Vet Sci. Mahidol: Wittawat Wiriyarat
- TRF and NSTDA for funding