SIgN Immunology Seminar

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Heterogeneous Lipid A structures of *Porphyromonas gingivalis* differentially modulate the Human Innate Immune Response

Porphyromonas gingivalis is a Gram-negative bacterial pathogen strongly associated with periodontal (gum) disease. In addition, *P. gingivalis* is also implicated in diabetes, cardiovascular disease, aspiration pneumonia and rheumatoid arthritis. Lipopolysaccharide (LPS) is a key virulence attribute of *P. gingivalis*. Lipid A is the 'bioactive center' responsible for "endotoxin" activity of LPS.

Lipid A structure greatly varies among Gram-negative bacteria. *E. coli* LPS represents the ''canonical'' hexa-acylated lipid A structure. However, *P. gingivalis* LPS displays remarkable heterogeneity with tetra- ($LPS_{1435/1449}$) and penta-acylated (LPS_{1690}) lipid A structures. Using cell-based models, we comprehensively investigated the biological activity of tetra and penta-acylated lipid A structures of *P. gingivalis* in comparison to hexa-acylated *E. coli* lipid A structure. *P. gingivalis* LPS_{1690} significantly upregulated the expression of IL-6, IL-8 and TNF- , suggesting that heterogeneous *P. gingivalis* LPS may differentially modulate the pro-inflammatory cytokines. *P. gingivalis* LPS_{1690} markedly induced MMP3 expression through p38 MAPK and ERK signal pathways, whereas TIMP1 was greatly up-regulated by *P. gingivalis* $LPS_{1435/1449}$. *P. gingivalis* LPS_{1690} induced TLR4 expression, whereas TLR2 was up-regulated by *P. gingivalis* $LPS_{1435/1449}$. NF-κB pathway played a dominant role in *P. gingivalis* LPS_{1690}-induced expression of IL-6 and IL-8. These findings show heterogeneous lipid A structures of *P. gingivalis* differentially interact with TLR2 and TLR4, and may determine the subsequent activation of signal transduction cascades that differentially modulate immuno-inflammatory response.

To obtain a holistic view of heterogeneous *P. gingivalis* lipid A and host interaction, a systems biology-based study through proteomics, metabolomics and bioinformatics approaches was undertaken. Pro-inflammatory proteins were induced by LPS_{1690} whereas anti-inflammatory proteins were up-regulated by $LPS_{1435/1449}$. Secretome analysis showed that immuno-inflammatory mediators, extra-cellular proteases and matrix proteins were differentially modulated by the heterogeneous lipid A structures. These findings demonstrate that multiple host responses seen in immuno-inflammation, oxidative stress and anti-oxidant defense may be differentially modulated by the heterogeneous lipid A structures of *P. gingivalis*. The present findings bring new insight into the molecular mechanisms of periodontal pathogenesis and other systemic diseases associated with *P. gingivalis*.

Host
Dr Puan Kia Joo
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Date
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Time
11am – 12pm

Venue
SIgN Seminar Room
Immunos Building
Level 4
Biopolis