Regulation of Cytokines and Chemokines during Lung Infection with Nontypeable *Haemophilus influenzae*

By

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Table of Contents

Publications Arising from Thesis

Conference Presentations and Posters

Clarke, J. L.: Cytokine and Chemokine regulation during Nontypeable Haemophilus influenzae lung infection (presentation). *University of Canberra, Corroboree, Canberra, 2004*

Clarke, J. L., Foxwell, A. R., Kyd, J. M., and Cripps, A. W.: Cytokine and Chemokine regulation during Nontypeable Haemophilus influenzae lung infection (Poster presentation). *Australian Society for Immunology Conference,* Adelaide 2004

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Clarke, J. L., Cripps, A. W., Foxwell, A. R. and Kyd, J. M.,: Immune regulation of chemokine and cytokine responses following Nontypeable *Haemophilus influenzae* infection (Conference proceedings). *9th International Symposium on Recent Advances in OM, 2007*

Abbreviations

APC	Antigen presenting cell
BAL	Bronchoalveolar lavage
CBA	Chocolate blood agar
ChoP	Phosphorylcholine
CFU	Colony forming unit
COPD	Chronic obstructive pulmonary disease
DEPC	diethyl pyrocarbonate
ELISA	Enzyme linked immunosorbent assay
GM-CSF	Granulocyte macrophage-colony stimulating factor
Hib	*Haemophilus influenzae* type b
ICAM	Intracellular adhesion molecule
IFN	Interferon
IL	Interleukin
IPP	Intra Peyer's patch
IP	Intra peritoneal
IT	Intra tracheal
LOS	Lipooligosaccharide
LPS	Lipopolysaccharide
MCP	Monocyte chemoattractant protein
MIP	Macrophage inflammatory protein
MLN	Mesenteric lymph node
NTHi	Nontypeable *Haemophilus influenzae*
OD	Optical density
OMP	Outer membrane protein
PAF	Platelet activating factor

PAMPs	Pathogen-associated molecular patterns
PBS	Phosphate buffered saline
PCR	Polymerase chain reaction
PMN	Polymorphonuclear leukocyte
RSV	Respiratory syncytial virus
SARS	Severe acute respiratory syndrome
SEM	Standard error of the mean
SIDS	Sudden infant death syndrome
SPF	Specific pathogen free
TLRs	Toll-like receptors
TNF	Tumor necrosis factor
URT	Upper respiratory tract
WBC	White blood cell
WKC	Whole killed cell

Summary

An animal model of respiratory infection was used to determine the effect of various factors, thought to influence the ability of the host to clear bacteria, on the host's innate response to an NTHi lung infection.

Mucosal immunisation with NTHi has previously been shown to enhance the clearance of NTHi from the lung in an animal model of infection through the increased recruitment of phagocytes. Comparisons of cytokine and chemokine kinetic profiles were made in order to determine differences between innate and acquired immune response and the way in which mucosal immunisation controls the innate immune response to NTHi. Increased production of pro-inflammatory cytokines and chemokines in the early stages of NTHi lung infection enhanced the ability to clear bacteria from the rat lung in the immune animals through the increased recruitment of phagocytes to the site. Mucosal immunisation was found to alter the cytokine and chemokine mRNA profiles of CD4+ and CD8+ cells, with increased levels of MCP-1 protein being detected in both types of immune cells.

An antecedent viral infection has been shown to increase the chance of developing a respiratory bacterial infection. The NTHi model of respiratory infection was used to characterise the effect that a viral infection had on the host response to the host's innate response to a bacterial infection and the ability to clear the bacteria. The host's ability to clear NTHi from the rat lung was enhanced by an antecedent viral infection through alterations to the innate immune response and the cytokine and chemokine kinetic profiles.

The use of a mutant strain of NTHi deficient in a component of Lipooligosaccharide (LOS), Phosphorylcholine (ChoP), was utilised as a tool to characterise the innate immune response to LOS. Animals challenged with the LOS mutant strain had a reduced inflammatory response to NTHi through the decreased production of pro-inflammatory cytokines and chemokines and the reduced recruitment of phagocytes to the site of infection.

This thesis has contributed valuable information to enable a better understanding of the host's innate immune response to respiratory infection. This study has identified the role of cytokines and chemokines in the innate response to a respiratory bacterial infection and the enhanced ability of the host to clear NTHi from the lung.