Immune mechanisms that underpin early-life
Chlamydia respiratory infection-induced chronic lung
disease

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Submitted in the fulfilment of the requirements for the award of a Doctor of Philosophy
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I hereby certify that the work embodied in this thesis contains published papers of which I am a joint author. I have included as part of the thesis a written statement, endorsed by my supervisor, attesting to my contribution to the joint publications.

I hereby certify that this thesis is in the form of a series of published papers of which I am a joint author. I have included as part of the thesis a written statement from each co-author, endorsed by the Faculty Assistant Dean (Research Training), attesting to my contribution to the joint publications.

Malcolm Ronald Starkey
December 2013
Acknowledgements

With all endeavours of this nature others provide a great deal of time and support. I would like to briefly acknowledge these individuals and express my sincerest gratitude.

Firstly, I would like to thank my primary supervisor Prof. Phil Hansbro, whose encouragement, support and supervision made this work possible. Thank you also to my co-supervisors Laureate Prof. Paul Foster and Dr. Jay Horvat. Your expertise, knowledge and advice have proven invaluable during my studies.

Thank you also to all the staff and students in the Microbiology, Asthma and Airways Research Group, the discipline of Immunology and Microbiology, the School of Biomedical Sciences and Pharmacy and members of the Hunter Medical Research Institute who have provided their assistance and friendship throughout the last several years. Special thanks go to Richard Kim, Dr. Ama-Tawiah Essilfie and Duc Nguyen.

I would very much like to thank my wife Nikalla, and two children Evanna and Xavier, who have inspired, encouraged, and supported me throughout my PhD. To these people I dedicate my thesis.
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Synopsis

Asthma is a chronic allergic inflammatory condition of the airways that affects >300 million people worldwide. The inflammatory responses that induce asthmatic episodes, at least in allergic asthmatics, are driven predominantly through the actions of activated mast cells, eosinophils and type 2 T helper (Th2) lymphocytes. These activated inflammatory cells and the mediators they release promote inflammatory responses that damage the airways and result in structural changes in lung tissue, and mucus secreting cell (MSC) hyperplasia and metaplasia. The inflammatory response is accompanied by exaggerated sensitivity of the airways to non-specific stimuli, a phenomenon known as airway hyperresponsiveness (AHR). These pathological processes result in a narrowing of the airways leading to widespread airflow obstruction and breathing difficulties associated with asthma.

*Chlamydiae* are atypical obligate intracellular bacteria that commonly cause asymptomatic infection and acute respiratory disease in human infants and adults. *Chlamydia* respiratory infections in early-life have been associated both clinically and experimentally with the development of reduced lung function and more severe asthma in later-life. Previous studies from our laboratory have shown that neonatal and infant, but not adult, *Chlamydia* respiratory infections in mice permanently alter the inflammatory phenotype and lung physiology to increase the severity of allergic airway disease (AAD) by increasing pulmonary interleukin-13 (IL-13) expression, mucus secreting cell (MSC) numbers and AHR. The aim of my PhD was to investigate the immune mechanisms that underpin these observations.

The first study identified a novel role for tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) in promoting *Chlamydia* respiratory infection-induced pathology in early life and subsequent chronic lung disease. Genetic deletion
or inhibition of TRAIL using neutralising antibodies protected against neonatal *Chlamydia* respiratory infection-induced histopathology, inflammation and MSC hyperplasia, as well as subsequent alveolar enlargement and impaired lung function.

The second study investigated the role of IL-13 in promoting early-life *Chlamydia* respiratory infection, infection-induced persistent AHR and severe AAD. IL-13-deficient mice had reduced infection, inflammation, MSC hyperplasia and AHR, which were restored by reconstitution of IL-13-deficient mice with exogenous IL-13. Surprisingly, infection of wild-type mice did not increase IL-13 production, but reduced IL-13 decoy receptor levels. Furthermore, neutralisation of IL-13 during infection prevented subsequent infection-induced severe AAD.

The third study investigated the role of hematopoietic cells in driving early-life infection-induced severe AAD, using bone marrow chimera studies. Neonatal, infant and adult mice were infected with *Chlamydia* and nine weeks after infection bone marrow was collected and transferred into recipient irradiated naïve mice. AAD was induced eight weeks after adoptive transfer. Reconstitution of irradiated naïve mice with bone marrow from mice infected as neonates suppressed the hallmark features of AAD including IL-13 levels in the lung, MSC hyperplasia and AHR. In stark contrast, reconstitution with bone marrow from mice infected as infants increased the severity of AAD by increasing IL-13 levels, MSCs and AHR. Reconstitution with bone marrow from infected adult mice had no effects.

Our novel findings indicate that neonatal and infant *Chlamydia* respiratory infections induce the development of chronic lung disease via distinct mechanisms at different ages. Our studies significantly contribute to understanding the association between early-life respiratory infections and the development of more severe asthma and may facilitate the development of more tailored treatments.
Publications arising from this thesis

Publications included in this thesis


Other publications included as an appendix at the end of this thesis


* denotes equal contribution to manuscript (i.e. co-first author)
Conference publications, presentations and awards

Conference publications


Conference presentations/invited seminars

1. Special seminar presentation at National Heart and Lung Institute, Imperial College London, United Kingdom. Title: Mechanisms of early-life infection-induced chronic lung disease.

2. Oral presentation (New Investigator award session) at 42nd Australasian Society of Immunology Annual Meeting, Melbourne, Australia 2012. Title: Tumor necrosis factor-related apoptosis-inducing ligand translates neonatal respiratory infection into chronic lung disease.

3. Oral presentation (block symposia) at the 8th Annual Newcastle Asthma meeting, Newcastle, Australia 2012. Title: Tumor necrosis factor-related apoptosis-inducing ligand translates neonatal respiratory infection into chronic lung disease.

4. Special Seminar presentation at Brigham and Women’s Hospital, Division of Rheumatology, Immunology, and Allergy, Harvard University, Boston, USA 2012. Title: Mechanisms of early-life infection-induced asthma.

5. Oral presentation (block symposia) at 99th American Association of Immunologists, Boston, USA 2012. Title: Constitutive IL-13 promotes respiratory chlamydial infection and infection-induced chronic airway hyper-responsiveness.
6. Oral presentation (BD Science communication prize) at 41st Australasian Society Immunology Annual Meeting, Adelaide, Australia 2011. Title: Constitutive IL-13 promotes respiratory chlamydial infection and infection-induced chronic airway hyper-responsiveness.

7. Oral presentation (block symposia) at the 7th Annual Newcastle Asthma meeting, Newcastle, Australia 2011. Title: Constitutive IL-13 promotes susceptibility to respiratory chlamydial infection and infection-induced severe asthma.

8. Oral presentation (block symposia) at the 6th Annual Newcastle Asthma meeting, Newcastle, Australia 2010. Title: Role of IL-13 in chlamydial infection and infection-induced asthma.

Fellowships and awards

1. National Health and Medical Research Council (NHMRC) early career fellowship. Awarded October 2013, starts January 2014, ends December 2017

2. International laboratory exchange award to visit the National Heart and Lung Institute Imperial College London. September 2013

3. Hunter Medical Research Institute education prize to visit Brigham and Women’s Hospital and Harvard Medical School, Boston. May 2012


5. CRC for asthma and airways travel award. July 2008
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AAD: Allergic airway disease
AHR: Airway hyperresponsiveness
APC: Antigen presenting cell
Arg-1: Arginase-1
BAL: Bronchoalveolar lavage
BALF: Bronchoalveolar lavage fluid
CD: Cluster of differentiation
cDNA: Complementary DNA
C. muridarum: Chlamydia muridarum
C. pneumonia: Chlamydia pneumoniae
C. trachomatis: Chlamydia trachomatis
DC: Dendritic cell
DcR1: Decoy receptor 1
DcR2: Decoy receptor 2
DNA: Deoxyribonucleic acid
Dpi: Days post infection
DR4: Death receptor 4
DR5: Death receptor 5
EB: Elementary body
ELISA: Enzyme linked immunosorbent assay
FACS: Fluorescence activated cell sorting
FeRI: The high affinity IgE receptor
FIZZ-1: Found in inflammatory zone 1
HDM: House dust mite
HPRT: Hypoxanthine-guanine phosphoribosyltransferase
H&E: Hematoxylin and eosin
Ig: Immunoglobulin
IFN: Interferon
ifu: Inclusion forming unit
IL: Interleukin
IL-4Rα: IL-4 receptor alpha
IL-13Rα1: Interleukin-13 receptor alpha 1
IL-13Rα2: Interleukin-13 receptor alpha 2
ILC2: Type 2 innate lymphoid cell
i.n: Intranasal
iNKT cell: Invariant NKT cell
iNOS: Inducible nitric oxide synthase
i.p: Intraperitoneal
JAK: Janus kinase
<table>
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<tr>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>mDC</td>
<td>Myeloid dendritic cell</td>
</tr>
<tr>
<td>MID1</td>
<td>Midline-1</td>
</tr>
<tr>
<td>MLN</td>
<td>Mediastinal lymph node</td>
</tr>
<tr>
<td>MMP</td>
<td>Matrix metalloproteinase</td>
</tr>
<tr>
<td>MOMP</td>
<td>Major outer membrane protein</td>
</tr>
<tr>
<td>mRNA</td>
<td>Messenger ribonucleic acid</td>
</tr>
<tr>
<td>MSC</td>
<td>Mucus secreting cell</td>
</tr>
<tr>
<td>NF-κB</td>
<td>Nuclear factor kappa-light-chain-enhancer of activated B cells</td>
</tr>
<tr>
<td>NKT cell</td>
<td>Natural killer T cell</td>
</tr>
<tr>
<td>Ova</td>
<td>Ovalbumin</td>
</tr>
<tr>
<td>PAS</td>
<td>Periodic acid–Schiff</td>
</tr>
<tr>
<td>PB</td>
<td>Persistent body</td>
</tr>
<tr>
<td>PBS</td>
<td>Phosphate-buffered saline</td>
</tr>
<tr>
<td>pDC</td>
<td>Plasmacytoid dendritic cell</td>
</tr>
<tr>
<td>PP2A</td>
<td>Protein phosphatase 2A</td>
</tr>
<tr>
<td>PVM</td>
<td>Pneumonia virus of mice</td>
</tr>
<tr>
<td>qPCR</td>
<td>Quantitative polymerase chain reaction</td>
</tr>
<tr>
<td>RB</td>
<td>Reticulate body</td>
</tr>
<tr>
<td>rIL-13</td>
<td>Recombinant interleukin-13</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>rTRAIL</td>
<td>Recombinant tumor necrosis factor-related apoptosis-inducing ligand</td>
</tr>
<tr>
<td>RSV</td>
<td>Respiratory syncytial virus</td>
</tr>
<tr>
<td>RV</td>
<td>Rhinovirus</td>
</tr>
<tr>
<td>SEM</td>
<td>Standard error of the mean</td>
</tr>
<tr>
<td>siRNA</td>
<td>Small interfering RNA</td>
</tr>
<tr>
<td>SPG</td>
<td>Sucrose phosphate glutamate</td>
</tr>
<tr>
<td>STAT6</td>
<td>Signal transducer and activator of transcription 6</td>
</tr>
<tr>
<td>TCR</td>
<td>T cell receptor</td>
</tr>
<tr>
<td>Th</td>
<td>T helper lymphocyte</td>
</tr>
<tr>
<td>Tg</td>
<td>Transgenic</td>
</tr>
<tr>
<td>TGF-β</td>
<td>Tranforming growth factor beta</td>
</tr>
<tr>
<td>TLR</td>
<td>Toll-like receptor</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumor necrosis factor</td>
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<td>Tnfsf10</td>
<td>Tumor necrosis factor superfamily member 10</td>
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