Immunoregulatory therapies for inflammatory diseases

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I hereby certify that the work embodied in this thesis has been done in collaboration with other researchers, or carried out in other institutions. I have included as part of the thesis a statement clearly outlining the extent of collaboration, with whom and under what auspices.

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Synopsis

Respiratory diseases such as asthma, chronic obstructive pulmonary disease (COPD) and influenza affect millions of people worldwide. The lack of effective therapies for these diseases means there is an urgent need to understand the immune mechanisms underpinning these diseases in order to develop more effective therapies.

Asthma is a chronic inflammatory disease of the airways characterised by recurring symptoms of wheezing, coughing and chest tightness. The development and progression of asthma is primarily due to the actions of activated mast cells, eosinophils and type 2 helper (Th2) lymphocytes upon exposure to allergens. These cells release mediators that result in inflammation, oedema and mucus hypersecretion, which are often accompanied by airway hyper-responsiveness (AHR). These features collectively lead to narrowing of the airways and airflow obstruction.

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease characterised by chronic bronchitis, emphysema and airflow limitation, which is not fully reversible. Active smoking of tobacco products remains the most important risk factor for COPD. Recruitment of inflammatory cells and mediators as a result of cigarette smoking leads to oxidative stress and a disruption in the balance between proteases and anti-proteases. Collectively this leads to parenchymal destruction, airway remodelling, narrowing of the airways and ultimately airflow limitation.

Influenza is one of the most important respiratory viral infectious diseases in the world. The virus causes annual epidemics and regular pandemics. Frequent genetic mutation of influenza viruses limits the efficacy of current vaccines and antiviral drugs.

The common theme and aim of my PhD was to investigate the role of novel immune pathways and factors that may underpin the development of asthma, COPD and control the severity of influenza virus infection. The first study demonstrates a novel role
for RelB expression in dendritic cells (DCs) in the development of allergic airway inflammation (AAI). Genetic deletion of RelB led to increased inflammatory cell influx, chemokine and Th2-associated cytokines in the lungs, and airway remodelling that is independent of allergen exposure. Adoptive transfer of RelB-sufficient DCs ameliorated AAI.

The second study investigated the benefits of targeting protein phosphatase 2A (PP2A) and the ubiquitin proteasome system (UPS) using immunomodulatory drugs in allergic airway disease (AAD). Enhancing PP2A activity with 2-amino-4-(4-heptylophenol)-2-methylbutanol (AAL(S)) is more efficient at suppressing hallmark features of AAD compared to fingolimod (FTY720), while inhibiting proteasome activity with bortezomib (BORT) suppresses certain features of AAD. Our study also demonstrates for the first time that enhancing PP2A and inhibiting proteasome activity at the same time has synergistic effects, and is able to suppress more features of AAD than either AAL(S) or BORT treatment alone.

The third study investigated the novel role of the anti-inflammatory molecule, tristetraprolin (TTP), in an experimental model of cigarette smoke (CS)-induced COPD. Our study identified a novel role for TTP in the pathogenesis of experimental COPD. We demonstrate that active TTP is able to reduce the severity of experimental COPD by suppressing CS-induced pulmonary inflammation, pro-inflammatory cytokine and chemokine expression, airway remodelling and lung function impairment.

The fourth study furthered our investigation into the role of TTP by investigating the importance of active TTP in a mouse model of influenza virus infection. We demonstrate for the first time that active TTP reduced the severity of infection by enhancing protective antiviral responses, decreasing pro-inflammatory cytokine and chemokine production, and suppressing phosphoinositide 3-kinase (PI3K) activity.
Collectively these studies have identified potential novel pathways and molecules that are implicated in asthma, COPD and influenza virus infection. Importantly, these studies have expanded our understanding of disease pathogenesis and demonstrate that therapeutically targeting these pathways and molecules may be novel therapeutic avenues for these respiratory diseases.
Publications arising from this thesis

Publications prepared for submission

These publications form the basis of this thesis:


* denotes equal contribution to the manuscript
Other publications


* denotes equal contribution to the manuscript
Conference publications


* denotes equal contribution to the manuscript
Conference presentations

- Oral presentation at 11th Annual Newcastle Asthma meeting, Newcastle, Australia, October 2015. Title: Role of tristetraprolin in respiratory diseases

- Oral presentation at 4th European Congress of Immunology, Vienna, Austria 2015. Title: RelB-deficient dendritic cells promote development of spontaneous allergic airway inflammation in mice. *(presented by Dr. Malcolm Starkey).*

- Oral presentation at Australian Respiratory Virology meeting, Canberra, Australia 2015. Title: Tristetraprolin is protective against influenza virus infection in mice. *(presented by Dr. Malcolm Starkey).*

- Oral presentation at 10th Annual Newcastle Asthma meeting, Newcastle, Australia, October 2014. Title: Role of RelB in allergic airway inflammation

- Oral presentation at 44th ASI annual meeting, Wollongong, Australia, December 2014. Title: RelB deficiency promotes allergic airway inflammation in mice
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Abbreviations

AAD: Allergic airway disease
AAL(S): 2-amino-4-(4-heptyloyphenol)-2-methylbutanol
AhR: Aryl hydrocarbon receptor
AHR: Airway hyperresponsiveness
APC: Antigen presenting cell
ARE: AU-rich element
ATP: Adenosine triphosphate
AU: Adenosine and uridine
BAL: Bronchoalveolar lavage
BM: Basement membrane
BMAL: Aryl hydrocarbon receptor nuclear translocator-like
BORT: Bortezomib
cDNA: Complementary deoxyribonucleic acid
cRNA: Complementary ribonucleic acid
CARD: Caspase activation and recruitment domain
Cbl-b: Casitas B lineage lymphoma B
CCCH: Cysteine-cysteine-cysteine-histidine
CCL: Chemokine (C-C motif) ligand
CD: Cluster of differentiation
CLOCK: Clock circadian regulator
COPD: Chronic Obstructive Pulmonary Disease
COX-2: Cyclooxygenase-2
CS: Cigarette smoke
CXC: Chemokine (C-X-C motif) ligand
DCs: Dendritic cells
DNA: Deoxyribonucleic acid
dpi: Days post infection
ELISA: Enzyme-linked immunosorbent assay
ERK: Extracellular signal-regulated kinase
FceRI: High affinity IgE receptor
FACS: Fluorescence activated cell sorting
FEV₁: Forced expiratory volume in 1 second
FVC: Forced vital capacity
FTY720: Fingolimod
GM-CSF: Granulocyte macrophage colony-stimulating factor
GOLD: Global Initiative for Chronic Obstructive Pulmonary Disease
H&E: Haematoxylin and eosin
HA: Haemagglutinin
HDM: House dust mite
HPRT: Hypoxanthine-guanine phosphoribosyltransferase
IκB: Inhibitor of κB
ICAM-1: Intracellular adhesion molecule 1
IDO: Indoleamine 2,3-dioxygenase
IFN: Interferon
Ig: Immunoglobulin
IKK: IκB kinase
IKK-i: IκB kinase-i
IL: Interleukin
ILC2: Type 2 innate lymphoid cells
i.n: Intranasal
i.p: Intraperitoneal
IPS-1: IFN-β promoter stimulator 1
LCMT1: Leucine carboxyl methyltransferase 1
IRF7: IFN regulatory factor 7
LPS: Lipopolysaccharide
LTβR: Lymphotoxin beta receptor
MACS: Magnetic-activated cell sorting
MAPK: Mitogen-activated protein kinase
mDCs: Myeloid dendritic cells
MG-132: carbobenzoxy-L-leucyl-L-leucinal
MHC: Major histocompatibility complex
MID1: Midline 1
miRNA: Micro RNA
MK2: MAPK-activated protein kinase 2
mRNA: Messenger ribonucleic acid
MMP: Matrix metalloproteinase
MSC: Mucus secreting cells
Muc5AC: Mucin 5AC
NA: Neuraminidase
NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells
NIK: NF-κB inducing kinase
NK: Natural killer
NLRP3: NOD-like receptor family pyrin domain containing 3
NS: Non structural
Nup475: Nuclear protein 475
OVA: Ovalbumin
PA: Polymerase acidic
PAMP: Pathogen-associated molecular pattern
PAS: Periodic acid-Schiff
PB: Polymerase basic
pBEC: Primary bronchial epithelial cell
PBMC: Peripheral blood mononuclear cell
pfu: Plaque forming units
PKC: Protein kinase C
PI3K: Phosphoinositide 3-kinase
PIP$_2$: Phosphatidylinositol 4,5-bisphosphate
PIP$_3$: Phosphatidylinositol (3,4,5)-trisphosphate
PPP: Phosphoprotein phosphatase
PP2A: Protein phosphatase 2A
PRR: Pattern recognition receptor
PTP: Protein tyrosine phosphatase
qPCR: Quantitative polymerase chain reaction
RIG-I: Retinoic acid-inducible gene I
RNA: Ribonucleic acid
RNP: Ribonucleoprotein
ROS: Reactive oxidant species
s.e.m: Standard error of the mean
siRNA: Small interfering RNA
SIPR1: Sphingosine-1-phosphate receptor
SNP: Single nucleotide polymorphism
STAT6: Signal transducer and activator of transcription-6
TANK: TRAF family member-associated NF-κB activator
TBK1: TANK binding kinase-1
TGF-β: Transforming growth factor beta
Th: T helper lymphocyte
TLR: Toll-like receptor
TNF: Tumour necrosis factor
TRAF: TNF receptor associated factor
TRAIL: Tumour necrosis factor-related apoptosis-inducing ligand
Tregs: Regulatory T cells
TSLP: Thymic stromal lymphopoietin
TTP: Tristetraprolin
TIS11: TPA-induced sequence 11
UCHL-1: Ubiquitin carboxyl-terminal hydrolase L1
US: United States
VCP: Valosin-containing protein
WT: Wild-type
ZFP36: Zinc finger protein 36
γδ T cell: Gamma delta T cell