

SYSTEMIC INFLAMMATION IN OBSTRUCTIVE AIRWAY DISEASE

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MD

A Thesis Submitted for the Degree of Doctor of Philosophy

School of Health and Medicine

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STATEMENT OF ORIGINALITY

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to the final version of my thesis being made available worldwide when deposited in the University's Digital Repository**, subject to the provisions of the Copyright Act 1968.

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26/05/2014

ACKNOWLEDGEMENT OF AUTHORSHIP

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 coauthor, endorsed by the Faculty Assistant Dean (Research Training), attesting to my contribution to the joint publications.

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Same casts, different scripts. It seems the same as it was four years ago when I was writing my acknowledgements at the completion of my Masters degree, but what I am now going to say is totally different. Four years ago, I decided to conduct my PhD study overseas, it was not an easy decision to make as I had known little about the world outside. I was so lucky that 'Newcastle' chose me among several candidates, and I chose 'Newcastle' among different offers, because I had learned from the website at that time of the advantages of clinical studies in this centre. Now, I am proud that I have been able to finish the journey and become a qualified PhD scholar.

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5. **Fu JJ**, McDonald VM, Baines KJ, Gibson PG. Airway IL-1 pathway activation and systemic inflammation predict future exacerbation risk in asthma and COPD. Under Review - *THORAX*. (Chapter 6)

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STATEMENT OF CONTRIBUTION OF OTHERS

I, Peter Gibson, attest that Research Higher Degree candidate, Juan-juan Fu, provided substantial intellectual input and contributions to the study design, patient recruitment, laboratory experimentation, data input, statistical analyses and manuscript preparation/writing for the papers entitled:

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LIST OF COMMONLY USED ABBREVIATIONS

ACQ	asthma control questionnaire
AFO	airflow obstruction
AHR	airway hyperresponsiveness
ASM	airway smooth muscle
BCR	B-cell receptor
BDR	bronchodilator responsiveness
BDP	beclomethasone dipropionate
BHR	bronchodilator hyper-responsiveness
BMI	body mass index
CAT	COPD Assessment Test
CCI	Charlson Co-morbidity Index
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
CVD	cardiovascular disease
C2R	chromotrope 2R
eCO	exhaled carbon monoxide
ELISA	enzyme-linked immunosorbent assay
eNO	exhaled nitric oxide
ER	emergency room
EPR	expert panel report
FEV ₁	forced expiratory volume in one second
FVC	forced vital capacity
GO	Gene Ontology
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Chronic Obstructive Lung Disease

HADs	Hospital Anxiety and Depression Scale
HRQoL	health-related quality of life
ICD	International Classification of Disease codes
ICS	inhaled corticosteroid
IL	interleukin
IQR	interquartile range
LABA	long-acting beta-agonists
LAMA	long-acting anticholinergics
LRTI	lower respiratory tract infection
LTRAs	Leukotriene antagonists
LTs	leukotrienes
MCID	minimum clinically important difference
MGG	May-Grünwald Giemsa
mMRC	Medical Research Council dyspnea questionnaire
MMP-9	metalloproteinase-9
OAD	obstructive airway disease
PC ₂₀	provocative concentration resulting 20% fall in the FEV ₁
PEF	peak expiratory flow
qPCR	quantitative polymerase chain reaction
RCTs	randomized clinical trials
ROS	reactive oxygen species
SAA	serum amyloid A
SABA	short-acting beta-agonist
SIRS	systemic inflammation response syndrome
SGRQ	St. George's Respiratory Questionnaire
TNF- α	tumor necrosis factor- α
6MWD	six-minute walk distance

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ABSTRACT

Obstructive airway disease (OAD) such as asthma and chronic obstructive pulmonary disease (COPD) are common respiratory conditions affecting people of all age and imposing significant socioeconomic burden. Distinct phenotypes and enhanced airway inflammation and immune dysfunction are typical features of OAD and have been widely studied. Airway inflammation has been shown to relate to adverse clinical outcomes such as exacerbations in asthma.

Systemic inflammation, characterized by minor increase in the circulating inflammatory cells or mediators, has been increasingly recognized as an important feature of COPD. The role of systemic inflammation in OAD is not well understood. While systemic inflammation is associated with COPD comorbidity and may be involved in the disease progression in terms of exacerbation and mortality in COPD, its presence in asthma and potentially in asthma-COPD overlap syndrome and the clinical relevance are still unknown. It is also unclear if there is an association between systemic inflammation and airway inflammation, and how this relates to disease progression.

The aim of this thesis was to investigate systemic inflammation in different phenotypes of OAD including asthma and COPD. The proportion of asthma-COPD overlap syndrome increases with age, therefore this specific phenotype was also assessed in the studies in which older patients were recruited in this thesis. The presence and the associations between systemic inflammation and clinical characteristics were assessed in OAD. In addition, the longitudinal changes in clinical outcomes among these different phenotypes of OAD were compared and linked to systemic inflammation. I also examined the association between airway inflammation and systemic inflammation linking to future exacerbation risk and sought to investigate the mechanisms behind the clinical relevance of systemic inflammation in COPD.

The findings of this thesis have extended our knowledge of the inflammatory mechanisms of OAD. Systemic inflammation and airway inflammation are both important features of OAD and relate to clinical prognosis in terms of exacerbation risk. These are important observations that revealed novel inflammatory mechanisms of OAD and have significant clinical implications. Targeting specific inflammatory pathways might provide novel therapeutic strategies for OAD.