university of groningen

UTS UNIVERSITY OF TECHNOLOGY SYDNEY

The role of accelerated ageing in aberrant lung tissue repair and remodelling in COPD

PhD thesis

to obtain the degree of PhD at the
University of Groningen
on the authority of the
Rector Magnificus Prof. C. Wijmenga
and in accordance with
the decision by the College of Deans

and

to obtain the degree of PhD of
University of Technology Sydney
on the authority of the
Faculty of Science

Double PhD degree

This thesis will be defended in public on

Tuesday 29 June 2021 at 11:00 hours

by

Roy Rolf Woldhuis

born on 23 June 1992
in Assen, the Netherlands

The studies presented in this thesis were performed within the framework of the Groningen University Institute for Drug Exploration (GUIDE), the Groningen Research Institute for Asthma and COPD (GRIAC), Woolcock Institute of Medical Research and University of Technology Sydney (UTS). The studies presented in this thesis were financially supported by the Australian National Health and Medical Research Council (NHMRC; grant number: APP1104704) and the Lung Foundation Netherlands (Longfonds; grant number: 3.2.12.044).

CERTIFICATE OF ORIGINAL AUTHORSHIP

I, ***Roy Woldhuis*** declare that this thesis, is submitted in fulfilment of the requirements for the award of ***Doctor of Philosophy*** in the ***School of life sciences*** at the University of Technology Sydney.

This thesis is wholly my own work unless otherwise referenced or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

I certify that the work in this thesis has not previously been submitted for a degree nor has it been submitted as part of the requirements for a degree at any other academic institution except as fully acknowledged within the text. This thesis is the result of a Collaborative Doctoral Research Degree program with ***The University of Groningen, Groningen, The Netherlands.***

This research is supported by the Australian Government Research Training Program.

Signature: Production Note:
Signature removed prior to publication.

Date: 14/09/2021

ABSTRACT

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide, while the prevalence is still increasing. Since the exact COPD pathogenesis is still unknown and no effective therapeutics are available to stop the progression of the disease, novel insights into the pathogenesis of COPD are urgently needed. Accelerated ageing has been postulated to play a role in COPD with characteristic of ageing demonstrated in lungs from COPD patients compared to age-matched smokers without COPD. Recently, extracellular matrix (ECM) dysregulation has been described as an additional ageing hallmark of the lungs. ECM dysregulation can cause aberrant lung tissue repair and remodelling. Lung fibroblasts and airway smooth muscle cells (ASMCs) are the major producers and regulators of the ECM and therefore play an important role in lung tissue repair and remodelling. The aim of this thesis was to elucidate the role of accelerated ageing in aberrant tissue repair and remodelling in COPD.

We analysed ageing markers and ECM changes in lung fibroblasts and ASMCs from COPD patients compared to ex-smoker controls without COPD matched for age, gender, and smoking history. In addition, we assessed the functional effects of induction of cellular senescence, which is a major ageing hallmark.

We found characteristics of accelerated ageing in COPD-derived fibroblasts compared to lung fibroblasts from matched controls, including higher levels of cellular senescence. The increase in cellular senescence in COPD-derived fibroblasts was associated with lower levels of the ECM protein decorin and higher levels of pro-inflammatory protein secretion. Induction of cellular senescence in lung fibroblasts also resulted in ECM changes, secretion of pro-inflammatory proteins and impaired tissue repair functions of the fibroblasts. Furthermore, ASMCs had higher levels of cellular senescence compared to lung fibroblasts from the same patients, but in ASMCs no differences were found between COPD and control. Finally, we showed that E-cigarette extract induces cellular senescence in lung fibroblasts, and the induction in cellular senescence resulted in impaired tissue repair functions. Therefore, we concluded that E-cigarettes, commonly used as smoking alternative or as smoke cessation aid, are not a safe alternative for tobacco smoking.

These studies indicate that accelerated ageing plays a role in aberrant tissue repair and remodelling in COPD and thereby contributes to the pathogenesis of COPD. Future studies should unravel the exact mechanisms that lead to accelerated ageing in COPD to discover therapeutics targets to develop therapies that target accelerated ageing in COPD patients.

STATEMENT OF AUTHOR CONTRIBUTION UNPUBLISHED CHAPTER 6

Roy R. Woldhuis[1,2,3,6], Jack Bozier[1,2], Maaike de Vries[4,6], Irene H. Heijink[3,5,6], Maarten van den Berge[5,6], Wim Timens[3,6], Corry-Anke Brandsma[3,6], and Brian G.G. Oliver[1,2]

Woolcock Institute of Medical Research[1], University of Technology Sydney[2], University of Groningen, University Medical Centre Groningen, Department of Pathology and Medical Biology[3], Department of Epidemiology[4], Department of Pulmonary Diseases[5], Groningen Research Institute for Asthma and COPD (GRIAC)[6]

Authors' contributions:
Conception and design: RRW, CAB, BGGO
Acquisition and analysis of data: RRW, JB, CAB, BGGO
Interpretation of data: RRW, MdV, IHH, MvdB, WT, CAB, BGGO
Drafting the manuscript: RRW, CAB, BGGO
All authors reviewed, edited, and approved the final manuscript.

By signing this document I declare that Roy R Woldhuis has contributed to a level that justifies first authorship on this manuscript

Jack Bozier
Signed ..... Date 17/12/2020

Production Note:
Signature removed prior to publication.

Maaike de Vries
Signed ..... Date 17/12/2020

Production Note:
Signature removed prior to publication.

Irene H. Heijink
Signed ..... Date 17/12/2020

Production Note:
Signature removed prior to publication.

Maarten van den Berge
Signed ..... Date 17/12/2020

Production Note:
Signature removed prior to publication.

Wim Timens
Signed ..... Date December 17, 2020

Production Note:
Signature removed prior to publication.

Corry-Anke Brandsma
Signed ..... Date 17/12/2020

Production Note:
Signature removed prior to publication.

Brian G. G. Oliver
Signed ..... Date 17/12/2020

Production Note:
Signature removed prior to publication.

STATEMENT OF AUTHOR CONTRIBUTION UNPUBLISHED CHAPTER 7

Roy R. Woldhuis[1,2,3,6]*, Jack Bozier[1,2]*, Baoming Wang[1,2], Irene H. Heijink[3,4,6], Maaike de Vries[5,6] Maarten van den Berge[4,6], Wim Timens[3,6], Corry-Anke Brandsma[3,6], Brian G.G. Oliver[1,2]
* Co-first authors

Woolcock Institute of Medical Research, Respiratory Cellular and Molecular Biology Group[1], University of Technology Sydney, School of Life Sciences[2], University of Groningen, University Medical Centre Groningen, Department of Pathology and Medical Biology[3], Department of Pulmonary Diseases[4], Department of Epidemiology[5] Groningen Research Institute for Asthma and COPD (GRIAC)[6]

Authors' contributions:
Conception and design: RRW, JB, BGGO
Acquisition and analysis of data: RRW, JB, BW, BGGO
Interpretation of data: RRW, JB, IHH, MvdB, WT, CAB, BGGO
Drafting the manuscript: RRW, JB
All authors reviewed, edited, and approved the final manuscript.
RRW and JB contributed equally.

By signing this document I declare that Roy R Woldhuis has contributed to a level that justifies first authorship on this manuscript

Jack Bozier
Signed ..... Production Note: Signature removed prior to publication. ..... Date 17/12/2020

Baoming Wang
Signed ..... Production Note: Signature removed prior to publication. ..... Date 17/12/2020

Irene H. Heijink
Signed ..... Production Note: Signature removed prior to publication. ..... Date 17/12/2020

Maaike de Vries
Signed ..... Production Note: Signature removed prior to publication. ..... Date 17-12-2020

Maarten van den Berge
Signed ..... Production Note: Signature removed prior to publication. ..... Date 17/12/2020

Wim Timens
Signed ..... Production Note: Signature removed prior to publication. ..... Date December 17, 2020

Corry-Anke Brandsma
Signed ..... Production Note: Signature removed prior to publication. ..... Date 17/12/2020

Brian G. G. Oliver
Signed ..... Production Note: Signature removed prior to publication. ..... Date 17/12/2020

TABLE OF CONTENTS