The role of Matrix Metalloproteinases in COPD

Submitted in Partial Fulfillment
of the Requirements of the Master Degree
in Chest Diseases

BY
Amira Ismail Mostafa Alm Eldin
M.B.B.ch.

Supervised by

Dr.
Nariman Abd El Rahman Helmy
Professor of Chest Diseases-Chest Department
Faculty of Medicine, Cairo University

Dr.
Laila Ahmed Rashed
Assistant Professor of Biochemistry
Faculty of Medicine, Cairo University

Dr.
Ahmed Mahmoud Abd Elhafez
Lecturer of Chest Diseases-Chest Department
Faculty of Medicine, Cairo University

Faculty of Medicine
Cairo University
2009

Acknowledgement

To ***ALLAH*** every thing in life is resumed, in this work, ***ALLAH*** has helped me a lot , if only one to be thanked , ***ALLAH*** is the first and the last , also those offered by ***ALLAH*** to advice and guide have to be thanked.

I wish to express my deepest gratitude to ***Prof. Dr. Nariman Helmy***, Professor of Chest Diseases, Cairo University, for her sincere guidance, kind supervision, and continuous encouragement through the whole work.

I am very grateful to ***Prof. Dr. Laila Rashed***, Assistant Professor of Biochemistry, Cairo University, for her precious supervision.

I am very grateful to ***Dr. Ahmed Abd El Hafez***, Lecturer of Chest Diseases, Cairo University for his constant assistance and valuable support.

I sincerely appreciate the aid of ***Dr. Samah Selim***; Assistant Lecturer of Chest Diseases, Cairo University, without her, this work would not have been completed.

Lastly I would like to thank my ***Father***, my ***Mother*** and my ***Husband*** for their guidance and support.

Acknowledgement

Abstract

The present study was conducted in the chest and biochemistry departments in Kasr EL Aini Hospital. It was done on 20 COPD patients, 10 healthy smokers, and 10 never smoker subjects. Exclusion criteria included a history of respiratory disease other than COPD or respiratory tract infection during the last 4 weeks before the study.

Each subject was submitted to:

1. Full history taking
2. Full clinical examination general and local examination
3. Pulmonary function tests (spirometry) before and after bronchodilatation (FEV1, FVC, FEV1/FVC, FEF 25%-75%) as % of predicted value.
4. Assay of matrix metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 in induced sputum.

Key Words:

Chronic Obstructive Pulmonary Diseases (COPD), Risk factors, Pathology, Pathogenesis and pathophysiology, Assessment and monitoring of COPD, Matrix metalloproteinase and tissue inhibitors of metalloproteinase.

List of Abbreviations

α 1-AT:α 1 anti-trypsin.

ANOVA: Analysis of Variance

ASM: Airway smooth muscle.

ATS: American Thoracic Society.

BAL: Bronchoalveolar lavage.

BDI: Baseline dyspnea Index.

BODE: Body mass index, obstruction, dyspnea and exercise.

BTS: British Thoracic Society.

COPD: Chronic Obstructive Pulmonary Disease.

COX-2: cyclooxygenase-2.

CRP: C-reactive protein.

CT: Computed tomography.

DTT: Dithiothreitol.

EBC: Exhaled breath condensate.

ECM: Extra cellular matrix.

ELISA: Enzyme-linked immunosorbent assay.

ERS: European Respiratory Society..

FEV1: Forced expiratory volume in the first second.

FENO: Exhaled nitric oxide.

FVC: Forced vital capacity.

GM-CSF: Granulocyte macrophage colony stimulating factor.

GOLD: Global initiative of chronic obstructive lung disease.

GRO-α: Growth related oncogene-α.

H_2O_2: Hydrogen peroxide.

IFN-γ: Interferon γ.

List of abbreviations

IL-1: Interleukin-1.

IL-6: Interleukin-6.

IL-8: Interleukin-8.

IL-9: Interleukin-9.

IP-10: INF-γ activated protein.

IPF: Idiopathic pulmonary fibrosis.

LPS: lipopolysaccharide.

LTB4: Leukotriene B4.

MCP-1: Macrophage chemo tactic factor.

MDI: Metered dose inhalers.

MEPHX1: Microsomal expoide hydrolase 1.

MIP-1α: Macrophage inflammatory protein-1 α.

MMP: Matrix metalloproteinase.

MMRC: Modified Medical research council.

NF-κB: nuclear factor-κB.

NO: Nitric oxide.

NSIP: Nonspecific interstitial pneumonitis.

OCD: Oxygen cost diagram.

PAF: Platelet-activating factor..

PDGF: platelet derived growth factor.

$PGE_{2:}$ prostaglandin E2.

ROS: Reactive oxygen species.

SD: Standard deviation.

SLPI: Secretory leukprotease inhibitor.

TGF-B: Transforming Growth Factor B.

TGFB1: Transforming growth factor beta 1.

TIMP: Tissue inhibitor of metalloproteinase.

List of abbreviations

TMB: Tetramethylbenzidine

TNF α: Tumor necrosis factor α.

TX: Thromboxane

Zn: Zinc.

List of figures

List of tables

Contents

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of chronic morbidity and mortality throughout the world.

Many people suffer from this disease for years and die prematurely from it or its complications. COPD is the fourth leading cause of death in the world, and further increases in its prevalence and mortality can be predicted in the coming decades ***(Lopez et al., 2006).***

Tobacco smoking continues to be a major cause of COPD, as well as of many other diseases. However, it is not the only cause of COPD, and it may not even be the major cause in some parts of the world.

Furthermore, not all smokers develop clinically significant COPD, which suggests that additional factors are involved in determining each individual's susceptibility**.** ***(Jindal et al., 2006)***

COPD is characterized by chronic airflow limitation that is not fully reversible .The airflow limitation is usually both progressive and associated with abnormal inflammatory response of the lungs to noxious particles or gases. Symptoms, functional abnormalities and complications of COPD can all be explained on

the bases of this underlying inflammation and the resulting pathology. ATS/ERS consensus states that although COPD affects the lungs, it also produces significant systemic consequences. ***(Gan et al., 2004)***

COPD is an inflammatory disease of the airways characterized by airways remodeling, due to an excess of ECM deposition in the airway wall. ***(Bousquet et al., 1992)***, which leads to fibrosis of the small airways in COPD ***(Thurbeck and W., 1990)***.

The Extracellular matrix (ECM) is a dynamic structure, and equilibrium between synthesis ***(Mosher et al., 1992)*** and degradation of ECM components is required for the maintenance of its homeostasis.

Although many proteases can cleave ECM molecules, Zn^{2+}-matrix metalloproteinases (MMPs) and their inhibitors are likely to be the normal physiologically relevant mediators of ECM degradation ***(Matrisian and L., 1992).***

Aim of the work

To investigate the role of MMP-9/TIMP in COPD and it's relation to airflow obstruction.

Chronic Obstructive Pulmonary Diseases(COPD)

INTRODUCTION AND DEFINATIONS

Historical Background

On the 18th century, Matthew Baillie provided the earliest illustrations and a brief description of emphysema ***(Baillie, 1808).***

Early in the 19th century, Laennec using air-dried inflated lung specimens, described emphysema. He suggested that peripheral airways were the primary site of obstruction in emphysema and speculated that loss of elastic recoil was a likely contributor to diminished airflow ***(Lannec, 1835).***

In the 1950s, Gough and his collaborators, using sections of whole inflation-fixed lungs mounted on paper; described centriacinar emphysema and differentiated it from panacinar emphysema ***(Gough, 1952).***

In the 1960s, the association of homozygous alpha-1 protease inhibitor deficiency with emphysema and animal model of emphysema induced by protease led to the concept of proteolytic destruction of the lung as a major factor ***(Laurell et al, 1963).***