



شبكة المعلومات الجامعية





شبكة المعلومات الجامعية

جامعة عين شمس

التوثيق الالكتروني والميكرو فيلم

قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأفلام قد أعدت دون أية تغييرات



يجب أن

تحفظ هذه الأفلام بعيدا عن الغبار

في درجة حرارة من ١٥-٢٥ مئوية ورطوبة نسبية من ٢٠-٤٠%

To be Kept away from Dust in Dry Cool place of
15-25- c and relative humidity 20-40 %



شبكة المعلومات الجامعية التوثيق الالكتروني والميكرو فيلم

بعض الوثائق الأصلية تالفة

Role of Matrix Degradation Enzymes in Aetiopathogenesis of Certain Bronchopulmonary Diseases

Thesis

Submitted By

Nabil Anwar

For Partial fulfillment of M.D
Degree in Internal Medicine

Under Supervision of

Prof. Dr. El Said Abou Gamrah

*Professor of Internal Medicine
Faculty of Medicine-Ain Shams University*

Dr. Magdi Farrag

*Assistant Professor of Internal Medicine
Faculty of Medicine -Ain Shams University*

Dr. Laila Ashour

*Assistant Professor of Chest Diseases
Faculty of Medicine-Ain Shams University*

Dr. Eman El-Gohary

*Lecturer of Clinical Pathology
Faculty of Medicine-Ain Shams University*

*Ain Shams University
2001*

ACKNOWLEDGEMENT

Thanks first and last to (God) to whom we owe his great care, support and guidance in every step in our life.

*I would like to express my deepest gratefulness to **Prof. Dr. El-Said Abou Gamrah** Professor of general Medicine Faculty of Medicine, Ain Shams University, for giving me the chance to work under his generous supervision and continuous encouragement.*

*I wish to offer my deepest thanks and my sincere gratefulness to **Dr. Magdi Farrag**, Assistant professor of general Medicine, Ain Shams University for his trustful help, advice and supervision.*

*I wish to offer my sincere gratefulness to **Dr. Laila Ashour**, Assistant Professor of chest diseases, Faculty of Medicine, Ain Shams University for her assistance and kind cooperation. Also, my thanks*

for every body in the chest department who helped me in finishing this work.

I wish to offer my profound appreciation and gratitude to **Dr. Eman El-Gohary** Lecturer of clinical pathology, Faculty of Medicine, Ain Shams University for her continuous interest, assistance and kind cooperation, supervision and great effort in every step in this work. Also, many thanks to every body in the clinical Pathology Department who helped me in finishing this work.

List of Contents

	Page
☛ Introduction	1
☛ Aim of the Work	2
☛ Review of Literature	3
★ The extracellular matrix	3
★ Matrix metalloproteinases family (Matrixins)	5
★ Tissue Inhibitor Metalloproteinases (TIMPs)	13
★ Role of MMPs & TIMPs in pathogenesis of many chest and systemic diseases	15
★ Matrix Metalloproteinase-9 (MMP-9)	55
★ Tissue Inhibitor Metalloproteinase-1 (TIMP-1)	61
☛ Subjects and Methods	64
☛ Results	74
☛ Discussion and Recommendations	112
☛ Summary	119
☛ References	122
☛ Arabic Summary.....	

List of Tables

Review of Literature & Patients and Methods

	Page
<i>Table (1):</i> Matrix metalloproteinase family	7
<i>Table (2):</i> Factors affecting MMPS production	12
<i>Table (3):</i> Comparison between TIMP-1 and TIMP-2	14
<i>Table (4):</i> Patients groups	65

Results

<i>Tables (1-48):</i> Showed the comparison between each group and the other groups regarding all the studied parameters (MMP-9, TIMP-1, the ratio and the age) using the logistic t-test	81-106
<i>Tables (49-51):</i> Showed the correlation study between MMP-9, TIMP-1 and ratio in each group using the ranked Spearman correlation test (r)	114-118
<i>Table (52):</i> Analysis of variance (ANOVA) test for discrimination between all groups regarding the studied parameters using F-ratio in descending order.	119
<i>Table (53):</i> Diagnostic performance of MMP-9, TIMP-1, and the ratio as a marker for lung cancer patients versus non cancer patients as a control at different decision levels	120

List of Figures

Review of Literature & Patients and Methods

	Page
<i>Fig. (1):</i> Composition and structure of extracellular matrix (ECM) are shown. The basement membrane is the composite of 3 layers: Lamina lucida, lamina densa, and lamina reticularis	4
<i>Fig. (2):</i> Domain structure of MMPs	9
<i>Fig. (3):</i> Scheme of proposed mechanisms of parenchymal destruction in tuberculous granuloma.	25
<i>Fig. (4):</i> The three modes of anticancer activity of matrix metalloproteinase inhibitors	29

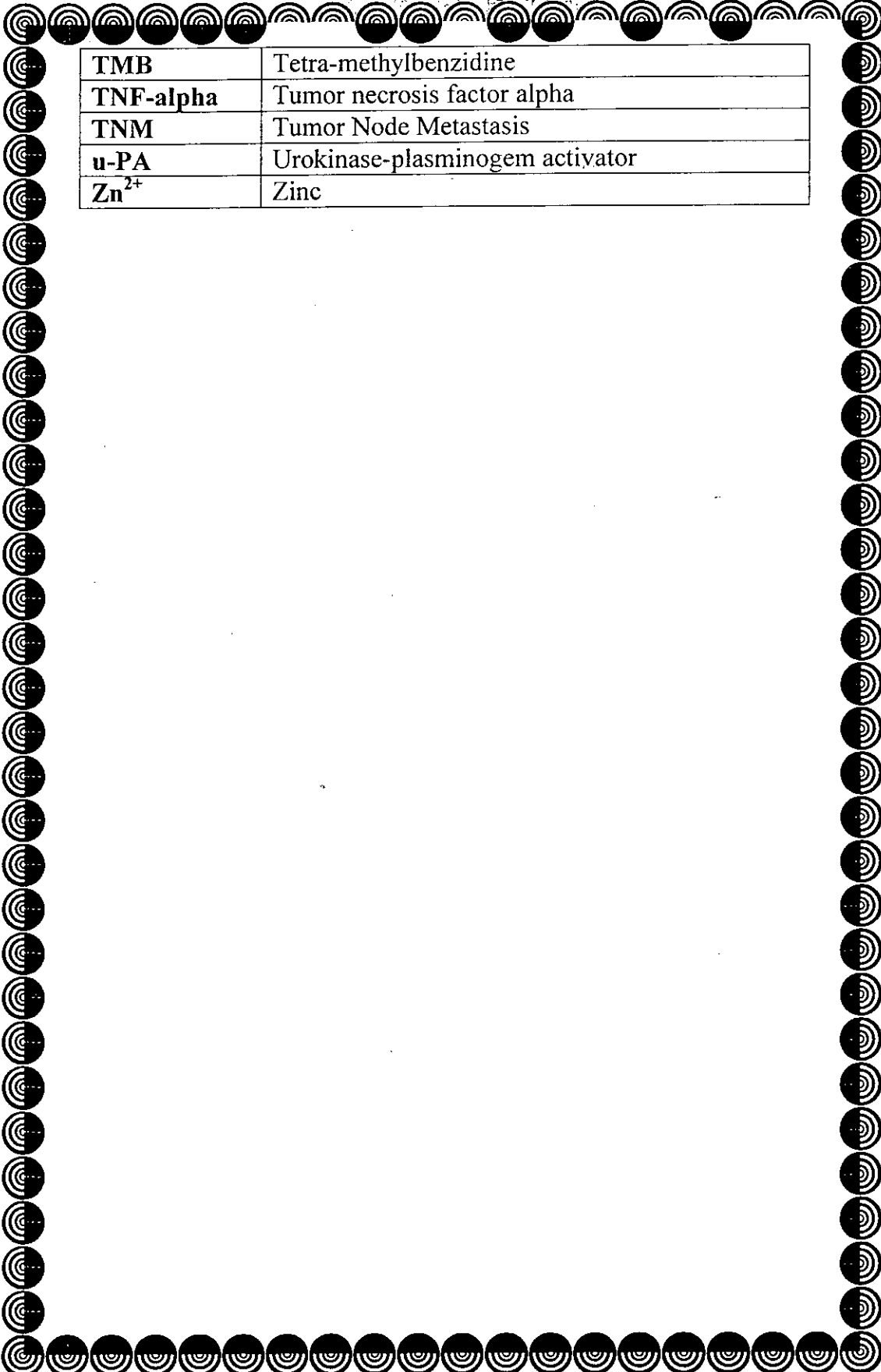
Results

<i>Fig. (1):</i> Statistical comparison between all studied groups regarding MMP-9 (ng/ml)	107
<i>Fig. (2):</i> Statistical comparison between all studied groups regarding TIMP-1 (ng/ml).	108
<i>Fig. (3):</i> Statistical comparison between all studied groups regarding ratio (MMP-9/TIMP-1)	109
<i>Fig. (4):</i> Receiver operating characteristic curve for MMP-9, TIMP-1 and MMP-9/TIMP-1	121

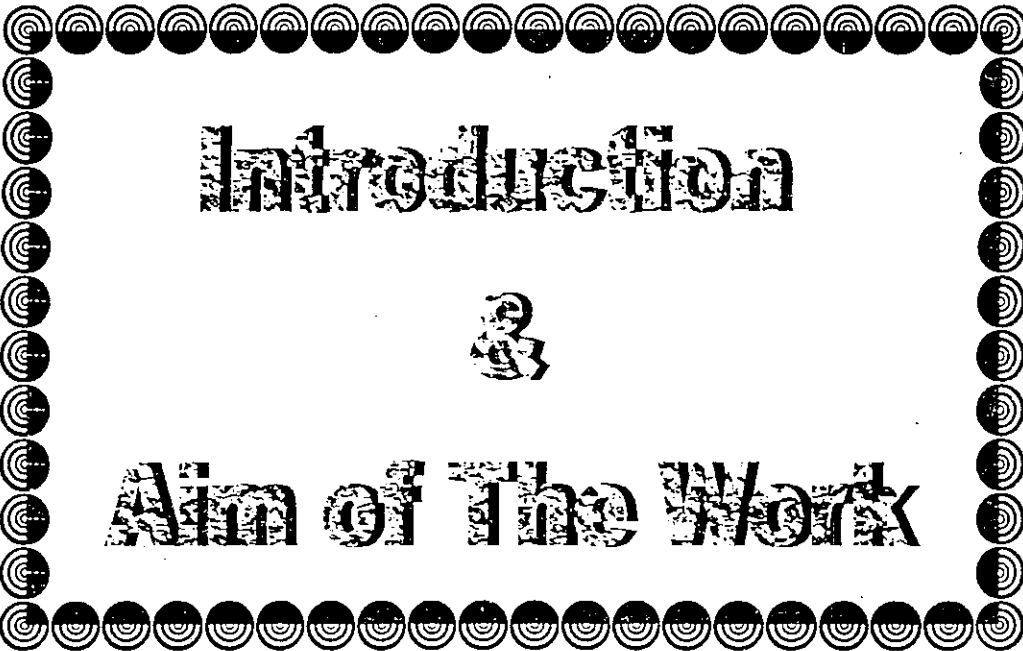
List of Abbreviations

AF	Amniotic fluid
AFP	α -feto protein
AM	Alveolar macrophage
AMI	Acute myocardial infarction
AMS	Alveolar macrophages
ANOVA	Analysis of variance
AP-1	Activator protein-1
ARDS	Adult respiratory distress syndrome
ATP	Adenosine triphosphate
BAL	Bronchoalveolar lavage
BALF	Bronchoalveolar lavage fluid
BBB	Blood brain barrier
bFGF	Basic fibroblast growth factor
BM	Basement membrane
Ca²⁺	Calcium
CCR5	Chemokine receptor 5
CDNA	Core DNA
CL	Collagenase
CSF	Cerebrospinal fluid
DNA	Deoxyribonucleic acid
EAN	Experimental autoimmune neuritis
EBV	Ebstein barr virus
EC	Endometrial carcinoma
ECM	Extracellular matrix
EDTA	Ethylene diamine tetra acetic acid
EGF	Epidermal growth factor
FEV₁	Forced expiratory volume-1
FIB	Fibroblast
GBS	Guillain-Barre Syndrome
GCR	Glucocorticoids receptor
Gel A	Gelatinase A
Gel B	Gelatinase B
GL	Gelatinase
H	Hour
HBEC	Human bronchial epithelial cells
HCCs	Hepatocellular carcinomas
HCG	Human chorionic gonadotrophin

HRP	Horseradish peroxidase
HSP	Hereditary spastic paraplegia
IFN-γ	Interferon- γ
IGF	Insulin-like growth factor
IL	Interleukin
IL-1	Interleukin 1
IL-1B	Interleukin 1B
IPF	Idiopathic pulmonary fibrosis
IPM	Interphotoreceptor matrix
Kda	Kilodalton
KS	Kaposi's sarcoma
LAM	Lipoarabinomannan
LMP1	latent membrane protein -1
M RNAs	Messenger ribonucleic acids
MMP	Matrix metalloproteinase
MMPs	Matrix metalloproteinases
Mr	Molecular weight
MS	Multiple sclerosis
MT1-MMP	Membrane type-1 metalloproteinase
n.d	Not determined
NGF	Nerve growth factor
NHL	Non Hodgkin's lymphomas
NPC	Nasopharyngeal carcinoma
PDGF	Platelet derived growth factor
PG	Proteoglycan
PKC	Protein kinase C
PMA	Phorbol myristate acetate
PNs	Peripheral nerves
PTH-rp	Parathyroid hormone related peptide
ROC	Receiver operating characteristic curves
SA	Status asthmaticus
SL	Stromelysin
SL-1	Stromelysin
STR-3	Stromelysin -3
TAG	T antigen
TGF-α	Transforming growth factor- α
TGF-B	Transforming growth factor-B
TIMPs	Tissue inhibitors of matrix metalloproteinases



TMB	Tetra-methylbenzidine
TNF-alpha	Tumor necrosis factor alpha
TNM	Tumor Node Metastasis
u-PA	Urokinase-plasminogem activator
Zn²⁺	Zinc

A decorative rectangular border composed of a series of concentric circles, each with a central dot, arranged in a grid-like pattern around the text.

Introduction

&

Aim of The Work

INTRODUCTION

Degradation of the extracellular matrix is controlled primarily by the matrix metalloproteinases (MMPs a family of zinc-dependent, secreted enzymes that collectively are capable of degrading the major components of the matrix by virtue of their individual substrate specificities). (*Ruth et al., 1998*).

The MMPs are regulated at the level of gene transcription, by latent proenzyme activation, and are inhibited by a family of secreted proteins known as tissue inhibitors of matrix metalloproteinases (TIMPs), which bind to the MMP active site and also to latent forms of the specific MMPs (*Birkedal et al., 1993*). The TIMP family consists of TIMP-1, TIMP- 2, TIMP-3 and the recently discovered TIMP-4 (*Greene et al., 1996 and Leco et al., 1997*).

Aim of the Work

The aim of this work is to measure the metalloproteinase enzymes and their inhibitors (TIMPs) in the bronchoalveolar fluid of patients having different bronchopulmonary pathology e.g