Matrix Metalloproteinases and TIMPs Expression in Pleural Effusion of Different Origins

Thesis Submitted for fulfillment of Master Degree in Pulmonology

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بسم الله الرحمن الرحيم

(قَالُواْ سُبْحَانَكَ لاَ عِلْمَ لَنَا إِلاَّ مَا عَلَّمْتَنَا إِنَّكَ أَنتَ الْعَلِيمُ الْحَكِيمُ)

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Abstract

Pleural effusion is a common clinical problem. The volume of the pleural fluid can increase dramatically with most pathologic conditions affecting the pleura. It is useful to differentiate the pleural effusion into transudates and exudates. Traditionally, such differentiation is made using Light's criteria, based on the protein and lactate dehydrogenase levels in pleural fluid and serum ***(Lee et al, 2006).***

Analysis of pleural fluid assists in the diagnosis of intra-thoracic and systemic disorders that cause pleural effusions. Nearly 75% of patients with pleural effusions gain either a definitive or presumptive diagnosis after a systematic analysis of pleural fluid. The need for further diagnostic studies depends on whether pleural fluid is classified by pleural fluid analysis as exudative or transudative in nature ***(Heffner, 2006).***

Proteolytic processes may play a role in the formation of pleural effusions by increasing vascular permeability, and therefore by facilitating fluid influx into the pleural space ***(Zucker et al, 1998)***. The presence and enzymatic activities of MMPs and TIMPs have been identified in pleural effusions ***(Hurewitz et al, 1992) & (Eickelberg et al, 1997).***

Key words:

MMPs, TIMPs, Pleural effusions

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List of abbreviations:

ADA: adenosine deaminase.

AFB: Acid fast bacilli.

AMA: Anti- myocardial antibody.

ANA: Anti-nuclear antibody.

ARDS: acute respiratory distress syndrome.

BAPE: Benign asbestos pleural effusion.

CA: cancer antigen.

CAPD: Continuous Ambulatory Peritoneal Dialysis.

CBC: Complete blood count.

CEA: Carcinoemberyonic antigen.

CHF: congestive heart failure.

CK 5-6: Cytokeratin 5/6

CT: computerized tomograpghy.

CXR: Chest X-ray.

ECM: extracellular matrix.

ICU: intensive care unit.

IL: Interleukine.

INF-γ: Interferon gamma.

LDH: Lactate dehydrogenase.

LE: Lupus erythematous cell.

MC: Myocobacterium culture.

MMP: Matrix Metalloproteinase.

MPE: malignant pleural effusion.

MRI: Magnetic resonance imaging.

MRSA: Methicillin resistant Staphylococcus aureus.

Mtb: Myocobacterium tuberclousis.

NT-Pro BNP: N-Terminal Pro- brain natriuretic peptide.

Pπ: oncotic pressure.

PA: Postero-anterior.

PCIS: Post Cardiac Injury Syndrome.

PE: pleural effusion.

PEEVO: Pleural effusion of extravascular origin.

PF: Pleural fluid.

PFA: Pleural fluid analysis.

pH: power of hydrogen ion.

Pmv: microvascular pressure.

PPD: Perifeid protein derivative.

PPE: Para pneumonic effusion.

Ppl: Pleural pressure.

RA: Rheumatoid arthritis.

SLE: Systemic lupus erythematous.

TB: Tuberculosis.

TGF-β: Transforming growth factor beta.

TIMP: Tissue inhibitor of metalloproteinase.

TNF-α: Tumor Necrosis Factor alpha.

TPE: Tuberclous pleural effusion.

VATS: Video Assisted Thoracoscopic Surgery.

Introduction

A pleural effusion refers to an abnormal accumulation of fluid in the pleural cavity, it is often a result of local pleuro- pulmonary diseases but can also complicate many systemic pathologies. Pleural effusion develops when the rate of pleural fluid formation exceeds that of its drainage. Establishing the underlying cause of pleural effusion is often challenging because a wide range of local and systemic disease can lead to pleural effusion formation. Pleural fluid samples should be analyzed to determine whether it is a transudate or exudate ***(Light, 2002).***

Matrix metalloproteinases (MMPs) are a family of extracellular proteinases defined by the presence of two conserved motifs in the lung. Essentially all cell types, including epithelial, interstitial, vascular, and inflammatory cells produce MMPs; however both the pattern and levels of MMPs expressed vary among cell types and situations. Although long thought to be responsible for turnover and degradation of extracellular matrix (ECM), matrix degradation per se is neither the sole nor the predominant function of these proteinases. Recent findings indicate that MMPs act on a variety of extracellular proteins, such as cytokines, chemokines, antimicrobial peptides, and other proteins, that regulate varied aspects of inflammation and immunity. The tissue inhibitors of metalloproteinases (TIMPs) are the primary endogenous inhibitors of MMPs. TIMPs indirectly regulate remodeling of (ECM) as well as cell signaling via ECM molecules. An imbalance between active MMPs and TIMPs in favor of enhanced MMP activity can lead to inappropriate ECM loss, or conversely, an imbalance favoring the TIMPs can abrogate MMP

activity leading to excess ECM deposition. Maintenance of MMPs-TIMPs balance is integral to normal lung development and function and a disruption in this balance has been implicated in numerous diseases of the lung ***(Parks, 2006).***

Proteolytic processes may play a role in the formation of pleural effusions by increasing vascular permeability, and therefore by facilitating fluid influx into the pleural space. The presence and enzymatic activities of MMPs and TIMPs have been identified in pleural effusions ***(Zucker et al, 1998).***

Tissue damage is a characteristic manifestation of infection by Mycobacterium tuberculosis (Mtb). Proteolysis by macrophage-secreted proteases has been implicated in such destructive processes ***(Kwang et al, 2005).***

In this regard, the proteolytic action of MMPs may be involved in the pathogenesis of tuberculosis, like many other diseases associated with tissue destruction. Several studies have reported that macrophages and monocytes release MMP-9 in response to Mtb or its cellular components ***(Quiding-Jarbrink et al, 2001) & (Friedland et al, 2002).***

MMPs have been known to play a role in the pathogenesis of malignancy ***(Nagase & Woessner, 1999) & (Kleiner et al, 1999).*** They have been reported to be expressed in lung cancer tissues and to be elevated in the sera and pleural effusions of lung cancer patients ***(Kwang et al, 2005).***

Iglesias et al, 2005 showed very high concentrations of MMP-1, MMP-9 and particularly MMP-8 in patients with empyema and complicated para-pneumonic pleural effusion (PPE). Elevated MMP-1 concentration may

be associated with its release by mesothelial cells stimulated by inflammatory mediators. An increase in MMP-8 and MMP-9 is a result of a higher activity of neutrophils, it indicates that these enzymes play an important role in the development of later complications.