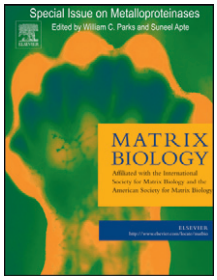
Review




# Matrix metalloproteinases in destructive lung disease

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http://dx.doi.org/10.1016/j.matbio.2015.02.002
***Edited by W.C. Parks and S. Apte***

## Abstract

Matrix metalloproteinases (MMPs) play essential physiologic roles in numerous processes ranging from development to wound repair. Unfortunately, given the broad substrate specificity of the MMP family as a whole, aberrant degradation of extracellular matrix proteins can result in destructive disease. Emphysema, the result of destroyed lung elastin and collagen matrix, is the prototypical example of such a destructive process. More recent data has highlighted that MMPs play much more elaborate physiologic and pathophysiologic roles than simple matrix protein cleavage. Key pathophysiological roles for MMPs in emphysema will be discussed herein.



## Introduction

The prototypical destructive lung disease is pulmonary emphysema, which is anatomically defined as the permanent enlargement of the peripheral airspaces of the lung distal to the terminal bronchioles [1]. Implicit in this definition is that the permanent airspace enlargement has arisen through the destruction of alveolar wall matrix structures, which is largely accomplished by matrix metalloproteinases (MMPs), and other matrix degrading enzymes [2]. The impact of aberrant MMP function in this regard is not trivial, as chronic obstructive pulmonary disease (COPD), of which emphysema is a major disease component, is currently the 3rd leading cause of death in the United States [3]. (See Fig. 1.)

The lung is a sophisticated matrix scaffold on which lung epithelium and endothelium reside [4]. The scaffolding is necessary to create the presence of millions of tiny air sacs, which allow for gas (oxygen and carbon dioxide) exchange. When the wall of an alveolus is destroyed, the air sacs coalesce to form larger ones. These enlarged airspaces empty more slowly, resulting in airflow obstruction, the hallmark of COPD [5]. The predominating theory regarding the nature of lung matrix destruction in emphysema is the proteinase–anti-proteinase hypothesis [6]. This theory originated from two separate reports—that instillation of elastolytic proteinases into the lungs of laboratory rodents induced emphysema [7]; and that of the five original subjects identified as having a deficiency of the proteinase inhibitor, alpha-one antitrypsin (A1AT), three of them had emphysema [8]. These findings led to the decades long assumption that an imbalance between A1AT and neutrophil elastase (NE) was the cause of cigarette smoke induced emphysema [9,10].

The discovery that MMPs were elaborated by cellular entities within the lung, and capable of degrading essentially all lung matrix components, including elastin, has led to the modification of the original theory [11]. Additionally, it is generally accepted that the proteinase–anti-proteinase hypothesis goes beyond simple matrix degradation, as MMPs perform many other functions that contribute to emphysema formation, including generation and elimination of chemotactic gradients, activation and degradation of other proteinases, and

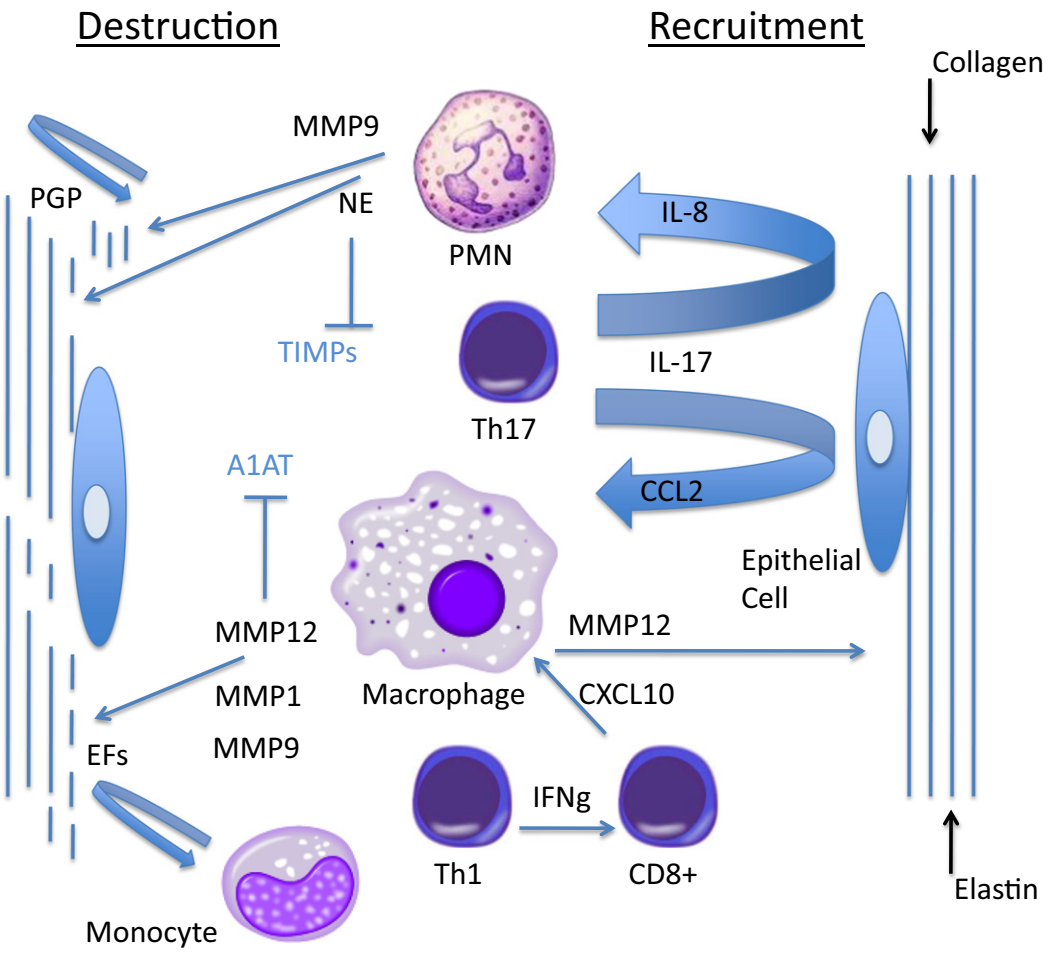


**Fig. 1.** Schematic of emphysema pathogenesis. Recruitment of inflammatory cells is depicted on the right. Th17 lymphocytes release IL-17, which interacts with its receptor, IL-17RA, on lung epithelial cells, inducing the release of CC and CXC chemokines. The presence of Th1 immunity drives the release of IFNγ inducible chemokines from $CD8^+$ lymphocytes, such as CXCL10. Interaction with CXCR3 on macrophages leads to the release of MMP12. Destruction of lung matrix is depicted on the left. The release of MMP12 generates EFs from elastic fibers, which are chemotactic for monocytes. Similarly, MMP9 activity nicks collagen fibers enabling prolyl endopeptidase to generate PGP, which is chemotactic for neutrophils. Collectively, the release of NE, MMP1, and MMP12 likely accounts for the majority of elastin and collagen degradation in emphysema.

alterations in cellular behavior independent of extracellular matrix [12–16]. These concepts will be discussed herein.

## Elastin degradation in emphysema

### MMP-12

Of all the MMPs, the evidence supporting a role for macrophage elastase (MMP12) in the pathogenesis of emphysema is the strongest. MMP12 is a relatively macrophage specific MMP, of the simple hemopexin domain type. It is not expressed to any large extent at baseline, such that it can only be identified in quiescent macrophages using electron microscopy, which reveals its sparse presence within intracellular pools [17]. It was initially described as the entity that conferred elastolysis to macrophages, which was later identified as an MMP [18,19]. Mmp12 expression is greatly increased in response to cigarette smoke exposure, due to a number of overlapping mechanisms. Activation of the plasmin/thrombin–proteinase activated receptor (PAR-1) cascade (itself a serine proteinase) leads to the expression of Mmp12, which is inhibitable by A1AT [20]. TGF-β signaling is intimately tied to Mmp12 expression, as $\alpha_v\beta6$ integrin deficient mice, incapable of TGF-β1 activation, display enhanced Mmp12 expression and Mmp12 dependent emphysema [21]. An important, though less direct pathway