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# The Role of Neutrophil Elastase Inhibitors in Lung Diseases

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In many respiratory diseases characterized by an intense inflammatory response, the balance between proteolytic enzymes (proteases, including elastases) and their inhibitors (proteinases inhibitors) is not neutral. Excess activity of neutrophil elastase (NE) and similar proteases has been reported to cause tissue damage and to alter the remodeling process in many clinical conditions such as pneumonia, respiratory distress, and acute lung injury (ALI). Several experimental NE inhibitors have been tested in preclinical and clinical studies of different conditions of inflammatory lung injury such as ALI and pneumonia, with contrasting results. This study reviews the literature regarding NE inhibitors in the field of respiratory diseases and reflects on possible future developments. In particular, we highlight potential gaps in the scientific evidence and discuss potential strategies for focusing investigation on antielastases in clinical practice through the selection of targeted populations and proper outcomes.

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Neutrophil elastase (NE) is one of the physiologic proteolytic enzymes (serine proteases) that are required for neutrophil function and are involved in the inflammatory response to tissue injury such as sepsis or arthritis. Certain proteases, for example E and cathepsin G, have a clear intracellular and extracellular antibacterial or antifungal activity.[1-3]

NE is a destructive elastase that attacks the extracellular matrix and modulates inflammation and tissue remodeling. Its involvement may be direct (tissue damage) or indirect (proinflammatory or proapoptotic), or it may just be a marker of leukocyte activation. The tissue damage and remodeling after an injury is the result of an imbalance between proteases and their inhibitors (Fig 1).[4]

Numerous studies have investigated the potential therapeutic role of NE inhibitors (endogenous or synthetic) in different models of inflammatory tissue damage, with contrasting results. The transfer of these findings to clinical practice remains a challenge. Here we present a critical analysis of the literature on NE inhibitors in different respiratory conditions that may contribute to guide future investigations.

**ABBREVIATIONS:** ALI = acute lung injury; α1-AT = alpha1 antitrypsin; CF = cystic fibrosis; EPI-hNE4 = engineered protease inhibitor, human neutrophil elastase 4; MNEI = monocyte neutrophil elastase inhibitor; NE = neutrophil elastase; PA = *Pseudomonas aeruginosa*; QoL = quality of life; RCT = randomized controlled trial

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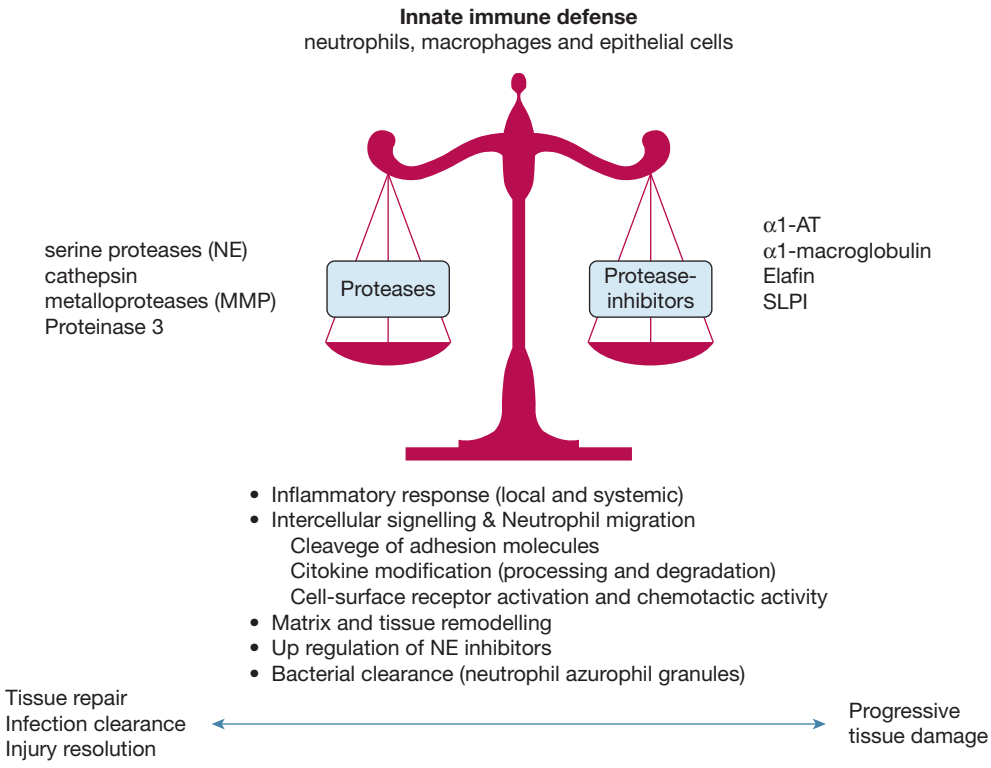


Figure 1 – *Innate immune defense. α1-AT = alpha1 antitrypsin; MMP = matrix metalloproteinase; NE = neutrophil elastase; SLPI = secretory leukocyte protease inhibitor.*

## Search Methodology

A broad search strategy was used to find English language publications indexed in PubMed and in the abstract books from the American Thoracic Society and European Respiratory Society congresses between 1996 and 2016. Relevant publications were selected manually from the following searches: human elastases in respiratory diseases and elastase inhibitors in respiratory diseases.

## Imbalance Between Proteases and Antiproteases in Respiratory Diseases

Different conditions of inflammatory lung injury such as pneumonia and cystic fibrosis (CF) are often characterized by a local imbalance between proteases (serine proteases, cathepsins, metalloproteases) and antiproteases (alpha1 antitrypsin [α1-AT], α2-macroglobulin, cystatins, tissue inhibitors of metalloproteinases). The proinflammatory imbalance is usually associated with tissue damage and systemic involvement.[5-7] NE is one of the major proteases involved in a range of conditions such as community-acquired pneumonia,[8] ventilator-associated pneumonia,[9] acute lung injury (ALI) and ARDS,[5,10] exacerbated COPD,[11] CF,[12] and bronchiectasis.[13,14]

A number of NE inhibitors such as elafin and secretory leukocyte protease inhibitor are physiologically produced at sites of tissue injury or by the liver (in the case of α1-AT), and their production is upregulated in response to inflammatory stimuli. They are produced by neutrophils, macrophages, and epithelial cells,[15,16] but some organs, such as the myocardium and the brain, are less prepared to counteract increased NE activity and are thus more predisposed to develop neutrophil-mediated injury.[4] To reduce the excess inflammatory response, various inhibitors of the neutrophilic elastase, ranging from nebulized α1-AT to systemic (oral or intravenous) or nebulized NE inhibitors (ONO-5046 [sivelestat]; AZD9668; engineered protease inhibitor, human NE 4 [EPI-hNE4 (depelstat; Debiopharm S.A.)]; monocyte NE inhibitor (MNEI); KRP-109, pre-elafin; BAY 85-8501; POL6014; and DX-890) have been tested in different diseases (Table 1).[17,18]

## Severe Pneumonia

In acute infections, an appropriate balance between proinflammatory and antiinflammatory mediators is required to resolve the inflammatory process.[19] Several studies in humans with severe community-acquired pneumonia or ventilator-associated pneumonia have