

EDITORIAL

Adding Weight to the Evidence: MMP-9 as a Predictor of COPD Development

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Received: 18 August 2025 | **Accepted:** 20 August 2025

Funding: The authors received no specific funding for this work.

The protease-antiprotease imbalance is central to COPD pathogenesis, particularly emphysema. The concept is rooted in the genetic predisposition to emphysema development caused by alpha-1 antitrypsin deficiency and experimental models based on protease instillation established in the 1960s. Beyond degrading extracellular matrix (ECM) and alveolar structures, proteases regulate inflammation, tissue remodelling, repair, and mediator activity through proteolytic cleavage. Among implicated proteases, MMP-9 is consistently elevated in lung tissue, sputum, BALF, and EBC of COPD patients (reviewed in [1]), and has emerged as a leading plasma biomarker, correlating with lung function and disease severity [2, 3]. Animal models of COPD support a causal role for MMP-9 in the development of emphysema, as overexpression of MMP-9, in particular in alveolar macrophages, which express excess MMP-9 in COPD patients [4], leads to airspace enlargement [5]. Although knockout of MMP-9 was not protective against cigarette smoke-induced emphysema [6], pharmacological inhibition of MMP-9/MMP-12 markedly reduced smoke-induced inflammation, emphysema, and airway remodelling in guinea pigs [7].

To support the role of MMP-9 in COPD initiation and progression, Ran et al. analysed data from the ECOPE study, a prospective, population-based cohort study conducted in China [8]. This study enrolled participants aged 40–80 years from the Guandong community for COPD screening [9]. Plasma MMP-9 levels were elevated in COPD and associated with symptoms, emphysema severity, air trapping, and impaired lung function. Higher baseline levels predicted faster lung function decline, greater exacerbation risk, and incident COPD over 2 years [8]. Strengths of the study include the relatively large sample size

(1328 participants, of which 1034 completed follow-up), the population-based prospective study design, and validation using a two-sample Mendelian randomisation study.

At baseline, plasma MMP-9 was higher in COPD than controls and associated with worse symptoms (CAT, CCQ) and impaired lung function (FEV₁% predicted, FEV₁/FVC), although levels did not differ by GOLD stage. Importantly, these results were corroborated by the two-sample Mendelian randomisation study, which used publicly available GWAS and eQTL databases. Fifty-nine SNPs with known association to expression of MMP-9 were significantly related to FEV₁ and FVC, providing external validation less prone to confounding. These negative correlations align with most prior studies, despite some conflicting reports [1]. The relation to emphysema reported by Ran et al. is consistent with literature and MMP-9-mediated ECM degradation and alveolar destruction, while respiratory oscillometry data suggest additional involvement in both central (R20) and small airway (R5-20) remodelling, supported by reports linking MMP-9 to small airway disease [10].

Discussing the physiological significance of higher plasma levels of MMP-9, one should keep in mind that plasma MMP-9 may both drive and reflect inflammation. MMP-9 can generate bioactive ECM fragments ('matrikines') and modulate cytokines such as TNF- α [11], but it is also released during immune cell activation (e.g., neutrophils, ...), leading to secondary accumulation in plasma [12]. Consistently, MMP-9 correlated with several circulating inflammatory markers, most strongly with IL-1 β , IL-6, and TNF- α , all key mediators of COPD progression. It can be speculated that these pro-inflammatory mediators, which are

known drivers of COPD progression, are responsible for enhancing MMP-9 expression, or that these mediators are activated by MMP-9. Weaker yet significant correlations with SP-D, CC16, and sRAGE suggest links to alveolar injury. Interestingly, while lower levels of these markers could reflect MMP-9–driven tissue destruction, SP-D showed a positive correlation, highlighting the complexity of these relationships.

In the prospective analysis, higher baseline MMP-9 levels were significantly associated with stronger declines of pre-bronchodilator FEV₁ and FVC, and post-bronchodilator FVC. These findings warrant further investigation into the involvement of MMP-9 in the progression of particular COPD phenotypes. Lack of correlation with FEV₁/FVC may reflect the short follow-up and slower decline of this ratio. While earlier work failed to link BALF MMP-9 to progression, plasma MMP-9 has consistently been reported as a predictor of lung function decline (reviewed in [1]). The inflammatory burden during exacerbations is a driver of lung function decline, and sputum, BALF, and EBC levels of MMP-9 are increased during these episodes [13]. The findings of the current study are furthermore in line with data from the COPDgene, SPIROMICS and another smaller study that also showed an increased future exacerbation risk in patients with elevated MMP-9 levels [14, 15].

The most important and novel observation by Ran et al., enabled by the population-based design, is that elevated plasma MMP-9 predicted incident, spirometry-defined COPD. As diagnosis often occurs after substantial lung function loss and current therapies only slow progression, a predictive biomarker is much sought after. A predictive biomarker would allow earlier interventions and could be used to stimulate a healthier lifestyle, such as smoking cessation, to prevent or delay disease onset. These findings, however, require replication and further exploration. It would be of particular interest to examine MMP-9 levels in relation to preserved ratio impaired spirometry (PRISM).

Collectively, the data published in *Respirology* strengthen the view that MMP-9 contributes to both initiation and progression of COPD, and highlight it as a putative pharmacological target. Despite interest and some preclinical success, no MMP inhibitors have been tested successfully in clinical trials. Clinical trials with broad-spectrum MMP inhibitors were terminated due to severe side effects. More selective approaches, including a monoclonal MMP-9 antibody (GS5745/Andecaliximab) and the dual MMP-9/MMP-12 inhibitor AZD1236, showed safety in COPD, but were discontinued.

Importantly, MMP-9 is unlikely to act alone—other MMPs (e.g., 1, 3, 7, 8, 12) and substrates are also implicated in COPD [1]. A more precise understanding of which enzymes drive specific stages and phenotypes will be key to realising protease-targeted therapy within a personalised medicine framework.

Conflicts of Interest

The authors declare no conflicts of interest.

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