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EDITORIAL

Mast cell chymase-1 and tryptases: therapeutic targets for COPD?

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is the 3rd leading cause of death worldwide [1–4]. It is characterized by progressive chronic bronchial inflammation that induces small airway remodeling and lung tissue damage in alveoli with emphysema, resulting in severe breathing difficulties [5]. Cigarette smoke (CS) inhalation is the primary cause of this disease. Other causes and risk factors include air pollution, indoor cooking, occupational exposure, and genetics. Patients with COPD patients have increased susceptibility to bacterial and viral infections, causing symptom exacerbation infections [5–9]. There is no cure for COPD, and available treatments only improve the symptoms. This is primarily due to the lack of understanding of the mechanisms involved in COPD pathogenesis. This has been largely due to the absence of short-term mouse models of cigarette smoke-induced COPD that accurately recapitulate the hallmark features of the human disease. Improving our understanding of how COPD develops, progresses and is exacerbated is critical for exploring novel treatments for the disease. Mast cells are a type of innate immune cells that play an important role in the immune system and respond to allergens, pathogens, and foreign particles [10]. These cells are located in connective tissues of the lungs and are involved in the pathogenesis of chronic inflammatory lung diseases, such as COPD. Mast cells can make mediators of their function *de* novo and contain many granules with pre-formed mediators such as histamines, cytokines, chemokines, and proteases [11]. These granules are released when the mast cells respond to foreign particles and pathogens, in a process termed degranulation [11]. Chymases and tryptases are two of the most important mast cell proteases. Our previous studies showed that their gene expression is increased in the lungs of COPD patients [12,13]. However, the mechanisms underlying the contributions of mast cell proteases in the pathological processes of COPD remain poorly understood. We recently elucidated the roles of mast cell chymases and tryptases in driving chronic inflammation-induced lung damage and emphysema in COPD [12,14–16]. Targeting these molecules may be an effective and urgently needed novel therapeutic option for this debilitating lung disease.

2. Mast cell chymase-1 (CMA1) as a therapeutic target for COPD

Chymases are serine proteases and potent inflammatory mediators released by mast cells after degranulation. They can cleave large numbers of proteins and peptides, including fibronectin, interleukins (IL)-13, −33, substance P, and latent transforming growth factor-β (TGF-β) with varying consequences ranging from protective functions by degrading pro-inflammatory substances to detrimental impacts by activating molecules that contribute to pathology. Chymases have numerous roles in host defense against pathogens, modulation of inflammation, regulation of homeostasis, and airway remodeling [17]. Chymase-1 (CMA1) is the only type of chymase in humans, while four types of chymases have been identified in mice, including mouse mast cell protease (mMCP)1, 2, 4, and 5 (Table 1) [21]. mMCP5 is murine equivalent of human CMA1. CMA1 has been implicated in various pathological processes, including inflammation, tissue repair, wound healing, and cardiovascular diseases [21,25]. The role of CMA1 in COPD is obscure. We recently showed that *CMA1* gene expression and the numbers of $CMA1^+$ mast cells are increased in the lung tissues of patients with severe compared to those with mild COPD and healthy controls [12]. *mmcp5* deficient (-/-) mice had reduced inflammation, small airway remodeling, emphysema-like alveolar enlargement, and impaired lung function in a highly human representative cigarette smoke (CS)-induced experimental model of COPD [12]. The study also showed that the co-culture of mast cells from $mmcp5^{-/-}$ mice with mouse lung macrophages reduced the protein level of tumor necrosis factor (TNF) in an *in vitro* model of COPD and the recombinant CMA1 protein induced human macrophages to release TNF [12]. This provides substantial evidence that CMA1 plays an important role in driving inflammation in COPD through the modulation of TNF release by macrophages (Figure 1). A previous study suggested that mast cell location in the lungs may have different roles in the COPD pathogenesis [26]. We have not observed that mast cell density is different in patients with COPD patients compared to controls, although mast cells are mainly located the around airways in these patients and in our experimental model [12]. Matrix metalloproteinases (MMPs) are key enzymes in regulating the production of extracellular matrix and contribute to small airway remodeling in COPD [27]. We found

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Table 1. Mast cell chymase and tryptases in human and mouse.

Name	Human	Mouse	Knock-out/transgenic mice phenotype	References
Chymases	Chymase-1 (CMA1)	Mouse mast cell protease (mMCP)5	• Heparin^{+} mast cells in the tongues of the mice are poorly granulated and lack mouse mast cell carboxypeptidase A protein • Abnormal mast cell physiology	[18] [19]
	–	mMCP1	• Abnormal mast cell morphology and increased susceptibility to parasitic infection in the gastrointestinal tract	[20]
	–	mMCP2	• None reported	
	–	mMCP4	• Loss of chymotryptic activity in the peritoneum and ear tissue • Abnormal blood coagulation	[21] [21]
Tryptases	Tryptase-β1 (TPSAB1)	mMCP7	• Abnormal mast cell differentiation and decreased susceptibility to induced arthritis	[22]
	Tryptase-β2 (TPSB2)	mMCP6`	• Increased susceptibility to bacterial and parasitic infection • Abnormal mast cell differentiation • Impaired eosinophil recruitment and neutrophil chemotaxis	[23,24] [22] [24]
	Tryptase-γ (TPSG1)	Protease serine member S31 (Prss31)	• Decreased lung compliance, airway resistance and tissue damping	[15]
	Tryptase- δ (TPSD1)	–	–	

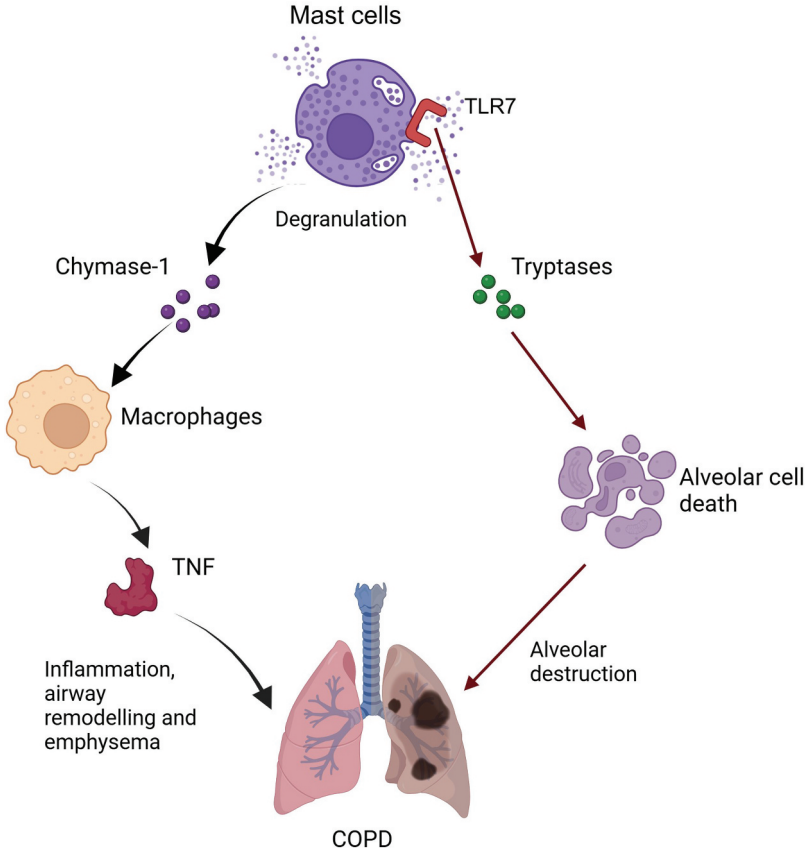

Figure 1. Proposed two mechanisms of how mast cell chymase-1 and tryptases may drive the pathogenesis of chronic obstructive pulmonary disease (COPD). The degranulation of mast cells releases chymase-1 that induces macrophages to secrete tumor necrosis factor (TNF). This promotes inflammation, small airway remodeling and emphysema and COPD. Also, toll-like receptor 7 (TLR7) is activated on the surface of mast cells. This leads to the release of mast cell tryptases, which induce alveolar cell death, emphysema and COPD. Created with BioRender.com.

that active MMP9 protein was decreased in the lungs of *mmcp5*$^{-/-}$ mice compared to WT controls in experimental COPD. This indicates that CMA1 induces MMP9 activity to regulate small airway remodeling in COPD. Importantly, the treatment of mice with a CMA1 inhibitor, RO5066852, protected them against CS-induced inflammation, remodeling, and emphysema in experimental COPD [12]. Chymase inhibition with RWJ-355871 also had promising effects by reducing lipopolysaccharide-induced airway inflammation in a mouse model [17]. This provides a proof concept that the inhibition of CMA1 may be an effective therapeutic strategy for COPD. The clinical study by targeting this molecule is required to be conducted in the future.

3. Mast cell tryptases in COPD

The role of tryptase-β1 (TPSAB1) in COPD has not been well documented. The major reason is a lack of proper tools to study the role of this serine protease. C57BL/6J naïve mice, which are the most common mouse strain in research, have the *mmcp7* gene (the murine equivalent of human *TPSAB1*) deleted [28]. Also, there are no reliable TPSAB1-specific antibodies to measure the protein level of this molecule in humans, explaining why most of the studies assess *TPSAB1* gene expression levels. These factors together limit the understanding of the role of mMCP7/TPSAB1 in COPD. A recent single cell (sc)RNA-sequencing study showed higher *TPSAB1* mRNA expression in bronchial epithelial samples from patients with eosinophilic COPD compared to those with low eosinophilic inflammation [29]. This suggests a potential role of TPSAB1 in driving inflammation in COPD. In an experimental emphysema model, CS induced the release of TGF-β from mast cells which led to the induction of tryptase expression (mMCP6) that could play a role in recruitment of neutrophils in the airways [30]. We elucidated roles for tryptase-β2 (TPSB2) in the regulation of both inflammation and emphysema in COPD. *mmcp6*$^{-/-}$*7*$^{-/-}$ double deficient mice had significantly reduced CS-induced inflammation, emphysema, and impaired lung function in experimental COPD than the wild-type. Mouse macrophages challenged with the recombinant TPSB2 protein had increased expression of COPD-related cytokines and chemokines, including TNF, chemokine C-X-C motif ligand-1 (CXCL1), and interlukin-1β [16]. We recently showed that CS activates mast cells through the toll-like receptor 7 (TLR7) localized on their surface and induces the release of TPSB2. That study also showed that imiquimod (a TLR7 agonist)-induced emphysema that was reduced in *mmcp6*$^{-/-}$*7*$^{-/-}$ mice [14]. Furthermore, mice that were treated with disodium cromoglycate (DSCG, a mast cell stabilizer) had lower levels of mMCP6 protein in their lungs [14]. Treated mice were also protected against experimental COPD with reduced inflammation, small airway remodeling, emphysema, and impaired lung function, indicating that this is a potential treatment for COPD. We also showed that mast cell tryptase-γ (TPSG1) also contributes to the pathogenesis of COPD. We showed that *Prss31*$^{-/-}$ (the murine equivalent of human TPSG1) mice were protected against CS-induced chronic inflammation, small airway remodeling, emphysema and impaired lung function, and experimental COPD [15]. Interestingly, the imiquimod challenge resulted in emphysema in the *Prss31*$^{-/-}$ mice [14], suggesting that TLR7 activation in mast cells may not contribute to the TPSG1 release in COPD [14].

4. Expert opinion

Mast cell chymases and tryptases are important mast cell proteases, and they have important roles in COPD pathogenesis. Numerous studies showed that the stabilization of mast cells to prevent their degranulation and release of their mediators and inhibiting mast cell protease activity, have positive impact on COPD by reducing inflammation, airway remodeling, emphysema, and improving lung function [12,14,16]. Short-term inhibition of mast cell degranulation may effectively relieve the symptoms of COPD, and inhibitors or antagonists that target excessive levels of specific proteases may be more beneficial and have fewer side-effects in the treatment of COPD. The location of mast cells in the lungs may also be important in the progression of COPD. Although we have not found that the mast cell populations are different in experimental COPD, they are mainly located around airways in the mouse model and in patients with COPD [12]. Mast cells are relatively rare in the lung. To capture the biological process that mast cells are involved in, requires serial sectioning of lung tissue. Consequently, 'omics technology, such as spatial transcriptomics will provide greater power to measure the levels of these mast cells and define their locations in the lungs of patients with COPD. We have elucidated potential mechanisms involved in CS mediated mast cell activation and their roles in pathogenesis and that TLR7 is a surface activator of mast cells in response to CS exposure in COPD [14]. However, TLR7 activation may not induce all types of mast cell proteases, such as TPSG1. It remains unclear how mast cells mediate other inflammatory cell activities involved in COPD pathogenesis, such as macrophage activation. The receptor or target molecules of CMA1 and tryptases in macrophages have not been identified in COPD. These will require further mechanistic studies for elucidation.

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Declaration of interest

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