Revisiting matrix metalloproteinase 12

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Revisiting matrix metalloproteinase 12: its role in pathophysiology of asthma and related pulmonary diseases

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Purpose of review
Matrix metalloproteinases (MMPs) are a family of over 20 zinc-dependent proteases with different biological and pathological activities, and many have been implicated in several diseases. Although nonselective MMP inhibitors are known to induce serious side-effects, targeting individual MMPs may offer a safer therapeutic potential for several diseases. Hence, we provide a concise overview on MMP-12, given its association with pulmonary diseases, including asthma, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis, and other progressive pulmonary fibrosis (PPF), which may also occur in coronavirus disease 2019.

Recent findings
In asthma, COPD, and PPF, increased MMP-12 levels have been associated with inflammation and/or structural changes within the lungs and negatively correlated with functional parameters. Increased pulmonary MMP-12 levels and MMP-12 gene expression have been related to disease severity in asthma and COPD. Targeting MMP-12 showed potential in animal models of pulmonary diseases but human data are still very scarce.

Summary
Although there may be a potential role of MMP-12 in asthma, COPD and PPF, several pathophysiological aspects await elucidation. Targeting MMP-12 may provide further insights into MMP-12 related mechanisms and how this translates into clinical outcomes; this warrants further research.

Keywords
asthma, chronic obstructive pulmonary disease, coronavirus disease 2019, matrix metalloproteinase 12, matrix metalloproteinase-12 inhibitor, pulmonary fibrosis

INTRODUCTION

Matrix metalloproteinases (MMPs) belong to a family of at least 20 zinc-dependent endopeptidases (proteases) with distinct, though partly overlapping, activities across several physiological and pathophysiological processes [1–3]. These bioactivities include immune and inflammatory responses [4,5], as well as degradation of components of the extracellular matrix (ECM) (e.g., elastin and fibrin) [6], tissue repair and remodeling, cell proliferation [7], and cell migration [8]. The activity of MMPs is delicately regulated by several transcriptional and posttranslational mechanisms. Upon release and activation, MMP activity is modulated by endogenous inhibitors within the extracellular compartment: tissue inhibitors of metalloproteinases (TIMPs) and α2-macroglobulin

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KEY POINTS

- MMPs are bioactive proteases implicated in a large variety of physiological processes and in several diseases.
- Several MMPs have been included in the pathophysiology of experimental lung disease in animals; these activities and properties may differ in humans.
- In humans, MMP-12 has been associated with several aspects of chronic pulmonary diseases, including asthma, COPD, IPF, and progressive pulmonary fibrosis of different cause (e.g., COVID-19); however, its precise role in the underlying disease mechanisms is not fully understood.
- Targeted inhibition should help to unravel the role of MMP-12 (and other MMPs) in the mechanisms underlying chronic pulmonary diseases.

[1]. In healthy state, MMP activity within the lungs remains limited, whereas in pulmonary disease several environmental triggers (pathogens, toxins, several mediators including growth factors and cytokines) can elicit MMP release from different cell types, and may thus cause an imbalance between MMPs and their endogenous inhibitors (the so-called protease/antiprotease imbalance), resulting in inflammation and remodeling (fibrosis) within the lungs [9,10].

Based on these properties and in line with ample evidence, MMPs have been implicated in the pathophysiology of several pulmonary diseases including asthma [11], chronic obstructive pulmonary disease (COPD) [12], idiopathic pulmonary fibrosis (IPF) [13▪▪], lung cancer [14] and lung injury [15] [e.g., as encountered in acute respiratory distress syndrome (ARDS) of any origin including severe coronavirus disease 2019 (COVID-19) [16▪▪]]. As a consequence, targeting different MMPs has been undertaken in animal disease models showing anti-inflammatory effects as well as modulating activity on several aspects of the remodeling process within the lungs [2,17]. So far, less data are available from human in-vivo studies, although interest in MMPs in the context of pulmonary medicine is currently increasing.

In this review, we discuss data underscoring a role of MMP-12 in pulmonary diseases associated with aspects of (chronic) inflammation and remodeling, that is, asthma, COPD, IPF, and other progressive pulmonary fibrosis (PPF), including possible sequelae of COVID-19, as well as its potential as a therapeutic target for these diseases.

MATRIX METALLOPROTEINASE-12 IN CHRONIC INFLAMMATORY AND FIBROTIC PULMONARY DISEASE

Evidence from animal data and human studies

Previously referred to as macrophage elastase, MMP-12 has been mainly detected in alveolar macrophages, whereas it is also produced by bronchial epithelial cells and airway smooth muscle cells. MMP-12 is a 54-kDa preproenzyme, which is processed into a 45-kDa and subsequently into a 22-kDa active form [18]. Experimental and clinical studies have implicated MMP-12 in the pathophysiology of several chronic inflammatory diseases including pulmonary diseases (esp., COPD, asthma, IPF, and PPF) [19–21], skin diseases such as cutaneous granulomas and psoriasis [22,23], arthritis [24], cancer [25–27], vascular diseases such as atherosclerosis [28], aneurysm [29,30], and neurological conditions including spinal cord injury [31], multiple sclerosis [32], intracerebral hemorrhage [33], and ischemic stroke [34].

In COPD, MMP-12 is markedly expressed by alveolar macrophages and represents the major elastolytic enzyme released by these cells [35]. Consequently, MMP-12 has been implicated in the pathophysiology of (cigarette-induced) chronic lung injury [36], particularly in emphysema and small airways disease, features of COPD and/or more severe asthma [37,38]. Indeed, MMP-12 is known to degrade elastin, a protein vital for the elastic recoil of the small airways, which may clarify its involvement in the mentioned pathophysiological features in persistent asthma and COPD [9]. Moreover, MMP-12 (or mixed MMP-9/12) inhibitors showed disease-modifying effects in mouse models of COPD [35,39]. Recent evidence from mouse models pointed toward an involvement of MMPs (including MMP-12) in the pathophysiology of obese asthma [40▪]. Although in animal models, MMP-12 undeniably shows proinflammatory activities, for example by recruiting neutrophils, it is unclear if similar properties and mechanisms equally apply in humans, where MMP-12 seems to switch off neutrophils by CXC chemokines inactivation [37].

In a large European case-control study of COPD, an MMP-12 gene variant was related to more severe disease, whereas no such associations were found for MMP-1 or MMP-9 [41]. In another COPD study, sputum MMP-12 levels and activity were directly associated with the extent of emphysema documented on CT scan [42]. In addition, increased MMP-12 levels were detected in the sputum from currently smoking and ex-smoking patients with

clinically stable COPD (GOLD I/II), whereas in asymptomatic, current, and former smokers, sputum MMP-12 levels were within a similar range as in nonsmoking healthy controls [38]. Similarly, increased levels of the degradation products of elastin, such as desmosine, were measured in the urine of patients with COPD and correlated with the rate of decline in lung function [43]. More recently, in a mixed study (combining animal and human data), Doyle *et al.* [44▪▪] confirmed the relationship between the presence of eosinophils and airspace enlargement consistent with emphysema in a type2 mouse model. Additionally, they showed that eosinophil-derived IL-13 promoted MMP-12 production in macrophages *in vitro*. These findings were consistent with their further observations of increased MMP-12 levels in the sputa of patients with chronic inflammatory airway disease with sputum eosinophilia and emphysema, which negatively correlated with forced expiratory volume in 1 s [44▪▪].

A multidimensional endotyping study of six different clusters of patients with severe asthma, showed an association between sputum MMP-1, MMP-3, MMP-8, and MMP-12 levels with severity of disease and positively correlated with sputum IL5 levels but negatively correlated with sputum IL-13 levels [45]. A study on gene polymorphisms showed association between an MMP-12 gene variant and susceptibility to asthma and disease severity in a Japanese population [46]. In another study including preclinical experiments and observations in asthmatic children and young adults, an association was found between the presence of an MMP-12 gene variant and disease severity [47]. Additionally, in an animal model of allergic asthma, that is, in Ascaris-sensitized sheep, they showed that MMP-12 inhibition was able to reduce both the early and late airway responses to inhaled allergen [47].

In pulmonary fibrotic disease, such as IPF and progressive pulmonary fibrosis (PPF) of different cause (e.g., as seen in COVID-19), the role of MMP-12 has not yet been fully established and current research shows contradictory data [48,49]. However, increased MMP-12 levels have been detected in bronchoalveolar lavage (BAL) fluid of IPF patients as well as in the serum of patients with systemic sclerosis and lung involvement. This could point toward a direct role of MMP-12 in the pathogenesis of pulmonary fibrosis, probably via activation of the TGF-β1 signaling pathway [50,51]. Alternatively, MMP-12 may also play a regulatory role in pulmonary fibrosis, downregulating the fibroproliferation, as in the study of Hu *et al.* [52] MMP-12 deficient mice exhibited significantly enhanced bleomycin-induced pulmonary fibrosis relative to that in wild-type mice as evaluated by analysis of collagen deposition, myofibroblast differentiation, and histopathology.

MMP-12 can also serve as a biomarker of severity of pulmonary fibrosis not only in IPF but for instance also in PPF as seen in systemic scleroderma. The higher the serum or BAL levels of MMP-12, the more advanced the fibrosis on radiologic imaging and the worse is the lung function [50,51].

MATRIX METALLOPROTEINASE-12 IN CORONAVIRUS DISEASE 2019-RELATED PATHWAYS

In the past year, the world was facing a global pandemic of the infection with the novel coronavirus SARS-CoV-2 (severe acute respiratory syndrome caused by coronavirus 2) causing the COVID-19. The increasing number of COVID-19 patients with various clinical manifestations and disease outcomes shaped our understanding of the disease pathophysiology and underlying mechanisms as well as the longer term sequelae which closely relate to the changes inflicted to several components of the immune system and other organs [53,54], especially the lungs [55,56]. COVID-19 is associated with several changes in the immune system parameters, especially in the T-cell compartment and downstream components often reflected in a typical laboratory pattern characterized by lymphopenia and eosinopenia [57]. Whether these changes are the consequence of COVID-19 or reflect the susceptibility to this infection is still under debate, as well as the prognostic and diagnostic value of these changes in relation to COVID-19 outcome [58,59].

The extent of lung involvement and damage play a crucial role in the prognosis and postinfectious stages of COVID-19 patients. In advanced stages of the disease, a severe acute lung injury (ALI) with ARDS develop as a result of the cytokine storm with subsequent pulmonary vascular leakage, accumulation of interstitial fluid and parenchymal lung damage often accompanied by thromboembolic events [60]. Several authors describe associations of SARS-CoV-2 infection with extensive inflammation, hypoxia, oxidative stress, mitochondrial dysfunction, DNA damage, and lung coagulopathy promoting endothelial dysfunction and microthrombosis [61]. Upon invasion into the respiratory epithelium, the virus induces the activation of several signaling cascades resulting in the release of several proinflammatory cytokines and mediators resulting in ALI. The subsequent activation of alveolar macrophages and neutrophils is followed by the release of reactive oxygen species, secondary mediators and proteases, including MMPs. MMPs are involved in ECM remodeling and tissue fibrosis

[10], typical features of severe COVID-19 pneumonia and post-COVID-19 pulmonary sequelae [62▪]. Despite scarce data linking MMPs directly to COVID-19, several reports exist on the involvement of MMPs in the pathophysiological sequelae during ALI and ARDS [63] (Fig. 1). Therefore, and based on their extensive properties within the processes involved in COVID-19 pneumonia and post-COVID-19 pulmonary fibrosis, it can be postulated that some MMPs would qualify as potential therapeutic targets for (post)COVID-19 [16▪▪] (Fig. 1). In this context and as an example, MMP-12 is involved in the breakdown of extra cellular matrix (by proteolysis of elastin) and has been associated with the development of the emphysema and fibrosis in certain pulmonary conditions [10,49,64]. Neutrophilia and activation of neutrophils are typical features of COVID-19. It seems that neutrophils are essential for the exacerbation of the immune response and hyperactivity and neutrophil extracellular traps formation plays a critical role in the development of the cytokine storm, sepsis, and COVID-19-related multiorgan failure [65]. Indeed, several inducers of MMP-12 gene expression and

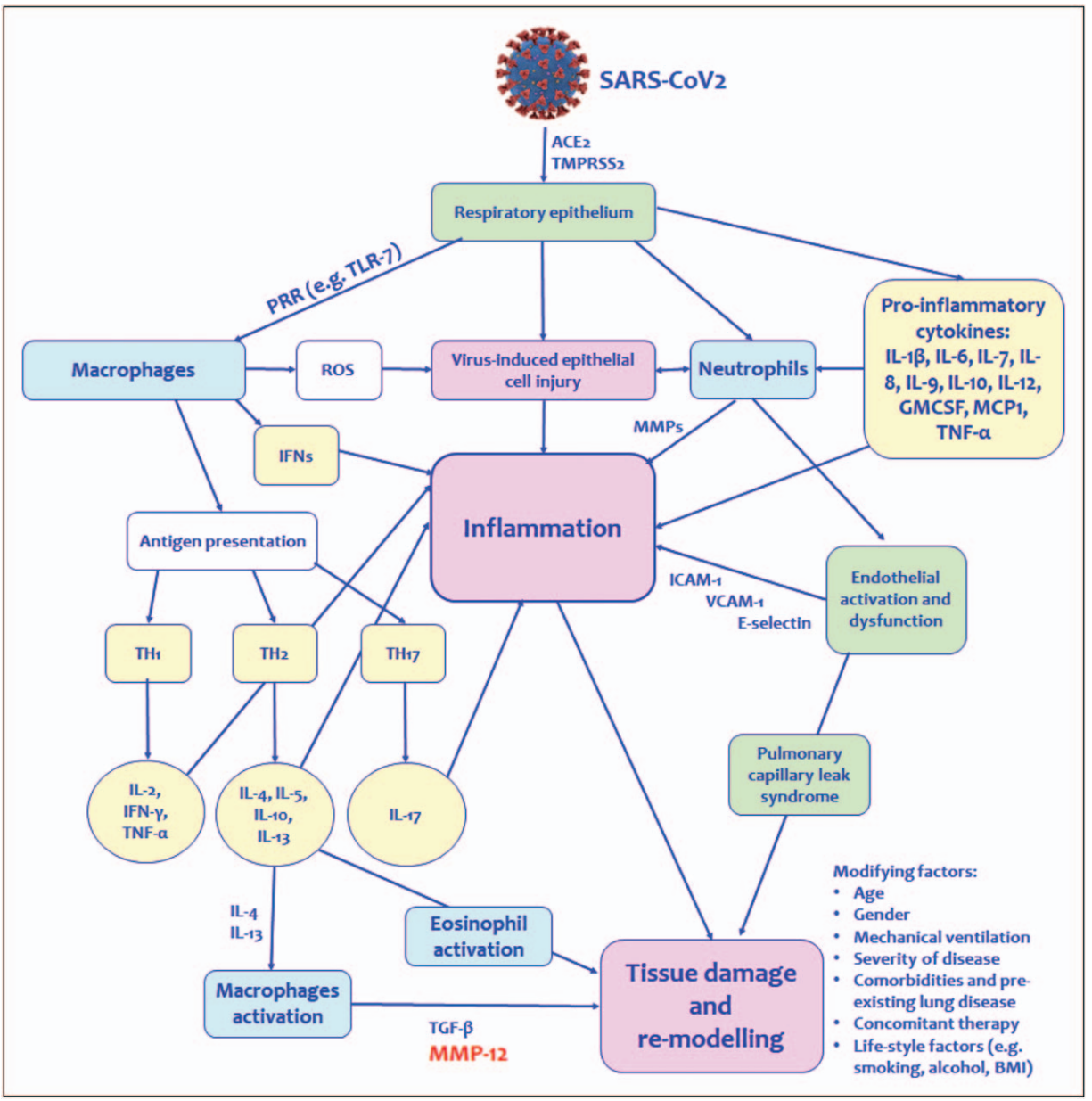

FIGURE 1. Simplified immune and inflammatory pathways (potentially) involving MMP-12 in the pathophysiology of ARDS. This process is modified by several extrinsic and intrinsic factors. MMP-12, Matrix metalloproteinase 12; ARDS, Acute respiratory distress syndrome.

secretion have been previously identified, for example, IL-1β, IL-6, IL-13 [66,67] which also have been associated with COVID-19 [68]. In addition to the MMP-12-mediated elastin proteolysis, pneumonia-induced extrahepatic vitamin K depletion contributes to the accelerated elastic fiber damage [69]. Among the cytokines studied in connection with several lung diseases, IL-13 seems of special importance. Currently, only few data are available on the relationship between IL-13 and COVID-19. Although Huang *et al.* [70] did not find any differences in IL-13 plasma levels between COVID-19 patients with or without need for ICU admission, a proportional association between IL-13 plasma concentration and SARS-CoV-2 was reported by another research group [71]. Interleukin-13 is increased during COVID-19 and predicts the need for mechanical lung ventilation [72]. Moreover, IL-13-dependent release of MMP-12 was shown to be essential for the development of airway eosinophilia [66] and together with the IL-4/13 contributes to the development of emphysema [44▪▪]. Apart from MMP-12, other MMPs may be involved in COVID-19-associated pathways and features – e.g. MMP-3 [73] or MMP-9 [74,75].

Despite the possible role of MMP-12 in COVID-19-associated lung damage and subsequent pulmonary fibrosis, some controversial aspects regarding its antiinflammatory and antiviral effects have been reported. In an animal model of wound healing of the cornea, MMP-12 inhibited corneal inflammation and neovascularization after injury by down-regulation of CCL2 and C-C chemokine receptor type 2 expression [76]. In another animal study, Marchant *et al.* showed that following viral infection, macrophages secrete MMP-12, which regulates the antiviral immunity via increased secretion of interferon alpha (IFN-α). Subsequently, MMP-12 has been shown to degrade extracellular IFN-α resolving the inflammation [77] and hence might act as a beneficial antiinflammatory agent under certain conditions. Therefore, the role of MMP-12 in the pathophysiology of COVID-19 as well as its potential as a therapeutic target in this infection could be double-edged and requires scrutinized research.

MATRIX METALLOPROTEINASE-12 INHIBITORS: INTERVENTIONS IN CLINICAL STUDIES OF PULMONARY DISEASES

Although a promising therapeutic target for chronic inflammatory airway disease, such as COPD and asthma, only a few clinical studies have been published on MMP-12 inhibitors.

In a multicenter, placebo-controlled study, Magnussen *et al.* [78] evaluated the safety and efficacy of an oral mixed MMP-9/MMP-12 inhibitor (AZD1236; 75 mg bis in die for 6 weeks) on top of concomitant COPD-pharmacotherapy in 74 COPD (GOLDII/III) patients. Apart from safety and tolerability, efficacy was assessed as a secondary parameter and included several clinical outcome measures: that is, symptoms (Clinical COPD Questionnaire score), rescue medication use, lung function measurements, 6-min walk test, body-mass index, airflow Obstruction, Dyspnea, and Exercise – index, as well as several biomarkers: that is, C-reactive protein, white blood cell differentials, IL-6, serum amyloid A, IL-8, TNF-α, and plasma and urine desmosine. After six weeks, no difference in any of the efficacy parameters was found between AZD1236 and placebo.

Similarly, an associated biomarker study by Dahl *et al.* [79] with the same MMP-12 inhibitor administered at the same dosing regime and treatment duration to patients with similar COPD characteristics as in the previous study [78], yielded overall negative findings, although a (statistically nonsignificant) reduction in urinary desmosine excretion and in sputum and blood lymphocytes were observed after 6 weeks of treatment with AZD1236 compared with placebo.

The major drawbacks of both studies consist the relatively short duration of treatment (6 weeks) in patients with initially stable disease and the fact that the drug effects were evaluated on top of concurrent controller medications. In the study by Magnussen *et al.* [78], one patient (out of 74 included) experienced a serious adverse event – otherwise, at the dose and dosing regimen given, the drug was overall safe and tolerable [79].

To the best of our knowledge, no published data exist in the open domain on MMP-12 inhibitors in patients with asthma or in pulmonary fibrosis. In clinicaltrials.gov, currently, only one phase IIa proof-of-concept study with an MMP-12 inhibitor intervention in asthma is being reported (NCT03858686), whereas no studies in COPD or pulmonary fibrosis are mentioned in this database.

SUMMARY AND FUTURE PERSPECTIVES/ CONCLUSION

Matrix metalloproteinases (MMPs) are bioactive proteases with distinct physiological and pathological properties and activities and consequently implicated in several diseases. MMP-12 has been associated with proinflammatory and tissue-remodeling pathways underlying chronic pulmonary diseases, including asthma, COPD, IPF, and progressive pulmonary fibrosis (PPF) of different cause (e.g., COVID-19).

Although animal data clearly point toward an important role of MMP-12 within the inflammatory and tissue remodeling pathways in the respiratory system, in humans, its role in the pathophysiology of chronic pulmonary diseases is not fully clarified. Furthermore, initial clinical studies with an MMP-12 inhibitor failed to show efficacy partly caused by several logistical drawbacks. In the future, selective and potent MMP-inhibitors could help to unravel the role of individual MMPs, including MMP-12, in the pathophysiology and treatment of specific pulmonary diseases.

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Conflicts of interest

K.A.E.: Acted as principal investigator and associate medical director at QPS, a CRO that received funding from various pharmaceutical companies for the conduct of clinical studies.
Z.D.: Apart from academic affiliations and assignments, until mid-2020, Z.D. acted as Executive and Scientific Medical Director at a phase I/II pharmacological unit (QPS-NL), which performs clinical studies for pharmaceutical companies. In the past three years, Z.D. received honoraria, consultancy, and speaker fees from Acucort, Astrazeneca, ALK, Aquilon, Boehringer Ingelheim, CSL, HAL Allergy, MSD, and Sanofi-Genzyme.
M.J.: M.J. in the past three years received honoraria, consultancy, and speaker fees from Novartis, Takeda, GlaxoSmithKline, Mundipharma, Stallergenes-Greer, ALK, CSL Behring, Sanofi-Genzyme, Mylan, and acted as a principal investigator in clinical trials for pharmaceutical companies (Pharming, BioCryst, Takeda).
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