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Editorial

Roles of Tissue Inhibitor of Metalloproteinase-1 in Severe Asthma

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▸ See the article "Tissue Inhibitor of Metalloproteinase-1 Enhances Eosinophilic Airway Inflammation in Severe Asthma" in volume 15 on page 451.

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A wide array of inflammatory cytokines and mediators play roles in immune response and chronic inflammation in severe asthma (SA). Monoclonal antibodies targeting some of these molecules have shown clinical efficacy in reducing exacerbations and improving asthma control in SA.[1] While biologic treatments, including anti-type 2 (T2) cytokines, such as interleukin (IL)-5, IL-4, and IL-13, and epithelial cell-derived alarmin thymic stromal lymphopoietin (TSLP), are now available in the clinical practice, many SA patients remain uncontrolled even with these treatments. Thus, a new therapeutic approach is needed to modulate inflammatory responses, not fully abrogated with current standard care and available biologics.

In this issue of *Allergy, Asthma & Immunology Research*, Cao and colleagues[2] provide compelling evidence that tissue inhibitor of metalloproteinase-1 (TIMP-1) plays a critical role in eosinophilic airway inflammation in asthma based on *in vivo* and *in vitro* experiments.[2] In addition, increased serum level of TIMP-1 in SA patients with high T2 inflammation in their analyses suggests that serum TIMP-1 could be a biomarker for T2-high SA, especially with an eosinophilic phenotype.

While TIMP-1 initially gained its name for its capability as an endogenous protease inhibitor, it is now appreciated as a multifaceted cytokine, which has various effects on immune response and inflammatory process.[3] Elevated levels of TIMP-1 have been observed in a wide range of acute and chronic infectious and inflammatory diseases, such as sepsis, coronavirus disease 2019, and psoriasis. TIMP-1 binds to its receptors (CD63, CD74, and CD44) and activates signaling pathways in various immune cells including T cells, B cells, NK cells, neutrophils, and macrophages. In terms of granulocytic inflammation, TIMP-1 is known to prolong the survival of neutrophils and activate neutrophilic inflammation via secretion of neutrophil elastase and myeloperoxidase, and formation of neutrophil extracellular traps.[4]

Compared with other inflammatory diseases, the roles of TIMP-1 in allergic disorders have not been understood clearly. A positive correlation was observed between TIMP-1-positive cells and mast cells in the nasal mucosa of patients with perennial allergic rhinitis after nasal allergen challenge with house dust mites.[5] Increased levels of serum TIMP-1 were also observed in patients with atopic dermatitis.[6] Subjects with asthma showed increased levels of TIMP-1 in sputum, bronchoalveolar lavage fluids, and airway tissue.[7-9] Moreover, TIMP-1 was higher in untreated asthma than glucocorticoids-treated asthma and likely to be increased with asthma severity, while there was no significant correlation between eosinophil count and TIMP-1.[8] So far, the roles of TIMP-1 were recognized as inhibitors of metalloproteinases, which break extracellular matrix and modulate airway remodeling. Therefore, the effects of TIMP-

1 expression in asthma were understood in the context of protease and protease inhibition relationships.[10] The ratio matrix metallopeptidase 9 (MMP-9) versus TIMP-1 in sputum and serum correlated with forced expiratory volume in 1 second (FEV1).[7,11] Low MMP-9/TIMP-1 ratio, which means excessive TIMP-1, was associated with poor response to corticosteroids treatment,[11] and airway wall thickening and reduced airway lumen area in computed tomography scans from the subjects with asthma.[12,13] Regarding long-term clinical course, the high MMP-9/TIMP-1 ratio showed a correlation with a fast decline in FEV1 over 5 years.[9]

Direct roles of TIMP-1 as an active player in allergic airway inflammation other than proteinase inhibitors were suggested from experimental studies using animal models. In an ovalbumin-induced asthma mouse model, TIMP-1 knockout mice showed increased airway hyperresponsiveness and eosinophilic inflammation with augmented expression of T2 cytokines, suggesting the protective roles of TIMP-1 in asthma.[14] Contrary to these observations, Cao *et al.*[2] reported intriguing results on the roles of TIMP-1 in airway inflammation of asthma in this issue. TIMP-1-treated mice showed increased infiltration of eosinophils with the release of eosinophil-derived neurotoxin, major basic proteins, and eosinophil extracellular traps. Furthermore, TIMP-1 treatment polarized macrophages into M2 phenotype, which may contribute to T2 inflammation in asthma. Given that the serum level of TIMP-1 is elevated in patients with eosinophilic fasciitis,[15] further research is needed to confirm the pro-inflammatory roles of TIMP-1 in eosinophilic inflammatory diseases. Moreover, the functions of TIMP-1 in T2-low and non-eosinophilic inflammation and airway remodeling should be determined in the future.

Biomarkers are valuable in classifying phenotypes and endotypes of SA and selecting optimal therapeutic agents, especially biologics.[16] For selecting optimal biologics or predicting treatment response, T2 inflammation is frequently determined by measuring blood and sputum eosinophils, fractional exhaled nitric oxide, and periostin.[17,18] Although TIMP-1 and MMP-9/TIMP-1 ratio were considered markers of airway remodeling until recently,[19] this study suggested that the serum level of TIMP-1 could be a reliable biomarker of T2 inflammation, not airway remodeling, in SA. For serum TIMP-1 to be used as a reliable biomarker for T2 inflammation in SA, standardization of the measurement methods and determination of reference values are needed in future studies. Furthermore, the clinical characteristics of TIMP-1 high SA should be identified using real-world data.

SA is a heterogenous and complex disease that cannot be controlled by targeting a single cytokine and inflammatory mediator. More novel therapeutic approaches and biomarkers need to be developed and utilized in clinical practice. Investigations using genomics, transcriptomics, proteomics, metabolomics, and microbiome studies from human samples and experimental studies would lead to the journey of finding new treatments and biomarkers.[20] Also, repositioning the therapeutic targets could be an effective approach for identifying novel treatment strategies.

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