

Stabilizing mast cells by commonly used drugs: a novel therapeutic target to relieve post-COVID syndrome?

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SUMMARY Regardless of the severity of coronavirus disease 2019 (COVID-19), a high proportion of patients struggle with persistent respiratory or systemic symptoms after recovery. This is called "post-COVID syndrome", for which pulmonary fibrosis is one of the pathogenesis. Besides T-lymphocytes and macrophages, mast cells also contribute to the development of cytokine storm and thus stimulate the activity of fibroblasts. Additionally, by the exocytotic release of fibroblast-activating factors, mast cells directly facilitate the progression of pulmonary fibrosis. In our previous basic studies, anti-allergic drugs (olopatadine, ketotifen), antibiotics (clarithromycin) and corticosteroids (hydrocortisone, dexamethasone) inhibited the process of exocytosis and showed their potency as highly effective mast cell stabilizers. Given such pharmacological properties of these commonly used drugs, they may be useful in the treatment of post-COVID-19 pulmonary fibrosis and in relieving the symptoms of post-COVID syndrome.

Keywords COVID-19, post-COVID syndrome, pulmonary fibrosis, mast cell

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In most cases, patients are asymptomatic or only present with mild to moderate symptoms, including fever, dry cough and shortness of breath. Nevertheless, some patients develop severe pneumonia or acute respiratory distress syndrome (ARDS), sometimes complicated by multiple organ dysfunction due to systemic thrombotic microangiopathy (1). Recently, regardless of the severity of the disease, a high proportion of patients with COVID-19 are reported to struggle with persistent respiratory or systemic symptoms after recovery (2,3). This so-called "post-COVID syndrome" includes dyspnea, chest pain, generalized fatigue and joint pain, for which pulmonary fibrosis is one of the pathogenesis (4,5).

Pulmonary fibrosis is the interstitial pulmonary disease characterized by the proliferation of fibroblasts, the excessive deposition of collagen and extracellular matrix, and the destruction of normal pulmonary architecture (6). For the development of idiopathic pulmonary fibrosis, several growth factors, such as transforming growth factor (TGF)- β , vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and epidermal growth factor (EGF), are generally considered to be responsible (7,8), since these growth factors promote the profibrogenic

process of the lung after injury. For the development of "post-COVID-19" pulmonary fibrosis, cytokine storm, which is characterized by the over-activation of leukocytes and the uncontrolled secretion of pro-inflammatory cytokines, is additionally thought to be responsible (9,10). These cytokines impair the recovery process from the lung injury and stimulate the activity of fibroblasts to produce collagen, and thus promote the progression of pulmonary fibrosis (11).

We have demonstrated in several animal studies that the overexpression of Kv1.3-channels in T-lymphocytes and macrophages is strongly associated with their over-activation and the progression of renal fibrosis (12,13). In these studies, margatoxin, a selective Kv1.3-channel inhibitor, actually suppressed the activity of the leukocytes and slowed the progression of renal fibrosis. On the other hand, in a series of patch-clamp studies, we have revealed the suppressive properties of nonsteroidal anti-inflammatory drugs (NSAIDs), anti-hypertensive drugs, anti-cholesterol drugs and anti-allergic drugs on lymphocyte Kv1.3-channels (14-16). Taking into account such pharmacological properties of these drugs, they may also be useful in the treatment of post-COVID-19 pulmonary fibrosis, in addition to their usefulness in suppressing cytokine storm (9).

Besides T-lymphocytes and macrophages, recent studies additionally indicate a large contribution of mast

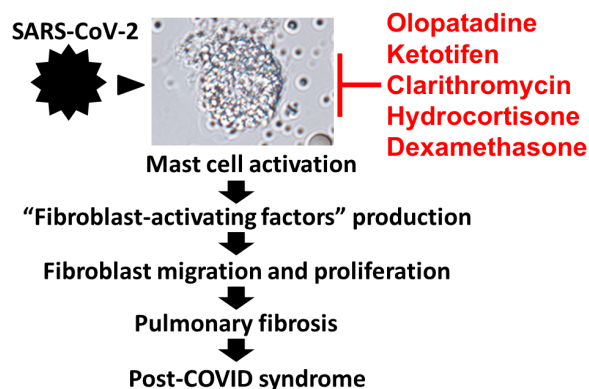


Figure 1. Mast cells in the development of pulmonary fibrosis and as the target of anti-allergic drugs, antibiotics and corticosteroids. Once mast cells are activated by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), they produce fibroblast-activating factors. These factors promote the migration and proliferation of fibroblasts and facilitate the progression of pulmonary fibrosis, causing post-COVID syndrome. Anti-allergic drugs (olopatadine, ketotifen), antibiotics (clarithromycin) and corticosteroids (hydrocortisone, dexamethasone) that stabilize mast cells suppress the progression of pulmonary fibrosis and relieve the symptoms of post-COVID syndrome.

cells to the pathogenesis of cytokine storm triggered by SARS-CoV-2 (17,18). Once activated by the virus, mast cells that reside in the respiratory mucous membrane produce pro-inflammatory cytokines, such as interleukin (IL)-1, IL-4, IL-5, IL-6 and tumor necrosis factor (TNF)- α , in addition to their exocytotic release of chemokines (19). Additionally, several studies revealed that mast cells directly facilitate the progression of pulmonary fibrosis by the exocytotic release of fibroblast-activating factors (20,21). In these studies, the factors promoted the migration and proliferation of fibroblasts and stimulated their activity to produce collagen (Figure 1).

Previous studies revealed that mast cells are also responsible for the development and progression of organ fibrosis, such as liver cirrhosis, systemic sclerosis and renal fibrosis (22-24). Therefore, based on these findings, these studies suggested the pharmacological efficacy of suppressing the mast cell activity in the treatment or protection against organ fibrosis. The pharmacological approaches that were taken were either directly stabilizing mast cells or indirectly inhibiting the chemokines released from mast cells. In our previous animal study, tranilast, one of the potent mast cell stabilizers, actually ameliorated the progression of peritoneal fibrosis complicated with chronic renal failure (25). On the other hand, in a series of patch-clamp studies, by monitoring the changes in the whole-cell membrane capacitance in mast cells, we provided *in vitro* evidence that anti-allergic drugs (olopatadine, ketotifen), antibiotics (clarithromycin) and corticosteroids (hydrocortisone, dexamethasone) strongly inhibit the process of exocytosis (26-29). Morphologically, these drugs actually suppressed the

degranulation from mast cells, showing their potency as highly effective mast cell stabilizers. Of note, prazosin, an α_1 -adrenergic receptor blocker, synergistically enhanced the mast cell-stabilizing property of adrenaline (30). Given such pharmacological properties of these commonly used drugs, they may also be useful in the treatment of post-COVID-19 pulmonary fibrosis and in relieving the symptoms of post-COVID syndrome (Figure 1).

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