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Title: Type II transmembrane serine protease matriptase is a mediator of pulmonary fibrosis

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Body: Idiopathic pulmonary fibrosis (IPF) is a devastating lung disorder which remains refractory to therapies. Recently, type II transmembrane serine proteases have emerged as key actors in pathophysiology, by proteolysis of cell surface receptors and/or cell environment, thereby orchestrating cell crosstalks. Among them, deregulation of the matriptase contributes to various proliferative disorders. Hence, we sought to investigate the role of matriptase in pulmlonary fibrosis. Matriptase expression and activity were analyzed in human lung material from controls and IPF patients. Human fibroblasts were stimulated with recombinant matriptase and the activation of key signaling pathways involved in IPF was analyzed. Using the murine model of bleomycin-induced pulmonary fibrosis, mice were administrated for 14 days with 0 or 0.5mg of camostat mesylate, a matriptase inhibitor, and the markers of tissue fibrosis in lung homogenate, and inflammatory cell influx in the bronchoalveolar lavage fluid (BALF) of the animals were assessed. We show that matriptase is upregulated in the lung and BALF of IPF patients compared to controls. In fibroblasts, matriptase induced the activation of p42/44, Akt, and Smad2/3 pathways. Finally, camostat administration in bleomycin-treated mice led to a significant decrease in mortality (39.3% versus 60.4% in bleomycin-treated group). Fibronectin and collagen expression, and inflammatory cell influx, were not significantly different from saline-treated animals in the camostat group.Taken together, matriptase seems instrumental in pulmonary fibrosis, and camostat mesylat could be a promising target for thetreatment of IPF.