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Commentary

Chronic Obstructive Pulmonary Disease

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STUDY DESCRIPTION

Chronic Obstructive Pulmonary Disease (COPD) includes emphysema and chronic bronchitis and is commonly caused by Cigarette Smoke (CS). Despite extensive knowledge about the pathologic changes in the lung epithelium, blood endothelium, and the cellular mechanisms for lung injury in the pathogenesis of COPD, the lung lymphatic vasculature has not been well evaluated. The lymphatics of the lungs and visceral pleura drain into the bronchopulmonary lymph nodes at the bifurcations of the larger bronchi. The main function of the lymphatic circulation is to drain fluid from tissues and return it to the vascular circulatory system. It is also involved in the immune system of the body, since lymphocytes and dendritic cells move through the lymphatic system to reach the lymphoid organs. The lymphatic function may play a role in the pathogenesis of disease, especially in the lungs, which are particularly dependent on lymphatic function.

It has been previously shown that mice with lymphatic dysfunction develop Lung Tertiary Lymphoid Organs (TLOs) and lung injury with many features of human emphysema including hypoxia, breakdown of elastin, and increased MMP-12 expression. TLOs are intricately associated with lymphatic vessels and resemble lymph nodes in their cellular organization and structure. They are a common occurrence in lung injury and inflammation, including in COPD, where they may also be associated with disease severity. Though lymphatic dysfunction is sufficient to cause TLO formation and lung injury that resembles emphysema in mice, it is not yet clear whether the TLOs that are seen in emphysema are associated with lymphatic dysfunction. In this study, I sought to uncover whether and to what extent lung lymphatic function is altered in the pathogenesis of emphysema and the mechanism by which this occurs.

Lung lymphatic vessel thrombosis is increased in emphysema compared to control smokers and is associated with severe disease. Using a mouse model, I found that tissue destruction and emphysema alone was not sufficient to cause lung lymphatic thrombosis. However, lung lymphatic thrombosis and dysfunction was associated with injury to the lymphatic endothelium and changes in the composition of lymph after CS exposure which occurs before the development of emphysema in mice. These data are the first to show a direct effect of CS on lung lymphatic function and to demonstrate lymphatic thrombosis in patients with emphysema.

Lymphatic thrombosis is generally rare and occurs far less frequently than thrombosis in the blood vascular system. This is because despite the presence of fibrinogen and coagulation factors, lymph is generally a hypocoaguable fluid that lacks platelets and has relatively strong fibrinolytic activity. Despite this, lymph does clot in pathologic conditions, and previously reported causes of lymphatic thrombosis include cancer (typically due to external compression and subsequent stasis), infections, heart failure, or chronic edema.

Thus, the effect of CS on the lymphatic vasculature may involve both direct injuries to the lymphatic endothelium as well as changes in the composition of lymph towards a prothrombotic state. In addition, it is conceivable that activated leukocytes that traffic in the lymphatics in the setting of CS exposure may play a role in lymphatic thrombosis and initiate the coagulation cascade. In scenario, lymphatic permeability, endothelial cell injury, and inflammation in the setting of impaired lymph flow coupled with the prothrombotic effects of CS would fulfil the tenants of 'Virchow's triad' and trigger thrombosis in these vessels.

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