Bronchial Mucosal Microcirculation in SARS-CoV-2 Infection: Role in Innate Humoral Defense?

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To the Editor.

The circulation furnishing human bronchi with oxygenized blood sems overlooked as regards possible roles in infection diseases. I thus welcome the advanced images reported by Ackerman et al. illustrating peribronchial and perivascular microvessels and showing evidence for excessive bronchiopulmonary shunting by the bronchial circulation in Covid-19 pneumonia (1). Arguably, a profuse mucosal microcirculation, supplied by the bronchial circulation, also needs attention in Covid-19.

Cooperation between mucosal microcirculation and overlying epithelial barrier.

Similar to superficial microcirculations of nasal and tracheal mucosae, but distinct from the pulmonary circulation, responsiveness of human bronchial mucosal microcirculation brings about local plasma exudation at mucosal challenge with toxins, including microbes (2,3). The involved microvascular-epithelial cooperation may be summarized: macromolecules extravasate through active formations/closures of endothelial gaps; extravasated bulk plasma moves up between epithelial cells; a minimal hydrostatic pressure increase impacts laterally on epithelial junctions; without sieving, plasma proteins/peptides traverse the pseudostratified epithelium (2-4).

Thanks to a conspicuous epithelial barrier asymmetry of human airways, plasma proteins/peptides traverse without compromising the normal epithelial defense barrier (2-4). In conducting airways plasma exudation thus comes forth as a physiological, first line, innate immune response at mucosal sites of challenge (2-4).

Early humoral antimicrobial defense in airways with intact epithelium.

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The non-sieved nature of plasma exudation means that coagulation-, complement-, natural antibodies-, cathelicidines- etc. -molecules have opportunities for joint operations on human intact airway mucosa (2,4). This power demands control. Thus, plasma exudation restricts to sites of toxin deposition and its duration is governed by active formation of endothelial gaps that close spontaneously unless challenge is increased (2,3).

Human nasal inoculation with rhinoviruses and coronavirus 229E causes plasma exudation (determined as fibrinogen in airway surface liquids) that associates with symptoms and lasts until resolution of infection (2,5).

As respiratory infections proceed down the airways, exudation of plasma proteins from the bronchial microcirculation would be a final out-post mucosal defense. In accord, high levels of fibrinogen were demonstrated in sputum samples from individuals with asthma infected with influenza AB (6). -Indeed, one may ask whether corticosteroid-insensitive plasma exudation has contributed to reduced risk for severe disease observed in cohorts of asthmatics in current and 2009 (H1N1-influenza) pandemics (2)?

Humoral defense at epithelial loss/regeneration.

The exudative nature of asthma is indicated by elevated baseline levels of alpha2-macroglobulin and IgM in bronchial surface liquids (2,3). Agreeing with epithelial barrier asymmetry, absorption of inhaled molecules has not been increased in asthma (3,4), nor may it be increased at viral infection (2).

However, epithelial shedding characterizes asthmatic bronchi. Hence, the unchanged absorption penetrability remains puzzling. Or, is plasma exudation the answer?

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In vivo-data, obtained in experimental test-systems with close structural and physiological similarities to human airways (3,4), suggest that airways mucosal microcirculations promptly contribute barrier functions at sites of epithelial loss: Patchy, asthma-like denudation (=no bleeding or basement membrane injury) promptly induces plasma exudation that creates and sustains a fibrin-fibronectin gel restricted to the site of epithelial loss. Under the biologically active, defense- and repair-promoting barrier-gel, all types of neighboring epithelial cells promptly dedifferentiate into rapidly migrating, tethered repair cells. As soon as a new cellular barrier of interdigitating repair epithelium is established, plasma exudation stops and the gel is shed. Hence, tiny patches of epithelial loss, as would occur in asthma and at viral infection, may not necessarily cause major barrier breaks (2,4).

Whereas Ackerman et al. (1) highlight bronchial circulation remodeling at advanced Covid-19, this letter concerns physiology of bronchial mucosal microcirculation at early-stages of respiratory viral infections. As discussed elsewhere (2-4), the present humoral defense aspects have gone under the radar and not yet been addressed in Covid-19 studies. In summary, exudation of proteins/peptides from bronchial mucosal microcirculation warrants attention in studies of factors that reduce progress of airway infections toward alveolar and pulmonary circulation injury and beyond.

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