New role for glyocalyx in lung

Aubrey E. Taylor  
Department of Physiology, University of South Alabama, Mobile, Alabama 36688

THE REPORT by Dull et al., the current article in focus (Ref. 1, see p. L986 in this issue), evaluates the effect of different polymers of arginine and lysine as models of neutrophil-derived inflammatory proteins. Their size and concentration responses on bovine cultured lung microvascular cells were studied relative to their ability to increase monolayer permeability. Arginine and lysine polymers >11 kDa caused endothelial barrier dysfunction as measured by a 70% decrease in trans-endothelial electrical resistance (TER), and, in addition, a specific enzyme that removed glycosaminoglycan receptors using a specific enzyme, heparinase III, decreased endothelial damage by 50%, but heparinase I produced no effect. The authors postulated from these studies that changes in actin organization and syndecan localization are responsible for the observed change in membrane permeability, since clustering of syndecans was attenuated by heparinase III. However, ML-7, which inhibits myosin light chain kinase, or a p38 MAPK inhibitor, failed to alter the damage of the endothelial barrier. The conclusion from this study is that endothelial cell heparan sulfate proteoglycans are key participants in inflammatory cationic signaling cytoskeleton reorganization and barrier dysfunction.

For several years, we have known that ischemia-reperfusion (I/R) or sepsis causes the release of cytokines by activated cells, and their release of IL-1, TNF-α, ICAM-1, and a large number of other factors as well as cells somehow results in damage to the endothelial barrier of lungs (1a−5). What is the physiological and cellular biological importance of this phenomenon? Dull et al. (1) clearly show that heparan sulfate proteoglycans are important components of the cationic peptides that induce signaling, linking the cytoskeleton to barrier dysfunction in endothelial cell monolayers.

Because blocking TNF-α, ICAM-1, etc., by pretreatment with specific antibodies inhibits or alters sepsis and I/R endothelial damage, it appears, then, that cytokines may also behave in a fashion to cause the cytoskeleton to reorganize and the endothelial barriers to become more porous and leaky to plasma fluid and proteins (5). The use of TER certainly provides a unique technique that can be used to quantify endothelial damage in monolayers, but we do not know the relationship between TER and barrier pore size changes, i.e., can TER be related to either protein leakage or fluid leakage or both? Can studies similar to Dull et al. (1) be done in isolated lungs to evaluate the pathophysiology and structural changes in inflammation by measuring TER across the alveolar capillary barrier in fluid-filled lungs? It appears that the approaches used in Dull et al. can be useful tools in intact lung studies and will most likely provide new insight into the structural changes that occur in endothelial and epithelial barriers of lungs during the inflammatory response.

However, one could certainly conduct dose-responses curves of different cytokines known to cause disruption of biological barriers as measured with TER to prove that the cationic effect observed in Dull et al. (1) is a specific mechanism used by specific cytokines to induce endothelial contraction and subsequent junctional disruption in sepsis and I/R. A large number of cytokines are known to be released during the immune response in lungs, yet we have not extended our knowledge of how these cytokines, beyond their involvement in several types of inflammatory and anti-inflammatory conditions, upregulate receptors that result in the pathophysiological process, changes seen in lung sepsis and inflammation associated with barrier disruption.

The interaction of the glyocalyx, as shown in Dull et al. (1), may likely provide the key to understanding how the inflammatory process occurs or does not occur when lungs are challenged by I/R and sepsis. However, one negative caveat could be that the in vivo endothelial barrier may not behave in the same fashion as found in endothelial monolayers. It is well known that endothelial cells in specific organs and different species certainly have developed immunological characteristics over the years that are related to their environments and produce inherent immune responses that are a product of both their past and present immune histories. But, it is very clear from the results in Dull et al. (1) that reorganization of the cytoskeleton of endothelial monolayers is affected by syndecan clustering, which causes the endothelial barrier permeability to be increased in a manner quite similar to that observed in many sepsis and I/R models of lung inflammation. We are often inclined to complicate a system when it may be as simple as a charge phenomenon that may cause the clustering of syndecans rather than produce up-regulation of receptors on certain sites that cause the effect, and that is what makes this paper interesting and important to the scientific community.

REFERENCES


