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## Glycocalyx perturbation: cause or consequence of damage to the vasculature?

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EARLY ELECTRON MICROSCOPIC observations identified an extracellular coating of anionic polysaccharides on the luminal surface of vascular endothelial cells. This coating was named glycocalyx by Bennet (2) in 1962 and was hypothesized to contribute to the transport properties of the capillary wall. Experimental data to support a physiological role for the endothelial glycocalyx remained lacking until 1979 when Klitzman and Duling (12) reported on low and variable capillary tube hematocrits in hamster striated muscle tissue and its modulation by pharmacological and metabolic stimuli. To account for a fourfold increase in individual capillary red blood cell content during functional hyperemia, Klitzman and Duling proposed that the endothelial glycocalyx represents a slow-moving plasma layer 1.2  $\mu\text{m}$  thick on the luminal surface of capillaries in control conditions. Regulation of the exclusion of blood from this relatively thick endothelial region could then contribute not only to control of capillary red blood cell filling and tissue oxygen supply but also to the controlled modulation of transcapillary solute exchange and tissue hydration. The concept of a relatively thick, permselective endothelial glycocalyx was supported experimentally by Vink and Duling, who directly visualized the exclusion of red blood cells from the capillary endothelial glycocalyx (24) and reported on its limited permeation by various dextrans in a molecular size and charge-dependent manner (25).

Numerous studies reported on the functional implications of glycocalyx perturbation by oxidized lipoproteins (4, 5) or sugar-degrading enzymes such as heparitinase, chondroitinase, and hyaluronidase (6, 8, 22). Loss of glycocalyx integrity is accompanied by impaired endothelial mechanotransduction of fluid shear stress (7, 14, 20), adhesion of platelets (23), and leukocytes (5, 9, 13) to the capillary and venular endothelial surface and leakage of plasma proteins and fluid from the vascular compartment (1, 10), resulting in swelling of the pericapillary interstitial space and consequent compression of the anatomic capillary lumen (21). Based on these findings, there is little doubt that glycocalyx perturbation results in impaired regulation of organ blood flow (8, 22), activation of coagulatory and inflammatory pathways (9), tissue edema (22), and loss of perfused capillary density (27). However, few data are available on the pathophysiological conditions that trigger the initial loss of vasculoprotective properties of the endothelial glycocalyx.

In this issue of *American Journal of Physiology–Heart and Circulatory Physiology*, Rubio-Gayosso et al. (19) report on the effects of ischemia and reperfusion of mouse striated muscle capillary blood vessels. It is demonstrated that immediately following reperfusion, the solute barrier properties of

the glycocalyx are impaired as reflected by enhanced access of large anionic dextrans to the endothelial surface. By monitoring the dextran-excluding properties of the endothelial glycocalyx, Rubio-Gayosso et al. provide new insight into the mechanisms that may mediate ischemia-reperfusion injury. It is demonstrated that the barrier properties of the endothelial glycocalyx are maintained by pharmacological inhibition of the oxygen radical producing enzyme xanthine oxidoreductase, which is associated with heparan sulfate glycosaminoglycans of the endothelial glycocalyx. Furthermore, competitive dissociation of xanthine oxidoreductase from the glycocalyx by heparin is also able to prevent ischemia-reperfusion-induced loss of glycocalyx barrier properties. Although many studies have demonstrated an important role for oxygen radical formation in mediating organ injury upon ischemia-reperfusion, this study sheds new light on the mechanisms by which oxygen radicals impair vascular function. Even more exciting is the observation that infusion of exogenous hyaluronic acid glycosaminoglycans before or shortly after the initiation of cremaster tissue reperfusion is able to partially prevent or even fully restore the impaired dextran-excluding barrier properties of the glycocalyx.

However, many questions remain to be answered. For instance, it is unclear why in this study a simple hyaluronan solution appears to be able to fully repair glycocalyx barrier properties, whereas in a previous study, Henry and Duling (8) needed to infuse a mixture of hyaluronan and chondroitin glycosaminoglycans to repair hyaluronidase-induced loss of glycocalyx barrier properties. Furthermore, it is absolutely unclear what the relative importance is of glycocalyx perturbation in mediating ischemia-reperfusion injury or what the impact is of prevention or reversal of glycocalyx perturbation on organ function following ischemia-reperfusion (3, 26). Nevertheless, this study by Rubio-Gayosso et al. (19) may stimulate many other studies on the potential contribution of impaired protective properties of the endothelial glycocalyx in mediating vascular dysfunction and disease. In a recent study, Nieuwdorp et al. (17) used a new method to measure systemic glycocalyx in humans and reported that hyperglycemia results in a pronounced 50% loss of its volume, which was associated with increased plasma levels of hyaluronan (17). Similar reductions in systemic glycocalyx volume are found in patients with Type 1 diabetes (16), and loss of glycocalyx appears more pronounced in diabetics with proteinuria. This finding is in agreement with a recent study by Jeansson and Haraldsson (11), demonstrating that the glycocalyx is an important contributor to the barrier properties of glomerular capillary endothelium.

Future studies will need to demonstrate whether increased glycocalyx permeability and/or loss of glycocalyx volume merely correlate with pathophysiological provocation of vascular integrity or whether loss of glycocalyx protective prop-

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erties actually causes vascular dysfunction and disease at the organ or systemic level. If so, the endothelial glycocalyx may prove to be a promising therapeutic target in the fight against acute, as well as chronic, vascular disease.

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