Glycocalyx: The Fuzzy Coat Now Regulates Cell Signaling

The glycocalyx is a fuzzy layer of glycoproteins and sugar moieties located on the external side of the plasma membrane of most cell types. The composition of the glycocalyx, which can be altered in disease, influences numerous properties of the cell membrane, including adhesion, cell-cell recognition, and exchange of information with the micro-environment.

Several lines of evidence suggest that the glycocalyx is important for the microvascular properties that sustain peritoneal dialysis. The glycan coating confers a negative charge to the endothelium, which plays a key role in flow- and mechano-sensation, interaction with leukocytes, and regulation of coagulation (1). The glycocalyx might also affect the peritoneal permeability for macromolecules through the interendothelial gaps (large pores), behaving as a barrier for large molecular weight solutes (2). Indeed, clinical situations that damage the glycocalyx, such as inflammation, ischemia/reperfusion and hyperglycemia, are all associated with an increased capillary permeability (1). Although the contribution of the glycocalyx to the size selectivity of the capillary wall remains debated (3), it is suggested that glycocalyx damage may facilitate the release of growth factors and cytokines that could then play a role in angiogenesis and

expansion of the interstitial cell matrix in the peritoneal membrane (4).

Using non-invasive imaging techniques to detect changes in glycocalyx dimension from *in vivo* recordings of the sublingual microcirculation, Vlahu *et al.* showed that dialysis patients had a loss of glycocalyx barrier properties, with possible shedding of its components (hyaluronan and syndecan-1) in blood (5). They suggested that the damaged endothelial glycocalyx could mediate an increased sensitivity of the vasculature to atherogenic stimuli, leading to endothelial dysfunction and increased risk for cardiovascular morbidity and mortality (5).

The long list of glycocalyx functions has now been extended to the signaling pathways originating at the cell membrane (6). In their study recently published in *Nature*, Paszek *et al.* demonstrated that the physical properties of the glycocalyx, i.e. its thickness and the gap between the membrane and the extracellular matrix, may affect intracellular signaling and contribute to cancer cell growth and survival. By combining large-scale expression analysis with modeling and experimental manipulation of membrane glycoproteins, the authors showed that areas of thick glycocalyx create restricted domains which favor the clustering of cell surface receptors including integrins. Because the integrins bind the extracellular matrix, such clusters promote adhesion, interaction with the matrix, and initiation of cell-survival signals which are involved in the metastatic spread of cancer cells. Similar observations were made when expressing the glycoprotein mucin-1 (MUC1), which is upregulated in different cancers, in non-malignant epithelial cells. The bulky glycocalyx promoted growth and survival of these cells by regulating the assembly of focal adhesions and the cross-talk between integrins and growth factor signaling (via extracellular signal-regulated kinase, phosphatidylinositol-3 kinase, and focal adhesion kinase pathways) (6).

The demonstration of the physical influence of the glycocalyx thickness on integrins and cell signaling may be relevant for many transmembrane receptors operating in various cell types and, by extension, for key biological processes (maintenance, repair, proliferation) taking place in the peritoneal membrane.

DISCLOSURES

The author has no financial conflicts of interest to declare.

Olivier Devuyst
Deputy Editor

REFERENCES

1. Reitsma S, Slaaf DW, Vink H, van Zandvoort MAMJ, oude Egbrink MGA. The endothelial glycocalyx: composition, functions, and visualization. *Pflugers Arch* 2007; 454:345–59.
2. Flessner MF. Endothelial glycocalyx and the peritoneal barrier. *Perit Dial Int* 2008; 28:6–12.
3. Rippe B. Free water transport, small pore transport and the osmotic pressure gradient three-pore model of peritoneal transport. *Nephrol Dial Transplant* 2008; 23:2147–53.
4. Devuyst O, Goffin E. Water and solute transport in peritoneal dialysis: models and clinical applications. *Nephrol Dial Transplant* 2008; 23:2120–3.
5. Vlahu CA, Lemkes BA, Struijk DG, Koopman MG, Krediet RT, Vink H. Damage of the endothelial glycocalyx in dialysis patients. *J Am Soc Nephrol* 2012; 23:1900–8.
6. Paszek MJ, DuFort CC, Rossier O, Bainer R, Mouw JK, Godula K, *et al.* The cancer glycocalyx mechanically primes integrin-mediated growth and survival. *Nature* 2014; 511:319–25.

doi: 10.3747/pdi.2014.00221