What is the Endothelial Glycocalyx?

By:
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Cardiovascular disease (CVD) is a chronic inflammatory disease[1,2,3,4,5,6] and the leading cause of death globally. CVD is driven by cardiovascular risk factors and inflammatory triggers.[1-7,8] The first step in the atherosclerotic process is endothelial dysfunction.[1-7,9] The "endothelial structure" is made up of the endothelial glycocalyx (EGX) and the endothelial cells (ECs).[9,10,11]

EGX damage precedes endothelial cell dysfunction.[9,10,11,12,13,14] In other words, you must violate the EGX for endothelial dysfunction to occur. The EGX's importance in CV health cannot be overstated. Therefore, this writing will briefly review the vascular endothelial glycocalyx's functions and structure.

Glycocalyx (EGX) functions

The vascular EGX has many physiologic functions. EGX functions include endothelial cell protection and signaling the endothelial cell to release nitric oxide (NO), barrier and filtration functions, facilitating shear stress from blood flow to the endothelial cells with responsive vasodilation, immune modulation, and regulating blood coagulation.

EGX barrier functions

The EGX serves as a barrier protecting endothelial cells from spontaneous leukocyte and platelet adhesion. Its negative charge repels red blood cells and large macromolecules, thus preventing access to the endothelial cells. A healthy EGX's importance is demonstrated by its action as a physical barrier to LDL particles and inflammatory cells like monocytes that evolve into macrophages and subsequently foam cells and plaque.[15]

EGX damage renders the endothelium "sticky" and permeable. This allows LDL, inflammatory cells, and platelets to penetrate or adhere to

the endothelium. Violating the glycocalyx, the first step in the atherosclerotic process, subjects the vulnerable endothelium to atherosclerotic plaque formation, stiff and rigid blood vessels, and possibly thrombosis and plaque rupture.[11,12,15]

EGX mechanotransduction functions

The glycocalyx signals the endothelium to release NO.[16] The glycocalyx is very sensitive to shear stress and blood flow patterns. High shear stress, as is seen with laminar blood flow in straight blood vessel segments, is associated with a robust and healthy glycocalyx that protects the endothelium, leads to endothelial nitric oxide synthase (eNOS) upregulation, and constant NO release and vasodilation.[10]

Low shear stress, as is found in complicated blood vessels segments like bifurcations, branch points, and curvatures, is associated with non-laminar, oscillatory, and turbulent blood flow. In these areas, the glycocalyx is thin with impaired glycocalyx barrier properties, i.e., decreased NO signaling, decreased NO release, and a predisposition to atherosclerosis.[10]

EGX immune modulation functions

The EGX has an important role in immune modulation. The EGX protects endothelial cells against damage by various oxidative stress mediators. Under healthy physiologic conditions, the EGX docks major enzymes. Extracellular superoxide dismutase, one of the most important enzymes, is bound to heparan sulfate and contributes to decreasing oxidative stress by quenching free radicals and maintaining NO availability. In addition, the EGX may modulate inflammatory responses by decreasing cytokine binding to cell surface receptors.[14]

EGX coagulation regulatory functions

Studies suggest that the EGX may play an important role in regulating coagulation. The EGX houses coagulation pathway mediators like antithrombin III, heparin cofactor II, thrombomodulin, and tissue factor pathway inhibitor.[14] For example, glypican has a high affinity for binding antithrombin III, which localizes antithrombin III to the endothelial cells surface.[17] In addition, Syndecan-4, which contains HS, specifically interacts with antithrombin III. Antithrombin III binds to syndecan-4's HS and stimulates endothelial cells to produce prostacyclin, which suppresses neutrophil and platelet adhesion to endothelial cells, thus supporting a possible decrease in inflammation and thrombus formation.[18]

Endothelial Glycocalyx Structure

The EGX is a negatively charged, heavily hydrated, sugar-rich, mesh-like layer with hair-like projections that blankets the vascular endothelium's inner wall facing the vascular lumen. The EGX consists of:

- **Core proteins (syndecans, glypicans),**
- **Glycosaminoglycans (GAGs, heparan sulfate [HS], chondroitin sulfate [CS]), and**
- **Hyaluronic acid (HA).**

The combination of core proteins (syndecans, glypicans) and GAGs (HS, CS) are termed proteoglycans. The GAGs are attached to the core proteins. These core proteins are anchored to the endothelial cell membrane that serves as the foundation for the remaining EGX components.[9-14]

In addition, plasma proteins like albumin are also embedded in the EGX, creating a concentration gradient. These plasma proteins are tightly bound to the EGX and contribute to its thickness, prevent EGX collapse, and support EGX-mediated vascular integrity.[10,13,14]

There are 4 syndecan subtypes which bind 3-5 heparan sulfate or chondroitin sulfate chains. The major vascular endothelial syndecan is syndecan-2. Most syndecans bind HS; however, the larger syndecan -1 and -3 can also bind CS. Syndecan-4 is important in regulating coagulation. There are 6 glypican subtypes that exclusively bind HS close to the endothelial cell surface. Also, CD44, a transmembrane protein, binds EGX's hyaluronic acid.[10]

Heparan sulfate bound to syndecans is the most

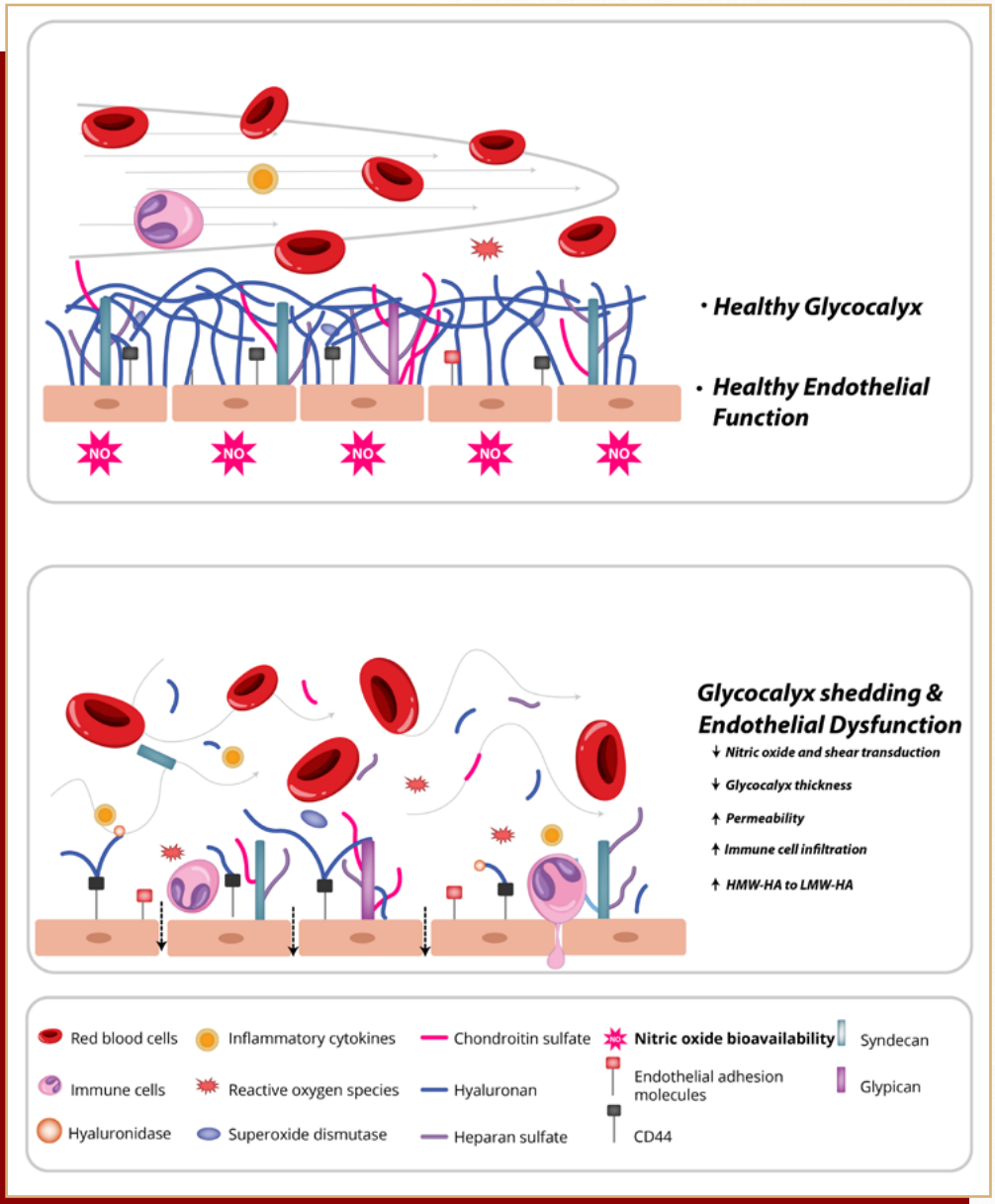

Figure.
The endothelial glycocalyx's main constituents are represented by the chondroitin sulfate, hyaluronan, heparan sulfate (blue and purple), showing the glycoproteins that make up this dynamic layer in the top image. Representative shedding of the endothelial glycocalyx is displayed in the lower image.

prominent EGX proteoglycan member expressed, accounting for 50-90%. The interactions between most syndecans and extracellular matrix molecules, growth factors, and/or cell adhesion molecules seem to be mediated by their heparan sulfate chains.[10]

Chondroitin sulfate is another abundant GAG in the EGX. The ratio of HS to CS is approximately 4:1. Hyaluronic acid is the only GAG not linked to a core protein. It can be bound to the endothelial cell membrane.[10]

Negatively charged heparan sulfate and chondroitin sulfate account for the EGX's biophysical properties and create inter-GAG repulsion forces protecting the endothelium. GAG length and negative charge both contribute to the EGX's extension into the vascular lumen.[13,14]

While syndecans are the main contributor to cell adhesion or shape change via their interaction with the cytoskeleton, glypicans mediate flow-induced endothelial nitric oxide synthase (eNOS) activation. In fact, studies with cultured endothelial cells have shown that EGX heparan sulfate breakdown alters shear stress and impairs nitric oxide production, the hallmark of endothelial dysfunction.[13]

Conclusion

The endothelial glycocalyx is a complex, fragile structure with pleiotropic functions including barrier and filtration, immune modulation, mechanotransduction, and regulating coagulation.

When the glycocalyx is damaged, these functions may become compromised. Therefore, it is easy to see why a healthy vascular endothelial glycocalyx is necessary for a healthy cardiovascular system.

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