An Introduction to Endothelial Glycocalyx --What is it and Why does it Matter?

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Background:

The human capillary system was designed to be leaky, allowing a significant part of the blood plasma to bathe the interstitial tissues and wash away the waste products of the cells. If this fluid were not reabsorbed, tissues would soon become hopelessly edematous and intravascular volume would decrease to the point of hypotension – unless many additional liters of fluid were consumed each day. However, in a healthy person, there is no accumulation of interstitial fluid. The fact that fluid distribution remains nearly perfectly balanced in normal individuals, with fluid uptake matched to capillary filtration volume is one of the most astounding aspects of human physiology. In 1896, Earnest Starling published a paper describing the mechanism by which the fluid exiting the arterioles is recycled back into the blood vascular system. Since then, generations of medical students have learned about the "Starling forces" by which it was believed that 90% of the capillary filtrate reentered the *venules* and only 10% re-entered the general circulation via the lymphatics. Although Starling made many important contributions to the understanding of human physiology, he was wrong about the mechanism of fluid reabsorption.[1] Thanks to advanced precision instrumentation, we now know that under normal conditions, 80 to 90% of the fluid leaving the arterioles is actually resorbed by **lymphatic system.** The key to this remarkable mechanism of fluid homeostasis is the **endothelial glycocalyx**.

What is the Endothelial Glycocalyx?

The endothelial glycocalyx acts as a one-way permeability layer (much like the fabric Gore-Tex) which allows fluid to exit the venule but limits fluid *reabsorption* – at least under normal conditions. What exactly is the glycocalyx (GCX) and why does it matter so much – particularly among patients with chronic wounds?

Although the presence of the GCX is not much discussed, it has been known about for many decades. In 1966, Dr. John Luft discovered that the endothelial cells of the capillary lumen had a "sugar husk" lining, called now the glycocalyx.[2] This lining is not passive but is functional, active, and dynamic. In an adult human, the GCX covers the totality of the approximately 60,000 miles of arterial, venous, and lymphatic vasculature, from the 2-centimeter diameter aorta to the 5-micron capillaries delivering oxygen and nutrients to the individual cells. At the microscopic level, the GCX resembles an "Amazonian forest" both vertical and horizontal stratification, although the structure is variable depending on the organ. It is thickest as a component of the

blood brain barrier (hence the term “barrier”) and thinnest in the alveolae of the lung where rapid diffusion of gas molecules is vital, and it has wide gap junctions in the liver and kidney, but tight junctions within the cerebral vasculature.[3]

The function and structure of the GCX can be described by the acronym “EPIC:” **E**ndothelial cell function (such as nitric oxide and other cytokine production), **P**ermeability layer (albumin and hyaluronic acid components), **I**nflammation quenching (prevention of white blood cell demargination), and **C**oagulation inhibition (platelet adherence inhibition and coagulation factor regulation).

In fact, the glycocalyx is like a computer, with hardware, software, and a power source. The GCX ***hardware*** includes albumin, the core proteins of glycoproteins and proteoglycans, and the glycosaminoglycans (GAGS) of heparan sulfate and hyaluronic acid (See Figure 1, Table 1).[4]

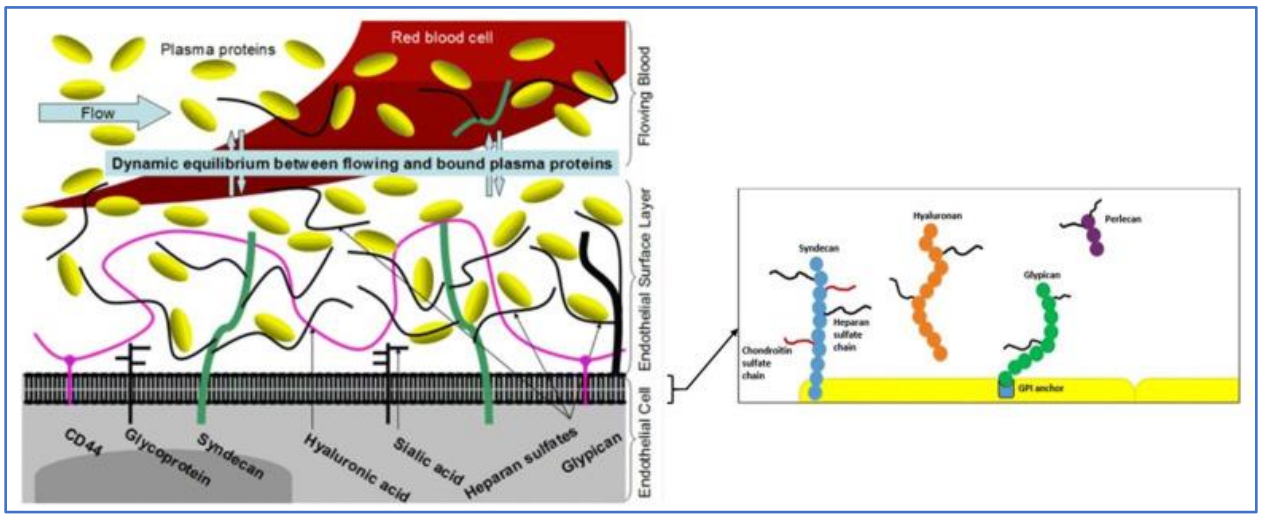

Figure 1: Structure of the endothelial glycocalyx illustrating proteoglycans and glycosaminoglycans[4,5]

Core protein	Core size (kDa)	Number of subtypes	Structural characteristics	Linked glycosaminoglycan (GAG)
Syndecan	19–35	4	Transmembrane protein	Heparan sulfate, chondroitin sulfate
Glypican	57–69	6	GPI-anchored protein	Heparan sulfate, chondroitin sulfate
Perlecan	400	1	Secreted	Heparan sulfate, chondroitin sulfate
Versican	370	1	Secreted	Chondroitin sulfate, dermatan sulfate
Decorin	40	1	Secreted	Chondroitin sulfate, dermatan sulfate
Biglycan	40	1	Secreted	Chondroitin sulfate, dermatan sulfate
Minecan	35	1	Secreted	Keratan sulfate

GPI glycosylphosphatidylinositol

Table 1: Characterization of proteoglycan core proteins in glycocalyx[4]

The GCX ***software*** consists of genetic, epigenetic, and single nucleotide polymorphisms which provide instructions regarding its function. The ***power source*** is our blood flow with laminar

movement causing micro and macro-oscillatory shear stress, and, through *mechanotransduction,* producing energy which impacts endothelial cell organelle function (See Figures 3 & 4).[6,7]

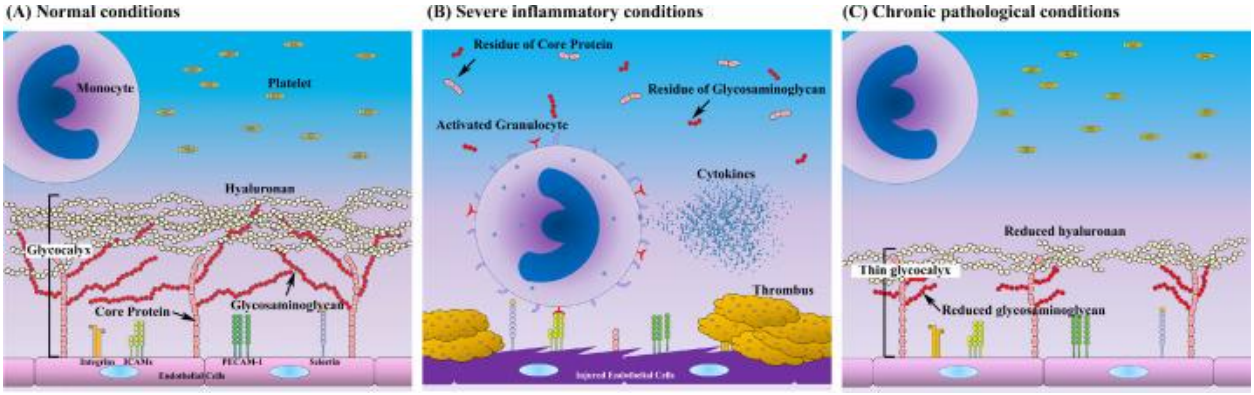

Fig 2. Schema of the endothelial glycocalyx in (A) normal conditions, (B) severe inflammatory conditions, and (C) chronic pathologic conditions. (A) The surface and surface receptors of the normal endothelium are covered by the endothelial glycocalyx, which is composed of a core protein, glycosaminoglycans, and hyaluronan. Only the core protein binds to the endothelial cells; glycosaminoglycans and hyaluronan do not directly interact with these cells (left panel). (B) Severe inflammatory conditions, such as a cytokine storm, can degrade the endothelial glycocalyx. This can lead to the exposure of both the surface and the surface receptors of the endothelial cells to the vascular lumen; this in turn enables the granulocytes and platelets to adhere to the endothelial cells and cause injuries and thrombus formation, which can block the blood flow (middle panel). (C) Chronic conditions, such as diabetes, CKD, and hypertriglyceridemia, can reduce the production of the glycocalyx components; this leads to a thinning of the glycocalyx structure, leaving it more vulnerable to damage by external stimuli (right panel).[6,7]

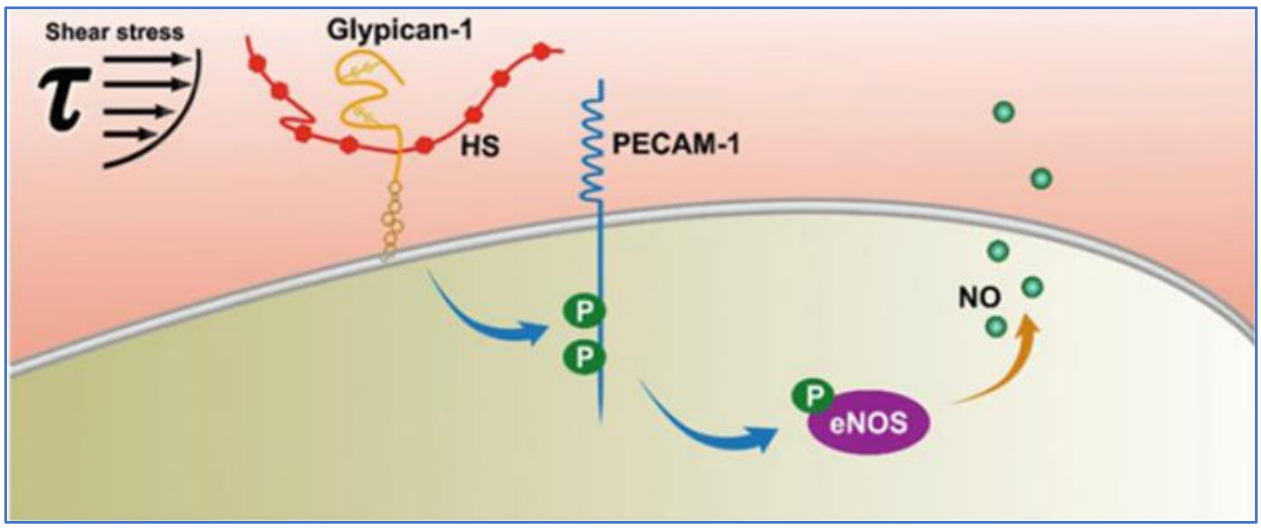

Figure 3: Shear-Induced Nitric Oxide Production *via* Heparan Sulfate and Glypican-1 Mechanotransduction and PECAM-1 Phosphorylation leading to eNOS activation and NO synthesis. Fluid shear stress is initially sensed by heparan sulfate proteoglycan glypican-1. That signal is transduced to the intracellular tail of PECAM-1 protein. PECAM-1 becomes activated by tyrosine phosphorylation. PECAM-1 activation triggers phosphorylation of eNOS and NO production increases.[9,10]

Under scanning electron microscopy, the GCX looks something like “drier lint” (See Figure 4 below)[6] but it is best imagined like seaweed waving with the tidal current or tall wheat stalks blowing in the wind.

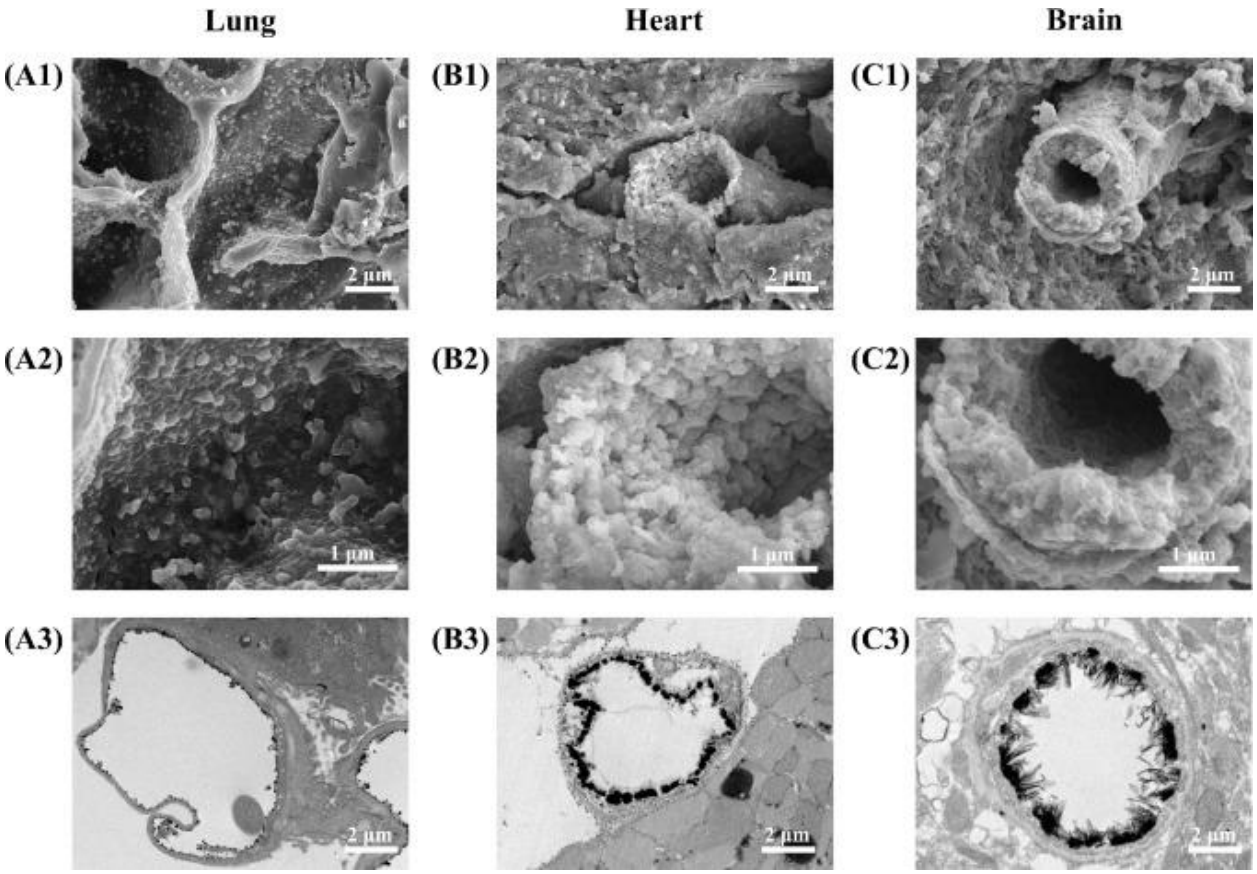

Figure 4. Scanning and transmission electron microscopy images of the ultrastructure of the continuous capillaries in the (A) lung, (B) heart, and (C) brain. Lanthanum nitrate staining is used to visualize the endothelial glycocalyx. (A2), (B2), and (C2) depict the higher magnification views of (A1), (B1), and (C1), respectively. (A3), (B3), and (C3) are the transmission electron microscopy images of the endothelial glycocalyx in (A), (B), and (C), respectively. Although the endothelial glycocalyx can be seen on the surface of the vascular endothelial cells in all images, its thickness varies greatly in each organ.[6,8]

The hardware, software, and power source of the GCX are all essential components for maximum function. When the hardware (molecular) components of the GCX are degraded or “shed,” its “EPIC” function is impaired, often resulting in dramatic localized or even systemic changes.[4] Many medical conditions can trigger the GCX shedding, causing vascular hyperpermeability (“excess leakage”).

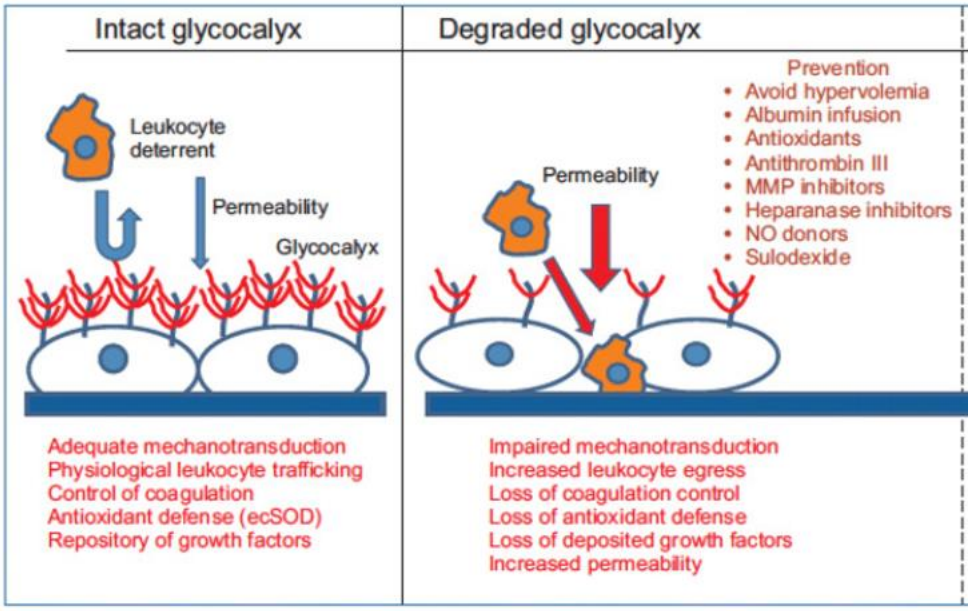

Figure 5: Pathologies/interventions associated with glycocalyx alterations. Adapted from Reference.[4,11]

Conditions associated with endothelial dysfunction include aging, sepsis, trauma, hyperglycemia/diabetes mellitus, hyperlipidemia, atherosclerosis, tobacco abuse, stroke, COVID, arterial hypertension and venous hypertension.[12,13,14]

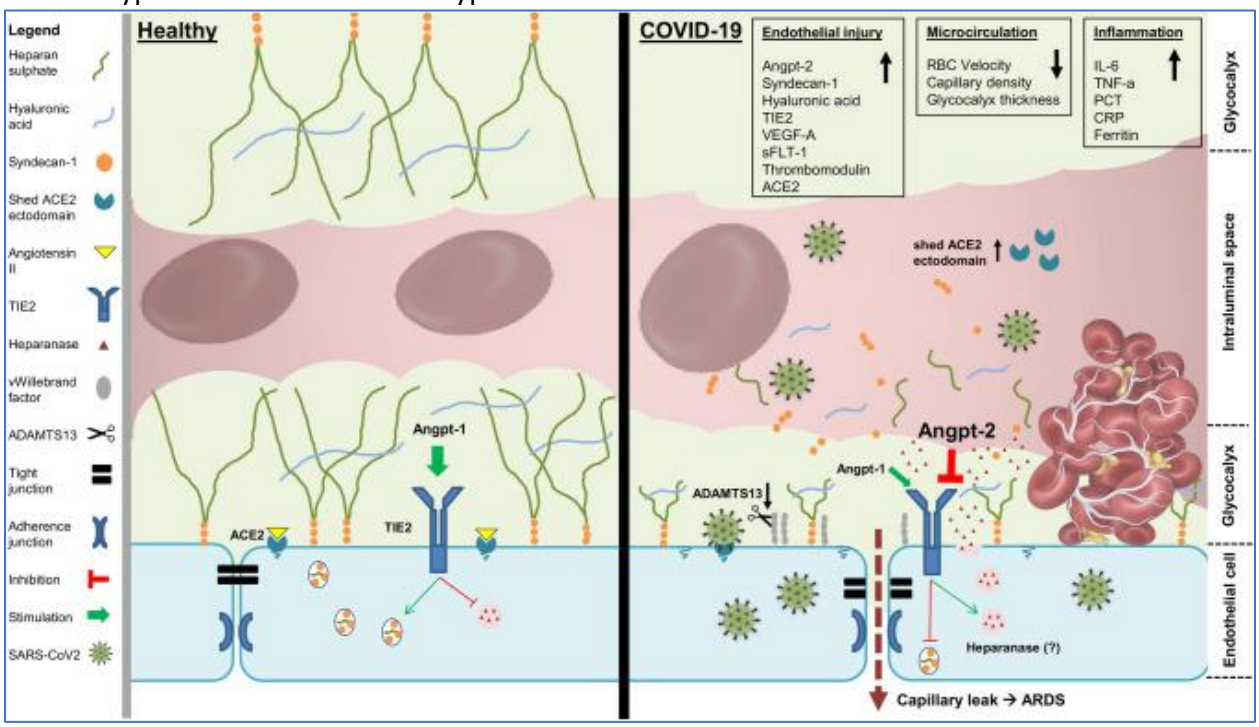

Figure 6: Endothelial, glycocalyx, and microcirculation damage in COVID-19.[12]

In fact, disruption to the GCX is a significant contributor to venous leg ulceration development (Castro-Ferreira et al. 2017).[15] When looking at the list of conditions that may affect GCX structure or function, it is no surprise that most patients with chronic wounds have some element of edema. Disruptions in GCX function may be part of the reason. In 2016, Drs. John Tarbell and Limarym Cancel provided an excellent summary of these pathophysiologic states in the article "Glycocalyx and its importance to human medicine", which includes a description of cancer's glycocalyx contributing to its progression and metastatic behavior.[16] With regard to cancer, there have been many recent papers discussing the way that abnormalities in the CCX can for example, mechanically push cells towards metastasis, deactivate immune cells, and rewire cellular metabolism towards sustained growth.[17,18,19]

Given the vital role of the lymphatics in fluid absorption, it is not surprising that lymphatics also have a GCX, demonstrated for the first time in a human specimen in 2022.[20] Drs. Peter Mortimer and Stanley Rockson called attention to the GCX in their now classic 2014 paper entitled "New developments in clinical aspects of lymphatic disease."[21]

The GCX and Nitric Oxide

It's not possible to describe the endothelial GCX function without discussing the role of nitric oxide. The endothelial GCX modulates vascular tone through the synthesis and release of several vasoactive substances, especially the vasodilator nitric oxide (NO). In 1998, the Nobel Prize in Physiology was awarded to Drs. Furchgott, Ignarro and Murad who identified that nitric oxide is a vital to human health, signaling molecule in the cardiovascular system. Endothelial NO synthase (eNOS), responsible for the synthesis of most of the NO, is localized within domains termed ***caveolae*** (a small "dent" in the plasma membrane composed of "lipid rafts" that function for intra-cellular signaling, see Figure 7).[22]

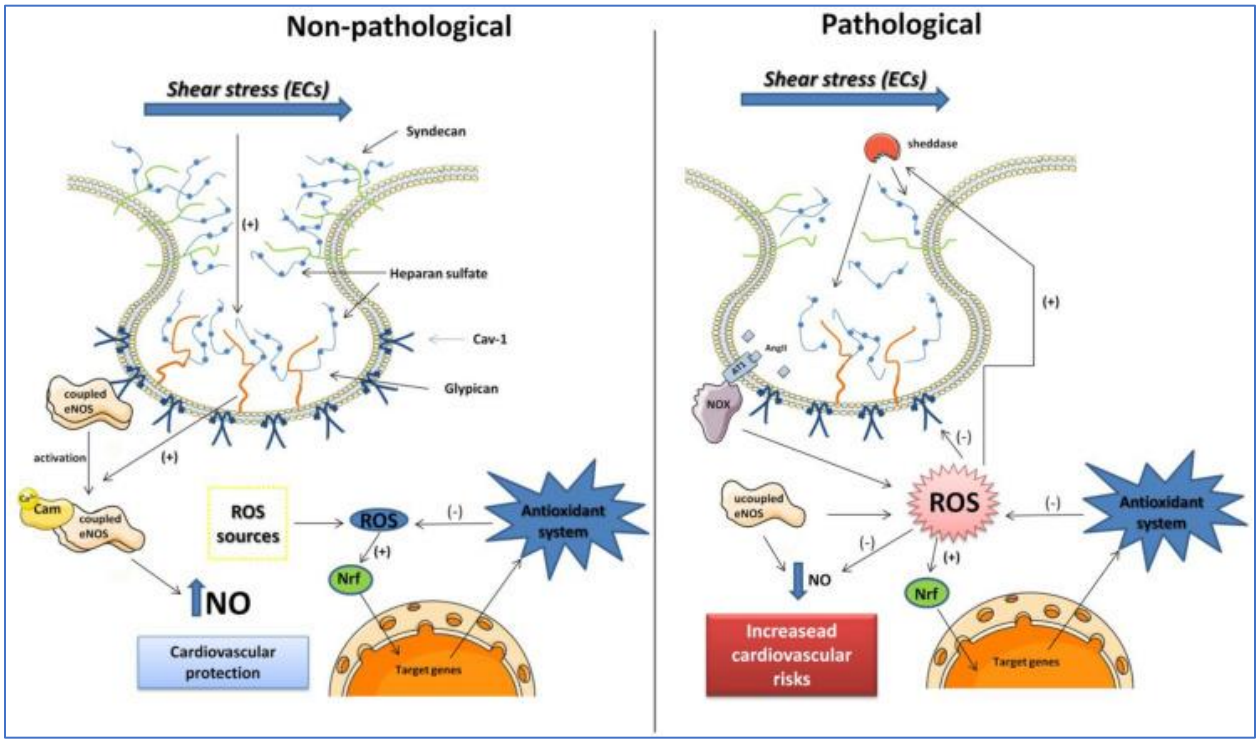

Figure 7: Schematic representation of caveola and glycocalyx proteins in endothelial cells (ECs) under non-pathological and pathological conditions. In non-pathological conditions, the glycocalyx proteins are intact and the coupled eNOS (dimeric form) is inactivated linked to Cav-1 protein. The eNOS is activated by shear stress mediated by Glypican-1 mechano-transduction as well as increase in calcium levels. The NO bioavailability can protect the cardiovascular system, and ROS produced by different sources stimulates the antioxidant system that also protects the cells of oxidative damage. In pathological conditions, the rise in ROS production mediated by pro-oxidant molecules as Ang II overtakes the antioxidant defenses. The ROS can degrade Cav-1, the eNOS is uncoupled (monomeric) that can be source of ROS, and NO bioavailability is reduced. ROS also stimulates the sheddases activity clivating the heparan sulfate from glypican and syndecan losing its ability to induce eNOS activation mediated by shear stress. Those frames with low NO levels can potentiate the cardiovascular risks.[22]

Powered by mechanotransduction, the GCX mediates the physiological activation of NO synthesis by shear stress. In pathologic states, the shedding of the glycocalyx changes in the structure of the caveolae, resulting in a significant decrease in eNOS activity. This reduces NO bioavailability and increases the generation of potentially harmful reactive oxygen species (ROS). Decreases in NO and increase in ROS are associated with cardiovascular disease and diabetes. The effect of GCX thinning or loss is relevant to many diseases , perhaps in large part due to reduction in NO and dysregulation of tissue blood flow.

How the GCX turns flow into energy

Additional transducers responsible for detecting and converting shear stress to NO production were identified a little over 10 years ago. In 2010, two genes - PIEZO 1 and PIEZO 2 were discovered which encode proteins that make up **mechanosensory channels**, resulting in the Nobel Prize in Medicine being awarded in 2021 to **Ardem Patapoutian** at Scripps for his teams' breakthrough discovery of the mechanosensory Piezo ion channels. These mechanosensory channels are present on the surface of the vascular endothelial cells, regulating the flow of ions in and out of cell and activating chemical signaling within the cell. This reaction lets cells maintain homeostais,[23] governs lymphatic valve development and maintenance,[24] and impacts varicose vein development.[25]

Can a damaged GCX be repaired?

Like our external skin cells, GCX turnover inside the endothelium is continuous. In health, the natural process of shedding and rebuilding maintains homeostasis and normal tissue/organ function. However, in many acute and chronic diseases, there is a mismatch and the GCX is shed faster than it can be rebuilt. Finding a way to restore the GCX might be considered the "Holy Grail" of vascular medicine. In 2021, Banerjee and Ebong's work provided an overview of GCX restorative developments (See Figure 8).[14] Additional work on diosmin and its effect on GCX restoration was published by Mitra et al from the Ebong lab (December of 2022 in *FASEB;* Diosmin and its glycocalyx restorative and anti-inflammatory effects on injured blood vessels).[26]

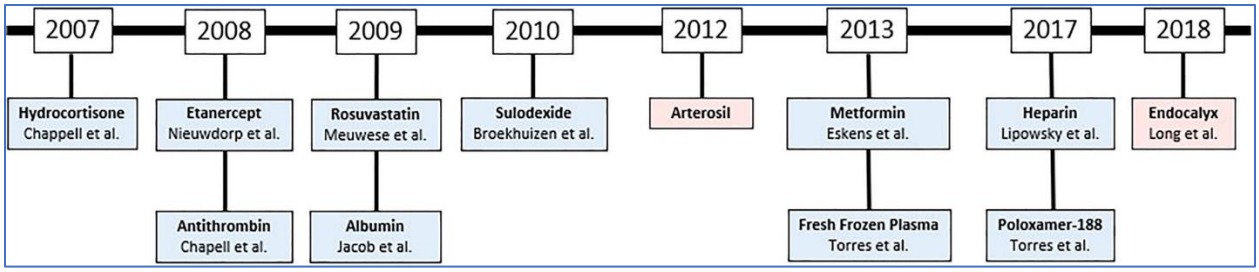

Figure 8: Chronological depiction of prominent EC GCX regenerative therapy developments. All reapplied therapies (blue) are ordered according to the year in which their beneficial effects on the EC GCX were published. Nutraceuticals (pink) Endocalyx and Arterosil are ordered according to the year of its patent approval and to the year it was first available for use, respectively. Of note, there is no published source confirming the earliest availability of Arterosil.[14]

Diosmin is a Micronized Purified Flavonoid Fraction (MPFF). MPFF is a leading veno-active compound indicated in the treatment of venous hypertension, venous leg ulcers, lymphedema, and hemorrhoids in Europe and internationally for over 40 years with multiple validating randomized controlled trials. Diosmin was shown in a mouse carotid artery model to support endothelial GCX integrity, which was attributed to its preservation of endothelial function as indicated by attenuated expression of inflammatory factors and restored vascular tone. The effects of MPFF could be related to functional GCX recovery, added to previously described anti-inflammatory properties with inhibition of leukocytes adhesion and migration. There is extensive research published demonstrating MPFF efficacy in chronic venous disease (CVD),[27,28,29] lymphedema, and in wound care as an adjunct to accelerate venous leg ulcers' healing. In fact, there are now societal guidelines which recognize maintaining the GCX as part of the standard of care.[30,31] That is why MPFF is considered a routine adjunctive treatment among patients with CVD, venous ulcerations, and lymphatic dysfunction.

Final Thoughts

The endothelial glycocalyx is essential and indeed "EPIC." Given the importance of the GCX in health and disease and its relevance to patients with chronic wounds, why is it not commonly discussed in clinical care? The answer is in part due to the general ignorance of the lymphatic system's critical and vital role in fluid homeostasis. It's hard to change decades-old, entrenched medical doctrine even when it's been proven wrong. It's not possible to update medical textbooks or medical school curricula as fast as medical knowledge is increasing. Discoveries about the GCX are happening so quickly that it is difficult for practicing physicians to keep up. It's also fair to say that clinicians are intimidated by this incredibly complex microscopic system which involves many unfamiliar medical terms. However, Medicine as a career is one of life-long learning. We need to understand the importance of the GCX, not just for our patients but for ourselves. We will all experience aging and we will likely develop some chronic disease process for which we need medical attention. Now that we are beginning to understand the importance of the lymphatics, the time has come to recognize the role of the GCX as an essential aspect of health maintenance and functional restoration. The future of our patients and our own health depends on an intimate understanding of the GCX.

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The Glycocalyx in Disease States

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