Endothelial Glycocalyx

April Summers

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Structure of the Endothelial Glycocalyx

- Complex gel between flowing blood and endothelial cell wall
- Interacts with plasma proteins and lipids
- Composition and dimensions fluctuate
  - Continuously replaces material sheared by plasma
    - Thickness varies from 0.1um and 1um

Structure of the Endothelial Glycocalyx

- Made of glycoproteins and proteoglycans
- Proteoglycans
  - Have a protein core
  - Attached: Negatively charged glycosaminoglycan (GAG) side chains
  - Some core proteins are firmly bound
    - Membrane spanning domain (syndecans)
    - Phosphatidylinositol anchor (glypicans)
  - Other core proteins are secreted after attachment of GAG sidechains
    - Perlecans
    - Versicans
    - Decorins
    - Biglycans
    - Mimecans

Structure of the Endothelial Glycocalyx

- Five types of GAG side chains
  - Heparan sulfate makes up 50-90%
  - Chondroiton
  - dermatan
  - keratin sulfates
  - Hyaluronic acid: only GAG not usually bound to a protein core and forms viscous solutions with water

Structure of the Endothelial Glycocalyx

- Glycocalyx forms a luminal mesh that provides endothelial cells with a framework to bind plasma proteins and soluble GAGs
- Glycocalyx is inactive but once plasma constituents are bound, it forms a physiologically active endothelial surface layer

Glycoproteins act as adhesion molecules and contribute to coagulation, fibrinolytic and hemostatic systems

- Cell adhesion molecules are divided into
  - Selectins (E and P)
  - Integrins
  - Immunoglobulins
- Histamine and thrombin stimulate P-selectin
- IL-1, TNFalpha, and LPS stimulate E-selectins
- Integrins bind to collagen, fibronectin, and laminin
- Immunoglobulins include ICAM1/2, VCAM, PECAM-1

Glycocalyx

- Net negative charge
  - Dependent on GAG side chain sulphation
  - Changes in sulphation patterns affect protein binding and vascular permeability
- Charged mesh acts as a macromolecular sieve
  - Repelling negatively charged molecules, white and red blood cells and platelets
  - Macromolecules >70kDa are excluded from the glycocalyx
  - Albumin is 67kDa and has a negative charge, but binds tightly to the glycocalyx due to its amphoteric nature
    - Binding reduced the hydraulic conductivity across the vascular barrier
    - Some albumin leaks through

Physiology of the endothelial surface layer

- Starlings forces- oncotic and hydrostatic pressures
  - Reduction in fluid extravasation by the glycocalyx
  - Three key components revised
    - Venous reabsorption
    - Rate of capillary filtration
    - Opposition to capillary filtration
  - Lymphatic flow is much less than capillary filtration rate calculated by Starling
    - Capillary filtration and reabsorption are less than originally thought
  - Why is capillary filtration so much less?
    - Colloid Osmotic Pressure

- Oncotic forces are only set up across the endothelial surface layer on the luminal aspect of the endothelial cell, not across the whole capillary wall

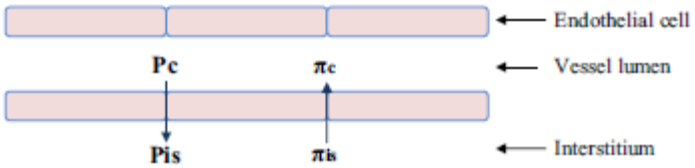

Figure 1 The Starling principle. Jv/A, volume filtered per unit area; Lp, hydraulic conductance; P_c, capillary hydrostatic pressure; P_{is}, interstitial hydrostatic pressure; σ, osmotic reflection co-efficient; π_c, capillary oncotic pressure; π_{is}, interstitial oncotic pressure [15].

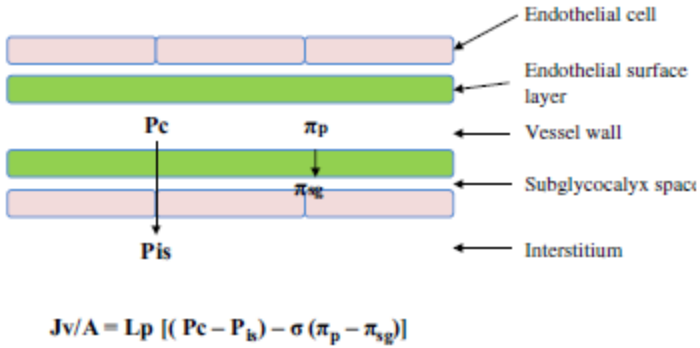

Figure 2 The revised Starling principle. Jv/A, volume filtered per unit area; Lp, hydraulic conductance; P_c, capillary hydrostatic pressure; P_{is}, interstitial hydrostatic pressure; σ, osmotic reflection co-efficient; π_p, oncotic pressure on plasma-side of endothelial surface layer; π_{sg}, oncotic pressure in subglycocalyx space [15].

Glycocalyx Model

- Fluid filtration is regulated at the point at which it begins within the capillary lumen by the endothelial surface layer
- Glycocalyx repels red blood cells
- Attenuates the interaction of platelets and leukocytes
  - Negative charge repels the cells and adhesion molecules are hidden within its structure
  - Molecules become more accessible during inflammation

Glycocalyx Model

- Endothelial surface layer protects endothelial cells from the shear stress of blood flow
  - Increased shear increases NO production → dilation of vessels
  - Increased shear can increase hyaluronic acid
- The binding of ligands and enzymes to the glycocalyx facilitates cellular signaling and enzymatic modification
  - Fibroblast growth factor
  - Lipoprotein lipase

Anticoagulant mediators can bind to the glycocalyx

- Antithrombin III- anticoagulant activity is enhanced by binding to heparan sulfate (GAG found in the glycocalyx)
- Heparin cofactor II activated by dermatan sulfate
- Thrombomodulin is produced by endothelial cells and contains chondroitin sulfate, which interacts with thrombin to activate the protein C pathway
- TF pathway inhibitor binds via heparin sulphates

Glycocalyx protects the endothelium

- Bind enzymes that scavenge oxygen radicals
- Enzymes help reduce oxidative stress and maintain NO bioavailability and prevent endothelial dysfunction

Damage to the endothelial surface layer

- Destruction can lead to:
  - Capillary leak
  - Edema
  - Accelerated inflammation
  - Platelet aggregation
  - Hypercoagulability
  - Loss of Vascular responsiveness

Damage to the endothelial surface layer

- Ischemia degrades the endothelial surface later
  - Denuded endothelial cells with shedding and washout of GAGs and increased transudate and permeability to colloids
- Vascular endothelium is one of the earliest sites involved in SIRS
  - Glycocalyx is damaged by TNF and LPS
  - Disruption of the glycocalyx exposes cell adhesion molecules

Damage to the endothelial surface layer

- Atrial stretch releases atrial natriuretic peptide (ANP)
  - Reduces plasma volume by increasing renal excretion
- Hyperglycemia degrades the glycocalyx
  - Mediated by oxygen radicals or the activation of glycocalyx degrading enzymes
- Normal renal function depends upon an intact glycocalyx

Protection and Repair of the endothelial surface layer

- Antioxidants rapidly reversed glycocalyx damage
  - Polyethylene glycol, NO, adenosine agonists, TNF alpha inhibitors, allopurinol, heparin, hyaluronan

Protection and repair of the endothelial surface layer

- Antithrombin III inhibits both coagulation and inflammation
  - Enhancing prostacyclin production
  - Inhibiting protease action
- Glucocorticoids can limit inflammatory damage to the glycocalyx by suppressing cytokine and chemokine production
  - Preventing migration of inflammatory cells and mast cell degranulation

Strategies to protect of repair the glycocalyx

- Suldodexide (commmercially available preparation of heparin sulfate and dermatan sulfate) partially restored the glycocalyx in diabetic patients
- Infusion of heparin sulfate reduced glycocalyx damage and subsequent leukocyte adhesion
- Rosuvastatin can partially restore glycocalyx volume in hypercholesterolemia

Strategies to protect of repair the glycocalyx

- Lidoflazine (Ca channel blocker) preserved the glycocalyx in patients undergoing cardiopulmonary bypass
- Hypervolemia damages the glycocalyx and triggers release of ANP
- Loss of albumin accompanies loss of the glycocalyx
- Albumin decreased net fluid extravasation compared with HES
  - Albumin dilates coronary arteries possibly by enhancing NO production in response to shear stress

Avoiding glycocalyx damage

- Avoiding hypervolemia and hyperglycemia
- Maintaining physiological concentration of plasma protein
- Antioxidant therapy, statins, corticosteroids etc