3.1.1

Healthy Endothelium – Endogenous Antiplatelets and Anticoagulants

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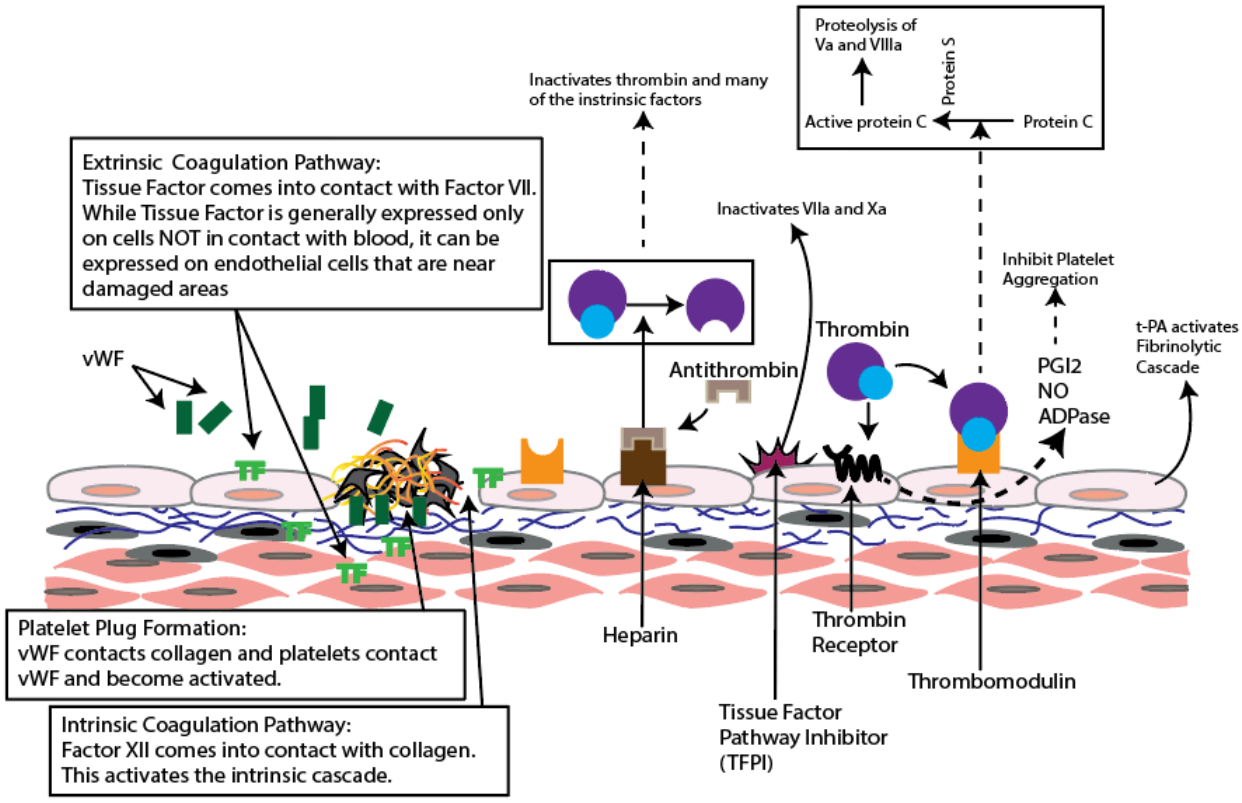

Image by JS 2015

This image shows a blood vessel wall and the many molecules involved in both forming and preventing blood clots. The left side of the image illustrates blood clotting while the right side shows the actions of mediators that inhibit blood clots.

Please watch the video Anticoagulants - Naturally Occurring

A healthy endothelium is very important to the successful physiology of proper blood flow and hemostasis. As you can see in the image above, the healthy endothelium on the right side releases a host of chemical mediators that work to

prevent blood clotting. We will discuss these substances in detail below.

Heparin and **heparin-like** molecules made by endothelial cells and nearby mast cells can be found along the vessel wall. These molecules make their way to the bloodstream where they bind and activate a protein called **antithrombin** (also commonly called **AT-III** or antithrombin III). AT-III is an inhibitor of thrombin, factor Xa and several other clotting factors such as XIIa, XIa, and IXa.

Tissue factor pathway inhibitor (TFPI) is manufactured by the vascular endothelium. It is mostly bound to the endothelial cell surface, but a small amount is released regularly to become a free form in the blood. The free form is able to bind factor Xa and inactivate it. Moreover, the TFPI/factor Xa complex can bind factor VIIa and inactivate it as well.

Endothelial cells have a G-protein coupled receptor for thrombin known as PAR-1 that when activated produces an anticoagulant response. Activation of this G-protein results in the production and release of prostacyclin, nitric oxide (NO) and ADPase.

- **Prostacyclin** – (also called prostaglandin I2 or PGI2) is a prostaglandin that is capable of inhibiting platelet activation. In a way, this prostaglandin is the antagonist to another prostaglandin called thromboxane (TXA2) that actually activates platelets.
- **Nitric oxide** – NO is able to cross platelet membranes and interact with enzymes in such a way that intracellular calcium is lowered. Activators of platelets (like ADP and TXA2) tend to increase intracellular calcium in platelets, so the ability of NO to lower platelet calcium works against the formation of platelet plugs.
- **ADPase** – (also called adenosine diphosphatase and apyrase) is generally found expressed on the endothelial cell surface where it binds up any nearby ADP and cleaves a phosphate from it to make AMP. Normally, intact ADP can bind to an ADP receptor called P2Y12 on platelets. Binding of ADP to P2Y12 results in an increase of platelet calcium levels and leads to activation of the platelet and granule release. Because ADPase breaks down ADP, platelet activation decreases.

Thrombomodulin is an integral membrane protein of healthy vascular endothelial cells. This protein acts as a cofactor for the activated thrombin enzyme from the clotting cascade. The thrombomodulin/thrombin complex is capable of cleaving a plasma protein called protein C. Protein C is synthesized in the liver and upon activation and combination with a second protein called protein S, it is capable of breaking down two important clotting cascade cofactors called factor Va and factor VIIIa.

tPA (tissue plasminogen activator) is an enzyme found on healthy endothelial cells or released very slowly into circulation that catalyzes the conversion of plasminogen to plasmin. Plasminogen is made by the liver and is found as an inert enzyme in the plasma. Once activated into plasmin, it is capable of breaking down the fibrin strands of a blood clot. This process is called fibrinolysis. tPA can be synthetically produced and given to patients with conditions such as pulmonary embolisms, thrombotic myocardial infarctions, and thrombotic strokes. This treatment is a form of thrombolysis and can greatly reduce the damage done to a tissue due to the formation of an unwanted blood clot. This treatment is generally given if the patient receives medical care within three hours of symptoms from the thrombotic blockage.

Notice that all of the above processes operate to prevent platelet plugs and blood clots. These antiplatelet and anticoagulant mechanisms work to keep the blood from forming unwanted and unnecessary clots. These mechanisms in the body are essential because unwanted clots can travel to smaller vessels, become lodged, and cause subsequent ischemia and tissue damage/death. However, if the endothelium is damaged, the anticoagulant properties of the endothelium are lost and a clot will result. The farther away you get from the damage and clot that is forming around a lesion, the healthier you will find the endothelium to be due to its intrinsic anticoagulation properties that prevent unwanted clot formation in the vasculature.