PLATELETS AND COAGULATION

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Following are some of the terms related to platelets coagulation. By the end of the lecture these terms will be clear to us.

1. Primary platelet plug
2. Coagulation
3. Platelet Adhesion
4. Platelet Activation
5. Platelet Aggregation
6. Secondary platelet/Hemostatic plug
7. Clot
8. Thrombus
9. Embolus

COAGULATION

Coagulation is a process by which soluble fibrinogen converts into insoluble fibrin.

Coagulation is a property of plasma.

PLATELETS

Platelets are membrane-bound cytoplasmic cells, without any nucleus.

Size of platelets → 2-3 microns

Life span of platelets → 8-10 days

WHY AND HOW OUR BLOOD IS KEPT IN FLUID FORM IN HEALTHY CVS?

Healthy blood's fluidity is maintained by certain factors which does not allow the platelets to aggregate. In the absence of platelet aggregation, no clots form and blood remains in fluid state.

Healthy endothelial cells produce certain products such as **nitric oxide (NO), prostacyclin (PGI_2) and ADP de-phosphatases**. These products are said to be **anti-platelet aggregating**

agents and do not allow the platelets to attach to the endothelial cells. PGI_2 are not only anti-platelet aggregators but also vasodilators. Factors due which blood is kept in liquid form are:

1. For a platelet to stick to endothelium, platelet receptors needs to be activated. **Nitric oxide and PGI_2** bind with platelets and inactivate platelet-receptors due to which the platelets cannot bind with endothelium.
2. ADP favors attachment of platelet to endothelium and as **ADP de-phosphatase** breaks down ADP, these platelets cannot attach to endothelium.
   Platelets love to bind with extra-cellular matrix which is beneath the endothelium and hence the endothelium serves as a biological partitian between platelets and extra-cellular matrix.
3. Healthy endothelium not only keep the platelets inactivated but also keeps the coagulation system under check. Healthy endothelium does not allow activated coagulated proteins to accumulate.
4. Healthy endothelial cells express proteins called **heparin sulfate**. **Anti-thrombin III,** a molecule produced by liver, sticks to the surface of heparin sulfate and becomes activated. Anti-thrombin III cuts down **thrombin** molecule. Anti-thrombin III can also inactivate activated-factor X and activated factor IX.
5. Endothelial cells also express **thrombomodulin,** which modulate the function of **thrombin**. Normally thrombin helps in coagulation. Once thrombomodulin binds to thrombin, thrombin activates **protein-C**, which digests activated factor V and VIII.
6. Healthy endothelium produce **tissue plasminogen activator.** It can convert **plasminogen** (coming from liver) into plasmin. **Plasmin** degrades fibrin, thereby inhibiting coagulation.

ENDOTHELIAL CELLS INJURING

Endothelial cells may be injured by:

1. Trauma
2. Radiations
3. Microbes
4. Drugs
5. Thermal injury
6. Cytokines
7. Antigen-antibody complexes, etc.

HOW INJURED ENDOTHELIAL CELLS BEHAVE?

If endothelial cells are significantly injured, then blood may leak out i.e. bleeding occurs. To prevent the undue bleeding, hemostasis process begins. The following initial processes takes place:

1. **Vasoconstriction**: The vascular constriction is an early response but for a short time. From surrounding nerve cells, vasoconstrictors are released and this is called neurogenic reflex vasoconstriction.
2. **Myogenic constriction** i.e. smooth muscle contraction takes place. Injured endothelial cells produce vasoconstrictors called endothelin. Endothelin acts on smooth muscles and contract them.
3. **Platelet Adhesion**: Injured endothelial cells produce **Von Willebrand factor** which attached to exposed collagen (since endothelial cells are damaged). Platelets get attached with Von Willebrand factor through special glycoprotein receptors named **gp-1b**. this process of adherence of platelets to the injured endothelium is called platelet adhesion.
4. **Platelet Activation**: As soon as platelets adhers, platelet activation takes place. The gp-1b signals the platelet to activate **phospholipase enzymes** in the platelet membrane. These phospholipases breaks down phospholipids into arachidonic acid and some of arachidonic acid will break down into thromboxin A_2. **Thromboxin A_2** is a vasoconstrictor as well as platelet-aggregator.
   Healthy endothelial cells produce PGI2 while activated platelet produce thromboxin A_2, both of which has opposite functions to each other.
   (FIY: Aspirin i.e. salicylic acid inhibits cyclo-oxygenase which is an enzyme that converts arachidonic acid into thromboxin A_2. Hence due to aspirin, thromboxin A_2 decrease, thereby decreasing platelet aggregation)
5. **Release of Platelet Granules** : When Von Willebrand factor activated platelet receptors, gp-1b. These receptors signals the platelets to move their granules towards the surface and start releasing their products.
   There are two granules in platelets
   a. Alpha Granules
   b. Dense Granules/ Delta Granules

   DELTA GRANULES :
   Delta granules release (mnemonic is SAC)
   1. SEROTONIN induce vasoconstriction.
   2. ADP is a platelet-activating chemical substance thereby activating nearby platelets.

3. CALCIUM – calcium ions are responsible for complete activation of several coagulation factors.

ALPHA GRANULES:

1. Coagulation factors
2. Fibrinogen
3. Platelet-derived growth factors : These growth factors leads to mitosis of smooth muscles and these growth factors attracts fibroblasts so multiplication of fibroblast takes place and collagen is produced, thereby healing the injured epithelium.

6. **Platelet Aggregation** : When platelets stick to each other, it is called platelet aggregation.
7. **Primary Hemostatic Plug:** The initial platelet plug is called primary hemostatic plug. Platelet surfaces start to express platelet factors which favor the coagulation process. The primary platelet plug, also known as hemostatic plug or platelet thrombus, is an aggregation of platelets formed during early stages of hemostasis in response to blood vessel wall injury. This plug closes off the opening formed due to rupture of blood vessel wall.
8. **Secondary platelet plug**: On primary platelet plug, a network of fibrin attaches and this tight plug with fibrin strings is called secondary platelet plug.

HOW FIBRINOGEN IS CONVERTED INTO FIBRIN STRANDS ON THE SURFACE OF PLATELET PLUG?

There are two pathways for coagulation:

1. Intrinsic pathway
2. Extrinsic pathway

Both intrinsic and extrinsic pathway convert soluble fibrinogen into insoluble fibrin.

INTRINSIC PATHWAY

Liver releases a lot of coagulation factors into blood. These coagulation factors move to the site where platelets are to be activated. First, factor XII is activated.

Activated Factor XII activates factor XI.

Activated Factor XI activates factor IX.

Activated Factor IX in presence of calcium, phospholipid and Factor VIII activates factor X.

Activated factor X acts on pro-thrombin and converts it into **thrombin**. This thrombin will convert **fibrinogen** into **fibrin** monomers. A lot of fibrin monomers get deposited on surface of platelets.

Meanwhile, thrombin also activates **fibrin stabilizing factor** (also called factor XIII). Factor XIII is an enzyme which produce cross linking of fibrin monomers. So a network of fibrins appear within the platelet plug and above the platelet plug. This platelet plug is now called secondary platelet plug. The secondary platelet strongly seals the injured epithelium.

EXTRINSIC PATHWAY

From injured area, tissue factors are produced which activate factor VII. An activated factor VII can perform two functions:

1. Can activate factor IX
2. Can activate factor X

Extrinsic pathway is a shorter/faster pathway than intrinsic pathway.

HOW FACTOR IX ACTIVATES FACTOR X?

Both factor IX and X should be sticking to phospholipids of platelets. Coagulation factors have negatively charged areas. Calcium reacts with these areas and fix the coagulation factors on phospholipid surface.

Calcium also helps two coagulation factors to stick with each other at **gamma-carboxylated glutamic acids**. Calcium interacts with negative carboxylate of both factors and attach the two factors together. Hence factor IX can now activate factor X.

Gamma-carboxylation of glutamic acid depends on vitamin K. In deficiency of **Vitamin K**, glutamic acid is not carboxylated and hence coagulation system cannot work.

THROMBUS

If secondary platelet plug is quite big and present in circulation, it is called thrombus.
A thrombus is a blood clot that forms in a vessel and remains there.

OCCLUSIVE THROMBUS

Sometimes a thrombus may completely block a blood vessel. The blood flow may be completely cut off which results in death of tissue supplied by that vessel. Such a thrombus is called occlusive thrombus.

EMBOLUS

An embolism is a clot that travels from the site where it formed to another location in the body.