Hematology

Medical Committee
The University of Jorda

- Histology
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- Dr. name : Saleem khreisha
- lecture number : 6
- Done BY : Noor Hammad

By: Amer ABU Shanab

Haemostasis

- This sheet includes
- ✓ 1- Two pathways of coagulation
- ✓ 2- CALCIUM ROLE IN HEMOSTASIS:
- ✓ 3-Normal fluidity of the blood
- ✓ 4- Clot retraction

In the last lecture, we talk about haemostasis (hemostasis), which is a process which causes **bleeding to stop** and In hemostasis , 3 reactions take place to prevent the blood loss.

- Vasoconstriction of blood vessel as well as neighboring endothelial cells.
- Platelet plug formation .
- Coagulation , clotting.

The coagulation cascade of hemostasis has **two initial pathways** and a common pathway which lead to **fibrin formation**.

Initial pathways are

1) Intrinsic
2) Extrinsic

#Additional points on the clotting system

- Both intrinsic and extrinsic pathways are necessary for normal hemostasis.
- Both pathways are activated when blood leaves the blood vessels for the tissues.
- Thrombin is a key factor in both the intrinsic and extrinsic systems, in a addition to its action on fibrinogen.
- The activation of the clotting mechanism along the shorter extrinsic pathway results in the rapid formation of thrombin. which feeds back to activate the intrinsic pathway through factors VII and V. Factor VII can activate factor X to active factor X, and !his forms an activation connection between both pathways.

Written by Noor Hamad

- Thrombin stimulates platelets to release ADP and TXA^2 and therefore enhances further aggregation of platelets.
- Thrombin is essential for platelet morphological changes during haemostasis, which lead to the formation of the primary haemostatic plug.

➢ INTRINSIC PATHWAY :

✓ Intrinsic; means that all the component are present in blood .

✓ This pathway is

- slow and weak (need minutes).
- long lasting and more important.

➢ steps of intrinsic pathway

- 1-Intrinsic pathway; begins with the exposure of **factor XII** (one of the coagulating factor in the blood) to negatively charged surface (contact with collagen fibers which are exposed after endothelial damage) and it's activated .

- 2-Activated factor XII along with two other factors ; HMW-K (**h**igh **m**olecular **w**eight –**k**ininogen) and Prekallikrein , play role in activation of factor XI

✓ Role of HMW –K ;
Is to bind prekallikerin and factor XI to keep them close to factor XII (keep them close to the surface of the injury .

✓ The deficiency of these 3 factors (factor XII+ HMW-K+ Prekallikrein) don't produce serious problems , because platelets are able to activate factor XI **DIRECTLY** without them.

✓ The deficiency of factor XI does produce serious problem.

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- 3. Activated Factor XI activates Factor IX in the presence of calcium.
- 4. Activated factor IX + Factor VIII + phospholipids + Calcium form a complex (The dr said that this complex will produce an enzyme that is responsible for activating factor X but we couldn't hear it) that activates factor X

Summary:

- Factor 12(XII) ……>factor 11(XI)… …..>factor9 (IX)… ……>factor 10(X)

  #Note→ Roman Numerals :
  1; I \ 2 ; II\3; III\4 ; IV\5 ; V
  6 ; VI\7; VII\8 ; **VIII**\9 ; **IX**
  10 ; **X** \11 ;**XI**\12; **XII**\13; XIII\14; XIV\15; XV

EXTRINSIC PATHWAY;

This pathway is

- ✓ **very fast and powerful**
- ✓ **occurs post to the tissue damage (occur within seconds)**
  - ➢ **steps of this pathway are:**

1. begins with the production of tissue factor (thromboplastin) , after the injury .

2. Tissue thromboplastin + factor VII + Calcium form a complex that activates factor X.

- We notice that, intrinsic and extrinsic pathways activate factor **X(10)** which starts the common pathway.

- Common pathway after factor X activation;

  - 1-Activated factor X + factor (V) + calcium + phospholipids ……form a complex called thrombokinase Which catalyzes the conversion of prothrombin to thrombin .
  - ThromboKinase complex = { act.factor10 + act.factor5 + PL + Ca }

  - .2-Thrombin converts fibrinogen to form fibrin

  - .3-Fibrin polymer is **insoluble** and **unstable**, need to be stabilized by the activation of factor XIII in the presence of thrombin and calcium.

  - 4- .At the end **insoluble stable** fibrin is produced

➢ CALCIUM ROLE IN HEMOSTASIS:

✓ Calcium is present in all steps of blood coagulation except the first 2 steps of the intrinsic pathway.

✓ if we remove calcium from the blood , blood don't coagulate.

✓ Calcium functions in the platelets :

- .1phospholipase activation

- 2 Activate secretion of granules
- 3. Contraction of Actomyosin (actin & myosin filaments).

❖ -Blood neither clots nor bleeds → Blood circulates normally (It has a Normal Fluidity)

-Factors that cause the normal fluidity of the blood:

A) Anti-coagulation system

B) Fibrinolytic system

➢Anti-coagulation system

- 1-Heparin from basophiles and mast cells. (Anticoagulant)

- 2-Clotting factors, mainly prothrombin and fibrinogen: present in the blood in **the inactive** form and during the circulation, they are removed (some of them) by the liver.

- 3-In everybody there are **minor clottings** that occur **normally** and dissolve **immediately**. From this process there are 2 advantages;
  - ✓ First, the clotting factors are used up in these minor clotting are reduced.
  - ✓ Second, the end products of degradation of the minor clottings (fibrin/ fibrinogen degradation products) function as Anti-coagulants.

- 4-The lining of the blood vessels are very smooth and not sticky to the platelets, also it's negatively charged & so repels the platelets.

- 5-There is a protein (anti-coagulant) in blood called **ANTI-THROMBIN III**, it inhibits the action of thrombin as well as factors it inhibits IX, X, XI , and XII.
- 6-Negative feedback of thrombin

  ✓ Thrombin bound to thrombomodulin activates **protein C**(an inhibitor of the coagulation cascade)
  ✓ . The activation of protein C is greatly enhanced following the binding of thrombin to thrombomodulin(an integral membrane protein expressed by endothelial cells)
  ✓ . Activated protein C **INACTIVATES** factors **V** and **VIII**.
  ✓ Binding of activated protein C to protein S leads to a modest increase in its activity. (both are vitamin K dependant)

(**Thrombomodulin binds to thrombin to activate protein C, and protein C doesn't function unless there is protein S (prot. S is a cofactor for prot. C), this complex functions as an anti-coagulant; inactivates factor V in the presence of Ca as well as factor VIII**.)

Note:

Thrombin functions;

1. Activation of factor VIII , V, XIII, and fibrinogen.
2. Activation of platelets.
3. Activation of protein C; play role in anticoagulation processes.

- 7-Two other proteins **α2-macroglubulin** and **α1-antitrypsin** contribute to the **anti-thrombin** effect of the plasma.

- If all these factors don't function, then fibrinolytic system begins.

➢ Fibrinolytic system

- Fibrinolytic system is a **physiological response** to the vascular injury.

- We mentioned that **factor XII** activates the intrinsic pathway of coagulation as well as the fibrinolytic system, and also it produces Bradykinin vasodilator

- Factor 12 (XII) activates the intrinsic pathway and fibrinolytic system→ this means that there is a balance between coagulation and fibrinolysis (dissolving the coagulation).

➢ **Fibrinolysis means**

✓ A fibrin clot, the product of coagulation, is broken down.Its main enzyme **plasmin** cuts the fibrin mesh at various places

✓ Plasmin is produced in an inactive form, plasminogen, in the liver

✓ There are plasminogen activators:

- **#Endogenous** →tissue plasminogen activators and contact phase (intrinsic pathway) of coagulation

- **#Exogenous** →urokinase (this enzyme is present in the plasma) and streptokinase (from streptococcus) >>> this (streptokinase) is called { The LIFE INJECTION } which immediately dissolves the thrombus.
- →These activators produce Plasmin <<>> Also note that there is α2-antiplasmin, so there is balance in the fibrinolytic system too.

- -PLASMIN lyses the fibrinogen, fibrin, factors V & VIII >> formation of fibrin/ fibrinogen degradation products will take place which in turn inhibits fibrin threads formation + platelet aggregation.
- When plasmin breaks down fibrin, a number of soluble parts are produced. These are called fibrin degradation products (FDPs). FDPs compete with thrombin, and thus slow down clot formation by preventing the conversion of fibrinogen to fibrin

➢ **NOTE**: in both systems, we need to inhibit factor V and factor VIII

Clot retraction

➢ **Is the "shrinking" of a blood clot over a number of days. In so doing, the edges of the blood vessel wall at the point of injury are slowly brought together again to repair the damage.**

➢ **Following coagulation, platelet contractile force on the fibrin network will compact on itself and hence reduce its total volume. The mechanism is termed clot retraction, and it is considered that its main physiological function is to clear the obstructed vessel for renewed blood flow**

- If the blood is left in the lab in tubes→ clot retraction will happen
- There's partial retraction that occurs either because of time or abnormality in the blood
- Clot retraction time: measures the ability of the blood clot to retract, it takes **1-2 hours** to have a partial clot retraction, whereas to have a complete clot retraction, the time needed (**24hours**).

- Blood without platelets can clot but clots weakly(weak coagulation) ;and that's because there are coagulation factors in the blood.

➢ #Two major factors (there are other factors) play a role in clot retraction:

- .1Platelets
- .2Calcium

➢ In thrombocytopenia, the clot retraction is deficient because platelets # is low.so clot retraction time will increase

General notes

✓ Sometimes, unwanted clots are formed in the blood vessels & they don't move forming→ **Thrombus.**

✓ This thrombus is either dissolved or sometimes under the effects of the circulation, it's pushed & removed from its attachment and circulates in the blood vessels.

❖ The circulating clot is called an **Embolus**.

❖ The embolus reaches narrow areas & if this embolus reached the heart or the brain, then this is a serious condition.

❖ Most heart attacks are caused by either:

- **Atherosclerosis:** the **accumulation** of lipids inside the blood vessels, so become relatively narrow.

- **Arteriosclerosis**: **losing the flexibility** of the arteries especially in old age, BUT if it happens during adulthood, there will be a disease, whereas in old age, it's considered to be normal to some extent to have arteriosclerosis, BUT still, it depends on the degree, if arteriosclerosis is too much even in old age, then for sure, there's a high risk for death.

#Probable Causes of thrombosis in humans :

1-injury to blood vessels→activation of intrinsic and extrinsic pathways of coagulation. In the extrinsic pathway , thromboplastin is needed, there is an inflammation (because of injury)and this will tract monocytes, which will produce thromboplastin .

2-infection, Cellulitis (bacterial infection involving the inner layers of the skin),infection in blood vessels.

3-Slowing of the blood stream after childbirth which result in platelet deposition .

*People are advised to walk in this case otherwise heparin is injected .

4-changes in the blood composition.