HEMOSTASIS AND BLOOD COAGULATION

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Q1: Explain extrinsic pathway.

ANSWER:

- Traumatized tissue release tissue factor(or tissue thromboplastin).
  Tissue factor composition:
  1. Phospholipid from membranes of tissue
  2. Lipoprotein complex that functions as proteolytic enzyme
- Liporotein complex + Factor VII + Ca^{+2} ions together activate Factor X
- Factor X_a + Phospholipids + Factor V form a complex called prothrombin activator
- Prothrombin activator converts prothrombin into thrombin in presence of Ca^{+2} ions.

Q2: Explain intrinsic pathway.

ANSWER:

- Blood trauma or contact of blood with collagen cause:
  1. Activation of Factor XII
  2. Release of platelet phospholipids
- Factor XII_a activates Factor XI
- Factor XI_a activates Factor IX
- Factor IX_a + Factor VIII + Platelet phospholipids + Factor III activates Factor X
- Factor X_a + Factor V + phospholipids form a complex called prothrombin activator
- Prothrombin Activators actiates cleavage of prothrombin into thrombin

Q3: How to prevent blood from clotting outside the body?

ANSWER:

1. Use of siliconized container
2. Heparin
3. By reducing calcium ion concentration
   a. By deionizing the calcium by causing it to react with citrate ion
   b. By precipitating the calcium with oxalate ion.

Q4: How blood is prevented from clotting in normal vascular system?

ANSWER: Factors for preventing blood from clotting in normal vascular system are:

1. The smoothness of endothelial cell surface
2. A layer of glycocalyx on endothelial cells
3. Thrombomodulin bound with endothelial cells. This thrombomodulin binds thrombin.
4. The thrombomodulin-thrombin complex activates a plasma protein, protein C, that acts as an anticoagulant by inactivating activated factors V and VIII
5. Prostacyclin (also called prostaglandin I_2 PGI_2), produced by endothelial cells. PGI_2 is a vasodilator as well inhibitor of platelet aggregation.
6. Production of NO by healthy endothelial cells

Q5: Which vitamin is good for blood clotting?

Answer: Vitamin K, as it is required by the liver for normal activation of prothrombin, as well as few other clotting factors.

Q6: How excessive spread of blood clot is prevented?

Answer: Anticoagulants that help remove thrombin from blood are:

1. Fibrin fibers – thrombin becomes adsorbed to fibrin fibers hence excessive spread of clot is prevented
2. Antithrombin III – inactivates thrombin
3. Heparin –a powerful anticoagulant when combined with antithrombin III

Q7: How blood clots are removed?

Answer: Blood clots are removed by the action of plasmin. Plasmin, activated form of plasminogen, digests fibrin fibers and some other protein coagulants such as fibrinogen, factor V, factor VIII, prothrombin and factor XII.

Q8: What conditions cause excessive bleeding in humans?

Answer:

1. Liver diseases such as hepatitis, cirrhosis, acute yellow atrophy
2. Vitamin K deficiency
3. Hemophilia
4. Thrombocytopenia (Platelet deficiency)

Q10: What are the causes of thromboembolic conditions?

ANSWER:

1. Roughened endothelial surface of a vessel
2. Slow movement of blood in blood vessels

POINTS FOR BLOOD MODULE

- The normal range of RBC count in men is 4.7 – 6.1 million RBCs per mm^3
  The normal range of RBC count in women is 4.2 – 5.4 million RBCs per mm^3
  People who reside at higher altitudes generally have a greater number of RBCs
- RBCs are produced from yolksac, liver, spleen, and lymph nodes throughout gestation.

The yolksac is the primary organ of RBC production during early weeks of gestation.
The majority of RBCs arise from liver during third trimester of gestation.
RBCs are produced by the bone marrow of all bones up until the age of 5 years.
After age 5, RBCs are only produced in the marrow of long bones and membranous bones up until the age of 20 years.
Beyond the age of 20 years, the bone marrow of long bones (except for the proximal portions of humerus and tibia) becomes fatty and stops producing RBCs. Hence, after the age of 20, RBCs are produced only in the bone marrow of membranous bones which include the vertebrae, sternum, ribs, and hip bones.

- Maturation failure in RBCs is caused by deficiency of Vitamin B12 or folic acid. If there is a lack or lesser amount of either vitamin, DNA synthesis is irregular or diminished. This condition clinically presents as reticulocytopenia (abnormal decrease in number of reticulocytes)
- Prothrombin is formed continuously by the liver. In case of the liver failing to produce prothrombin, the plasma prothrombin concentration falls too low to provide normal blood coagulation. Hence, it takes longer time for blood clotting, which means the prothrombin plasma concentration time is increased.
  Vitamin K is required by the liver for normal activation of prothrombin. Vitamin K deficiency causes bleeding due to a shortage in the production of clotting factors.
- Each gram of Hb can combine with 1.34 ml of oxygen if Hb is 100% saturated.
  In an average man, a maximum of about 20 ml of oxygen can be carried by Hb in each 100ml of blood, and in women 19 ml of oxygen can be carried.
- Interleukin-3 promotes growth and reproduction of virtually all different types of committed stem cells
- **Pernicious Anemia** is a rare blood disorder characterized by the inability of the body to properly utilize Vitamin B_{12}. Most causes result from the lack of gastric protein known as intrinsic factor, without which Vitamin B_{12} cannot be absorbed.
- Blood loss anemia i.e. after rapid hemorrhage – Microcytic hypochromic anemia
- Aplastic anemia due to bone marrow dysfunction
- Loss of Vitamin B12, Folic acid or intrinsic factor leads to megaloblastic anemia
- Cytoplasm of platelets have:
  - Actin and myosin molecules
  - Thrombosthenin
  - Calcium ions
  - Mitochondria and enzyme systems for forming ATP and ADP
  - Prostaglandins
  - Fibrin – stabilizing factor
  - Growth gactor
- The thrombin acts as enzymes to convert fibrinogen into fibrin fibers
- Prothrombin activator can be formed by extrinsic or intrinsic pathway
- Plasmin digests fibrin fibers and some other protein coagulants, such as fibrinogen, factor V, factor VIII, prothrombin and factor XII
- **Hemophilia A** or classic hemophilia (85%) – caused by abnormality or deficiency of Factor VIII
  Hemophilia B – caused by deficiency of Factor IX
- **Mechanism of Hemostasis**:

1. Constriction of blood vessel
2. Formation of a temporary platelet plug
3. Activation of coagulation cascade
4. Formation or fibrin plug or the final clot

- Normal percentages of different types of WBCs

Neutrophils	62%
Lymphocytes	30%
Monocytes	5.3%
Eosinophils	2.3%
Basophils	0.4%

- Life span of blood cells in blood:

RBCs	120 days
Granulocytes	4 – 8 hours
Monocytes	10 – 20 hours
Platelets	10 days

- Normal values:
  - PCV (Hematocrit) – 45%
  - Red cell count in 1 ml of blood – 5 million
  - Hb Concentration – 15% of total volume
    15 g in 100 ml
    33% in one RBC (one-third of RBC)
  - MCV (volume occupied by one RBC) = 90 ± 10 fl
  - MCH (Hb present in single RBC) = 30 pg
  - MCHC (concentration of Hb in PCV) – 33%
- **Hemoglobin Formation:**
  - Succinyl Co-A + Glycine → Pyrrole
  - Four Pyrrole → Porphyrin ring
  - Porphyrin ring + Iron → Heme
  - Heme + Globin → Hb Chain
  - Four Hb Chains → Hb molecule
- Total Iron = 4 -5 g
  - Hemoglobin – 65%
  - Stored as Ferritin – 15 – 30%
  - Myoglobin – 4%
  - Other heme compounds – 1%
  - Combined with protein transferrin in blood plasma – 0.1%
- The extrinsic pathway is activated by external trauma that causes blood to excape from the vascular system and ensues after tissue thromboplastic activates Factor VII
  The intrinsic pathway is activated by trauma inside the vascular system by platelets, exposed endothelium, collagen, or chemicals. This pathway ensues after activation of Factor XII.
- Types of Hb:
  - **HbA**: two alpha-globin chains and two beta-globin chains
  - **HbF:** two alpha-globin chains and two gamma-globin chains
  - **HbA2**: two alpha-globin chains and two delta-globin chains

- **HbA1c**: two alpha-globin chains and two beta-globin chains with glucose

- **C3b** is primarily responsible for opsonization of bacteria.
- Helper T-cells are divided into T_{H1} and T_{H2} cells that are responsible for secreting lymphokines called interleukins.
- **C5b6789** complex functions as a membrane attack complex (MAC) causing lysis of gram-negative bacteria, human cells displaying foreign epitopes, and viral envelopes.
- B lymphocytes are known to be pre-processed in the liver during midfetal life and in the bone marrow during late fetal life and after birth.
- RBCs, most WBCs and platelets are produced in the bone marrow.
  Two types of WBCs i.e. B cells and T cells (lymphocytes) are also produced in lymph nodes and spleen, in addition to being produced in bone marrow.
  T cells mature in thymus gland.
- Human endothelial cells synthesize, store and secrete von Willebrand factor and coagulation factor VIII.
- The most potent stimulator of erythropoietin is hypoxia i.e. lack of oxygen
- Eosinophils respond in allergic reaction and parasitic invasion
- Basophils are responsible for allergic reactions. They release histamine which causes vasodilation. Basophils contain anticoagulant heparin which prevents blood from clotting too quickly.
- IgM is the major class of antibodies secreted into the blood in the early stages of a primary antibody response, on first exposure to an antigen.
- **Margination** is the accumulation and adhesion of leukocytes to the epithelial cells of blood vessel walls at the site of injury in the early stages of inflammation.
- Hookworm infection is an infection of the intestines that can cause an itchy rash, respiratory and GIT problems and eventually **iron deficiency anemia** and **microcytic hypochromic anemia** due to ongoing loss of blood.
- The most common cause of hypochromic microcytic anemia is an iron deficiency in the blood.
- **Hyperchromic microcytic anemias** are rare. They may be caused by genetic condition known as congenital spherocytic anemia. This is also called hereditary spherocytosis.
- **Hypochromic anemia** may be caused by Vitamin B6 deficiency from a lower iron intake, diminished iron absorption, or excessive iron loss. It can also be caused by hookworm infections, therapeutic drugs, copper toxicity, and lead poisoning.
- Heparin has little or no anticoagulant properties. But when combined with antithrombin III, the effectiveness of antithrombin III for removing thrombin increases a hundredfold.
  Heparin is normally in low concentrations in the blood.
  Thrombin removal from the circulation is instantaneous when excess heparin is present.
  Heparin is produced by many cells with the largest quantities formed by basophilic mast cells.
- CLOTTING FACTORS

Factor I	Fibrinogen
Factor II	Prothrombin
Factor III	Tissue Thromboplastin
Factor IV	Calcium ions
Factor V	Labile factor
Factor VII	Stable Factor

Factor VIII	Antihemophilic Factor
Factor IX	Christmas Factor, or plasma thromboplastin component
Factor X	Stuart-Prower Factor
Factor XI	Plasma thromboplastin Antecedent (PTA)
Factor XII	Hageman Factor
Factor XIII	Fibrin Stabilizing Factor

- Primary immunoglobulin of the newborn is the maternal IgG as this is the only immunoglobulin to cross the placental barrier.
  On the other hand, IgM is synthesized by the newborn in the early postnatal period, followed by IgA and IgG
- Vitamin K dependent coagulation factors are Factor II, VII, IX, X
- Gamma-globulins are formed in lymph nodes and in the cytoplasm of plasma cells
- Complement C5a is the most potent plasma-derived chemotactic factor
- Microcytic anemia is a common feature of thalassemia
- The classical complement pathway typically requires antigen-antibody complexes for activation whereas the alternative pathway can be activated by C3 hydrolysis, foreign materials, pathogens or damaged cells.
- The complement component activated by both pathways is C3.
- **Opsonins** are extracellular proteins, that when bound to substances or cells, induce phagocytes to phagocytose the substances or cells with the opsonins bound. Thus, opsonins acts as tags to label things in the body that should be phagocytosed by phagocytes.
- **Type I Hypersensitivity** (or immediate hypersensitivity) is an allergic reaction provoked by re-exposure to a specific type of antigen referred to as an allergen e.g. anaphylaxis, allergic asthma, allergic conjunctivitis, allergic rhinitis (hay fever) etc.
  Type II Hypersensitivity is antibody-mediated, and also known as cytotoxic hypersensitivity due to complement activation and activation of membrane attack complexes e.g. rheumatic fever, hemolytic anemias, thrombocytopenia, autoimmune diseases, transfusion reactions due to mismatched blood types
  Type III Hypersensitivity occurs when there is accumulation of immune complexes (antigen-antibody complexes) that have not been adequately cleared by innate immune cells, giving rise to an inflammatory response and attraction of leukocytes. Such reactions may progress to immune complex diseases e.g. systemic lupus erythematosus.
  Type IV Hypersensitivity reaction occurs from a transplant or skin graft rejection.