

Chapter 19b
Blood, cont'd

White Blood Cells

WBCs account for less than 1% of blood volume. There are two major histological categories of WBCs...the granulocytes and the agranulocytes.

GRANULOCYTES are Basophils, Eosinophils and Neutrophils (BEN)

- **Basophils** account for less than 1% of the WBCs, and they take up basic dye...you see mostly the granules on the histology slide. Basophils release HISTAMINE, so they are part of the allergy response. Basophils circulate around, and their buddies, the Mast Cells are in tissues. An example of a Mast Cell is a Langerhans cell.
- **Eosinophils** account for 2-4% of WBCs and they take up acidic dye (granules show up red.) They have a bi-lobed nucleus that pretty much looks like two nuclei, or an alien face. These cells are phagocytic, but don't kill their prey by phagocytosis. They use phagocytosis to clear up cellular debris, but for dealing with pathogens they attack it as a group and release their deadly enzymes. Eosinophils are high in response to PARASITE INFECTION!
- **Neutrophils** account for the majority of WBCs...50-70%. They do not take up dyes! They are going to be present when you have a BACTERIAL INFECTION. Though they are smaller than the macrophages, there are so many of them that they can get the job done. They are also phagocytic, and they contain lysosomal enzymes as well as bactericides.

AGRANULOCYTES are Lymphocytes and Monocytes

- **Lymphocytes** are rather small compared to other leukocytes, but they have a huge round nucleus and you can't see much of the cytoplasm. They mostly live in lymphatic tissues, and there are three types:
 - **B-Lymphocytes (B-cells)**
 - **T-Lymphocytes (T-cells)**
 - **NK Cells (macrophages)**

} Specific immune response
} Nonspecific immune response
- **Monocytes** have a large heart-shaped nucleus. These cells circulate temporarily but eventually enter tissues as MACROPHAGES. They are phagocytic!

Specific and non-specific (general) immunity

General immunity: Granulocytes (Basophils, Neutrophils and Acidophils)
Monocytes

An example of general immunity is inflammation. It occurs the same way for every injury, no matter where it is or how severe it is. The secretion of histamine causes inflammation...the basophils and mast cells secrete histamine!

Specific immunity: T-lymphocytes (cell-mediated immunity)
B-lymphocytes (humoral immunity)

The T-cells are involved in cell-mediated immunity, meaning they get involved in hand-to-hand combat with the pathogens. They come directly into contact with the invading cells and destroy them!

The B-cells are involved in humoral immunity, which means they secrete antibodies (immunoglobulins) to do the dirty work for them. The antibodies then attack!

Unique characteristics of WBCs (leukocytes)

- WBCs are true cells. They have a nucleus and can divide/repair
- Most WBCs are phagocytic
- Large populations of WBCs are found in CT proper and lymphatic tissues
- They are the only blood cells that can leave circulation and enter tissues through a process called diapedesis
- They are called to action via chemotaxis...attraction to specific chemical stimuli

Production of WBCs

All blood cells start with the stem cell which is the HEMOCYTOBLAST. It then branches to the two less-specialized stem cells...the MYELOID stem cell produces the granulocytes and the monocytes. The LYMPHOID stem cell produces lymphocytes.

The committed cell for each cell type is:

- MYELOBLAST produces eosinophils
- MYELOBLAST produces neutrophils
- MYELOBLAST produces basophils
- MONOBLAST produces monocytes
- LYMPHOBLAST produces lymphocytes

Chemical messengers known as CSF (colony stimulating factors) tell the developing cells what kind of cell to specify.

- EPO tells the progenitor cell to make erythroblasts.
- EPO tells the blast cell to make erythroblasts
- GMCSF tells the progenitor cell to make granulocytes and monocytes
- GCSF tells the blast cell to make granulocytes
- MCSF tells the blast cell to make monocytes

So, the pathway for the production of blood cells for each of the cell types is as follows:

Pluripotent Stem Cell	Stem Cell	Committed Cell	Produces	Process
Hemocytoblast	Myeloid S.C.	Proerythroblast	Erythrocyte	Erythropoiesis
Hemocytoblast	Myeloid S.C.	Myeloblast	Basophil	Leukopoiesis
Hemocytoblast	Myeloid S.C.	Myeloblast	Eisonophil	Leukopoiesis
Hemocytoblast	Myeloid S.C.	Myeloblast	Neutrophil	Leukopoiesis
Hemocytoblast	Myeloid S. C.	Monoblast	Monocyte	Leukopoiesis
Hemocytoblast	Lymphoid S.C.	Lymphoblast	Lymphocyte	Leukopoiesis
Hemocytoblast	Myeloid S.C.	Megakaryoblast	Platelet	Thrombocytopoiesis

We can also make a synthetic GCSF (filgrastin or Neupogen). It is used by cancer patients to help them develop more neutrophils to support the immune system during chemotherapy. Recall that neutrophils are the major phagocyte in circulation.

WBC disorders:

- Leukopenia = not enough WBCs (results from chemotherapy)
- Leukocytosis = too many WBCs...can be because you are fighting an infection, or because of cancer causing the abnormal production of WBCs.

Production of Platelets (thrombocytopoiesis)

The production of platelets begins with the HEMOCYTOBLAST, and the committed cell is the MEGAKARYOBLAST. It then becomes a PROMEGAKARYOCYTES, but this is not a platelet yet! Next, it is a MEGAKARYOCYTE, which breaks off into pieces to become about 4,000 platelets. Platelets are “little pieces” of cells! These little pieces squeeze through capillary wall in the bone marrow to go out into circulation.

The **granules of platelets** are chemical messengers and enzymes that are involved in hemostasis...they create a plug until the tissue is fully repaired. They do this by facilitating clot formation and converting fibrinogen to fibrin. The chemical messenger for this pathway is thrombopoietin (TPO)...TPO stimulates the development of platelets.

Hemostasis

Hemostasis is the process of stopping bleeding! It consists of three general phases:

1. Vasoconstriction just upstream from the break. This is an immediate response that lasts about 30 minutes. Smooth muscles cells have a “vascular spasm” when they are damaged...this is another way of saying they undergo vasoconstriction. This constriction buys us time while we complete phase 2. Besides slowing the flow of blood, a few other things happen at this time:
 - a. The endothelial cells release their chemical messenger (endothelin) that reinforce the smooth muscle spasm and cause a proliferation of cells and fibers for tissue repair.
 - b. The endothelial cell membrane becomes sticky, which helps platelets plug adhere to the injury site
 - c. The basal lamina is exposed to blood flow
2. Platelet plug formation takes about 1 minute, but also starts immediately. In this stage the platelets adhere to the site of injury on exposed collagen fibers + basal lamina + sticky endothelial cells. This process is called “platelet aggregation” and it creates a platelet plug. Though not a great seal (it still needs the fibrin mesh), the platelets release:
 - a. Ca^{++} which promotes aggregation in a positive feedback loop
 - b. Serotonin which enhances vasoconstriction of the vessel
 - c. ADP which enhances aggregation and secretion, attracting more platelets. Also a positive feedback loop
 - d. Clotting factors, which enhance vessel repair
 - e. PDGF (platelet derived growth factor) that enhances vessel repair

- f. Thromboxane A₂, which stimulates aggregation and secretion as well as secretion...it is inhibited by aspirin (aspirin is an antiprostaglandin).

This plug formation is regulated locally by prostacyclin from the endothelial cells, which work as a negative feedback loop to prevent the clot from getting too big and encroaching on non-injured tissues.

3. Coagulation is a delayed response...delayed by about 30 seconds and takes about 5 minutes to complete. The reason it takes so long is that there are about 30 different clotting factors that all work in a complicated pathway to convert fibrinogen to fibrin. There are two components to the process...the extrinsic pathway (stimulated by trigger outside the blood) and the intrinsic pathway (stimulated by trigger in the blood), and they converge at Clotting Factor 10. From there, prothrombinase converts prothrombin to thrombin, and thrombin converts fibrinogen to fibrin. The final product in the coagulation phase is the fibrin mesh.

Procoagulants are things that promote clot formation. These factors include Ca²⁺ and various plasma proteins called proenzymes...these are activated in the chain reaction.

Anticoagulants are things that inhibit clot formation. These provide control in the form of negative feedback. Examples are heparin (from basophils and mast cells), Thrombomodulin (from endothelial cells) and Prostacyclin.

The EXTRINSIC PATHWAY is faster and originates from the vessel wall. The **INTRINSIC PATHWAY** is not as fast, but is more robust. Though clotting can be initiated by either one, they usually work together and converge at a common pathway. The end result of both of them working together is that once prothrombinase is produced, then clotting happens very fast...in about 10-15 seconds.

The prothrombinase pathway is: Prothrombinase stimulates the synthesis of prothrombin which leads to thrombin, which leads to fibrinogen becoming fibrin, which creates the fibrin mesh! Recall that Vitamin-K is needed for the synthesis of prothrombin, and that fibrinogen is the dissolved plasma protein.

Post Hemostasis is clot retraction and repair...this happens within 30-60 minutes. In this stage...

1. Contractile proteins within the platelets contract, which pulls the vessel edges closer together...this is called "clot retraction."
2. Endothelium and smooth muscle regenerate and repair. This is stimulated in part by platelet-derived growth factor (PDGF), which is one of the chemical messengers from the platelet granules
3. Once healed, fibrinolysis removes the temporary clot. This is mediated by the enzyme plasmin.

Disorders of Hemostasis

There are two major types of disorders of hemostasis...thromboembolytic disorders and bleeding disorders.

Thromboembolytic disorders have to do with inappropriate clot formation. When an abnormal clot forms on a vessel wall this is called a THROMBUS. If it breaks off and floats downstream it is called an EMBOLUS. When it lodges and blocks the blood flow causing all kinds of damage, this is called an EMBOLISM. Embolisms cause strokes and heart attacks.

Bleeding disorders have to do with abnormal bleeding due to the inability to form clots.

- Thrombocytopenia is a platelet deficiency. This is caused by damaged bone marrow which can't function properly.
- Insufficient procoagulants can also affect one's ability to make clots. This happens with liver disease/dysfunction and Vit-K deficiency. Recall that the liver produces most of the blood proteins, including fibrinogen. No fibrinogen is a very bad situation to be in.
- Hemophilias are genetic bleeding disorders that have similar signs and symptoms of the ones listed above. The individual is missing a clotting factor (it only takes one missing factor to screw up the pathway). Sometimes this factor can be given exogenously, or the person has to get frequent plasma/whole blood transfusions.

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