Lecture 1b: Hematopoiesis

Hematopoiesis: The process whereby the blood cell components [red blood cells (erythrocytes or RBCs), white blood cells (leukocytes or WBCs), and platelets (thrombocytes)] are produced in the body. Figure 1 shows that all the cell types originate from a common precursor (hematocytoblast). Consequently, the different cell types are produced down different paths and can be stimulated or inhibited differently. Figure 2 depicts the different shapes of RBC, platelets and WBCs. Per microliter of blood, humans normally have approximately 5 million RBCs, 150,000-400,000 platelets, and 4,000-11,000 WBCs. The lower levels of WBCs (compared to the other blood components) make them more vulnerable to depletion, especially in the setting of cancer chemotherapy.

Figure 1. General scheme for blood cell formation (hematopoiesis).
Figure 2. General appearance of a RBC, a platelet, and a WBC. The shape of RBCs optimizes flexibility while that of platelets optimizes clotting efficiency.

**RBCs (erythrocytes):** primarily for oxygen transport

RBC production can be stimulated by low oxygen content in blood which can be detected by the kidneys. In response, the kidneys secrete the protein erythropoietin (Epo) which specifically stimulates greater RBC production; more on recombinant Epo (e.g. Epoetin) later. Mature RBCs (erythrocytes) are much smaller than their parent cells and they contain no nucleus. However, RBCs are very rich in the oxygen carrier hemoglobin.

Interestingly, the marrow of essentially all the bones can perform erythropoieses until around the age of 5. The large leg bones (tibia and femur) contribute to erythropoieses until the mid 20s. Afterward, only the vertebrae, sternum, pelvis, ribs and cranial bones contribute. RBCs are estimated to have a life-span of about 120 days.

**Anemia:** the condition of abnormally low functional hemoglobin.

**Polycythemia:** the condition of abnormally high RBCs.

**WBCs (leukocytes or leucocytes):** primarily part of the immune system to fight infection and there are many subtypes. The life-span of WBCs ranges from hours to several days or a week.

- **Granulocytes** (polymorphonuclear leukocytes): have the appearance of granules in their cytoplasm upon staining. These granules are typically packets of membrane bound enzymes that act mainly to digest (lyze) foreign materials such as bacteria, fungi, parasites.

  There are three subtypes of granulocytes (named after their staining properties) which generally target different pathogens:

  - **Neutrophils:** typically target bacteria and fungi and destroy these pathogens by phagocytosis
  - **Eosinophils:** typically target parasites and involved in allergic inflammatory responses
  - **Basophils:** typically store histamine for release during inflammation response
Neutropenia: low levels of neutrophils.

Leukopenia (leucopenia): low levels of leukocytes

-Agranulocytes (morphonuclear leukocytes): appear not to have granules but still contain lysozomes which can lyze foreign materials.

Again, there are three subtypes of agranulocytes:

Lymphocytes: a large subset of cell types that includes B cells, T cells* (see below), and NK (natural killer) cells; they are actually more abundant in the lymphatic fluids than in blood.

Monocytes: can perform a similar role to neutrophils and capable of phagocytosis, but can also present pieces of pathogens to T cells to help them recognize the pathogens later and mount a more rapid immune response.

Macrophages: similar to monocytes and capable of phagocytosis; actually are monocytes that have migrated from the blood into tissue; they retain their immunity role in the tissues; monocytes that have migrated specifically into liver tissue are special macrophages called Kupffer cells.

*More on T cells:

- CD8+ (Cytotoxic T cells): attack virus infected cells and tumor cells
- CD4+ Th (T helper) cells: activate and regulate T and B cells
- γδ T cells: bridge between innate and adaptive immune responses; also phagocytosis
- Regulatory T cells (Trgs): returns the functioning of the immune system to normal operation after infection; prevents autoimmunity

Figure 3. Some mechanisms of communication between T cells and cancer cells.
A greater understanding of regulation of the immune system and how cancer cells can specifically take advantage of “negative” regulation of T cells has allowed the development of new immune-therapies. Two new therapies that do this are below:

**Ipilumumab (Yervoy):** an anti-CTLA4 monoclonal antibody that prevents interaction of B7 with CTLA4. Approved for metastatic melanoma.

**Pembrolizumab (Keytruda):** an anti-PD1 monoclonal antibody that prevents interaction of PD-L1 with PD-1. Received accelerated approval September 2014. Also approved for metastatic melanoma.

**Platelets (thrombocytes):** very important in clot formation during bleeding; average life span is 8-9 days.

**Thrombocytopenia:** low levels of platelets; typically not as big a concern as leucopenia, neutropenia, or anemia in cancer therapy.