Lecture 8: Hematopoiesis

Objectives

1. Understand the overall process of hematopoeisis
2. Describe the different attributes and functions of RBCs, WBCs and platelets

Hematopoiesis: The process whereby the blood cell components such as 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 RBCs, platelets and WBCs. Per microliter of blood, humans normally have approximately 5 million RBCs, and 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.

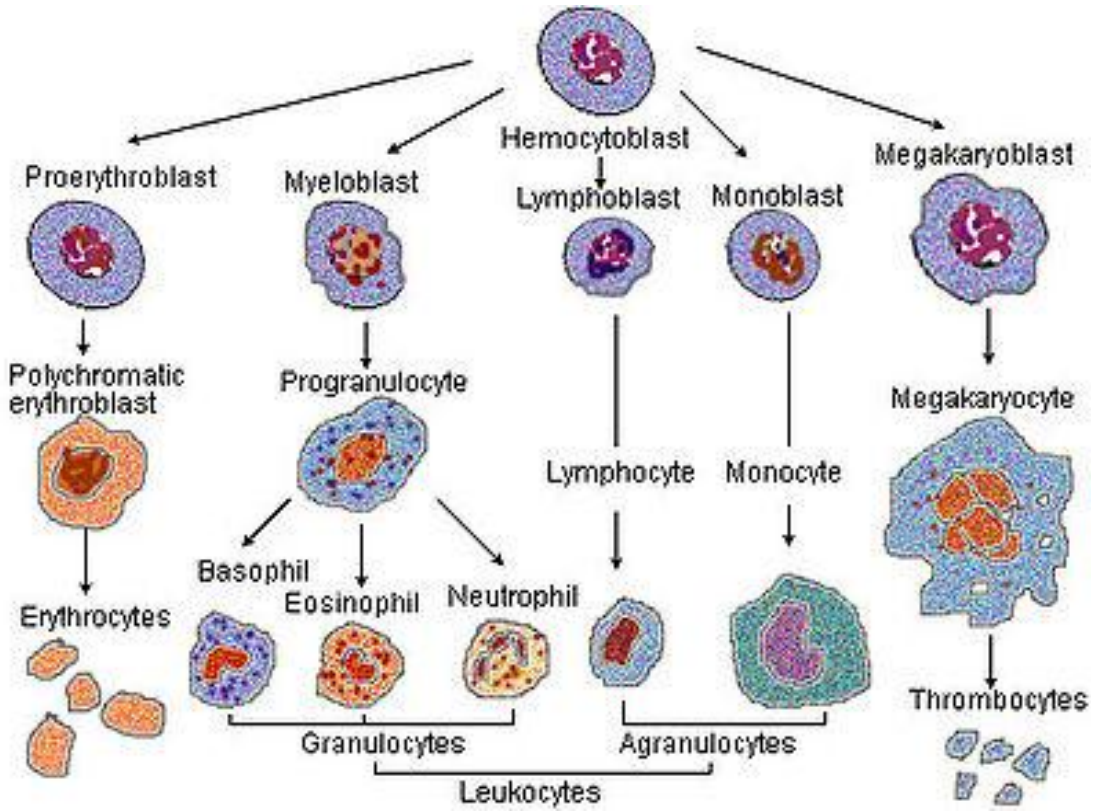

Figure 1. General scheme for blood cell formation called hematopoiesis

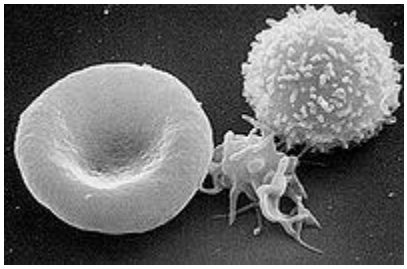

Figure 2. The general appearance of a RBC, a platelet, and a WBC; the shape of RBCs optimizes flexibility and that of platelets optimizes clotting efficiency, while the surface of WBCs enhances antigen recognition and signaling

RBCs (erythrocytes): primarily for oxygen transport

RBC production (erythropoiesis) can be stimulated by low oxygen content in the blood. Low levels of oxygen in the blood 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 hemoglobin which carries oxygen.

Interestingly, the marrow of essentially all the bones, liver and spleen can perform erythropoiesis until around the age of 5. After the age of 20, the ends of large leg bones (tibia and femur), vertebrae, sternum, pelvis, ribs and cranial bones contribute to erythropoiesis (Figure 3). RBCs are estimated to have a life-span of about 120 days.

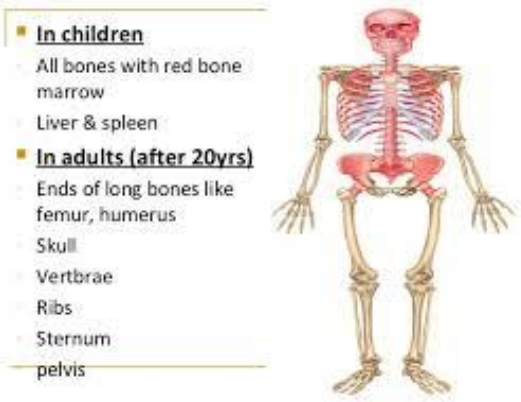

Figure 3. Locations of erythropoiesis as a function of age

Anemia: The condition of abnormally low functional hemoglobin (can be secondary to low RBCs)

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
We will discuss specific drugs to elevate WBCs or neutrophils in a later lecture.

-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 they 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

A greater understanding of the 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 (Figure 4). Both CTLA4 and PD-1 are "negative" regulators of T cells. The T cell receptor and MHC are the classic "positive" regulation or activation mechanism for T cells.

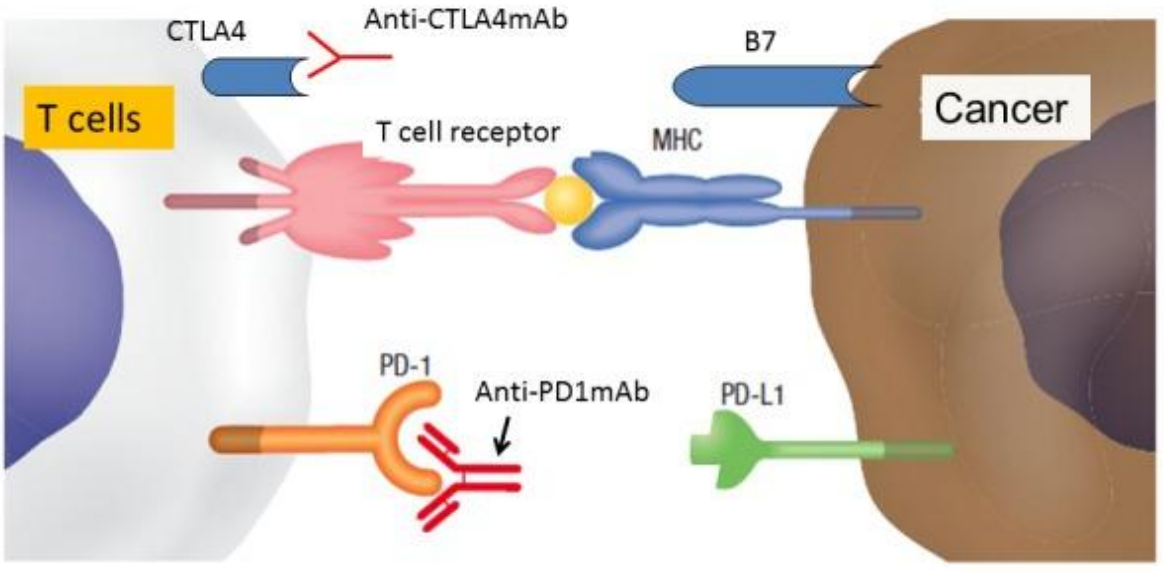

Figure 4. Several mechanisms of communication between T cells and cancer cells

We will discuss specific drugs (monoclonal antibody drugs) to specifically activate T cells in a later lecture. This field of oncology is also called "immuno-oncology" and you might have heard the term. Lately it has been in the news frequently because of several new drug approvals.

Platelets (thrombocytes): very important for 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.

We will discuss specific drugs to elevate platelets in a later lecture.