Toxic Responses of the Blood Lec:5

BLOOD AS A TARGET ORGAN

Hematotoxicology is the study of adverse effects of drugs, nontherapeutic chemicals, and other chemicals in our environment on blood and blood-forming tissues. The delivery of oxygen to tissues throughout the body, maintenance of vascular integrity, and provision of the many affector and effector immune functions necessary for host defense require a prodigious proliferative and regenerative capacity. Each of the various blood cells (erythrocytes, granulocytes, and platelets) is produced at a rate of approximately one to three million/s in a healthy adult and several times that rate in conditions where demand for these cells is high, as in hemolytic anemia or suppurative inflammation.

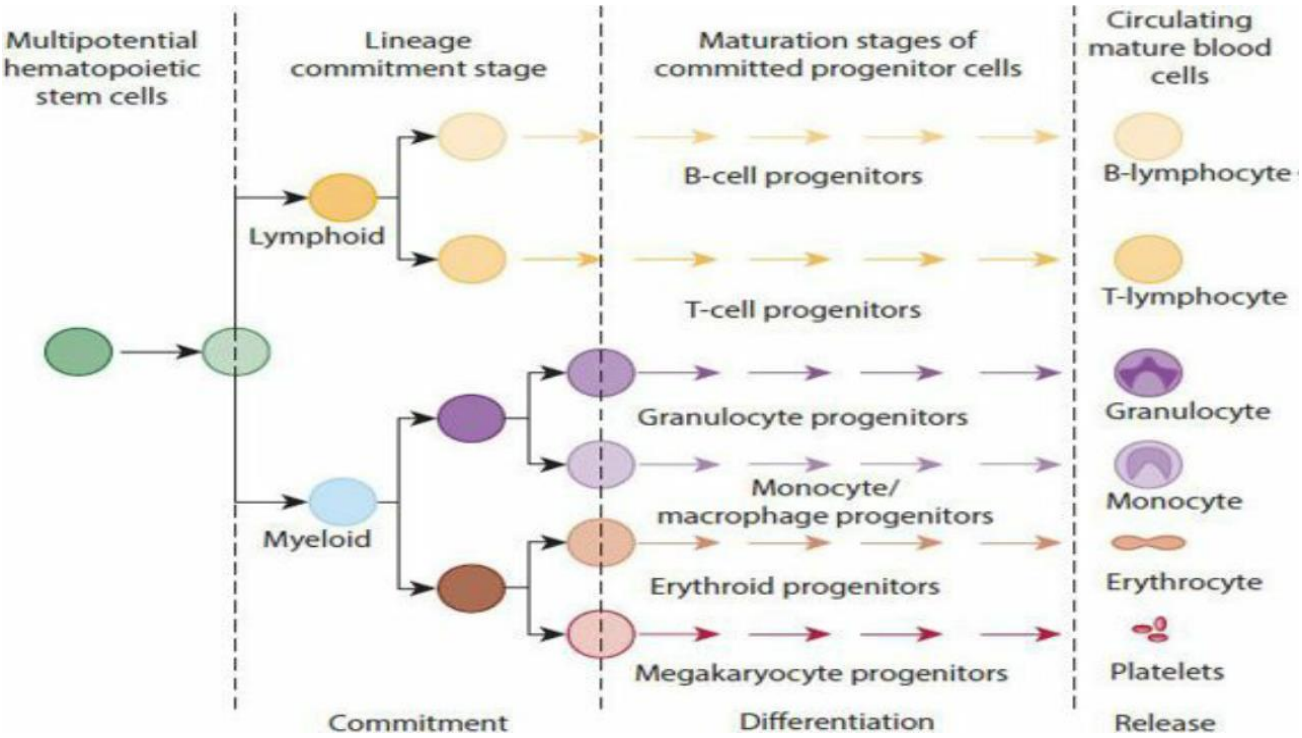
As with intestinal mucosa and gonads, this makes hematopoietic tissue a particularly sensitive target for cytoreductive or antimitotic agents, such as those used to treat cancer, infection, and immune-mediated disorders. This tissue is also susceptible to secondary effects of toxic agents that affect the supply of nutrients, such as iron; the clearance of toxins and metabolites, such as urea; or the production of vital growth factors, such as erythropoietin and granulocyte colony-stimulating factor (G-CSF). The consequences of direct or indirect damage to blood cells and their precursors are predictable and potentially life-threatening. They include hypoxia, hemorrhage, and infection.

Hematotoxicity may be regarded as *primary,* where one or more blood components are directly affected, or *secondary,* where the toxic effect is a consequence of other tissue injury or systemic disturbances. Primary toxicity is regarded as among the more common serious effects of xenobiotics, particularly drugs. Secondary toxicity is exceedingly common, due to the propensity of blood cells to reflect a wide range of local and systemic effects of toxicants on other tissues.

HEMATOPOIESIS

The production of blood cells, or hematopoiesis, is a highly regulated sequence of events by which blood cell precursors proliferate and differentiate to meet the relentless needs of oxygen transport, host defense and repair, hemostasis, and other vital functions described previously. The bone marrow is the principal site of hematopoiesis in humans and most laboratory and domestic animals.

While the central function of bone marrow is hematopoiesis and lymphopoiesis, bone marrow is also one of the sites of the mononuclear phagocyte system (MPS), contributing monocytes that differentiate into a variety of MPS cells located in liver (Kupffer cells), spleen (littoral cells), lymph nodes, and other tissues.



TOXICOLOGY OF THE ERYTHRON

The Erythrocyte

Erythrocytes (red blood cells [RBCs]) make up 40% to 45% of the circulating blood volume and serve as the principal vehicle of transportation of oxygen from the lungs to the peripheral tissues. In addition, erythrocytes are involved in the transport of carbon dioxide from tissues to the lung, maintenance of a constant pH in blood, and regulation of blood flow to tissues. Xenobiotics may affect the production, function, and/or survival of erythrocytes. These effects are most frequently manifest as a change in the circulating red cell mass, usually resulting in a decrease (anemia). Occasionally, agents that increase oxygen affinity lead to an increase in red cell mass (erythrocytosis), but this is distinctly less common. Shifts in plasma volume can alter the relative concentration of erythrocytes/hemoglobin and can be easily confused with true anemia or erythrocytosis.

Evaluation of a peripheral blood sample can provide evidence for the underlying mechanism of anemia. The usual parameters of a complete blood count (CBC)−including the RBC count, hemoglobin concentration (Hbg), and hematocrit (also referred to as packed cell volume [PCV])−can establish the presence of anemia. Two additional parameters helpful in classifying an anemia are the mean corpuscular volume (MCV) and the reticulocyte count. Increased destruction is usually accompanied by an increase in reticulocytes (young erythrocytes containing residual RNA), which are easily enumerated using appropriate stains.

Alterations in Red Cell Production

Erythrocyte production is a continuous process that is dependent on frequent cell division and a high rate of hemoglobin synthesis. Human adult hemoglobin (hemoglobin A), the major constituent of the erythrocyte cytoplasm, is a tetramer composed of two α-globin and two β-globin chains, each with a heme residue.

Abnormalities that lead to decreased hemoglobin synthesis are relatively common (eg, iron deficiency). An imbalance between α- and β-chain production is the basis of congenital thalassemia syndromes and results in decreased hemoglobin production and microcytosis. Xenobiotics can affect globin chain synthesis and alter the composition of hemoglobin within erythrocytes.

Synthesis of heme requires incorporation of iron into a porphyrin ring. Iron deficiency is usually the result of dietary deficiency or increased blood loss. Drugs that contribute to blood loss, such as nonsteroidal anti-inflammatory agents, with their increased risk of gastrointestinal ulceration and bleeding, may potentiate the risk of developing *iron deficiency anemia.* Defects in the synthesis of porphyrin ring of heme can lead to *sideroblastic anemia,* with its characteristic accumulation of iron in bone marrow erythroblasts. The accumulated iron precipitates within mitochondria causing injury.

Hematopoiesis requires active DNA synthesis and frequent mitoses. Folate and vitamin B 12 are necessary to maintain synthesis of thymidine for incorporation into DNA. Deficiency of folate and/or vitamin B 12 results in *megaloblastic anemia.* A number of xenobiotics may contribute to a deficiency of vitamin B 12 and/or folate leading to megaloblastic anemia. Examples: Azathioprine, Chloramphenicol, Colchicine, Cotrimoxazole, 5-Fluorouracil, Hydroxyurea, 6-mercaptopurine, methotrexate, Phenytoin, Vinblastine.

Drug-induced *aplastic anemia* may represent either a predictable or idiosyncratic reaction to a xenobiotic. This life- threatening disorder is characterized by peripheral blood pancytopenia, reticulocytopenia, and bone marrow hypoplasia.

Examples: Carbamazepine, Captopril, Chloramphenicol, Chlorpromazine, Dapsone, Furosemide, Lithium, Phenobarbital, Phenytoin, Sulfonamides.

Alterations in Erythrocyte Survival

The normal survival of erythrocytes in the circulation is about 120 days. Very little protein synthesis occurs during this time, as erythrocytes are anucleate when they enter the circulation and residual mRNA is rapidly lost over the first one to two days in the circulation. Consequently, senescence occurs over time until the aged erythrocytes are removed by the spleen, where the iron is recovered for reutilization in heme synthesis.

Nonimmune Hemolytic Anemia

Oxidative Hemolysis

Molecular oxygen is a reactive and potentially toxic chemical species; consequently, the normal respiratory function of erythrocytes generates oxidative stress on a continuous basis. The major mechanisms that protect against oxidative injury in erythrocytes include NADH diaphorase, superoxide dismutase, catalase, and the glutathione pathway.

The most common enzyme defect associated with oxidative hemolysis is G-6-PD deficiency, a relatively common sex-linked disorder characterized by alterations in the primary structure of G-6-PD that diminish its functional activity. It is often clinically asymptomatic until the erythrocytes are exposed to oxidative stress. The stress may come from the host response to infection or exposure to xenobiotics.

Dapsone, ascorbic acid, methylene blue, nalidixic acid, nitrofurantoin, Phenazopyridine, Primaquine, Sulfacetamide, Sulfamethoxazole are induces this type

Immune Hemolytic Anemia

Immunologic destruction of erythrocytes is mediated by the interaction of IgG or IgM antibodies with antigens expressed on the surface of the erythrocyte. In the case of autoimmune hemolytic anemia the antigens are intrinsic components of the patient’s own erythrocytes. A number of mechanisms have been implicated in xenobiotic- mediated antibody binding to erythrocytes Some drugs, of which penicillin is a prototype, appear to bind to the surface of the cell, with the “foreign drug acting as a *hapten* and eliciting an immune response. The antibodies that arise in this type of response only bind to drug-coated erythrocytes.

Other drugs, of which quinidine is a prototype, bind to components of the erythrocyte surface and induce a conformational change in one or more components of the membrane. A third mechanism, for which α-methyldopa is a prototype, results in production of a *drug-induced autoantibody* that cannot be distinguished from the antibodies arising in idiopathic autoimmune hemolytic anemia.

TOXICOLOGY OF THE LEUKON

Components of Blood Leukocytes

The leukon consists of leukocytes, or white blood cells. They include granulocytes, which may be subdivided into neutrophils, eosinophils, and basophils; monocytes; and lymphocytes. Granulocytes and monocytes are nucleated ameboid cells that are phagocytic. They play a central role in the inflammatory response and host defense. Unlike the RBC, which resides exclusively within blood, granulocytes and monocytes generally pass through the blood on their way to the extravascular tissues, where they reside in large numbers.

Granulocytes are defined by the characteristics of their cytoplasmic granules as they appear on a blood smear. Neutrophils, the largest component of blood leukocytes, are highly specialized in the mediation of inflammation and the ingestion and destruction of pathogenic microorganisms. Eosinophils and basophils modulate inflammation through the release of various mediators.

Toxic Effects on Granulocytes

Effect on Proliferation

The high rate of proliferation of neutrophils makes their progenitor and precursor granulocyte pool particularly susceptible to inhibitors of mitosis. Such effects by cytotoxic drugs are generally nonspecific, as they similarly affect cells of the dermis, gastrointestinal tract, and other rapidly dividing tissues. Agents that affect both neutrophils and monocytes pose a greater risk for toxic sequelae, such as infection. Such effects tend to be dose-related, with mononuclear phagocyte recovery preceding neutrophil recovery.

Myelotoxicity is commonly seen with cytoreductive cancer chemotherapy agents. Most act to inhibit DNA synthesis or directly attack its integrity through the formation of DNA adducts or enzyme-mediated breaks.

Idiosyncratic Toxic Neutropenia

Of greater concern are chemicals that unexpectedly damage neutrophils and granulocyte precursors—particularly to the extent of inducing *agranulocytosis,* which is characterized by a profound depletion in blood neutrophils to less than 500/μL. Such toxicity occurs in specifically conditioned individuals, and is therefore termed idiosyncratic.

Mechanisms of Toxic Neutropenia

The incidence of xenobiotic-induced immune neutropenia is considerably less than that of immune hemolytic anemias. In immune-mediated neutropenia, antigen‑antibody reactions lead to destruction of peripheral neutrophils, granulocyte precursors, or both. As with RBCs, an immunogenic xenobiotic can act as a hapten, where the chemical must be physically present to cause cell damage, or may induce immunogenic cells to produce antineutrophil antibodies that do not require the drug to be present. Also like immune hemolytic anemia, drug-induced *autoimmune* neutropenia has been observed.

LEUKEMOGENESIS AS A TOXIC RESPONSE

Human Leukemias

Leukemias are proliferative disorders of hematopoietic tissue that are monoclonal in origin and thus originate from individual bone marrow cells. Historically they have been classified as myeloid or lymphoid, referring to the major lineages for erythrocytes/ granulocytes/thrombocytes or lymphocytes, respectively. poorly differentiated phenotypes have been designated as “acute,” whereas well- differentiated ones are referred to as “chronic” leukemias.

Leukemogenic Agents

Most *alkylating agents* used in cancer chemotherapy can cause MDS and/or acute myelogenous leukemia AML. Of the *aromatic hydrocarbons,* only benzene has been proven to be leukemogenic. Treatment with *topoisomerase II inhibitors,* etoposide and teniposide can induce AML.

Toxic Effects on Platelets

The Thrombocyte

Platelets are essential for formation of a stable hemostatic plug in response to vascular injury. They initially adhere to the damaged wall. Activation of the GP IIb/IIIa receptor permits fibrinogen and other multivalent adhesive molecules to form cross-links between nearby platelets, resulting in platelet aggregation. Xenobiotics may interfere with the platelet response by causing thrombocytopenia or interfering with platelet function; some agents are capable of affecting both platelet number and function.

Thrombocytopenia

Like anemia, thrombocytopenia may be due to decreased production or increased destruction. Thrombocytopenia is a common side effect of intensive chemotherapy, due to the predictable effect of antiproliferative agents on hematopoietic precursors. It is a clinically significant component of idiosyncratic xenobiotic-induced aplastic anemia. Indeed, the initial manifestation of aplastic anemia may be mucocutaneous bleeding secondary to thrombocytopenia.

Exposure to xenobiotics may cause increased immune mediated platelet destruction through any one of several mechanisms. Some drugs function as haptens, binding to platelet membrane components and eliciting an immune response that is specific for the hapten. The responding antibody then binds to the hapten on the platelet surface, leading to removal of the antibody-coated platelet from the circulation.

A second mechanism of immune thrombocytopenia is initiated by xenobiotic-induced exposure of a neoepitope on a platelet membrane glycoprotein. This elicits an antibody response, with the responding antibody binding to this altered platelet antigen in the presence of drug, resulting in removal of the platelet from the circulation by the mononuclear phagocytic system.

Toxic Effects on Platelet Function

Platelet function is dependent on the coordinated interaction of a number of biochemical response pathways. Major drug groups that affect platelet function include nonsteroidal anti-inflammatory drugs, β-lactam-containing antibiotics, cardiovascular drugs, particularly β-blockers, psychotropic drugs, anesthetics, antihistamines, and some chemotherapeutic agents.

Xenobiotics may interfere with platelet function through a variety of mechanisms. Some drugs inhibit the phospholipase A 2 /cyclooxygenase pathway and synthesis of thromboxane A 2 (eg, nonsteroidal anti-inflammatory agents). Other drugs appear to interfere with the interaction between platelet agonists and their receptors (eg, antibiotics, ticlopidine, clopidogrel). As the platelet response is dependent on a rapid increase in cytoplasmic calcium, any chemical that interferes with translocation of calcium may inhibit platelet function (eg, calcium channel blockers). Occasionally, drug-induced antibodies will bind to a critical platelet receptor and inhibit its function.