Bone Marrow

In the adult, bone marrow is the major organ for production of erythrocytes, platelets, granular leukocytes, and monocytes. Many lymphocytes also are produced in the marrow and reside in the lymphatic tissues secondarily. In toto, the bone marrow constitutes an organ that rivals the liver in weight and in humans is estimated to account for 4% to 5% of body weight.

Types

Bone marrow is an extremely cellular connective tissue that fills the medullary cavities of bone. On gross inspection, it may have a red or yellow color. Red marrow is actively engaged in the production of blood cells and represents the active or hemopoietic marrow. The red color is due to the content of red cells and their pigmented precursors. Yellow (fatty) marrow is inactive, and its principal cellular components are fat cells. Fat cells also are scattered sparingly throughout the red marrow. The amount and distribution of fatty marrow vary with age and the need for blood cells. All bones contain active marrow in the late fetus and neonate, but active marrow gradually is replaced by fatty marrow during postnatal development and aging. Beginning in the shafts of long bones, fatty marrow gradually replaces red marrow until, by adulthood, almost all the marrow in the limbs is the fatty type. Active marrow remains at the ends of the long bones and in the ribs, sternum, clavicles, vertebrae, pelvis, and skull. Fatty marrow forms about 50% of the total marrow. Fatty marrow is very labile and easily replaced by active marrow. Yellow marrow serves as a reserve space for the expansion of active marrow to meet increased demands for blood. Active marrow first replaces the fat cells scattered within the red marrow itself, but if demands for blood remain high or are increased, red marrow gradually encroaches into the areas of fatty marrow. Prolonged or increased demands then are met by expansion of hemopoiesis into other organs or tissues such as the spleen, liver, or lymph nodes. Blood formation in tissues other than the bone marrow is called extramedullary hemopoiesis and occurs in some pathologic states.

Structure

Bone marrow is a specialized connective tissue that, on the basis of its fiber content, can be classed as a reticular connective tissue. A loose, spongy network of reticular fibers and associated cells fills the medullary cavities of bone and provides a supporting framework (stroma) for the hemopoietic cells. The network of fibers and cells is continuous with the endosteum of the bone and is intimately associated with blood vessels that pervade the marrow. Within the meshes of the reticular fiber network are all the cell types normally found in blood, their precursors, fat cells, plasma cells, and mast cells. These constitute the free cells of the marrow. The reticular cells are fixed cells that have no special phagocytic powers and do not give rise to precursors of hemopoietic cells. They are modified fibroblasts responsible for the formation and maintenance of reticular fibers. Reticular cells have large, palely stained nuclei and irregularly branched cytoplasm that extend long slender processes along the reticular fibers.

Vasculature

In long bones, the nutrient artery enters the marrow cavity through the nutrient canal and gives off central nutrient (longitudinal) branches that run centrally in the marrow cavity toward the ends of the bone. These are supplemented by branches from epiphyseal and periosteal arteries. Along its course, the central nutrient artery provides numerous branches that pass toward the boney wall. Some of these branches enter the bone to supply osteons; others turn back to the marrow and join the venous system directly by uniting with sinusoids.
Sinusoids (venous sinuses) are thin-walled vessels, 15 to 100 μm in diameter, that form an extensive and complex network throughout the marrow. They are lined by thin, flattened endothelial cells that are closely apposed and joined by zonula adherens and gap junctions. A basal lamina is absent or discontinuous, with only scattered patches present on the basal surface. The endothelium is incompletely wrapped by a loose coat of adventitial reticular cells whose broad, branching processes merge with the reticular mesh that supports the hemopoietic cells. The adventitial reticular cells contain ribosomes, granular endoplasmic reticulum, and bundles of microfilaments located just beneath the plasmalemma. The proportion of endothelium covered by these cells varies with the functional state of the marrow and may be reduced to one-third when there is heavy cell traffic across the sinusoidal wall. Sinusoids are the first venous elements. They pass toward the center of the marrow cavity and join the central longitudinal vein either directly or after union with other sinusoids to form collecting sinusoids. Thus, in the marrow, blood flows from the center to the periphery and back to the center. The central longitudinal vein also is thin-walled and consists of a low endothelium, a thin but complete basal lamina, and a thin outer layer of supporting reticular cells. The venous blood drains from the marrow by a main vein that exits through the nutrient canal, where it narrows abruptly. The blood supply appears to be "closed"--that is, there is endothelial continuity between venous and arterial components.

Distribution of Marrow Elements

The hemopoietic elements form irregular cords between the sinusoids, and collectively, these cords of blood-forming cells make up the hemopoietic compartment; the blood vascular components are referred to as the vascular compartment. In smears, marrow cells appear to be randomly distributed, but in serial sections, some ordering of the cells can be seen. Fat cells, though generally scattered, tend to concentrate toward the center of the marrow, where they cluster about the larger blood vessels. The vascular arrangement of the marrow results in a concentration of small vessels, especially sinusoids, at the periphery, and the hemopoietic cells are largely confined to the area near the vessels, close to the endosteum. Erythrocytes develop in small islets close to the sinusoids with some ordering of the cells within a cluster according to their stage of development. The most mature cells occupy the outer rim of the islet. Macrophages are commonly associated with developing red cells and often lie in the center of an erythroblastic islet surrounded by several layers of red cells. Cells that give rise to platelets (megakaryocytes) are closely applied to the walls of sinusoids and frequently project small cytoplasmic processes through apertures in the sinusoidal wall. Developing granulocytes form nests of cells that tend to locate at some distance from the sinusoids. Formation of blood cells occurs extravascularly: the cells form outside the blood vessels and enter the circulation through the sinusoids. The blood cells must penetrate the outer investment of reticular cells and cross the endothelial lining to gain access to the lumen. In areas of active passage of cells, the reticular sheath is much reduced, and the vessel appears to consist only of an

endothelium. Blood cells penetrate the endothelium through apertures in the cytoplasm and not by insinuating themselves between adjacent endothelial cells. The openings are relatively large, 1 to 3 μm in diameter. They are not permanent structures and develop only in relation to and during the actual passage of cells.

Stem Cells

The hemopoietic cells of the marrow encompass various developmental stages, from a primitive stem cell to the mature circulating elements in the blood. A stem cell can be defined as a cell that can maintain itself through self-replication and also can differentiate into a more mature cell type.

There is much evidence that bone marrow contains a pluripotent stem cell capable of giving rise to all the different types of blood cells. Mice given a lethal dose of irradiation soon die from loss of blood cells due to destruction of the hemopoietic organs. However, transfusion of bone marrow soon after exposure to radiation averts death, and both the marrow and the lymphatic tissues are reconstituted by functional cells derived from the transfused marrow. During recovery, macroscopic nodules appear in the spleen; these spleen colonies represent islets of proliferating hemopoietic cells and contain undifferentiated and maturing blood cells. The cells in the marrow inoculum that give rise to the spleen colonies are called colony-forming units (CFU). Some colonies consist only of cells of the erythrocyte line, others contain developing granulocytes or developing megakaryocytes, but many are mixed colonies that contain developing cells of all three lines. The unicellular origin of mixed colonies has been shown by transfusing donor cells that have been irradiated just sufficiently to form unique chromosome markers but not enough to destroy their abilities to replicate. When these cells form spleen colonies, all the constituent cells bear the same marker as the inoculated cells and therefore must have arisen from the same CFU. The unique chromosome marker also appears in cells that are repopulating the thymus and lymph nodes, indicating that the CFU has the potential for forming cells of lymphatic lineage as well. Cultures of cells from granulocytic and mixed colonies produce monocytes and macrophages that also carry the marker chromosome. The reconstituted marrow of these "rescued" animals, when injected into new recipient animals, produces spleen colonies that still carry the marker chromosomes. Cells from spleen colonies give rise to new spleen colonies when injected into irradiated animals. Even colonies that are purely erythrocytic or granulocytic can give rise to colonies of all types. Thus, the CFU is not only capable of differentiation but also of self-renewal, therefore fulfilling the definition of a stem cell. The bone marrow must contain pluripotent stem cells capable of feeding into the erythrocyte, granular leukocyte, megakaryocyte, monocyte, and lymphocyte lines. In addition to pluripotent stem cells, bone marrow contains stem cells that have a more restricted capacity for development. These restricted stem cells are committed to the development of one specific cell line. Experimental evidence supports the existence of restricted stem cells for erythrocytes (CFU-E), granular leukocytes (CFU-G), and megakaryocytes (CFU-Meg). Most studies suggest a common precursor for granulocytes and monocytes (CFU-GM). Restricted stem cells arise from pluripotent stem cells, are rapidly proliferative, but have limited capacity for self-renewal. Pluripotent stem cells are capable of extensive replication but are only slowly proliferative and actually represent a reserve cell. It is the restricted stem cells that provide for the immediate, day-to-day replacement of blood cells. Based on size, sedimentation velocities, and response to erythropoietin, three categories of restricted erythropoietic stem cells have been defined, and by their growth rates, size, and sedimentation characteristics, two CFU-GM are known. Within a given cell line, the various categories of committed stem cells represent

progressions of development from more primitive, but restricted, stem cells to cells that are the immediate precursors of the classic, cytologically recognizable precursor cells. While the existence of a pluripotent stem cell is certain, its morphology is in doubt; there is evidence, however, that it may be similar in appearance to a lymphocyte. Fractionation of bone marrow on sedimentation columns has shown that CFUs (stem cells) are contained in a fraction whose cells have a size and weight comparable with those of lymphocytes. The number of marrow stem cells can be increased by administering antimitotic drugs that destroy hemopoietic cells capable of division. Since pluripotent stem cells are only slowly proliferative, they are spared, and their relative numbers in the marrow are greatly increased. Stem cells can be enriched further by density gradient centrifugation, and as shown by their ability to produce spleen colonies, stem cells increase in number in proportion to an increase in cells with lymphoid appearance. These lymphocyte-like cells have been called candidate stem cells. While the morphology generally is similar to that of a small lymphocyte, the nucleus is more irregular and less deeply indented than in most lymphocytes, and the chromatin is more finely dispersed. Mitochondria are few in both types of cells but are smaller and more numerous in the candidate stem cell. Free ribosomes but no granular endoplasmic reticulum or lysosomes are present. The earliest hemopoietic cells are those in the blood islands of the yolk sac, and there is evidence that undifferentiated cells from the yolk sac circulate in the fetus and successively seed the liver, spleen, and marrow. As hepatic hemopoiesis declines, the number of circulating stem cells increases, suggesting a large-scale migration of stem cells into the marrow. Cells of blood islands do contain CFUs and can restore all the hemopoietic organs in an irradiated animal.