Symposium on Blood Disorder in Systemic Diseases*

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(1) Disorders of Hemopoiesis in Systemic Diseases

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1. Regulation of hemopoiesis and stem cells in human beings.

Recent development of cloning techniques of human hemopoietic cells in semisolid culture media made it possible to directly analyze the mechanism of derangements of hemopoiesis. Cultures of human hemopoietic cells are now available for the erythroid, granulocyte-macrophage, and eosinophil precursors and their common ancestor, multipotent stem cells, respectively. The erythroid precursors form erythroid burst and erythroid colonies. Erythroid bursts are derived from more immature precursors called burst forming unit, erythroid (BFU-E); while erythroid colonies are derived from the progenies of BFU-E called colony forming unit, erythroid (CFU-E). Erythroid bursts usually consist of erythroid subcolonies. Formation of erythroid bursts requires the presence of humoral factor or factors called burst promoting activity (BPA) and erythropoietin (Ep), while CFU-E-derived colony formation requires Ep alone. The source of BPA is lectin-stimulated lymphocyte conditioned medium and many other materials while Ep is believed to be derived mainly from kidneys. Granulocyte-macrophage (GM) colonies are derived from their precursors GM-colony forming units (GM-CFU). Formation of GM colonies requires colony stimulating factors (CSF) which are produced by various kinds of cells such as kidneys, human peripheral leukocytes, lungs, placentas etc. CSF are also obtained from human urine and serum.

Eosinophil colonies are formed in the similar semisolid media later than GM colonies by the stimulation of CSF or lectin-stimulated leukocyte conditioned media. Eosinophils are also detected in GM colonies, meaning that neutrophils, macrophages and eosinophils have common or closely related pregenitors.

The colony forming techniques of human megakaryocytes have been reported from several institutes. It has, however, not become common because of the difficulties of the identification of human megakaryocytes in culture. The progenitor of megakaryocytes are called colony forming unit, megakaryocytes (CFU-M).

Colonies consisting of granulocytes, macrophages, erythroblasts and megakaryocytes are formed in the presence of lectin-stimulated lymphocyte conditioned media and other hemopoietic factors. They are derived from multipotent stem cells called mixed colony-forming units (CFU-mix). It has been suggested that CFU-mix belongs to a multipotent stem cell population.

*Presented at the 79th Annual Meeting of the Japanese Society of Internal Medicine, April 5th, 1982, in Tokyo.

known as the colony forming unit in spleen (CFU-S), which has been first demonstrated by a transplantation experiment of lethally irradiated mice.

2. Systemic diseases that affect hemopoiesis.

When we consider the pathogenesis of hemopoietic disorders we can distinguish the abnormalities of hemopoietic cells from those of hemopoietic factors. Main systemic disorders that can be the causes of hemopoietic disorders are: (1) endocrine diseases such as pituitary, thyroid and adrenocortical dysfunctions, (2) chronic inflammatory diseases and collagen diseases such as SLE and RA, (3) renal diseases, (4) hepatic diseases and (7) miscellaneous. (8) Besides these systemic disorders, drugs that are frequently used to treat them, such as steroid hormones, lithium, anticonvulsants and anticancer drugs, are also important in the pathogenesis of hemopoietic disorders in systemic diseases.

Among them we describe several selected items related to stem cells from our experiences.

(a) Androgens and anabolic steroids are known to stimulate hemopoiesis and are widely applied to the therapy of aplastic anemia. It is also effective on in vitro erythroid colony formation when applied with erythropoietin. They directly stimulate stem cells or enhance the activity of Ep. In Cushing disease and other adrenocortical hyperfunctions, marked granulocytosis occurs without any sign of infection. Besides the release of neutrophils from marginal pools, they seem to directly stimulate granulopoiesis. Application of hydrocortisone to the system of GM colony formation caused an increase in the number of neutrophil colonies.

(b) Formation of GM colonies by bone marrow cells from the patients with systemic lupus erythematoses (SLE) was markedly reduced. The number of colonies reflected the status of the diseases. Addition of lymphocytes (or sera) from the patients with SLE and RA caused the depletion of GM colony formation by normal marrow cells. Erythroid colonies were also reduced in some cases with marked anemia. These results may be related to some abnormal changes of the immune system.

(c) Chronic renal failure is usually associated with severe anemia. It is generally accepted that the major cause of anemia is the lack of Ep produced in the kidney. Addition of uremic serum to the culture results in complete disappearance of erythroid colonies when added alone, and a marked reduction in colony formation when added with Ep. These results show the presence of inhibitory factor(s) in uremic serum. Spermine is one of the candidates of these inhibitors.

(d) Hemopoietic disorders detected in hepatic diseases are much more complicated. Some documented causes of anemia are hemolysis due to the changes of lipid metabolism, hemorrhage, derangement of serum protein production and hyponutrition that may affect hemopoiesis. It is, however, not clear if there are any specific mechanisms that affect hemopoiesis in hepatic dysfunction.

(e) Polycythemia and leukocytosis are occasionally observed in some cases of tumors of liver, kidney, cerebellum, lung, thyroid and so on. Transplantation of these tumors into nude mice evoked marked erythrocytosis or leukocytosis, which disappear after the resection of the tumors. These tumors are proven to be producing Ep or CSF. More detailed descriptions will be done in this symposium by Ohsawa and Asano.

Causes of anemia observed among the patients with malignancy are complicated as in cases of hepatic diseases.

(f) Marked polycythemia is observed in the patients with hypoxia due to respiratory and cardiovascular diseases. Polycythemia is caused by overproduction of Ep due to anemia.

3. Conclusion

Perturbances of homeostasis due to systemic diseases make the changes of many factors that affect hemopoiesis through complicated processes. They directly involve stem cells or indirectly influence the production of hemopoietic factors. So called "hemopoietic cell microenvironment" may play another role. We should further analyze in details by purifying the stem cell populations as well as by separation and purification of the stimulators and inhibitors. (Supported in part by the Grant-in-Aid for Scientific Research from The Ministry of Education, Science and Culture).