REVIEWS

Dynamic Theory of Hemopoiesis Regulation

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A fundamental feature of hemopoiesis is production of a large number of cells per time unit [4,77], which is compensated by death of the corresponding number of blood cells. Additional requirement for mature cells in different pathological states leads to excessive strain of the hemopoietic system, in particular, massive recruitment of hemopoietic precursors necessary for repopulation of the low-differentiated cell niches [4, 67,90]. These situations regularly arise in all complex organisms and could completely deplete the stem cell pool [90,113,117], if they responded to each stimulation. These considerations led to a conclusion on the existence of local mechanisms responsible for quantitative regulation of hemopoiesis at the level of committed and partially differentiated precursors and limiting the reaction of polypotent stem cells to indirect nervous and humoral stimuli. This regulation is executed by a complex of cell, extracellular, and humoral factors located in immediate proximity to hemopoietic elements and termed as hemopoietic or hemopoiesis-inducing microenvironment (HIM) [106,123,125]. According to current concept, HIM is formed by different cells and their products both in the stroma and parenchyma of hemopoietic organs. HIM components include some populations of T lymphocytes and macrophages (mobile elements), and fibroblasts and fibroblasts-produced extracellular matrix components, resident macrophages, adipocytes, endothelial cells, elements of microcirculatory bed and nerve fibers [83, 94,95,106,120,121].

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Elements of HIM regulate hemopoiesis via both cytokine production and direct contacts with hemopoietic cells [57,119]. Direct cell-cell interaction is used for transmission of regulatory signals and compounds, migration and homing of precursor cells in specific regions of the hemopoietic tissue, and for presentation of hemopoietic growth factors in a biologically available form [106,125].

It should be noted that this regulation can be both positive and negative (inhibition of proliferation and differentiation) depending on subpopulation of HIM cells and their functional state [20,57,92,119].

Early hemopoietins alone or in combination with other factors are involved into stimulation of proliferation and differentiation of early hemopoietic precursors or induce division of polypotent hemopoietic stem cells resting in the G_0 phase [110,114]. They include interleukin-3 (IL-3) produced by activated T lymphocytes, Steel factor, IL-1, IL-6, IL-11, and Flt-3-ligand produced by macrophages, stromal mechanocytes, endotheliocytes, and adipocytes, and granulocyte-macrophage colony-stimulating factor produced by practically all HIM cells [80,107,108,111,116].

T lymphocytes produce lineage-restricted cytokine IL-5 regulating eosinophil proliferation and differentiation [80,81]. Resident bone marrow macrophages and monocytes secrete erythropoietin and IL-6 stimulating proliferation of erythroid precursors; T lymphocytes, products of erythrocyte degradation, and some other factors can potentiate this effect [27,67, 112]. Late hemopoietins are produced by macrophages, fibroblasts, and endothelial cells and include granulocyte and macrophage colony-stimulating factors, involved in the regulation of granulocyto- and mono-

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cytopoiesis, respectively [27,57,80,96,115]. Moreover, stromal cells and specialized macrophages synthesize types I, III, and IV collagens, reticular fibers, fibronectin, laminin, tenascin, and other protein components of extracellular matrix [106, 118].

A complex of glycosaminoglycans, components of the connective tissue extracellular matrix, and extracellular proteins are considered as a structure responsible for concentration of hemopoietic islets and modulation of their functions [93,95,121]. Thus, extracellular matrix of the bone marrow tissue is a physiologically active medium and acts as an important regulator of hemopoiesis.

Basing on published data and our findings, we proposed a scheme of the regulation of hemopoiesis by cytokines produced by HIM cells (Fig. 1).

At present, there are ample data on different aspects of the blood system function in health and pathology. However, little is known on regularities and mechanisms of the function of the hemopoietic tissue as an integral dynamic system adequately reacting to internal and environmental stimuli. This understanding cannot be reached without systemic approach to this problem [24,84,124].

Working for many years in this direction, we used in our studies various experimental models of pathological processes (immobilization stress, infectious inflammation, blood loss, cytostatic, radiation, neurotic damages, spontaneous leukemia, *etc.*) and assessed functional activity and interaction between of the main compartment of the hemopoietic tissue and regulatory systems (distant and local) [8,27,28,48,57,99]. It should be noted that hemopoietic tissue is a convenient model for studying tissue regeneration. Therefore, principal mechanisms regulating its activity under optimal conditions and in extreme situations can provide a basis for creating a theory of tissue adaptogenesis [24].

Integral analysis of our experiments and published data led us to a conclusion on the existence of a universal complex system of hemopoiesis regulation including interrelated distal and local regulatory structures [24,27,99].

Extreme factors (inducing or not inducing hypoplasia of the hemopoietic tissue) trigger successive activation of the regulatory cascade of hemopoiesis. Adaptive response of the hemopoietic tissue depends on central neuroendocrine mechanisms [8,28,63,64], which realize their effects via universal stress-realizing (autonomic nervous system, pituitary-adrenal axis, opioid peptides) and stress-limiting systems (GABAergic system, opioid peptides, *etc.*) [18,27, 67,76], the sympathoadrenal system being the main autonomic regulator of hemopoiesis [66].

Activation of the pituitary-adrenal [68] and sympathoadrenal [28] systems induces hyperplasia of the bone marrow hemopoietic tissue (primarily due to stimulation of erythro- and granulomonocytopoiesis) and increases peripheral blood cell count. Activation of hemopoiesis under these conditions is associated with migration of T regulators to the bone marrow [56] stimulated by glucocorticoids and catecholamines [25,98]. At present, the phenotype and the main properties of T cells controlling hemopoiesis are well studied [10,34-37,45,46,70,105]. T cells activate resident macrophages and stromal mechanocytes in HIM [14,15,40,50,61,122] responsible for proliferation and differentiation of hemopoietic precursors from polypotent to mature cells [26,67]. Moreover, hormones produced by adrenal medulla and cortex directly (via receptor-mediated pathways) and indirectly (through T lymphocytes, macrophages, stromal mechanocytes) synchronize and stimulate proliferative and differentiation activities of hemopoietic cells [24,31,33,86, 98]. A peculiar tropism of β-adrenergic stimuli to erythroid and α-adrenergic stimuli to granulocyte-macrophage hemopoietic mechanisms reported in previous studies [33,87] was then confirmed by correlation analysis [27]. The adaptive response of the hemopoietic tissue depends on the relation between stress-realizing and stress-limiting systems, which have analogous target cells in the blood [19,24,32,105].

Elements of HIM (macrophages and stromal mechanocytes) in cooperation with T lymphocytes determine proliferative and differentiation state of hemopoietic precursors by stimulating production of humoral regulators (cytokines, glycosaminoglycans) [11, 21,25,38,39,47,49,69,86,91] and cell-cell interactions increasing the number of cell associations (hemopoietic islets) [33,67]. The elevated content of IL-1 and IL-3 is the most early reaction of HIM to extreme influences [25]. On the other hand, the number of horizontal (within the hemopoietic system) and vertical (with higher regulatory systems) correlations increases, which reduces plasticity of the compensatory and adaptive mechanisms of hemopoiesis under the effect of varying environmental influences [27].

It should be noted that various shifts in the hemopoietic system observed under various pathological conditions and mechanisms of these shifts are usually similar and nonspecific. Nevertheless, a particular response of the blood system is determined by the nature of stimulus. For instance, immobilization stress equally stimulates erythro- and granulomonocytopoiesis [99], while inflammation affects primarily white blood cells [59], which can be explained by the key role of neutrophils, mast cells, and monocytes in the development and solution of inflammation [22,57,58,60,78,103]. However, similarly to other stress reactions, acute inflammation is also accompanied by stimulation of erythropoiesis due to functional activation of HIM

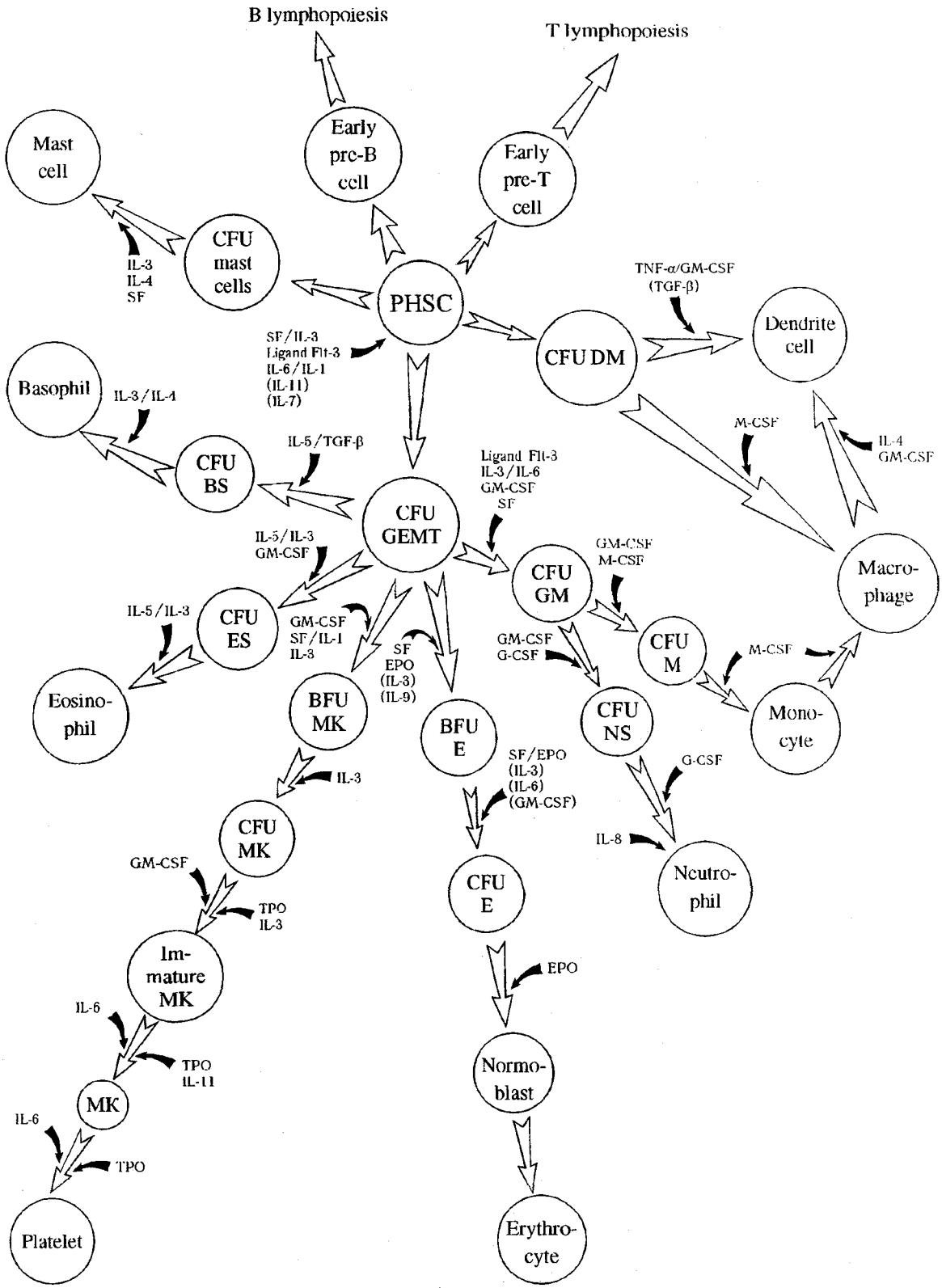

Fig. 1. Regulation of hemopoiesis with cytokins. Here and on Figs. 2-5: IL: interleukins; CSF: colony-stimulating factors: GM: granulocyte-macrophage; G: granulocyte; M: macrophage; TPO: thrombopoietin; TGF: transforming growth factor; TNF: tumor necrosis factor; SF: Steel factor (stem cell factor); EPO: erythropoietin: PHSC: polypotent hemopoietic stem cell; CFU: colony-forming units; DM: dendrite cells and macrophages; GEMT: granulocyto-, erythrocyto-, monocyto-, and thrombocytopoiesis, GM: granulomonocytopoiesis; M: monocytopoiesis; E: erythropoiesis; MK: megakaryocyte; NS: neutrophil stem; ES: eosinophilic stem; BS: basophilic stem of granulocytopoiesis; BFU: early precursors; HI: hemopoietic islets.

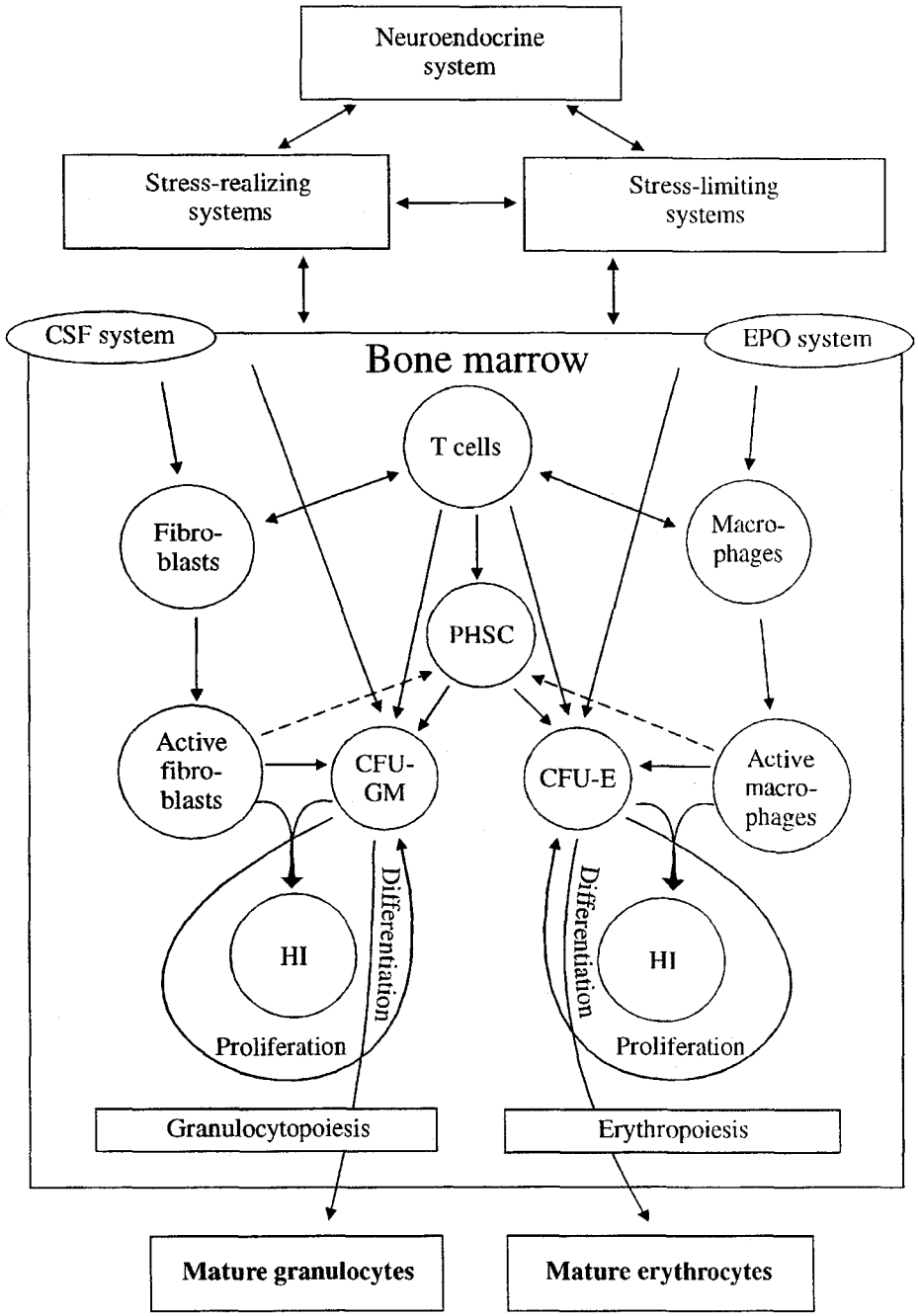

Fig. 2. Regulation of hemopoiesis under the effect of extreme factors.

erythron [23,59,79]. On the contrary, massive blood loss is accompanied by stimulation of the erythron due to circulatory and hemic hypoxia [16,101, while stimulation of granulomonocytopoiesis is less pronounced.

Basing on these data we propose a scheme of regulation of hemopoiesis (Fig. 2). It should be emphasized that the most convincing evidence in favor of theoretical and practical value of this scheme was obtained in studying the mechanisms of regulation of hemopoiesis on the models of cytostatic- and radiation-induced myelosuppression. During hypoplasia of the hemopoietic tissue induced by extreme factors (treatment with cytostatics, ionizing radiation, *etc.*) the dynamics of hemopoietic recovery depends not only on the direct suppressive effect of toxic agents on hemopoietic cells [77], but also on disturbances in the regulatory systems, particularly, in HIM elements [41, 42,51,54,100-102].

For instance, priority recovery of hemopoietic islets in the bone marrow and their enhanced formation by mature macrophages, as well as effective coup-

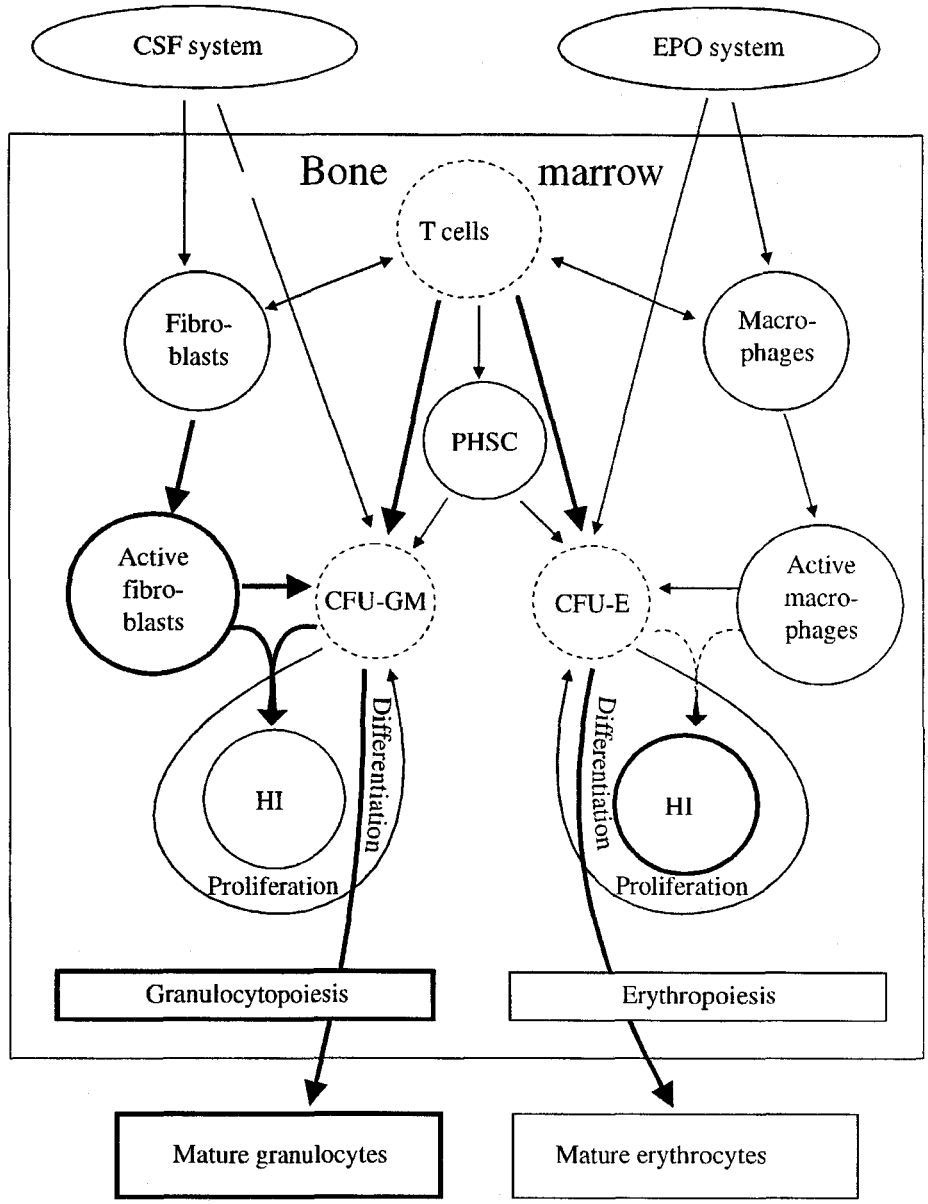

Fig. 3. Regulation of hemopoiesis in hemosuppression caused by anthracycline antibiotic (adriamycin). Here and in Fig. 4 and 5: fine lines: negligible effect, dashed line: inhibition; bold line: activation.

ling of stromal mechanocytes with hemopoietic precursors provide the basis for active differentiation of committed precursors and rapid regeneration of the hemopoietic tissue after treatment with the anthracycline antibiotic adriamycin [51,72]. Intense proliferation of hemopoietic precursors [52] results from enhanced production of hemopoiesis-stimulating factors by HIM elements in the early period after cytostatic treatment [53] due to active repopulation of HIM (Fig. 3).

Treatment with the alkylating agent cyclophosphamide also led to rapid recovery of structural and functional organization of the bone marrow and early stimulation of secretory activity of adherent myelokaryocytes in cooperation with T cells [7,12,53], which accelerated differentiation of granulocyte-macrophage precursors [52]. These processes sharply increased the content of neutrophil granulocytes in the bone marrow [72,97]. The long-term depression of erythrokaryocytes can be explained by pronounced damaging effect of the alkylating agent on committed hemopoietic precursors of the erythroid lineage (Fig. 4).

Long-term suppression of granulocyte and erythroid hemopoietic stems after treatment with the antimetabolite 5-fluorouracil [73,97] is accompanied by accumulation of hemopoietic precursors in the hemopoietic tissue [27] due to their disturbed maturation [52]. This phenomenon can be explained by active

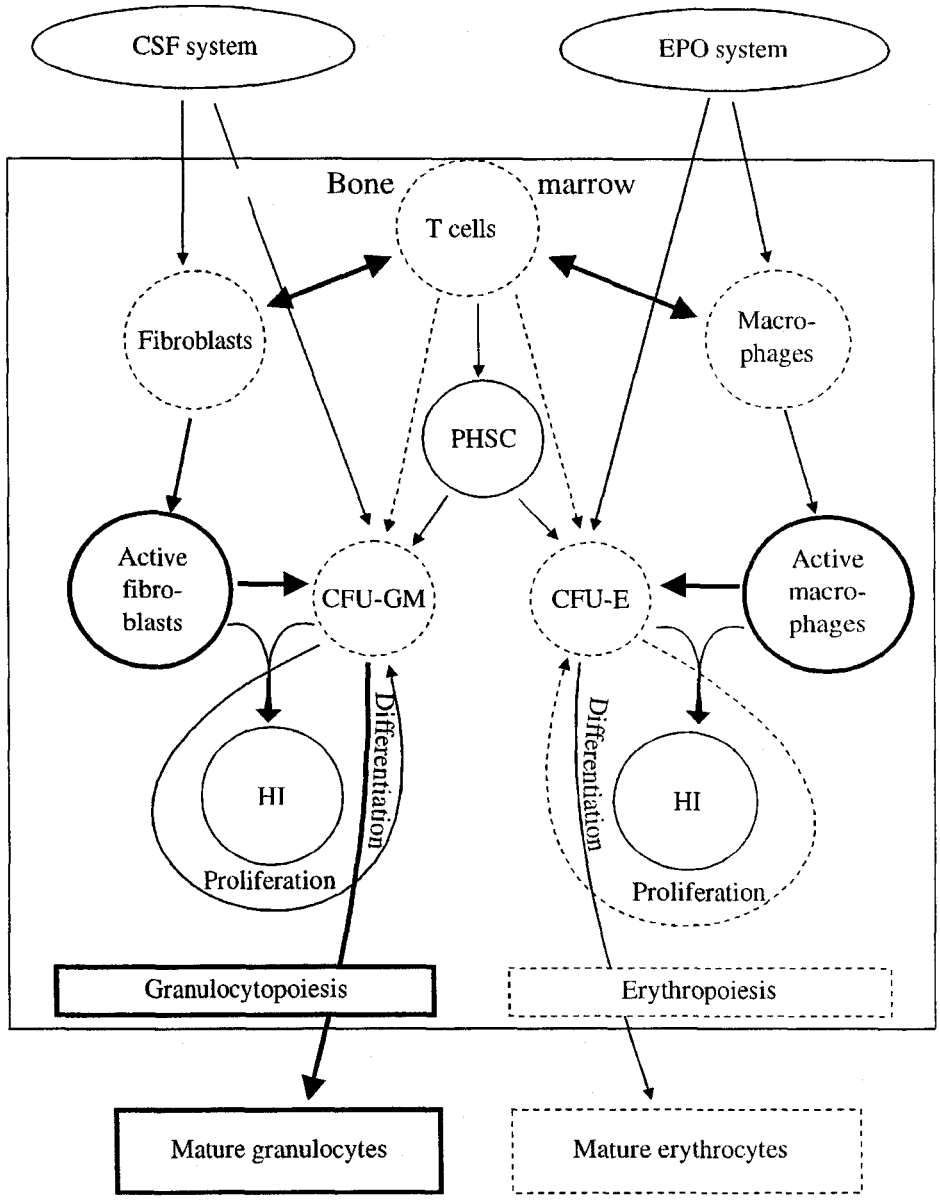

Fig. 4. Regulation of hemopoiesis in hemosuppression caused by alkylating agent (cyclophosphamide).

proliferation of hemopoietic precursors against the background of disturbed (due to crude dissociation of precursors and stromal elements of HIM) structural and functional organization of the bone marrow [27, 73]. This stimulation of proliferation of clonogenic cells occurs due to enhanced secretion of hemopoietic growth factors by T cells during the later stages of the experiment due to their accumulation and interaction with adherent cells in hemopoietic organs (Fig. 5).

Thus, the intensity of growth and differentiation of hemopoietic cells depends on the damaging effect of cytostatic drugs on different HIM elements [13]. For instance, 5-fluorouracil primarily disturbs functional activity of mononuclear phagocytes, while T lymphocytes are relatively resistant to this drug [27, 53,71]. Cyclophosphamide exerts a pronounced toxic effect on T cells [71]. Both these preparations uncouple cooperative interaction of T lymphocytes and macrophages in the regulation of the cell cycle of polypotent stem cells, which leads to their predominant proliferation (5-fluorouracil) or differentiation (cyclophosphamide). Pathological disintegration of hemopoiesis was also observed after radiation exposure [93]. Under conditions of disturbed cell-cell cooperation between different HIM components, the function of the hemopoietic tissue is determined by the spectrum of produced humoral substances (cytokines, glycosaminoglycans). In other words, under these con-

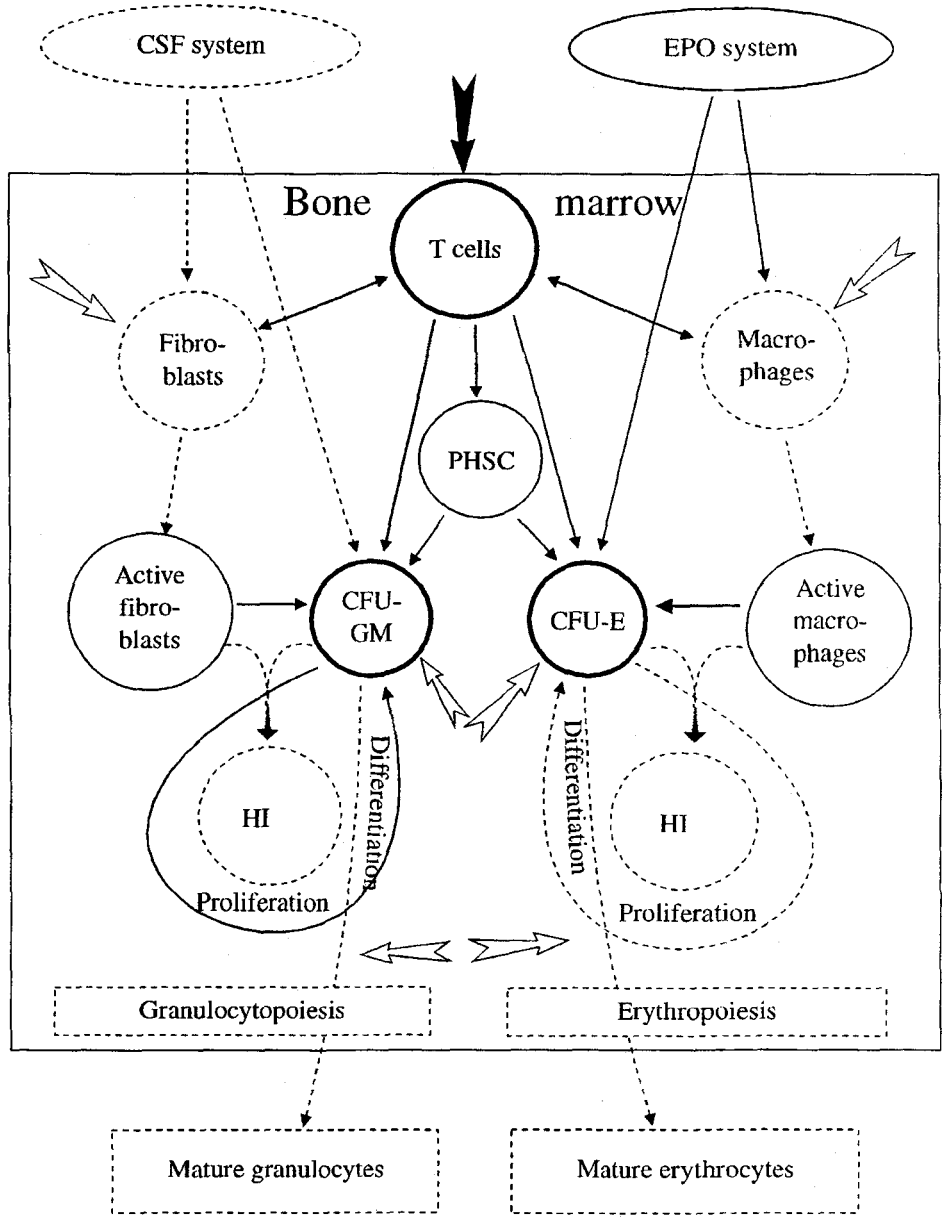

Fig. 5. Regulation of hemopoiesis in hemosuppression caused by fluoropyrimidine antimetabolite (5-fluorouracil). Activating (dark arrow) and inhibiting (open arrows) effects of the sympathetic nervous system.

ditions T lymphocytes can regulate cell proliferation (in particular, via IL-3), while adherent cells control cell differentiation (probably, through IL-1).

The existence of common nonspecific cross-points (migration of T lymphocytes to the bone marrow, activation of HIM and hemopoietic precursors) for stress and myelosuppression induced by extreme factors, in particular, radiation injury [2,7,20,41,43,44,48,62] poses the question on universal neuroendocrine mechanisms regulating physiological and emergency regeneration of the hemopoietic tissue.

Hemopoiesis-inhibiting factors (cytostatics, radiation, *etc.*) disturb structural and functional integrity of the hemopoietic tissue and possess a pronounced neuroendocrine component associated with activation of stress-realizing systems of the organism [88,97]. In comparison with factors producing no myelosuppression, under these conditions, hemopoiesis is in a more closely correlation dependence on autonomic transmittory (primary, catecholamine) control [27]. However, in contrast to pure stress-reaction, the positive causal relationship between the sympathoadrenal and blood systems is disrupted. Uncoupling of hemopoietic mechanisms characteristic of hemopoiesis-suppressing stimuli is potentiated by adrenergic influences inhibiting recovery of damaged hemopoietic precur-

sors and HIM elements against the background of stimulation of relatively resistant cells of the blood system. These processes attenuate regeneration of the hemopoietic tissue.

For instance, after treatment with high doses of 5-fluorouracil catecholamines potentiate cytostatic-induced inhibition of proliferation and differentiation of erythroid and, to a lesser extent, granulocyte-macrophage colony-forming units (CFU) (Fig. 5) [87]. Catecholamines stimulate homing and improve functional activity of T lymphocytes relatively resistant to 5-fluorouracil, but on the other hand they inhibit recovery of HIM (number and secretory capacity of adherent cells and their ability to form hemopoietic islets though cell-cell interactions) [26,65]. This impairs cooperation of HIM cell in the regulation of proliferation and differentiation of stem cells [65] and determines long-term regeneration dynamics typical of 5-fluorouracil [85]. The same vector of regulatory (suppressive/stimulating) effects of catecholamines is observed after treatment with high doses of cyclophosphamide to tumor-bearing or healthy experimental animals [27,97]. Other stress-realizing hormones glucocorticoids produce similar modulating effects on hemopoiesis under conditions of cytostatic treatment.

Another principal question is the role of local and distant regulatory systems in the maintenance of hemopoiesis base in the norm, *i.e.*, under optimal conditions. We believe that neuroendocrine substances, including transmitters of the autonomic nervous system [27,57], hormones produced by the adrenal cortex [57, 67], and opioid peptides [18] had no direct effects on proliferation and differentiation of hemopoietic precursors under conditions of steady-state hemopoiesis (*i.e.* the system function autonomously). In particular, modulation of functional activity of the neuroendocrine apparatus (adrenal cortex and medulla, opioidergic system) in animals not exposed to extreme factors had no significant effect on hemopoiesis [24]. T lymphocyte deficiency modeled in intact animals (*i.e.* deficit of an important messenger of distal and local hemopoietic regulatory systems also had practically no effect on parameters of the blood system [99]. Nevertheless, the existence of an anatomical unit, so-called neuroreticular complex [109] implying the involvement of nerve terminals in the formation of HIM, suggests the possibility of indirect regulation of intact hemopoiesis by higher regulatory centers. This regulation can be effected via modulation of the metabolism, oxygen consumption, and erythropoietin secretion [82,89] via trophogenic influences on metabolic processes [93] in HIM cells, which, in turn, regulate proliferation and differentiation of hemopoietic elements [126]. A low level of humoral hemopoiesis regulators produced by stromal bone marrow cells under normal conditions [5] probably determines their dominant role in renewal of cell populations via cell-cell interactions. The minimum number of horizontal (within the bone marrow) and vertical correlation relationships [26,27] reflects unchanged organism's requirements in functionally mature blood cells under optimal conditions.

In summary, it should be noted that the validity of the proposed theory of dynamic regulation of hemopoiesis is confirmed in applied studies. For instance, it provided the basis for using neuropharmacological substances in the treatment of postcytostatic myelosuppression in clinical practice [27]. Some highly effective hemostimulators, glycosaminoglycan derivatives, were created [9], the use of recombinant cytokines is pathogenetically substantiated [75], and the mechanisms of somatization of neurosis [63] and the development of leukemia [5] are now studied.

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