GENERAL PATHOLOGY AND PATHOLOGICAL PHYSIOLOGY

Role of Mast Cells in Regulation of Erythropoiesis during Inflammation

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Using the mouse model of acute infectious peritonitis caused by *Escherichia coli*, we have shown that preliminary osmotic elimination of peritoneal mast cells markedly affects the erythron reaction and its mechanisms during inflammation. Activation of local regulatory mechanisms of erythropoiesis (hemopoiesis-inducing microenvironment) and less pronounced hyperplasia of the erythron in the bone marrow were noted.

Key Words: *inflammation; erythropoiesis; mast cells*

Our previous studies show that must cells modulate the intensity of granulomonocytopoiesis during inflammation [4]. It was also shown that inflammation is characterized by marked stimulation of erythropoiesis and on days 6-9 of inflammation by hyperplasia of erythron in the bone marrow due to activation of proliferation and differentiation of committed erythropoiesis precursors, hemopoiesis-inducing microenvironment (HIM) of the bone marrow, and the erythropoietin system [2].

The aim of the present study was to evaluate the role of mast cells in the regulation of erythropoiesis in inflammation.

MATERIALS AND METHODS

Experiments were carried out on 204 male CBA mice weighing 18-20 g. The model of inflammation was infectious peritonitis caused by *Escherichia coli* strain ATCC 25922 inoculated intraperitoneally in 0.3 ml isotonic NaCl solution in a dose of 0.5 LD_{50} [4]. The mice were decapitated at various times of the inflammatory process, and the total number of myelokaryocytes per femur and myelogram were counted. In the bone marrow, committed erythropoietic precursors, erythroid colony-forming units (CFU-E) [10], and hemopoietic islets [1,9] were counted, and erythropoietic activity of blood serum and conditioned media of adherent and nonadherent bone marrow cells was determined [12]. Conditioned media were obtained by culturing adherent or nonadherent myelokaryocytes (2×10^6 cells/ml) in complete RPMI-1640 medium supplemented with 10% fetal bovine serum for 24 h in the presence of 10 μg/ml lipopolysaccharide from *E. coli* serotype 0111:B4 (Sigma) or 5 μg/ml concanavalin A (ConA, Sigma). Mast cells were eliminated by intraperitoneal injection of 1.8-2 ml distilled water 10 days before peritonitis [7,11].

RESULTS

Natural inflammation was characterized by a short-term rise of erythroid elements in the bone marrow by hour 12 and hyperplasia of the erythron on days 6-9. In the absence of mast cells, the number of erythrokaryocytes rose considerably on day 1 (Fig. 1, *a*), i.e., erythron hyperplasia practically did not develop.

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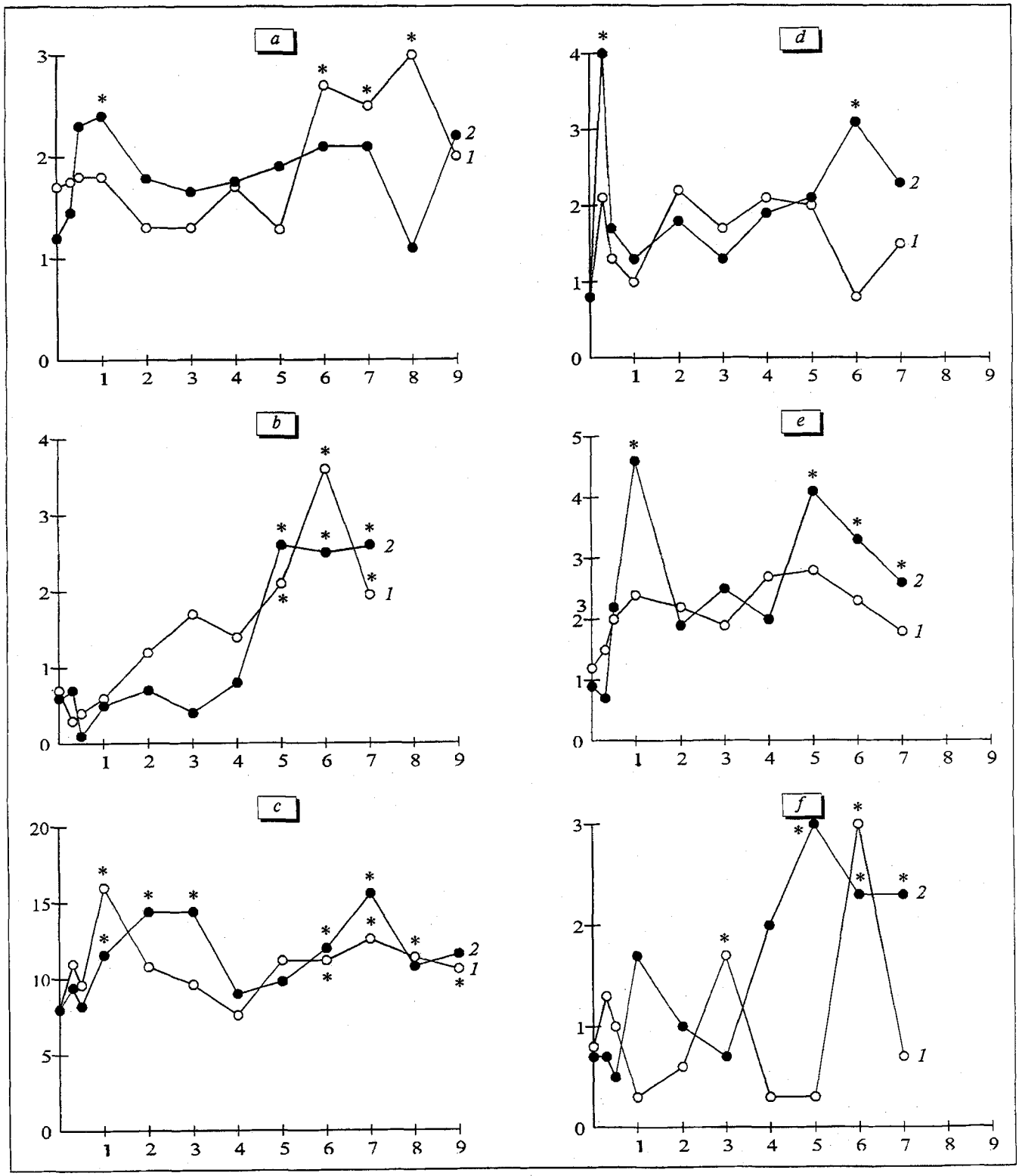

Fig. 1. Content of erythroid cells (×10^6/femur, *a*), erythroid colony-forming units (per 10^5 cells, *b*), macrophage-positive hemopoietic islets (×10^3/femur, *c*) in the bone marrow. Erythropoietic activity of adherent (per 10^5 cells, *d*), and nonadherent (per 10^5 cells, *e*) myelokaryocytes and blood (per 10^5 cells, *f*) in mice with acute infectious peritonitis induced under natural conditions (*1*) and in the absence of mast cells (*2*). Abscissa: days. *p=0.05 compared with the control.

The number of CFU-E surpassed the initial value on days 5-7 in both cases; however, in the absence of mast cells this parameter was slightly lower than on days 3 and 6 in natural inflammation (Fig. 1, *b*).

The dynamics of macrophage-positive islets (represented primarily by erythroid islets [1]) was similar in both series, but in the absence of mast cells the increase in the number of these islets was more prolonged in its first phase and more pronounced in the second phase and exceeded that observed in natural inflammation on days 2-3 and 7 (Fig. 1, *c*).

Erythropoietin-stimulating activity (EPA) in supernatants of lipopolysaccharide-stimulated adherent myelokaryocytes in inflammation induced in the absence of mast cells surpassed that observed under natural conditions on hour 6 and day 6 (Fig. 1, *d*); EPA in supernatants of ConA-stimulated nonadherent myelokaryocytes surpassed the level observed in natural inflammation after 24 h and on days 5-7 (Fig. 1, *e*).

Thus, elimination of mast cells markedly affects the erythron reaction and its mechanisms in inflammation. We noted a more strained functioning of local mechanisms of hemopoiesis regulation involved into the formation of HIM. This manifests itself in a larger number of hemopoietic islets, structural and functional associations, and the sites of proliferation and differentiation of hemopoietic cells from committed precursors to mature forms [1,9]. The production of EPA-factors, which are responsible for stimulation of proliferation and differentiation of committed erythroid precursors [12], by adherent and nonadherent bone marrow elements was noted. However, despite the more strained functioning of local regulatory mechanisms of erythropoiesis, hyperplasia characteristic of natural inflammation did not develop. This is consistent with the absence of marked hyperplasia of the granulomonocytic series in the bone marrow in inflammation induced in the absence of mast cells, despite a more pronounced early activation of HIM and stimulation of granulomonocytopoiesis [4,5].

The more strained functioning of HIM during the second phase of its activation (corresponding to bone marrow hyperplasia in natural inflammation) probably represents a compensatory reaction to the absence of an adequate effect (a rise of CFU-E and erythroid hyperplasia), i.e., a feedback mechanism. Presumably, these bioactive substances normally produced by mast cells are involved into realization of the effect of EPA (HIM) on proliferation and differentiation of committed erythroid precursors.

It should be noted that elimination of mast cells induced less pronounced changes in erythropoiesis than in granulomonocytopoiesis, which can be attributed to the key effector role of granulocytes and monocytes in inflammation [8].

This agrees with the concept that the hemopoietic response depends on the nature of damaging factor and the main pathological process. For instance, immobilization stress equally stimulates erythro- and granulomonocytopoiesis, while in acute bleeding, the erythron response dominates [3].

The erythron response in inflammation indicates that changes in hemopoiesis under these conditions are nonspecific and characteristic of stress, which accompanies inflammation. Changes in the regulation of erythropoiesis in inflammation induced in the absence of mast cells are more pronounced in the earlier period, which implies a stress-dependent pattern of this reaction.

We should also point to a delay in the rise of blood EPA in inflammation induced in the absence of mast cells: it surpassed the initial level on days 5-7 *vs.* days 3 and 6 in natural inflammation (Fig. 1, *f*). Blood EPA reflects the functioning of the erythropoietin system, which provides the main remote control of erythropoiesis. Delayed activation of this system is probably responsible for the absence of an adequate erythron hyperplasia in the bone marrow. It cannot be excluded that disturbed regulation of erythropoiesis proves the participation of mast cell-derived bioactive products in coordination (interaction) of remote and local regulatory mechanisms. It has been previously found that inflammation in the absence of mast cells is characterized by a delayed rise of colony-stimulating activity in the blood [5]. Since EPA and colony-stimulating activity in inflammation are also provided by activated monocyte-derived macrophages [8], the delayed rise of EPA and colony-stimulating activity in the blood can be attributed to inhibited migration and reduced functional activity of monocytes in the inflammation focus and in the blood [4,6].

REFERENCES

1. E. D. Gol'dberg, A. M. Dygai, Yu. M. Zakharov, *et al.*, *Gematol. Transfuziol.*, No. 3, 20-23 (1990).
2. E. D. Gol'dberg, A. M. Dygai, N. A. Klimenko, *et al.*, *Byull. Eksp. Biol. Med.*, **120**, No. 10, 382-384 (1995).
3. A. M. Dygai and V. P. Shakhov, *Role of Cell-to-Cell Contacts in Regulation of Hemopoiesis* [in Russian], Tomsk (1980).
4. N. A. Klimenko, A. M. Dygai, E. V. Abramova, *et al.*, *Byull. Eksp. Biol. Med.*, **112**, No. 9, 305-307 (1991).
5. N. A. Klimenko, A. M. Dygai, B. Yu. Gumilevskii, *et al.*, *Gematol. Transfuziol.*, No. 4, 16-19 (1992).
6. N. A. Klimenko and G. Yu. Pyshnov, *Byull. Eksp. Biol. Med.*, **115**, No. 1, 29-30 (1995).
7. P. U. Lipshits and N. A. Klimenko, *Ibid.*, **84**, No. 12, 660-664 (1977).
8. A. N. Mayanskii and D. N. Mayanskii, *Essays on the Neutrophil and Macrophage* [in Russian], Novosibirsk (1989).
9. P. R. Crocer and S. Gordon, *J. Exp. Med.*, **162**, 993-1014 (1985).
10. N. N. Iscove, F. Sieber, and K. N. Winterhalter, *J. Cell. Physiol.*, **83**, 309-315 (1974).
11. Y. Kanakura, A. Kuriu, N. Waki, *et al.*, *Blood*, **71**, 573-580 (1988).
12. D. Metcalfe, *Hemopoietic Colonies*, Berlin (1977).