Effect of Mast Cells on Interleukin-1 Production by Exudate and Bone Marrow Macrophages in Inflammation

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A modulatory effect of mast cells (MC) on hemopoiesis in inflammation was demonstrated in our previous investigations [5]. It was established that this effect may be achieved via a modulation of the leukocyte function in a focus of inflammation and may be mediated by the hemopoiesis-inducing microenvironment of the bone marrow [5,6].

The present study was performed for a further examination of the mechanisms of MC effect on hemopoiesis in inflammation. The effect of MC on the production of interleukin-1 (IL-1) by exudate and bone marrow macrophages was studied, because IL-1 plays a key role in the activation of hemopoiesis both by leukocytes from the focus and by the hemopoiesis-inducing microenvironment [3,8].

MATERIALS AND METHODS

The experiments were carried out on 204 male CBA mice weighing 18-20 g (Rassvet nursery, Tomsk) in the fall and winter in the morning. The model of inflammation was acute infectious peritonitis, performed by i.p. injection of $1/2LD_{50}$ *E. coli* (strain ATSS 25922) 24-h culture in 0.3 ml saline [5]. The animals were decapitated at different times of inflammation. The exudate was obtained by flushing the peritoneal cavity with 2 ml saline containing 5 IU/ml heparin. The bone marrow was flushed from the femur with 1 ml 3% acetic acid. The viability of the cells was determined using trypan blue staining [4]. The IL-1 assay was performed in exudate and bone marrow adhesive cell-conditioned medium after Mizel's method [10]. Conditioned medium was prepared by cell cultivation for 24 h in RPMI-1640 culture medium containing 10% fetal calf serum with lipopolysaccharide of *E. coli* strain 0.111B4 (Sigma, USA, 10 μg/ml). The removal of MC was induced by i.p. injection of 1.8-2.0 ml sterile destilled water 10 days before peritonitis was induced [7,9].

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RESULTS

There was a biphasic augmentation (by the 6th-12th h and by the 3rd day) of IL-1 production by the exudate macrophages under natural conditions of inflammation with a maximum toward the 6th h (Fig. 1, *a*). In the absence of MC this was also maximal after 6 h and significantly increased after 12 hours. However, later it did not differ from the initial level (Fig. 1, *a*), which is in agreement with the data on a reduced accumulation of monocytes in inflammation with MC removed [5].

Bone marrow macrophage IL-1 production was also markedly stepped up and showed a wavelike variation for the typical development of inflammation (Fig. 1, *b*). It was enhanced on the 1st, 4th and 7th day. At the same time, in animals with MC removed it was already higher by the 6th hour of

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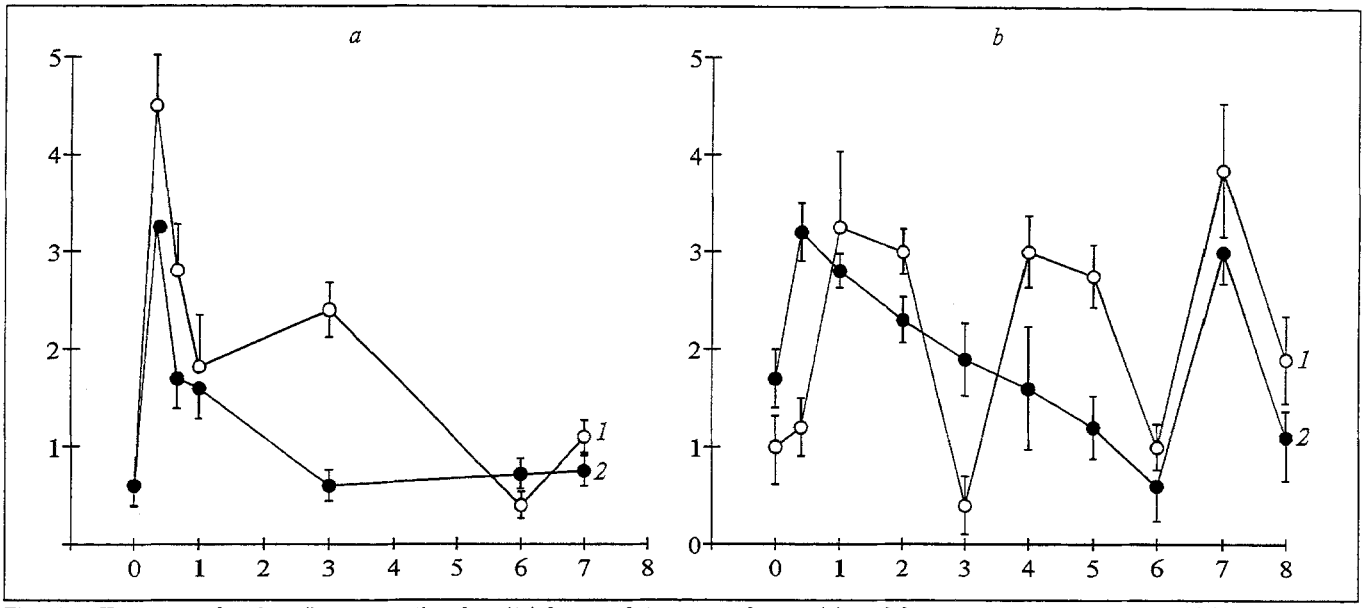

Fig. 1. IL-1-production (in conventional units) by exudate macrophages (*a*) and bone marrow macrophages (*b*) in dynamics of acute infectious peritonitis (days) in mice for natural development of inflammation (*1*) and in the absence of peritoneal MC (*2*).

inflammation and subsequently did not differ statistically from the initial level (Fig. 1, *b*).

Thus, the removal of MC results in an earlier increase of IL-1 production by bone marrow macrophages and in the abolishment of its repeated increase by either exudate or bone marrow macrophages. These findings are consistent with the data on an earlier activation of hemopoiesis, but a less expressed bone marrow hyperplasia, in particular, of its erythrocytic portion, in inflammation without MC [5].

The obtained results attest to the fact that the modulatory effect of MC on hemopoiesis in inflammation realizes itself mostly via variations in IL-1 synthesis by exudate and bone marrow macrophages. Under natural conditions of inflammation the MC stimulate the functional activity of the monocytes and macrophages in the focus of inflammation, leading to a repeated elevation of IL-1 production. In its turn, this reincrease probably provides for the further activation of bone marrow macrophages and initiation of their own IL-1 production, which induces a proliferation and differentiation of the hemopoietic stem cells. As this takes place, the effect of IL-1 from either the inflammation focus or the bone marrow (lymphocyte-activating factor) may be realized by the lymphokines produced by T cells, which are involved in the regulation of hemopoiesis during inflammation. As we demonstrated previously, the development of bone marrow hyperplasia is preceded by a pronounced accumulation of T lymphocytes in the hemopoietic tissue. T-cell elimination results in an abolishment of the second (corresponding to the period of bone marrow hyperplasia) peak of colony formation (CFU-GM, CFU-E), and in the suppression of the colony-stimulating and erythropoietic activity not only by the nonadhesive, but also by the adhesive myelokaryocytes [1,2].

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