Interleukin-18 Induces Acute Biphasic Reduction in the Levels of Circulating Leukocytes in Mice

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We investigated the acute hematological changes caused by interleukin-18 (IL-18) in mice. Intraperitoneal administration of IL-18 (2 μg/mouse) resulted in biphasic decreases in the number of leukocytes in the blood. The first phase of decrease occurred within 2 h of IL-18 administration and was followed by a transient increase at 5 h. The second phase of decrease occurred at around 6 h, reaching a nadir which lasted for more than 24 h. In mice deficient in inducible nitric oxide (NO) synthase, the first phase of decrease was not observed although the second phase of decrease was observed. In mice deficient in gamma interferon (IFN-γ) or in mice depleted of natural killer cells and incapable of producing IFN-γ, IL-18 had no effect on the number of circulating leukocytes. Levels of nitrite and/or nitrate in the serum were elevated within 2 h after IL-18 administration, followed by a decrease in the basal level and a second increase at 6 h. Levels of IL-18 receptor mRNAs also showed biphasic changes in correlation with the changes in serum IFN-γ levels. These results suggest that the changes in the leukocyte number following IL-18 administration are mediated by NO and IFN-γ, with NO being involved in the first phase of reduction and IFN-γ being involved in both phases.

Interleukin-18 (IL-18), which was discovered as a gamma interferon (IFN-γ)-inducing factor, carries out various biological activities in immune and inflammatory reactions (5, 12, 20, 26). Up-regulation of natural killer (NK) cell-mediated cytotoxicity, induction of Fas ligand, and development of type 1 T-helper (Th1) cells were the first major actions of IL-18 to be demonstrated. Recently, IL-18 has been shown to induce Th2 cytokines such as IL-4 and IL-13 (9). In addition, IL-18 has been reported to exhibit an antitumor effect (17), enhance eosinophil recruitment in pulmonary inflammation (34), and stimulate nitric oxide (NO) formation (8, 11).

Biological actions of IL-18 are mediated by its specific receptor. The IL-18 receptor consists of an α-chain (IL-18Rα) and an accessory protein-like molecule (IL-18Rβ), both of which have been cloned as IL-1β receptor-related molecules (3). IL-18 is similar to IL-1β in that it exhibits biological activities by using signaling systems consisting of MyD88, IRAK, TRAF 6, and NF-κB (24). IL-18 resembles IL-1α in many other functions and is now classified as a proinflammatory cytokine in the IL-1 family (6).

It has been shown that administration of proinflammatory cytokines in mice or rats results in changes in the number of circulating leukocytes. For instance, tumor necrosis factor alpha (TNF-α) and granulocyte-macrophage colony-stimulating factor have been shown to decrease levels of circulating lymphocytes and neutrophils in rats (32, 33). Administration of IL-1β has been reported to reduce the number of circulating leukocytes in rats (32).

Although IL-18 resembles IL-1β in various functions, it is not known whether IL-18 induces hematological effects similar to those seen with IL-1β. In this study, we administered IL-18 to mice and analyzed changes in the number of circulating blood cells. We found that IL-18 causes a reduction in the leukocyte number in a biphasic manner. These changes in the leukocyte number were partially or completely abolished in mice deficient in inducible NO synthase (iNOS) or IFN-γ, respectively, suggesting that the hematological effects of IL-18 may be mediated by NO and IFN-γ.

**MATERIALS AND METHODS**

**Experimental animals.** C57BL/6 mice and iNOS-knockout mice were purchased from Japan SLC Inc. (Shizuoka, Japan) and Jackson Laboratory (Bar Harbor, Maine), respectively. Both IFN-γ- and TNF-α-knockout mice were kindly provided by Y. Iwakura (Tokyo University). They were kept under conditioned air at 22 ± 2°C. All experimental procedures were approved by the Animal Care Committee of the Hyogo College of Medicine.

**Cytokine administration.** Recombinant mouse IL-18 and IL-12 (both provided by Hayashibara Biochemical Laboratories, Okayama, Japan) were dissolved in phosphate-buffered saline containing heat-inactivated normal mouse serum (0.5%). IL-18 (2 μg) and IL-12 (10 ng) were administered in a bolus singly or in combination into the peritoneal cavity of each mouse at a total volume of 0.2 ml/mouse.

**Blood cell count.** At appropriate times (0.5, 1, 2, 4, 6, and 24 h) after cytokine administration, mice were sacrificed by excess ether anesthesia and blood samples were collected in vacuum test tubes containing lithium heparin and EDTA for hematocyte counting. Red blood cells, leukocytes, and platelets in
each blood sample were stained with hematoxylin-cosin stain and counted under a microscope.

Depletion of the NK cell levels in vivo. In order to deplete the levels of NK cells in vivo, mice were intravenously injected with rabbit anti-asialo GM1 antibody (0.5 mg/mouse; Wakо Pure Chemical Industries, Ltd., Osaka, Japan). Four days later, these mice were subjected to the experimental conditions. To confirm the effect of the anti-asialo GM1 antibody treatment, splenocytes (10⁶ cells) were treated with a combination of fluorescein isothiocyanate-conjugated anti-mouse CD3 antibody (clones 145-2C11 and PM-01084D; BD-Pharmingen, San Diego, Calif.) and phycoerythrin-conjugated anti-mouse IL-2R-β-chain antibody (clones TM-β1 and PM-01925B; BD-Pharmingen) for 30 min on ice and then analyzed by flow cytometry on a fluorescence-activated cell sorter (FACSCalibur; Becton Dickinson, Cowley, United Kingdom). NK cells were visualized as a population of CD3-negative and IL-2R-β-chain-positive cells by the computer program Cell Quest (version 3.01; 1996; Becton Dickinson).

ELISA. Concentrations of IL-18 in serum were measured by an enzyme-linked immunosorbent assay (ELISA) kit purchased from Medical and Biological Laboratories (Tokyo, Japan). IFN-γ and IL-12 p70 were analyzed by ELISA development systems purchased from BD-Pharmingen. Serum NO₂⁻ and/or NO₃⁻ levels were determined by a kit consisting of Greiss reagents (Dojin Chemical Laboratories, Kumamoto, Japan). All the procedures were performed according to the manufacturer’s instructions.

Analysis of IL-18 receptors by RT-PCR. For reverse transcriptase (RT)-PCR, total mRNA was extracted from splenocytes by Isogen, a reagent for RNA extraction (Nippon Gene Co., Ltd., Tokyo, Japan) according to the manufacturer’s instructions. First-strand cDNA was synthesized with the GeneAmp RNA PCR kit (Perkin-Elmer) and 32 cycles of PCR in a GeneAmp DNA thermal cycler (model 9700; Perkin-Elmer). Primers for murine IL-18Rα, IL-18Rβ, and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) were synthesized by Sawady Technology (Tokyo, Japan) (Table 1). Each PCR cycle consisted of 45 s of denaturation at 94°C, 45 s of annealing at 58°C, and 2 min of extension at 72°C. After the final cycle, the temperature was held at 72°C for 7 min to allow reannealing of the amplified products. The PCR product was separated by electrophoresis in a 2.0% agarose gel, stained with ethidium bromide, and analyzed by densitometry in an ATTO (Tokyo, Japan) densitograph. The intensities of IL-18Rα and IL-18Rβ bands were normalized against that of GAPDH.

Statistical analysis. Data were analyzed by Dunnett’s test for multiple comparisons. A P value of < 0.05 was considered to represent a statistically significant difference. Results were expressed as the means ± standard errors of the repeated experiments.

RESULTS

IL-18 induces a biphasic reduction of circulating leukocytes. Administration of IL-18 (2 μg/mouse) in mice caused a biphasic reduction in the number of circulating leukocytes. The first reduction (~45%) occurred within 1 h after IL-18 administration and was followed by a recovery to the original level in 3 to 5 h (Fig. 1a). The second phase reduction occurred at 6 h, with the leukocyte counts remaining low for more than 24 h (Fig. 1b). Administration of IL-12 (10 ng/mouse) resulted in an approximately 25% reduction in the leukocyte number within 1 h, which remained relatively unchanged for 24 h (Fig. 1b). Combined administration of IL-12 and IL-18 also resulted in a monophasic reduction in the levels of leukocytes to 50% of the initial level (Fig. 1c). There was no synergism between IL-18 and IL-12 with respect to the hematological effect.

Analysis of the leukocyte population revealed that levels of

### TABLE 1. Sequences of specific primers for RT-PCR

| Target gene | Type of primer | Primer sequences | Annealing temp (°C) | Size (bp) |
|-------------|----------------|------------------|---------------------|-----------|
| IL-18Rα     | Sense          | 5'-CGT GAC AAG CAG AGA TGT TG-3' | 58                 | 428       |
|             | Antisense      | 5'-ATG TTG TCG TCT CCT TTC TG-3' |                     |           |
| IL-18Rβ     | Sense          | 5'-ATG CTC TGT TTG GCC GTG GT-3' | 58                 | 427       |
|             | Antisense      | 5'-CTG TCT TGA TAC AAC AGG CCA-3' |                     |           |
| GAPDH       | Sense          | 5'-CCA TCA CCA TCT TCC AGG AGC GAG-3' | 55                 | 347       |
|             | Antisense      | 5'-CAC AGT CTT CTG GGT GCC AGT GAT-3' |                     |           |

FIG. 1. Time course of the changes in leukocyte counts in mice after administration of IL-18 (a), IL-12 (b), and their combination (c). IL-18 (2 μg/mouse), IL-12 (10 ng/mouse), or a combination of the two was administered in a bolus into the peritoneal cavity of each mouse, and at the indicated times, blood was collected and leukocytes were counted. Symbols and bars represent means ± standard errors (n = 3 to 6), respectively. Open and filled circles express the leukocyte numbers before and after IL-18 treatment, respectively. *, P < 0.05; and **, P < 0.01, compared with that for the value before treatment (Dunnett’s test for multiple comparison).
neutrophils (Fig. 2a) and lymphocytes (Fig. 2b) were reduced as a result of IL-18 administration. The reduction was more pronounced in the neutrophil fraction than in the lymphocyte fraction. IL-18 did not affect the number of red blood cells (Fig. 2c) or platelets (Fig. 2d).

Time course of appearance of IL-18 and IL-12 in blood. In our preliminary experiments (unpublished data), we found that IL-18 (2 μg/mouse) injected in a bolus into the peritoneal cavity moved into the blood within 15 min after administration. The concentration of IL-18 in serum was 217 ± 23 ng/ml and 275 ± 20 ng/ml 30 and 45 min after the administration of IL-18, respectively (Fig. 3a). These results are consistent with the long half-life of IL-18 (16 h) observed in our earlier experiments (unpublished data). IL-12 (10 ng/mouse) similarly administered into mice also rapidly moved into the blood flow, reaching the maximum level in 1 h (Fig. 3b). However, IL-12 levels rapidly decreased, essentially disappearing 5 h later (Fig. 3b).

Hematological effects of IL-18 in various knockout mice. In IFN-γ-knockout mice, IL-18 administration exerted no effect on the circulating leukocyte count (Fig. 4a). In NO-knockout mice, on the other hand, IL-18 caused a monophasic reduction in the number of circulating leukocytes 6 h after administration. This corresponded to the second phase reduction observed in normal mice (Fig. 1a and 4b). In TNF-α-knockout mice, IL-18 caused a biphasic reduction of the leukocyte counts in a manner somewhat similar to that for normal mice (Fig. 4c).

Induction of IFN-γ and NO in serum. Induction of IFN-γ and NO, known mediators of hematological responses, into the serum was analyzed in mice after the administration of IL-18, IL-12, or their combination. Administration of IL-18 caused a marked induction of IFN-γ, which reached a peak level at 2 h. The IFN-γ level then rapidly decreased to a basal level within the next 2 h but increased again to a moderate level at 6 to 24 h (Fig. 5b). In contrast, administration of IL-18 and IL-12 together resulted in only low levels of induction of IFN-γ in the first 4-h period, followed by high levels of IFN-γ induction at 6 h, which lasted until 24 h (Fig. 5c) (19).

Administration of IL-18 caused increases in levels of nitrite.
and/or nitrate, metabolites of NO, in serum, which reached a maximal level at 4 h and then decreased gradually (Fig. 6). On the other hand, TNF-α was not detected in the serum at any of time points analyzed after IL-18 administration (data not shown).

Effects of NK cell depletion on IL-18-induced changes in the number of circulating leukocytes and levels of IFN-γ and nitrite and/or nitrate. Flow cytometric analysis showed that in normal mice, 2.81% of cells in the spleen are NK cells that are CD3 negative and IL-2Rα positive. The treatment of mice with the anti-asialo GM1 antibody caused an almost complete disappearance of these cells (from 2.81% to 0.16%) (Fig. 7a). Treatment of these mice with IL-18 resulted in increases in the number of leukocytes at 2 and 4 h followed by decreases from the original level (Fig. 7b). Thus, in mice treated with anti-asialo GM1 antibody, an early rapid decrease in the leukocyte number observed in normal mice (Fig. 1a) did not occur. No induction of IFN-γ and nitrite and/or nitrate by IL-18 was observed in the mice treated with anti-asialo GM1 antibody (data not shown).

FIG. 4. Effect of IL-18 on the leukocyte count in IFN-γ-knockout (a), INOS-knockout (b), and TNF-α-knockout (c) mice. IL-18 (2 μg/mouse) was administered in a bolus intraperitoneally in IFN-γ-, INOS-, and TNF-α-knockout mice. At the indicated times, blood was collected and leukocytes were counted. Columns and bars represent means and standard errors (n = 3), respectively. **, P < 0.01, compared with that for the value at time zero (Dunnett’s test for multiple comparison).

Changes in IL-18R mRNA levels after IL-18 administration in mice. We analyzed the expression of IL-18 receptor mRNAs in splenocytes in mice at different times after the administration of IL-18. IL-18Rα mRNA levels were reduced to an undetectable level at 2 h after IL-18 administration but increased moderately at 4 and 6 h (Fig. 8, upper panel). IL-18Rβ mRNA levels were also reduced but to a lesser extent (Fig. 8, lower panel). These changes corresponded to the changes in serum IFN-γ levels after IL-18 administration (Fig. 5a). On the other hand, no changes in the expression of both IL-18Rα and IL-18Rβ mRNAs were observed in the splenocytes of IFN-γ-deficient and NK-depleted mice (data not shown).

FIG. 5. Time course analysis of IFN-γ levels in serum after administration of IL-18 (a), IL-12 (b), and their combination (c) in mice. IL-18 (2 μg/mouse), IL-12 (10 ng/mouse), or a combination of the two was administered in a bolus intraperitoneally in mice. At the indicated times, blood was collected and serum IFN-γ levels were measured by ELISA. Columns and bars represent means and standard errors (n = 3 to 5), respectively. *, P < 0.05; and **, P < 0.01, compared with that for the value at time zero (Dunnett’s test for multiple comparison).
DISCUSSION

Proinflammatory cytokines IL-1β and TNF-α have been proposed to play a role in hematological changes accompanying acute inflammation, such as lymphopenia and neutrophilia (29, 32, 33). Earlier, it was observed that daily administration of IL-18, like IL-1β, induced neutrophilia in mice by 10 days (22). However, in this study, we found that bolus administration of IL-18 resulted in the acute reduction of circulating leukocyte numbers in a biphasic manner in C57BL/6 mice. No such effect was observed in IFN-γ-knockout mice, suggesting that the IL-18-induced reduction in the number of leukocytes was mediated by IFN-γ. IL-18 has been reported to induce TNF-α, which has been reported to cause a reduction in the number of circulating lymphocytes 6 h after administration in rats (25, 31). In this study, however, we found no induction of TNF-α in the serum samples of mice treated with IL-18 (data not shown), suggesting that it was unlikely that TNF-α was involved in IL-18-induced leukocyte reduction. In addition, we observed that IL-18 induced the reduction in leukocyte levels
in TNF-α-knockout mice in a manner similar to that in the wild-type mice.

Leukopenia, often observed in patients receiving IFN therapy, has been suggested to be due to the suppression of lymphocyte recruitment (16). It has been demonstrated that the leukopenia induced by IFN-γ is due to the enhancement of the expression of CD62L (L-selectin) in leukocytes and CD54 (intercellular adhesion molecule-1) in endothelial cells (18, 35). These molecules have been shown to be profoundly involved in leukocyte migration (7, 15). We found in this study that the depletion of NK cells by using anti-asialo GM1 antibody resulted in the abolition of the IL-18-induced production of IFN-γ as well as the reduction of leukocyte numbers. This suggests that the cellular source of IFN-γ mediating the effects of IL-18 is the NK cells. Since NK cells constitutively express IL-18 receptor (13), it is conceivable that these cells are stimulated by exogenously administered IL-18 to secrete IFN-γ. In support of this, we observed that the single administration of IL-18 induced the secretion of IFN-γ into the bloodstream.

Induction of IFN-γ by IL-18 has been reported to require collaboration with IL-12 (14, 23, 30). Our results may be explained if we assume that IL-18 injected intraperitoneally functions with endogenous IL-12.

NO plays several roles in host defense against infection, maintenance of vascular tone, tissue injury, and neurotransmission (2). In this study, we found that single administration of IL-18 induced the production of low levels of NO. IL-18, when administered to mice in combination with IL-12, causes the production of a large amount of NO in an IFN-γ-dependent manner (4). Activation of transcription factors IRF-1 and NF-κB is required for the efficient induction of iNOS mRNA (10, 27, 28). Since IL-18 stimulates IFN-γ production, it is probable that IL-18 activates IRF-1 via IFN-γ. In addition, IL-18 has been shown to activate NF-κB and NF-AT (30). Thus, IL-18 is likely involved in iNOS induction and in support of this, we detected NO metabolites in serum in a micrometer range 4 to 6 h after the administration of IL-18. Our observation that depletion of NK cells by anti-asialo GM1 antibody treatment completely abolished NO synthesis as well as IFN-γ production induced by IL-18 suggests that NK cells are involved in NO synthesis through IFN-γ production.

In iNOS-knockout mice, IL-18 induced only the second phase of reduction of leukocytes, suggesting that NO produced by IL-18 is responsible for the early reduction (first phase reduction) of leukocytes. It has been reported that inhaled NO gas reduces the leukocyte count in rabbits (21). Taken together, these results suggest that IL-18 rapidly induced NO production that causes quick reduction in leukocyte levels.

IFN-γ, on the other hand, is likely involved in both the first and second phases of reduction of leukocyte numbers because the biphasic increase in serum IFN-γ levels corresponded to the biphasic decreases in leukocyte levels after IL-18 administration. The transient decrease in IFN-γ levels 4 h after IL-18 administration might be due to the reduction in IL-18 receptor expression because similar decreases were observed in levels of IL-18Rα and IL-18Rβ mRNAs at that time. The reduction in IL-18 receptor expression was not observed in the IFN-γ-deficient mice which had received IL-18, suggesting that IFN-γ produced after IL-18 administration is involved in this change. Reduction of IL-18 receptor expression following IL-18 treatment may also be a feedback inhibitory loop for IFN-γ signaling to prevent excessive Th1 responses (overproduction of IFN-γ) through IL-18 and its receptors.

In humans, IL-18 has been reported to induce chemokines (1, 25), raising the possibility that IL-18 may exert hematological effects through chemokines. Our analysis of macrophage inflammatory proteins 1α and 1β after the administration of IL-18 in mice showed that IL-18 in fact induced these chemokines. However, the kinetics of induction did not correlate with changes in the leukocyte number, suggesting that these factors are not directly involved in the IL-18-induced changes in the leukocyte number.

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