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ORIGINAL ARTICLE

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Effect of interleukin 11 on normal and pathological thrombopoiesis

Abstract Interleukin 11 (IL-11) is a stromal cell-derived cytokine that has multiple effects on hematopoietic and nonhematopoietic systems. In vitro, it enhances the growth of early progenitors and promotes megakaryocytopoiesis and erythropoiesis. In healthy animals, IL-11 administration stimulates megakaryocyte maturation and increases peripheral platelet counts. IL-11 accelerates the recovery of peripheral neutrophil, erythrocyte, and platelet counts in mice that have undergone cytoablative treatment. Therefore, IL-11 may be useful clinically as an agent promoting recovery from hematopoiesis. However, its clinical use in patients with hematological malignancies may be restricted because IL-11 has been reported to stimulate some leukemia and myeloma cells. In the United States, phase I trials have shown that IL-11 accelerates recovery from chemotherapy-induced or bone-marrow transplantation (BMT)-induced thrombocytopenia. In Japan, phase II trials studying the thrombopoietic effect of IL-11 in patients with solid tumors postchemotherapy, in patients undergoing BMT, and in patients with aplastic or refractory anemia are now under way. Recently, thrombopoietin (TPO) has been cloned, and its thrombopoietic effect and accelerating effect on platelet count recovery in thrombopoietic states have been demonstrated in animal models. The physiological effect of TPO is restricted to hematopoiesis; therefore, it may have fewer side effects than IL-11. However, in addition to its hematopoietic effect, IL-11 administration to mice that have undergone cytoablative therapy significantly decreases morbidity and mortality due to chemotherapy-related endogenous infections caused by gut microorganisms. Therefore, IL-11 can be used in patients postchemotherapy and post-BMT not only to promote platelet recovery but also to prevent life-threatening infections. The use of in-vitro-expanded hematopoietic stem cells for BMT or as target cells for gene therapy is one of the most exciting areas in the field of medicine. Since IL-11 can expand hematopoietic progenitor-cell populations when used in combination with other cytokines, it may be useful as an ex vivo hematopoietic progenitor-cell-amplifying agent

Key words Interleukin 11 (IL-11) · Megakaryocytopoiesis · Thrombopoiesis · Platelet

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Introduction

Proliferation and differentiation of hematopoietic cells are regulated by a family of molecules referred to as colony-stimulating factors (CSFs) and interleukins (ILs). IL-11 has recently been isolated and cloned from an immortalized primate marrow stromal cell line on the basis of its stimulatory effect on IL-6-dependent plasmacytoma cells [23]. Recombinant human IL-11 (rhIL-11) has subsequently been cloned from a human fetal lung fibroblast cell line [23].

IL-11 has multiple effects on hematopoietic and nonhematopoietic systems (Table 1), including the liver, gastrointestinal tract, lung, heart, central nervous system, bone, joint, and immune system [1, 6–9, 14, 19, 20, 23, 24]. IL-11 has various effects on hematopoiesis, affecting cell types ranging from early progenitor cells to mature blood cells. Its stimulatory effect on megakaryocytopoiesis and platelet production may be most noteworthy because no cytokine available to date has been used clinically as a thrombopoiesis-stimulating agent. In this report, we describe the in vitro and in vivo effects of IL-11, particularly on megakaryocytopoiesis and platelet production, and discuss possible future clinical applications of rhIL-11.

Table 1 Physiological effects of IL-11

Hematological effects:
Promotion of proliferation and differentiation of multilineage progenitor cells
Stimulation of proliferation of granulocyte-macrophage progenitor cells
Stimulation of proliferation of early and late erythroid progenitor cells
Promotion of proliferation and maturation of megakaryocytes
Induction of neutrophilia and thrombocytosis
Acceleration of recovery from neutropenia, anemia, and thrombocytopenia
Inhibition of lipoprotein lipase activity and adipocyte differentiation
Stimulation of the growth of myeloid leukemia cells
Autocrine growth factor in megakaryoblastic leukemia cell lines
Stimulation of the growth of myeloma and plasmacytoma cell lines
Nonhematological effects:
Enhancement of antigen-specific antibody responses
Induction of airway hyperresponsiveness
Involvement in the formation of pulmonary inflammation
Acceleration of the recovery of gastrointestinal mucosa after chemotherapy
Induction of cardiac hypertrophy
Enhancement of gastrointestinal absorption of iron
Promotion of neuronal development
Inhibition of bone formation by osteoblasts
Stimulation of osteoclast development
Stimulation of the production of metalloproteinase tissue inhibitor by chondrocytes and synoviocytes
Induction of acute-phase protein synthesis

In vitro and in vivo effects of IL-11 on megakaryocytopoiesis and thrombopoiesis

When rhIL-11 is added to mouse or human bone marrow cells in the presence of IL-3 in vitro, the number and size of megakaryocyte colonies and the ploidy of the megakaryocytes increase [2, 25]. Therefore, IL-11 is a maturation-promoting factor for megakaryocytes. Injection of rhIL-11 at 2 μg/kg i.p. into healthy mice every 12 h for 5 days increased the number of peripheral platelets (Fig. 1). Furthermore, the size and ploidy of megakaryocytes in the bone marrow were increased by IL-11 administration (Tables 2, 3). The number of megakaryocytes and progenitors [i.e., colony-forming unit-megakaryocyte (CFU-Meg)] in the bone marrow did not increase in this study, although other investigators have reported increases in the numbers of megakaryocytes and CFU-Meg in the spleen and of CFU-Meg in the bone marrow [22]. In addition, the number of white and red blood cells did not increase in this study, although leukocytosis in mice after IL-11 treatment has been reported [11].

IL-11 is known to accelerate the recovery of peripheral neutrophils, platelets, and red blood cells in mice that have undergone cytoablative treatment [5, 18]. Therefore, IL-11 may be useful clinically as an agent to promote hematopoietic recovery. However, its use may be restricted in chemotherapy-treated leukemia and myeloma patients, as it may promote leukemia and myeloma cell growth and may act as an autocrine factor in megakaryoblastic leukemia cells [13, 16, 27].

Table 2 Effect of IL-11 on murine bone-marrow megakaryocyte count and size[a]

Group	Megakaryocyte count		Megakaryocyte diameter (μm)
	Count (/mm^3)	Corrected count	
2 μg × 2 × 1 day	84.77 ± 5.15	10.73 ± 0.87	20.65 ± 0.60
Control	82.15 ± 4.13	10.89 ± 0.71	19.68 ± 0.66
2 μg × 2 × 2 days	87.23 ± 4.38	10.81 ± 0.51	21.28 ± 0.63
Control	82.67 ± 8.45	10.84 ± 1.30	20.01 ± 0.62
2 μg × 2 × 3 days	97.62 ± 3.08	10.68 ± 0.46	24.36 ± 0.57
Control	77.67 ± 5.03	10.41 ± 0.75	19.61 ± 0.43
2 μg × 2 × 4 days	95.23 ± 4.54	10.75 ± 0.51	23.18 ± 0.43
Control	82.38 ± 3.97	10.85 ± 0.45	19.84 ± 0.41
2 μg × 2 × 5 days	94.15 ± 5.23	10.74 ± 0.64	23.10 ± 0.55
Control	77.00 ± 3.51	10.34 ± 0.53	19.54 ± 0.50

[a] IL-11 at 2 μg was injected i.p. into mice every 12 h for 1–5 days. Control mice received an identical dose of heat-inactivated IL-11. Data represent mean values ± SD (n = 3). The megakaryocyte count was corrected using a standard method 12

Clinical trials of rhIL-11

Phase I trials in the United States have indicated that IL-11 accelerates recovery from chemotherapy-induced or bone-marrow transplantation-induced thrombocytopenia [3, 10]. These studies also demonstrated that significantly fewer rhIL-11-treated than -untreated patients required platelet transfusions. In Japan, phase II trials studying the effect of rhIL-11 in patients with thrombocytopenia due to chemotherapy or BMT and underlying disorders such as aplastic or refractory anemia are now under way. Preliminary data from the aplastic and refractory anemia studies showed

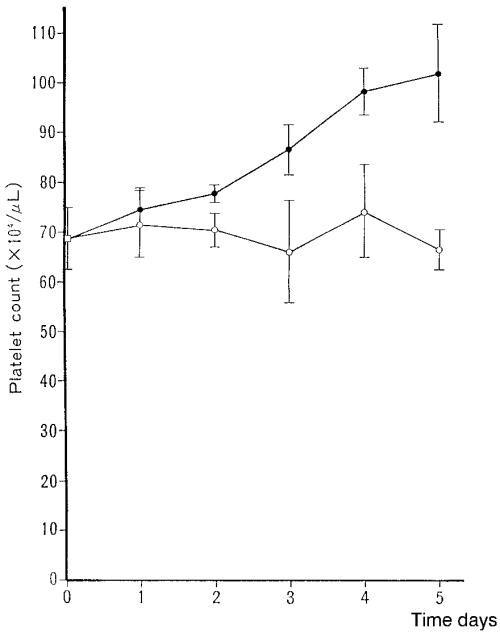

Fig. 1 Effect of IL-11 on the circulating platelet count in mice. IL-11 at 2 μg was injected i.p. every 12 h for 5 days. As a control, heat-inactivated IL-11 at 2 μg was injected i.p. *Black circles* IL-11 treatment, *white circles* heat-inactivated IL-11 treatment, *white squares* pretreatment platelet count

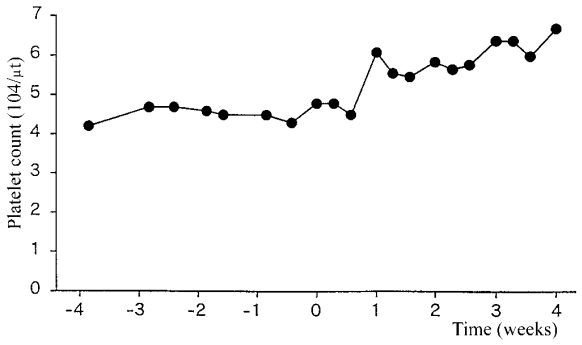

Fig. 2 Change in peripheral platelet counts measured in a patient with aplastic anemia. rhIL-11 at 50 μg/kg per day was injected s.c. for 14 days

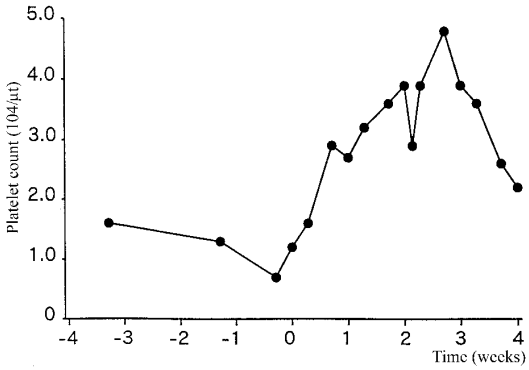

Fig. 3 Change in peripheral platelet counts measured in a patient with refractory anemia. rhIL-11 at 75 μg/kg per day was injected s.c. for 14 days

Table 3 Effect of IL-11 on the ploidy distribution of murine bone-marrow megakaryocytes[a]

	Ploidy class (%)			
Group	8 N	16 N	32 N	64 N
1 day	7.9	47.4	43.4	1.3
Control	21.7	50.0	27.2	1.1
2 days	10.9	43.9	42.0	3.2
Control	18.6	54.7	25.5	1.2
3 days	7.7	40.0	44.6	7.7
Control	19.4	51.0	28.6	1.0
4 days	6.5	38.9	52.0	2.6
Control	23.9	53.1	21.2	1.8
5 days	6.7	34.5	56.3	2.5
Control	24.5	56.1	18.7	0.7

[a] IL-11 at 2 μg was injected i.p. into mice every 12 h for 1–5 days. Control mice received an identical dose of heat-inactivated IL-11

increased platelet counts in some patients. Figure 2 shows the thrombopoietic effect of rhIL-11 in a patient with aplastic anemia. IL-11 administration at 50 μg/kg per day for 14 days produced an approximately 1.5-fold increase in the platelet count. In a patient with refractory anemia, administration of IL-11 at 75 μg/kg per day for 14 days produced an approximately 5-fold increase in the platelet count as compared with pretreatment levels, and the count remained elevated for >2 weeks after treatment (Fig. 3).

Clinical applications of rhIL-11

Preliminary clinical trial results suggest that rhIL-11 is a promising thrombopoietic agent. However, caution should be employed in future clinical trials because unpredictable side effects may occur.

Recently, clinical trials of IL-6 in patients with thrombocytopenia have been performed and clinical trials of thrombopoietin (TPO) have been initiated [4]. IL-6 has physiological effects similar to those of IL-11, probably because these cytokines share a common transducer, GP130 [26]; however, IL-11 has the possible advantage of being capable of accelerating recovery of erythropoiesis in animal models [5, 18]. The physiological effects of TPO are limited to hematopoiesis, and its thrombopoietic effect in mice has been demonstrated to be greater than that of other cytokines, including IL-11 and IL-6 [15]. Therefore, clinical trials may show that TPO has fewer side effects and a greater thrombopoietic effect than IL-11 or IL-6.

It should be noted, however, that IL-11 has been reported to stimulate recovery of small-intestinal mucosal cells injured by cytoablative therapy [6]. Serious infection during chemotherapy is related to damage to the small-intestinal mucosal barrier, allowing entry of gastrointestinal flora into the blood. IL-11 treatment of mice that had undergone cytoablative therapy produced significant increases in survival associated with IL-11-induced recovery of the small-intestinal mucosa, which decreased the incidence of bacterial infection due to gut organisms. Therefore, IL-11 might be useful not only to promote platelet recovery but also to prevent life-threatening infections that arise from the gastrointestinal tract.

The use of in-vivo-expanded hematopoietic stem cells for BMT or as target cells for gene therapy is one of the most exciting areas in medicine. In vitro studies have demonstrated that IL-11 can stimulate the proliferation of murine hematopoietic progenitors and maintain hematopoietic stem cells when used in combination with stem-cell factor (SCF) and IL-3 [21]. IL-11 can stimulate primitive human hematopoietic cells and expand the early hematopoietic progenitor-cell pool when used in combination with SCF, IL-3, and granulocyte-macrophage CSF [17]. Therefore, IL-11 may also be useful as an ex vivo hematopoietic stem-cell-amplifying agent.

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