REVIEW ARTICLE

Interleukin-11: A Multifunctional Growth Factor Derived From the Hematopoietic Microenvironment

By X.X. Du and D.A. Williams

HEMATOPOIETIC cells develop both in vitro and in vivo in direct contact with a variety of cells making up the hematopoietic microenvironment (HM). Seminal observations by Dexter et al[1] in 1976 described an in vitro culture system that mimics somewhat these cellular interactions. Subsequently, investigators from many laboratories have identified macrophages, endothelial cells, fibroblasts (advential reticular cells), and adipocytes that are key cellular components of this microenvironment.[2] Although the exact role of the HM in determining hematopoietic stem and progenitor cell behavior is not fully known, multiple possible functions have been theorized.[3] As currently envisioned, the HM provides direct cell-cell contact between supporting and hematopoietic cells, provides anchorage for both growth factors and hematopoietic cells, supplies specific positive and negative growth regulatory factors, and probably provides for multiple cellular communications within what we have termed a "local area network"[4] (Fig 1). Within this network, stromal cells probably play a key role by both producing growth regulatory proteins and secreting complex extracellular matrix proteins for stabilization of growth factors in high local concentration with adherent hematopoietic stem and progenitor cells. The behavior of both the hematopoietic cells and the stromal cells is likely modulated by signals from other cells in this local network.

In an effort to study stromal cells in the HM in detail, our laboratory began a series of studies in which we used recombinant retroviral vectors that transferred and expressed immortalizing oncogene cDNAs in an effort to generate permanent stromal cell lines from the bone marrow, fetal liver, and yolk sac of mice, primates, and humans.[5-8] Generation of permanent stromal cell lines had previously been accomplished by a variety of cell culture methods. Using this technology, several bone marrow stromal cell lines were generated from the medullary cavity of nonhuman primates. One such cell line, PU-34, was noted to maintain multilineage hematopoiesis for several weeks in vitro, and maintained megakaryocytes in culture during this period of time.[7] This cell line was subsequently used for detailed analysis of growth factor production, which ultimately led to the cloning of interleukin-11 (IL-11).[9]

CLONING AND GENOMIC CHARACTERIZATION

Conditioned media from PU-34 was noted to stimulate the proliferation of a murine plasmacytoma cell line, T1165. Although T1165 cells were known to respond to IL-6 and PU-34 produced IL-6, residual stimulatory activity could consistently be demonstrated on T1165 cells even with excess quantities of neutralizing antibodies to IL-6. This residual activity in the presence of antibodies to IL-6 became the basis for the "expression cloning"[10] of IL-11 using a cDNA library generated from PU-34. The resulting cDNA encodes a predicted protein of 199 amino acids with a 21 amino acid leader sequence (Fig 2).[9] Unlike many growth factors, the predicted protein contained no cysteine residues nor potential N-linked glycosylation sites. Similar to many growth factors, the 3′ untranslated (UT) mRNA contained multiple ATTTA repeats that are important in the regulation of mRNA stability.[11] Although the IL-11 cDNA was cloned based on IL-6–like bioactivity, no sequence homology exists between IL-11 and IL-6 either at the DNA or protein level. Using the cloned cDNA as a probe, IL-1–induced PU-34 cells demonstrated two RNA transcripts of 1.5 and 2.5 kb because of alternate polyadenylation sites. Subsequently, the cDNA was cloned independently by Kawashima et al[12] based on the ability of the expressed protein to inhibit adipogenesis in 3T3-L1 cells (see below). Protein expressed from the cDNA migrates with an apparent molecular mass of 21 to 22 kD.

McKinley et al characterized the human IL-11 genomic sequence in 1992.[13] The gene is contained in 7 kb of genomic sequence, contains 5 exons and 4 introns, and maps to chromosome 19q13.3-19q13.4. Interestingly, this area of chromosome 19 contains several genes involved in phospholipid metabolism. The 5′ region of the gene contains multiple sequences known to be involved as *cis*-regulatory elements in the expression of other genes. These include AP-1 sites (the DNA binding site for *fos/jun* complexes), SP-1, CTF/NF-1, and interferon binding (IFN/1) sites. As noted above, the 3′UT region of IL-11 has multiple repeats of the mRNA instability motif (ATTTA) and *Alu* repeats. Interestingly, this region also contains a sequence similar to the IL-1 response element of IL-6. Although IL-11 expression is known to be induced by IL-1, phorbol myristate acetate (PMA), and the calcium ionophore A23187, little functional analysis of the promoter sequence has been reported to date.

LIGAND BINDING AND RECEPTOR STUDIES

Although the receptor for IL-11 has not yet been cloned, studies on specific binding have been reported. From these studies it is clear that IL-11 is among several growth factors that use gp130 as a signaling mechanism, including IL-6, leukemia inhibitory factor (LIF), oncostatin M, and ciliary neurotrophic factor (CNTF).[14-17] At least three of these fac-

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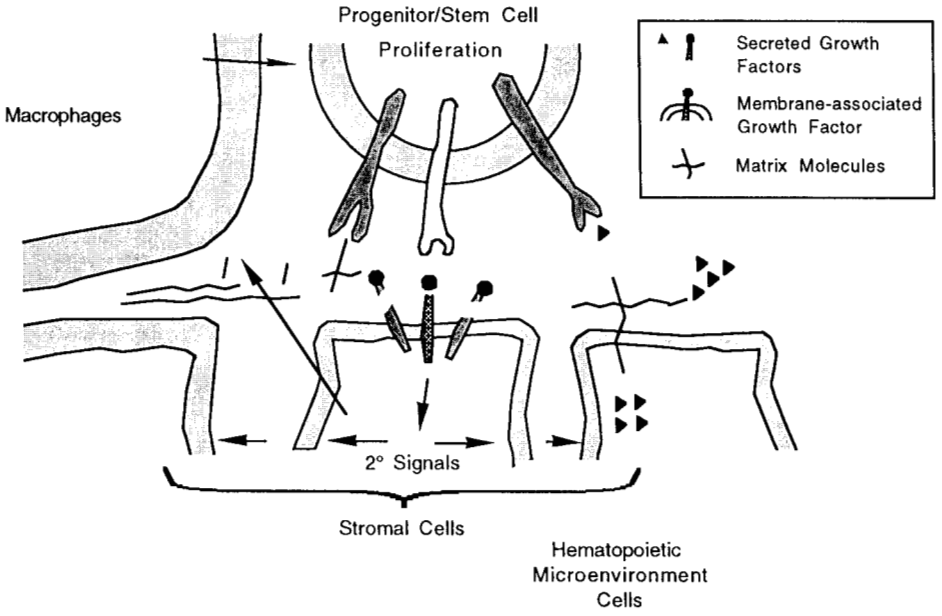

Fig 1. Schematic view of cellular interactions in the hematopoietic microenvironment forming a local area network between supporting stromal cells, macrophages, and progenitor/stem cell populations. (Modified and reprinted with permission from Gordon and Greaves.[59])

tors (IL-6, IL-11, and LIF) have been implicated as stimulatory proteins for early hematopoietic stem/progenitor cells. IL-11 binds to murine 3T3-L1 cells with a Kd of 3.5 × 10^{-10} mol/L.[18] The binding protein appears to be a single polypeptide with an apparent molecular mass of 151 kD and approximately 5,000 sites/cells are present on these cells. Ligand binding is associated with phosphorylation on tyrosine of a number of proteins of 44 to 152 kD, depending on the cell type examined.[18,19] Several early response genes, including tis11 and junB, appear to be expressed after IL-11 stimulation. IL-6 does not cross-compete for binding to 3T3-L1 cells or other cells in which competition has been examined.

IN VITRO EFFECTS OF IL-11

Megakaryocytopoiesis and thrombopoiesis. As a single agent, IL-11 has no influence on murine megakaryocyte colony formation in serum-free semisolid (methylcellulose) cultures,[20,21] but can stimulate the proliferation of the human megakaryoblastic cell lines (CMK and MegJ) in a dose-dependent fashion.[22] IL-11 does synergize with IL-3 to enhance the growth of both murine and human megakaryocyte colonies.[9,21,23,24] IL-11 also increases the size of IL-3–stimulated megakaryocyte colonies as well as the size and DNA content (ploidy) of constituent megakaryocytes.[21,23,24] IL-11 and IL-3 stimulate the formation of a significant numbers of both colony-forming units-megakaryocyte (CFU-MK; derived from human $CD34^+/HLA\text{-}DR^+$ cells) and burst-forming units-megakaryocyte (BFU-MK; derived from human $CD34^+/HLA\text{-}DR^-$ cells) colonies.[25] These data indicate that IL-11 promotes multiple stages of human and murine megakaryocytopoiesis and thrombopoiesis, including both the production and maturation of megakaryocytes.

Hematopoietic stem and multipotential progenitor cells.

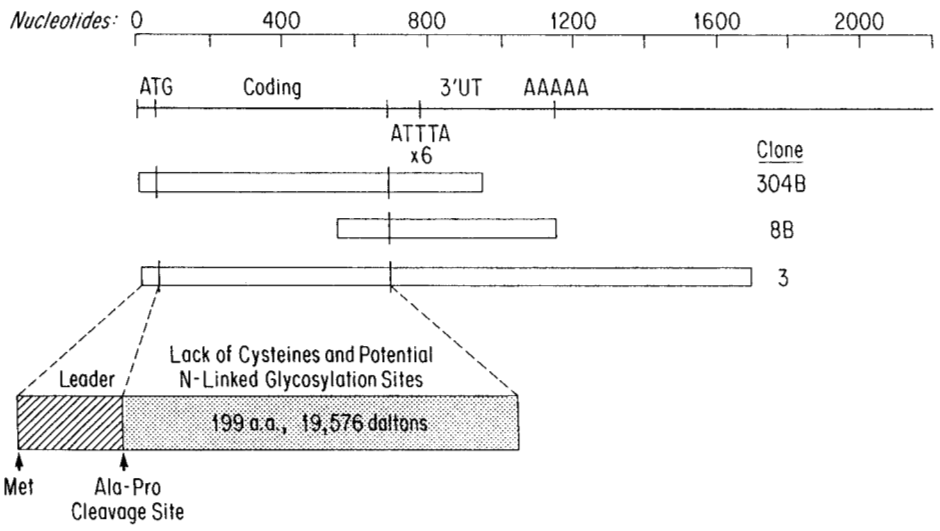

Fig 2. Schematic representation of overlapping IL-11 cDNA clones derived from PU-34 cDNA library and predicted protein encoded by these cDNAs.[9]

IL-11 alone has little effect on murine blast formation, CFU-granulocyte, erythrocyte, macrophage, megakaryocyte (CFU-GEMM) colony formation, or colony formation derived from human $CD34^+/HLA\text{-}DR^-$ cells,[26,27] although Keller et al[26] have noted some additive effects of IL-11 with IL-3 on colonies formed from purified human bone marrow containing large numbers of the latter cell type. There are no significant differences in the content of high proliferative capacity–colony-forming cells (HPP-CFC) and long-term repopulation stem cell content between IL-11–treated and control murine in vitro long-term bone marrow cultures.[28] In contrast, both the content of day-12 CFU-spleen (CFU-S) and committed myeloid progenitors are increased significantly in these cultures. In human long-term suspension cultures (nonstromal based) initiated with $CD34^+/HLA\text{-}DR^-$ $CD15^-$ cells, IL-11 alone is incapable of supporting the survival of long-term culture-initiating cells (LTC-IC) after 2 weeks of culture.[29] However, IL-11 acts synergistically with other cytokines, such as IL-3, stem cell factor, (SCF) or the combination of IL-3 and granulocyte colony-stimulating factor (G-CSF) to expand primitive LTC-IC populations that are capable of sustained production of large numbers of hematopoietic cells and generation of HPP-CFC.[29] IL-11 with IL-3, IL-4, and SCF increases murine blast and CFU-GEMM colony formation derived from day-2 post–5-fluorouracil (FU) marrow cells in vitro.[30,31] The effects of IL-11 on both murine and human stem and/or early progenitors may be caused by the entry of dormant stem cells into the cell cycle.[32]

Myelopoiesis. When added to normal murine bone marrow cells in vitro, IL-11 alone or in combination with IL-3 supports colony formation predominantly of granulocyte/macrophage type in a dose-dependent manner.[31,33] IL-11 also supports multilineage colonies (CFU-GEMM) derived from bone marrow harvested 2 days after 5-FU treatment.[30,31] IL-11 stimulates myeloid progenitor growth from human unfractionated bone marrow cells at 100 ng/mL and from purified $CD34^+/HLA\text{-}DR^+$ cells at a dose range from 10 to 400 ng/mL.[26] IL-11 has additive effects on CFU-granulocyte-macrophage (CFU-GM) colony formation from $CD34^+/HLA\text{-}DR^+$ cells in combination with IL-3, SCF, M-CSF, and GM-CSF.[26,27] In contrast, IL-11 has additive effects on colony formation from primitive highly purified $CD34^+/HLA\text{-}DR^-$ cells only with IL-3.[26] As single agent, IL-11 induces cycling of human fetal multilineage colonies (CFU-Mix), CFU-GM, and BFU-erythroid (BFU-E).[34]

Lymphopoiesis. IL-11 stimulates the generation of mouse spleen sheep red blood cell (SRBC)-specific plaque forming cells in a dose-dependent manner in vitro.[9,35] Depletions of $Thy\text{-}1.2^+$ or $L3T4^+$(CD4) cells dramatically decrease this IL-11–induced enhancement of SRBC-specific plaque-forming cells.[35] This suggests that L3T4(CD4)$^+$ T cells, but not Lyt-2(CD8)$^+$ T cells are required in IL-11–stimulated antibody responses.[35] Similarly, Anderson et al[36] have demonstrated that IL-11 or IL-6 addition to mixtures of human B cells, $CD4^+/45RA^-$ T cells, monocytes, and pokeweed mitogen leads to increased DNA synthesis and Ig secretion by B cells. Neutralizing anti–IL-6 monoclonal antibody only partially blocks IL-11–related increments in Ig secretion. These studies suggest that IL-11 promotes the differentiation of B lymphocytes by selective stimulation of $CD4^+/45RA^-$ T cells and monocytes, in a manner similar to IL-6. A component of the IL-11 effect on B-cell differentiation may be through stimulation of IL-6 production.[36] IL-11, in combination with SCF or IL-4, supports the generation of B cells in the primary colonies from marrow cells of 5-FU–treated mice, an effect similar to IL-6.[37]

Erythropoiesis. IL-11, when combined with SCF and erythropoietin (Epo) in vitro, can stimulate the growth of macroscopic erythroblast colonies containing erythroid progenitors capable of forming CFU-E–like colonies with a high frequency.[38] In addition, IL-11 synergizes with IL-3 in serum-containing cultures to stimulate BFU-E growth in a dose-dependent fashion, even in the absence of exogenous Epo. IL-11 alone supports the maturation of less-primitive CFU-E from fetal liver or bone marrow cells and from the cells replated at low density from macroscopic erythroblast colonies. IL-11 with Epo has proliferative activity on CFU-C derived from highly enriched $CD34^+CD33^-HLA\text{-}DR^-$ human bone marrow cells, leading to BFU-E colonies.[27] These data suggest that IL-11 may act directly both on primitive erythroid progenitor cells and on terminal differentiation of the erythroid precursor.

IL-11 effects on blast cell lines and leukemic cells. IL-11 stimulates the proliferation of several murine plasmacytoma cell lines, including T1165, T10, B9, and B9-Ty1, in a dose-dependent manner and the IL-11–induced stimulation of these cells cannot be neutralized by anti–IL-6 antibody.[9,19,39] In contrast to these mitogenic effects of IL-11 on murine plasmacytoma cell lines, exogenous IL-11 does not increase DNA synthesis or Ig secretion of several human myeloma cell lines examined or freshly isolated human myeloma cells.[40] Moreover, there are no increases in IL-11 mRNA expression, protein secretion, or protein capable of binding IL-11 on the cell surface of human myeloma cell lines or freshly isolated myeloma cells in these studies. These data suggest that IL-11 dose not play a role, either in an autocrine or in paracrine fashion, in the growth of human myeloma cells or derived cell lines.[40] In contrast, IL-11 in combination with IL-3, GM-CSF, or SCF does support myeloid leukemia cell line colony growth and triggers acute myeloblasts from patients with acute myeloblastic leukemia into S-phase. Several acute pre-B–lymphocytic leukemia and acute T-lymphocytic leukemia cell lines fail to respond to IL-11.[41]

IL-11 effects on acute-phase reactants. IL-11 induces the production of acute-phase reactants both in vitro and in vivo. Similar to IL-6 and LIF, IL-11 stimulates the production of type 1 (α1-acid glycoprotein, complement component C3, haptoglobin, and hemopexin) and type 2 (thiostatin and fibrinogen) acute-phase proteins in a dose-dependent fashion in rat hepatoma (H-35) cells and rat hepatocytes.[42] In human HepG2 hepatoma cells, IL-11 increases microsomal heme oxygenase, the rate-limiting enzyme in heme catabolism, mRNA in a dose- and time-dependent fashion.[43] This response is also similar to the responses observed with IL-6, whereas IL-11 has a significantly weaker effect than IL-6 on the induction of haptoglobin mRNA, a major acute-phase protein.[43]

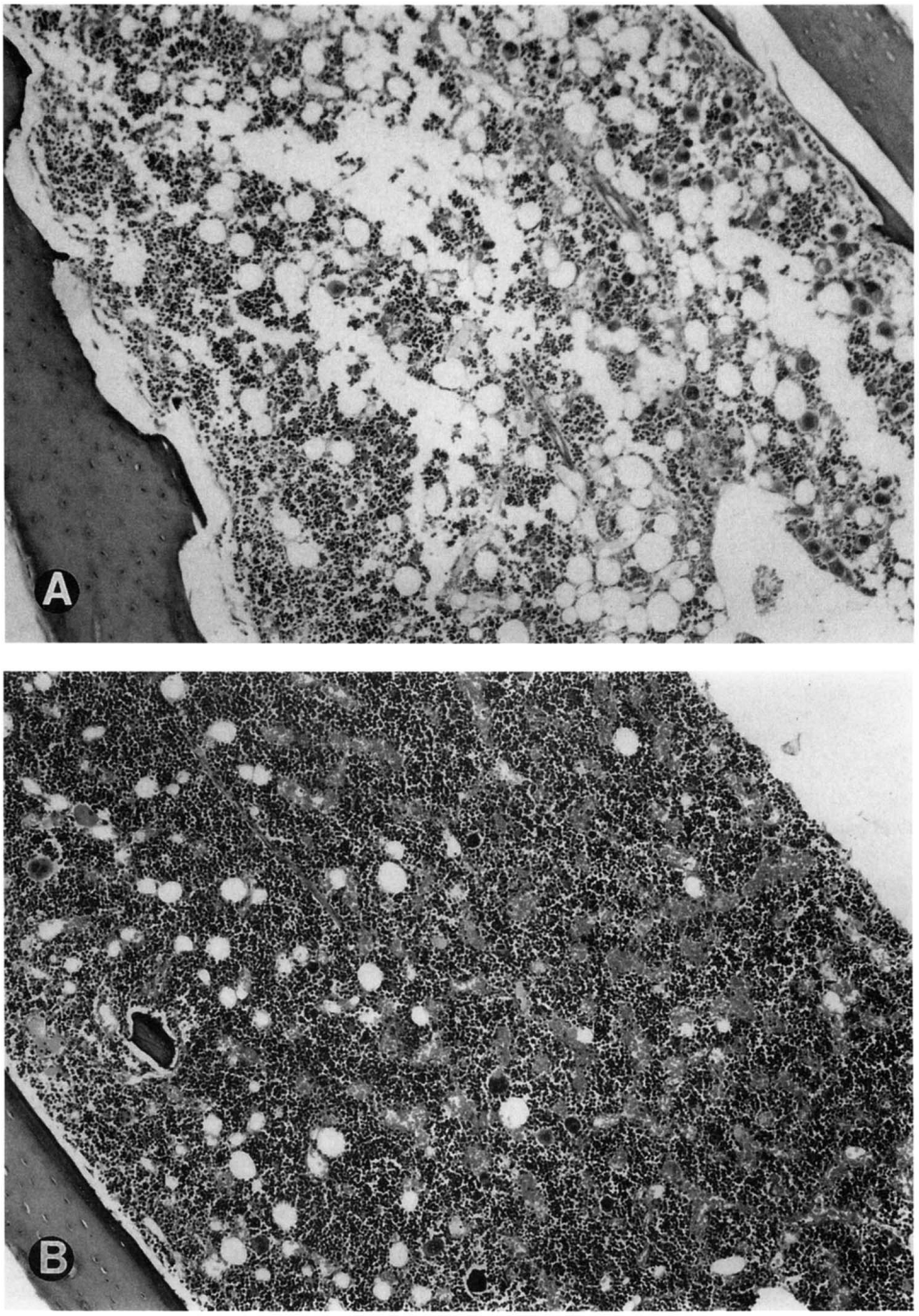

Fig 3. Effect of IL-11 administration to mice after BMT. Sections of mice femurs from (A) control (vehicle-treated); (B) mouse treated with 150 μg/kg;

Effect on nonhematopoietic cells. IL-11 directly inhibits the process of adipogenesis in murine 3T3-L1 cells and suppresses the heparin-releasable lipoprotein lipase (LPL) activity of differentiated 3T3-L1 adipocytes in a dose-dependent manner.[12] IL-11 can also inhibit adipocyte differentiation induced by insulin and dexamethasone in these cells. IL-11 inhibits adipose accumulation of H-1/A cells, a cell line derived from the adherent cell layer of a 14-week-old Dexter bone marrow culture.[44] Moreover, IL-11 markedly inhibits adipose accumulation in the adherent layer of human long-term bone marrow cultures because of a block in the differentiation of preadipocytes.[26]

IL-11 is also an inducible cytokine in connective tissue cells.[45] Stimulation of human articular chondrocytes and synoviocytes with either IL-1 or transforming growth factor-β1 (TGF-β1) induces the expression of both IL-11 mRNA transcripts. These increases in mRNA expression parallel increases in secretion of IL-11 protein, which migrates at an apparent molecular mass of 22 kD. IL-11 does not induce either catabolic responses of chondrocytes (such as the pro-

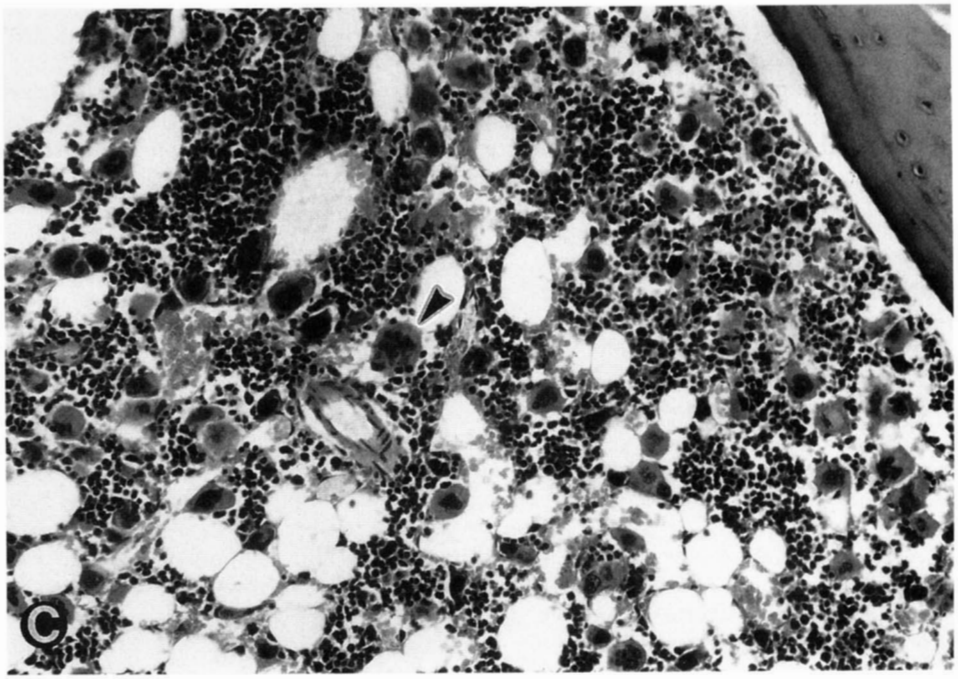

Fig 3. (Cont'd) and (C) mouse treated with 250 μg/kg. Arrowheads denote megakaryocytes. (a) and (b), original magnification × 200; (C), original magnification × 400.

duction of stromelysin activity, a matrix metalloproteinase) or the proliferation of chondrocytes and synoviocytes. IL-11 does induce the synthesis of the tissue inhibitor of metalloproteinase-1. Through this effect, IL-11 potentially balances IL-1β–induced extracellular matrix breakdown (by production of stromelysin) and may have a protective effect on connective tissues.

IL-11 can also promote neuronal differentiation of an immortalized neural stem and progenitor cell line (MK31) from dissociated embryonic (day 17) mouse hippocampus.[46] IL-11 alone or in combination with TGF-α enhances cellular polarity, neurite outgrowth, and nuclear enlargement and complexity of MK31 cells. Moreover, IL-11 alone or with TGF-α promotes cellular expression of the phosphorylated form of the high molecular weight mature neurofilament protein (NFH-P), with reduced expression of nestin and NF66. IL-11 alone can induce inward currents and propagation of immature action potentials in MK31 cells. These data indicate that IL-11 induces intermediate stages of neuronal maturation in the mammalian brain.

IN VIVO EFFECTS OF IL-11

Normal animals. IL-11 treatment results in marked stimulation of megakaryocytopoiesis in both small rodents and nonhuman primates.[20,47-49] In normal mice, IL-11 administration increases megakaryocyte progenitors, stimulates megakaryocyte endoreplication, and increases peripheral platelet counts.[47] Similar results have been reported in rats treated with IL-11, with a dose-dependent increase in platelet counts and increased bone marrow megakaryocyte size and ploidy.[20] IL-11 treatment can increase circulating platelet concentrations in nonhuman primates by enhancing the size and maturation rate of bone marrow megakaryocytes.[48]

IL-11 has no effect on peripheral leukocyte counts, erythrocyte counts, and hematocrits when administered to normal mice and rats.[20,47] Similar to these effects in rodents, IL-11 treatment elicited no changes in peripheral leukocyte counts in nonhuman primates (cynomolgus monkeys), but did induce a moderate, transient anemia. There was recovery of red blood cell counts and hemoglobin concentration in these animals by day 28 of treatment. Reticulocyte counts were significantly increased after 28 days of IL-11 treatment in cynomolgus monkeys.[48]

IL-11 administered in vivo enhances the cycling rates of BFU-E and CFU-GEMM from both bone marrow and spleen of normal mice when cultured in the presence of Epo and pokeweed mitogen mouse spleen cell conditioned media.[50] Although there are no increases in peripheral leukocyte and erythrocyte counts, IL-11 treatment elicited significant increases of absolute numbers of CFU-GM, BFU-E, and CFU-GEMM from both bone marrow and spleen.

IL-11 treatment in vivo also results in a dose-dependent increase in the number of spleen SRBC-specific plaque-forming cells as well as serum SRBC-specific antibody titer in both the primary and secondary immune responses.[35] IL-11 administration also elevates the plasma concentration of acute-phase reactants in normal rats, but to a lesser degree than IL-6 treatment. Also in contrast to IL-6, IL-11 has no effect on body weight gain in rats.[20]

Preclinical animal models. In contrast to the effects of IL-11 administration in normal mice and some preclinical models, IL-11 significantly increases peripheral total leukocyte counts in mice receiving syngeneic bone marrow transplants (BMT model) and in sublethally irradiated (nontransplanted) mice.[51] In these models a dose-dependent increase of peripheral platelet counts was also seen. The increased total leukocyte counts reflects mainly an acceleration of neutrophil recovery. IL-11–treated BMT mice demonstrated a

shortened period of neutropenia (by at least 7 days) compared with vehicle-treated mice.[51] BMT mice treated with the combination of IL-11 and SCF show additive increases in total leukocyte counts and platelet counts as well as increased hematocrits (instead of the mildly decreased hematocrits seen in BMT mice treated with IL-11 alone).[52]

IL-11 administration is also associated with increases of bone marrow and spleen cellularity and megakaryocyte numbers (Fig 3), CFU-GM, CFU-Mix, and megakaryocyte progenitors (CFU-MK) content in BMT mice. Although IL-11 treatment is associated with mild anemia, BFU-E content in bone marrow and spleen are not decreased. In contrast to the effect of IL-11 on the number CFU-S_{12} in murine long-term bone marrow culture in vitro,[28] IL-11 administration in vivo has little effect on CFU-S_{12} content in either bone marrow and spleen of BMT mice.[51,52]

Lethally irradiated mice transplanted with syngeneic bone marrow cells infected with a retrovirus expressing the human IL-11 cDNA show no changes in total circulating leukocyte counts despite a greater than 20-fold increase in myeloid progenitor content in spleen. These mice also demonstrate systemic effects of chronic IL-11 exposure, including loss of body weight (due to loss of fat) accompanied by a hyperactive state, thymic atrophy, inflammation of eyelids, and increased acute-phase reactants (haptoglobin level).[53]

In mice treated with combined chemotherapy (5-FU at 150 mg/kg) and radiation therapy (sublethal irradiation), IL-11 administration markedly decreases morbidity and mortality caused by endogenous infection from gut organisms.[54] The increased survival is associated with a rapid repair of gut intestinal villus structures. IL-11 administration is associated with increases in the mitotic index of cells in the small intestine crypt, the location of villus stem and progenitor cells. The frequency of staining of these cells with a monoclonal antibody to proliferating cell nuclear antigen (PCNA) is also increased. In this combined modality model, IL-11 results in a mild increase in peripheral platelet counts, but has no effect on leukocyte recovery in the first 10 days postirradiation. The data suggest that IL-11 directly or indirectly stimulates repair of small intestinal epithelial cells after radiation/chemotherapy-induced damage, an effect that may be caused by increased proliferation of crypt stem and progenitor cells.

In another combined modality model, mice received 500 cGy sublethal irradiation followed by a single injection of the chemotherapeutic drug carboplatin (1.2 mg/mouse). This regimen produces a severe and prolonged period of anemia and thrombocytopenia with no rebound thrombocytosis. Administration of IL-11 for 20 days results in the stimulation of multilineage hematopoiesis in bone marrow and spleen. The number of megakaryocyte, erythroid, granulocyte, and macrophage progenitors from bone marrow and spleen measured on day 15 and day 30 after myelosuppression was increased. IL-11 blunted the platelet and hematocrit nadirs and shortened the period of thrombocytopenia and anemia in this model.[55]

IL-11 administration to mice immunosuppressed by cyclophosphamide treatment accelerates the recovery of both peripheral neutrophils and platelets.[50] In this model, IL-11 augments the number of spleen SRBC-specific plaque-forming cells as well as serum SRBC-specific antibody titer. These data are consistent with the effects of IL-11 on immune cells in vitro.

Human studies. The results of the initial phase I trial of IL-11 in humans have recently been reported.[56,57] Women with advanced-stage breast cancer (stage IIIb or IVBC) undergoing high-dose chemotherapy (cyclophosphamide and doxorubicin) were treated with increasing doses of IL-11 both before therapy and after each of four cycles of combined chemotherapy.[58] The patients received 10, 25, 50, 75, and 100 μg/kg/d of rhIL-11 administered subcutaneously on days 3 through 14. IL-11 was well tolerated at doses of 10, 25, and 50 μg/kg/d. IL-11 administration was associated with higher mean platelet counts in the doses greater than or equal to 25 μg/kg/d. Higher doses of IL-11 were associated with prevention of cumulative platelet nadirs in later cycles of chemotherapy. There were no significant changes in total leukocyte counts or differential counts. IL-11 administration was associated with significant increases in bone marrow megakaryocyte numbers and a shift in megakaryocyte ploidy (modal 32N to 64N). A modest increase in bone marrow cellularity was noted at the higher doses administered. Both the number and cycling status (by PCNA staining) of immature erythroid and myeloid precursors were increased.[57] A reversible and non–dose-related decrease in hemoglobin concentration (mean, 20%) was observed as early as day 3 of treatment. Hemoglobin concentration returned to normal after completion of treatment. Similar to the experience with IL-6, IL-11 administration increased the plasma concentration of acute-phase reactants, including C-reactive protein, fibrinogen, and haptoglobin, at all doses. Fever was not a prominent side effect with IL-11 administration. Reversible edema, fatigue, and myalgias were seen in all patients treated with 75 μg/kg/d IL-11. One patient suffered a hemorrhagic central nervous system (CNS) infarct on the first cycle of 50 μg/kg/d of IL-11.[56,58]

SUMMARY

IL-11 is a unique growth factor derived from cells making up the HM. Although cloned based on IL-6–like bioactivity, IL-11 and IL-6 have distinct biologic profiles (Table 1). IL-11, like many recently cloned growth factors, has pleiotropic effects on hematopoietic cells presumably depending on the cytokine and cellular environment into which it is introduced. However, some general findings are consistent (Table

Table 1. Comparison of IL-11 and Il-6

	IL-11	IL-6
Molecular weight (kD)	23	26
Glycoprotein	No	Yes
Sequence	No homology	
T-cell proliferation	No	Yes
CTL differentiation	No	Yes
Erythropoiesis	Yes	No
Myeloma cell proliferation	No	Yes
Induction of haptoglobin in HepG2 cells	+	+++

Table 2. Summary of Pharmacologic Effects of IL-11

- Increased platelet counts in all models examined
  - —Increased platelet progenitors (BFU-MK, CFU-MK)
  - —Shift to higher ploidy, when examined
- Increased leukocytes, primarily neutrophils, depending on model
  - —Increased myeloid progenitors in all models
- Data suggest potent effect on multilineage progenitor cell population in bone marrow
- Mild anemia in some models, although increased erythroid progenitors/precursors also seen in some models
- Increased acute-phase reactants noted in both in vitro and in vivo models

2). In addition, IL-11 has significant effects, either primary or secondary, on nonhematopoietic cells, including neurons, small intestine crypt progenitor/stem cells, and preadipocytes. The institution of human trials with IL-11 will provide important information on the pharmacologic effects of IL-11 on human hematopoietic cells in the context of frequently used chemotherapy protocols. The physiologic role(s) of IL-11 are unknown but will become clear (at least in the mouse) with gene targeting experiments underway in several laboratories.

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