Experimental Hematology Today-1988

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Editors

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Preface

Experimental Hematology Today—1988 represents a selection of the outstanding papers presented at the 17th Annual Meeting of the International Society for Experimental Hematology in Houston, Texas, August 21–25, 1988. The manuscripts were selected after a careful review by the local program committee and finally by the editors of the book. The book is divided into six parts dealing with molecular involvement in hematopoietic precursor proliferation, growth factors, specific cell regulators, genetic manipulation, regulation of leukemogenesis, and bone marrow transplantation.

The first part, chaired by Dr. Bradley, presents recent interesting findings on "Hematopoietic Regulation by Cytokines." Dr. Zipori heads part II, entitled "Hematopoietic Cellular Growth Regulation." Reports in this chapter discuss the interaction of stromal cells with hematopoietic stem and progenitor cells. Part III deals with "Granulopoietic Regulators" and is chaired by Dr. Pluznik. Papers in part IV, introduced by Dr. Evinger-Hodges, relate to findings dealing with means of gene transfers into hematopoietic progenitor cells. Dr. Ruscetti chairs part V, which deals primarily with "Regulation of Leukemogenesis." Finally, part VI comprises papers dealing with recent discoveries in "Bone Marrow Transplantation." Dr. Dicke is the very able leader of this section.

The present yearbook of experimental hematology reflects the diverse interests of basic and clinical hematologists. As such, it should be of considerable value to all biomedical scientists.

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Contents

Part I. Hematopoietic Regulation by Cytokines

Chairperson: T.R. Bradley

1 Interleukin 1 in Hematopoiesis

C.L. Epstein

This paper will review some of the important events in the development of our understanding of Interleukin-I (IL-1), and will cover discovery and characterization, in vitro and in vivo animal studies, and will speculate on the role of IL-1 in the clinic.

IL-1 was cloned at Immunex using two separate techniques - 1) hybrid selection from macrophage cDNA library using sized mRNA, and 2) using oligonucleotide probes derived from N-terminus amino acid sequence information obtained from purified IL-1 protein. Both techniques yielded proteins which possessed activities attributed to IL-1[1,2]. However, these proteins proved not to be identical.

The two gene products, termed IL-1α and IL-1β, are both 30KD molecular weight in their primary gene transcript form, and, in vivo, are processed to a 17.5 KD length. They share homology at only 25% of their amino acid sequence[2]. The homology is scattered rather evenly throughout the sequence leading to the conclusion that there might have been a mutual forbearer gene. IL-1α and IL-β bind competitively to the same receptor. IL-1α in its full length gene transcript (30KD molecular weight form) binds equally well as the 17.5KD form, as measured by percent inhibition of binding of radiolabeled IL-1α. However, it shows that IL-1β is active only in its processed (17.5KD) form. This IL-1β competes with IL-1α for the binding site[3]. In side-by-side equal-dose studies to date, there have been no demonstrated differences between IL-1α and IL-1β. Therefore, this paper will consider them as equivalent and will refer to both proteins as IL-1.

The receptor for IL-1 is an 80KD glycosylated cell surface protein[4] which we have recently cloned[5]. It binds both IL-1α and IL-1β, and is expressed in all cells responding to IL-1. Very recent work by Sims and colleagues has demonstrated that the N-terminus 319 amino acids have a structure reminiscent of the immunoglobulin superfamily with three external domains. There is a region consisting of 20 uncharged amino acids which is presumed to be the transmembrane region[5].

Within the past two years, investigations have led to the conclusion that IL-1 is identical to hematopoietin-1. Mochizuki and co-workers[6] found, using hematopoietin-1 from medium conditioned by the human bladder tumor cell line 5637 and an in vitro 5FU bone marrow proliferation assay, that hemopoietin-1 activity was indistinguishable from that of IL-1. HBT 5637 was shown to express mRNA coding for IL-1. Hematopoietin-1, co-purified with IL-1, and monoclonal antibodies directed against IL-1α neutralized the activity of hemopoietin-1.

In general, IL-1 was then believed to place stem cells in cycle, thus protecting against the effects of radiation and chemotherapy, to induce CSF production, to synergize with CSFs, and to induce CSF receptor expression.

IL-1 also has multiple other effects which may be significant in clinical applications. Among these are synergism with IL-2 to generate LAK activity (Grimm, personal communication). Work at Immunex has demonstrated that it induces fibroblast proliferation, acts as a chemo-attractant to leukocytes, and demonstrates angiogenic activity. In addition, we have shown that it potentiates the primary humoral response to a variety of antigens.

Figure 1 is a diagram showing the sites of action of IL-1 and other cytokines. The activity on IL-1 on lymphopoiesis appears to be limited to

the generation of the lymphoid stem cell. The activities on the generation of other hemopoietic cells is much more complicated, and it appears to have effects in generating cells of varying maturity.

Some of the earliest work on IL-1 was done by Neta and co-workers[7,8] who investigated IL-1 as a radioprotectant. They found that when IL-1 was given 20 hours prior to irradiation, the mice became more radioresistant. The effect was dependent on the interval between IL-1 therapy and the dose of radiation. When IL-1 was given 45 hours or 4 hours preradiation, the effect was diminished, and dosing 1 hour after radiation did not show a protective effect.

These observations were confirmed in Talmadge's laboratory by Castelli and co-workers[9] and extended to treatment with cyclophosphamide. Mice given sublethal doses of cyclophosphamide were treated with IL-1 at varying times relative to the dose of cyclophosphamide. Optimal CFU-C recovery in the femur occurred when cyclophosphamide was given as a single dose 20 hours prior to radiation, or 48 hours after. Single doses at 2 hours and 24 hours post-cyclophosphamide showed decreased CFU-C on day 4, but increased CFU-C by day 8, when compared to the cyclophosphamide-treated controls. Treatment schedules beginning on day 1 or day 2 and extended over several days, resulted in increased numbers of CFU-C. These results supported the theory that IL-1 has protective (optimally when given 20 hours pre-cyclophosphamide or radiation) or restorative (when given once or more post-cyclophosphamide or radiation) effects on bone marrow progenitor cells.

In order to study whether the effects of pretreatment with IL-1 could be explained by the induction of other cytokines, Neta's group[7,10] compared treatment with IL-1 with treatment with other cytokines. IL-1 given 20 hours prior to radiation improved survival better than GM-CSF, gamma interferon or IL-2. Subsequent work[11] has demonstrated that in vivo, administration of IL-1 20 hours preradiation results in placing GM-CSF-responsive cells into cycle. This supports that theory that the pretreatment of cells with IL-1 prior to radiation (or chemotherapy) may confer its protective effect by placing the cells into cycle, as cells in S phase are said to be less sensitive to radiation than normal cells[12].

Morrissey and co-workers[13] have studied CFU-GM in mice which were sublethally irradiated, then treated b.i.d. with IL-1 intraperitoneally, b.i.d. IL-1 increased the number of CFU-GM over control animals which were untreated. In addition, on day 4, there were more cells in the IL-1-treated animals, which were responsive to GM-CSF, IL-3, and G-CSF, than seen in the control animals treated with these same cytokines. Peripheral polymorphonuclear leukocytes were increased on days 5 through 20. However, in this model, chronic IL-1 administration (postirradiation through day 20) led to hypoplasia of the thymus. MSA-treated control mice rapidly recovered thymic cellularity following radiation, unlike the IL-1-treated mice. In addition, IL-1 treatment resulted in diminishing the number of pre-B cells in the marrow. Responses of the spleen cells to T cell and B cell mitogens were decreased, suggesting that chronic IL-1 therapy may have limited clinical drawbacks.

Unpublished extension of this work (Morrissey, personal communication) has shown that in normal mice given IL-1 for 4 days, thymic cellularity was decreased by 90%, but recovered rapidly following cessation of treatment. In addition, serum corticosteroids increased. The decrease in thymocytes occurred in the CD4+/CD8+ population. They propose that the decrease in thymic cellularity is a result of the demonstrated increase in serum corticosteroids which is know to cause cell intrathymic death, presumably by activation of a calcium-dependent endonuclease. Finally, Neta and co-workers[14] studied the effect of combining CSFs on the survival of mice after lethal radiation. GM-CSF alone was ineffective, but in combination with IL-1 was more effective than IL-1 alone or G-CSF alone. The combination of G-CSF and IL-1, although better than either of the two alone, was not as good as IL-1 plus GM-CSF.

A number of other combination studies are currently being performed in order to clarify the effects of the cytokines, and how they may best be used in the clinic. Preliminary reports by Moore and co-workers (personal communication) indicate that IL-1 treatment may improve the hematologic reconstitution in the 5FU-treated mouse, and that combination with G-, GM-, and IL-3 may be better than single-agent therapy.

There is speculation that IL-1 may be useful in the setting of bone marrow transplantation. Recent studies with GM-CSF indicate that, at least in some clinical trials, it provides enhanced engraftment[15]. However, Blazar and co-workers (personal communication) in Minnesota have had less striking results., We speculate that this is due to the 4HC purging treatment that the center uses. 4HC dramatically decreases the population which is responsive to GM-CSF. Therefore, the use of IL-1 in this setting, which may help to increase the population of cells ranging from the pluripotent stem cell down to committed

cells which can respond to GM-CSF, may be appropriate in this situation.

However, the use of IL-1 in the setting of malignancies will require studying various malignant cells to examine their potential for responding by proliferating to IL-1. Referring back to Figure 1, it would appear that the lymphoid malignancies might be particularly appropriate for IL-1 therapy as cells beyond the lymphoid stem cell are not believed to proliferate in response to IL-1. Thus, one possibility would be to treat bone marrow cells in culture with IL-1, either preceding or following treatment with an agent such as 4HC, or both. This might a) protect the stem cell from the effects of 4HC, and b) encourage the replication and differentiation (perhaps in combination with other cytokines) of these cells to enhance engraftment. A variety of other clinical settings can be imagined. However, given the time course of beneficial IL-1 effect we have seen in vivo in animal models it may be necessary to develop new chemotherapeutic or radiotherapeutic schedules to result in optimal effects.

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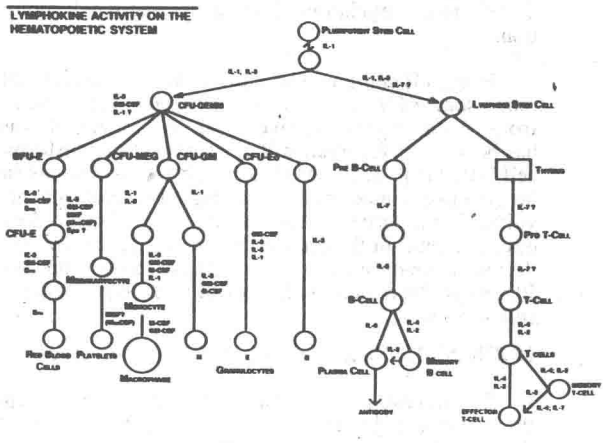

Fig. 1. Effects of various lymphokines and colony stimulating factors (CSFs) on the hematopoietic system. (Courtesy Immunex Corporation)