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Transforming Growth Factor β: Possible Roles in the Regulation of Normal and Leukemic Hematopoietic Cell Growth

Jonathan R. Keller, Garwin K. Sing, Larry R. Ellingsworth, and Francis W. Ruscetti

Biological Carcinogenesis Development Program, Program Resources, Inc. (J.R.K.) and Laboratory of Molecular Immunoregulation, Biological Response Modifiers Program (G.K.S., F.W.R.), NCI-Frederick Cancer Research Facility, Frederick, Maryland, 21701; Collagen Corporation, Palo Alto, California 94303 (L.R.E.)

We have recently demonstrated that transforming growth factor (TGF)-β1 and TGF-β2 are potent inhibitors of the growth and differentiation of murine and human hematopoietic cells. The proliferation of primary unfractionated murine bone marrow by interleukin-3 (IL-3) and human bone marrow by IL-3 or granulocyte/macrophage colony-stimulating factor (GM-CSF) was inhibited by TGF-β1 and TGF-β2, while the proliferation of murine bone marrow by GM-CSF or murine and human marrow with G-CSF was not inhibited. Mouse and human hematopoietic colony formation was differentially affected by TGF-β1. In particular, CFU-GM, CFU-GEMM, BFU-E, and HPP-CFC, the most immature colonies, were inhibited by TGF-β1, whereas the more differentiated unipotent CFU-G, CFU-M, and CFU-E were not affected. TGF-β1 inhibited IL-3-induced growth of murine leukemic cell lines within 24 h, after which the cells were still viable. Subsequent removal of the TGF-β1 results in the resumption of normal growth. TGF-β1 inhibited the growth of factor-dependent NFS-60 cells in a dose-dependent manner in response to IL-3, GM-CSF, G-CSF, CSF-1, IL-4, or IL-6. TGF-β1 inhibited the growth of a variety of murine and human myeloid leukemias, while erythroid and macrophage leukemias were insensitive. Lymphoid leukemias, whose normal cellular counterparts were markedly inhibited by TGF-β, were also resistant to TGF-β1 inhibition. These leukemic cells have no detectable TGF-β1 receptors on their cell surface. Last, TGF-β1 directly inhibited the growth of isolated Thy-1-positive progenitor cells. Thus, TGF-β may be an important modulator of normal and leukemic hematopoietic cell growth.

Key words: hematopoiesis, transforming growth factor β, colony-stimulating factors, leukemic cells, interleukin-3

A family of polypeptide growth factors that regulates cell growth has recently been identified and includes 1) two distinct forms of transforming growth factor beta

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(TGF-β), TGF-β1 and TGF-β2 [1–3], which have been shown to be multifunctional regulators of cell growth; 2) inhibin, which suppresses follicle-stimulating hormone secretion; 3) Mullerian inhibitory substance, which causes regression of the Mullerian duct in the male embryo; and 4) the predicted product of the Drosophilian decapentaplegic gene complex [2]. The cDNA sequences for this family of growth factors indicate that the mature proteins are synthesized from the carboxyl-terminal half of larger precursors, and share homologies to each other within this region and, in particular, show conservation in seven out of nine cysteines [1]. TGF-β1 has been purified to homogeneity from platelets, placenta, kidney, and bone and is a 25-kilodalton (Kd) disulfide-linked homodimeric protein whose sequence is remarkably conserved with a single amino acid substitution between mouse and man [1].

TGF-β1 was originally identified in the supernatants of transformed fibroblasts by its ability to induce the anchorage-independent growth of NRK 49F fibroblasts in soft agar. More recently, it has been shown to enhance the proliferation of two mesenchymal cell types, osteoblasts, responsible for new bone formation, and Schwann cells, involved in the repair of peripheral nerves and synthesis of myelin [3]. TGF-β1 has also been described as a potent inhibitor of proliferation of a variety of cell types in vitro including epithelial cells, embryonic fibroblasts, endothelial cells, and T and B lymphocytes [3]. Thus, it has been postulated that TGF-β1 may act as an autocrine or paracrine negative regulator of cell growth.

TGF-β is also known to exert biological effects unrelated to cell proliferation, including the induction of extracellular matrix proteins such as collagen and fibronectin in human, rat, mouse, and chicken fibroblasts [4], and the inhibition of the degradation of extracellular matrix proteins. Local injection of TGF-β1 in vivo results in a strong fibrotic response including activation of fibroblasts to produce collagen. Also, TGF-β1 accelerates the healing of incisional wounds in rats. Therefore, TGF-β1 has been proposed to play a role in inflammation and wound healing [4].

Immunohistochemical studies using antibodies to the N-terminus of TGF-β1 to localize the production of TGF-β1 showed that TGF-β1 is produced by cells in centers of active hematopoiesis including fetal liver and bone marrow, and active lymphopoiesis in the Hassall's corpuscles [5]. Therefore, experiments were designed to determine whether TGF-β1 might be involved in regulating normal hematopoietic cell growth and differentiation.

RESULTS

For these studies, we employed the bone marrow soft agar colony assay, which measures the clonal growth of hematopoietic progenitors and has historically been used to determine the factors and conditions required for normal hematopoietic cell growth and differentiation. This assay has facilitated the identification and cloning of the colony-stimulating factors (CSFs) [6], which are polypeptide growth factors that enhance the proliferation and differentiation of hematopoietic cells in vitro. Using this assay and purified CSFs, we designed experiments to determine whether TGF-β1 could enhance or inhibit the growth of hematopoietic cells in vitro.

Effect of TGF-β on Normal Bone Marrow Progenitor Cell Growth

The initial experiments to examine the effect of TGF-β1 on the growth of hematopoietic cells used ^{3}H-thymidine proliferation assays with freshly aspirated

murine bone marrow cells cultured in microtiter wells for 72 h in the presence of the various CSFs. For these studies, homogeneous TGF-β1 purified from bovine bone was used. In contrast to two recent reports [7,8] stating TGF-β2 had no effect on hematopoiesis, our comparative study of the effects of TGF-β1 and TGF-β2, each purified from two different sources, showed little or no difference between the two. Thus, all the results presented here will have used TGF-β1. The CSFs employed were interleukin 3 (IL-3), which promotes the colony formation (CFU) of mixed lineage colonies that include granulocytes (G), macrophages (m), megakaryocytes (M), and erythroid cells (E) (CFU-GEMM); granulocyte/macrophage-CSF (GM-CSF), which promotes the growth of granulocytes and macrophages (CFU-GM); granulocyte-CSF (G-CSF), which promotes granulocyte growth; and erythropoietin (EPO), which promotes the terminal differentiation of erythroid cells. The results demonstrate that TGF-β1 alone has no effect on the proliferation of hematopoietic cells but can inhibit between 50% and 70% of the IL-3-driven bone marrow proliferation in a dose-dependent manner with an ED_{50} of 5–10 pM. In contrast, G-CSF-, GM-CSF–, and EPO-driven proliferation is unaffected by TGF-β1. To determine what progenitors and which lineages may have been affected by TGF-β1, bone marrow cells were plated in soft agar in the presence of the CSFs. IL-3-induced colony formation was inhibited in a dose-dependent manner with an ED_{50} of 5–10 pM, while G-CSF- and GM-CSF-driven colony formation were unaffected (Table I). Finally, even though the colony formation induced by IL-3 was significantly inhibited by TGF-β1, clusters of differentiated myeloid cells were consistently observed.

Since the inhibition of IL-3-driven proliferation was incomplete and ranged from 50% to 70% and since clusters of differentiated cells were observed in soft agar assays containing IL-3 and TGF-β1, we hypothesized that TGF-β1 might selectively regulate early hematopoietic progenitor cell growth. To test this hypothesis, we studied the effect of TGF-β1 on the growth of the most primitive CFU found in normal marrow populations, the multipotential CFU, CFU-GEMM. The CFU-GEMM develops in response to two signals—namely, IL-3, which provides the early signal, and EPO, which promotes the terminal differentiation of erythroid cells. In addition, we examined the primitive erythroid lineage colony, the burst-forming unit (BFU-E), which also uses the same two growth signals, IL-3 and EPO. As shown in Table I, TGF-β1 is a potent inhibitor of CFU-GEMM and BFU-E formation; however,

TABLE I. Effect of TGF-β1 on Murine Hematopoietic Colony Formation in Soft Agar*

		No. of colonies		
CSF	TGF-β1	CFU-GM	CFU-GEMM	BFU-E
None	+ or −	0	0	0
IL-3	−	52 ± 5	0	0
IL-3	+	6 ± 3	0	0
IL-3 + EPO	−	58 ± 3	5 ± 2	11 ± 3
IL-3 + EPO	+	4 ± 2	0	0
GM-CSF	−	113 ± 12	0	0
GM-CSF	+	387 ± 11	0	0
G-CSF	−	20 ± 4	0	0
G-CSF	+	25 ± 4	0	0

*Colonies were scored after 6–8 days of incubation and are expressed as the mean of triplicate experiments. The growth factors were supplemented to the cultures at the following concentrations: TGF-81 (10 ng/ml), IL-3 (50 U/ml), EPO (2 U/ml), GM-CSF (1 ng/ml), and G-CSF (100 U/ml).

TGF-β1 had no effect on erythropoietin-driven proliferation of splenocytes from phenylhydrazine-treated mice (spleen cells are highly enriched for erythroblasts [9]) or erythroid colony formation, CFU-E, from normal bone marrow. Taken together, the results suggest that TGF-β1 selectively inhibits the growth of early progenitor cells, while the proliferation and differentiation of the more committed or differentiated progenitors are unaffected.

To determine if TGF-β1 could also regulate human hematopoietic cells, comparative studies were performed on freshly aspirated human bone marrow. In proliferation assays, TGF-β1 inhibited 50–70% of the IL-3- and GM-CSF-driven proliferation in a dose-dependent manner with an ED_{50} of 5–15 pM. In contrast, G-CSF driven proliferation was unaffected. Similar results were observed in the colony assays, in that TGF-β1 inhibited GM-CSF and IL-3 induced CFU-GM, CFU-GEMM, and BFU-E progenitor cell growth, while G-CSF-induced colony formation was unaffected (Table II). In addition, similar to results seen with murine hematopoietic cells, clusters of terminally differentiated progeny of a single lineage were consistently seen in cultures containing TGF-β1 and GM-CSF or IL-3. However, in contrast to results with murine hematopoietic cells, human GM-CSF-induced colony formation was inhibited by TGF-β1. This may reflect differences in the two species, since human GM-CSF, unlike murine GM-CSF, is a potent inducer of the more primitive progenitors including CFU-GEMM [10]. Therefore, these results are consistent with the concept that TGF-β1 selectively regulates early hematopoietic progenitor cells while the more differentiated and committed progenitors are unaffected.

Effect of TGF-β1 on Primitive Murine Progenitor Populations

To determine whether the effect of TGF-β1 on hematopoietic cells was direct or indirect, pure populations of hematopoietic progenitors were isolated from heterogeneous populations of murine bone marrow cells. This was accomplished using a previously described system which demonstrated that IL-3 was required for the induction of Thy-1 antigen expression on Thy-1-negative (Thy-1−) bone marrow cells. Single-cell analysis of fluorescence-activated cell sorted (FACS) Thy-1+ cells has shown that these cells have the potential to differentiate to the various hematopoietic cell types, and contain progenitors with multipotent, bipotent, and unipotent differentiation potential [11]. Therefore, two aspects of this system were studied—first, what are the effects of TGF-β1 on IL-3-induced Thy-1 antigen expression; and second, does TGF-β1 inhibit the growth of isolated Thy-1+ progenitor cells in soft

TABLE II. Effect of TGF-β1 on Human Hematopoietic Colony Formation in Soft Agar*

		No. of colonies		
CSF	TGF-β1	CFU-GM	CFU-GEMM	BFU-E
None	+ or −	0	0	0
GM-CSF + EPO	−	62 ± 23	9 ± 3	43 ± 8
GM-CSF + EPO	+	3 ± 2	0	0
IL-3 + EPO	−	15 ± 2	8 ± 2	37 ± 7
IL-3 + EPO	+	11 ± 1	0	0
G-CSF	−	48 ± 5	0	0
G-CSF	+	49 ± 4	0	0

*Colonies were scored after 14 days and the results are expressed as the mean of triplicate experiments. The growth factors were supplemented to the medium at the following concentrations: TGF-β1 (10 ng/ml), GM-CSF, IL-3, and G-CSF (10 ng/ml).

agar colony assays? As shown in Table III, TGF-β1 inhibited IL-3-induced Thy-1 antigen expression in a dose-dependent manner with an ED_{50} of 5–10 pM. When these cultures were examined morphologically using a Jenner's stain, there was an absence of myeloid blast cells normally present in cultures supplemented with IL-3. Next, to demonstrate the direct action of TGF-β1 on hematopoietic progenitor cell growth, Thy-1+ progenitors were isolated by fluorescence-activated cell sorting from bone marrow cultures grown for seven days in medium supplemented with IL-3, and then plated into soft agar colony assays. As previously demonstrated [12], IL-3 induces the formation of mixed-lineage colonies that contain granulocytes, macrophages, and mast cells as well as pure monolineage colonies of each cell type. However, in addition to the previous results, Thy-1+ progenitors also give rise to CFU-GEMM in cultures supplemented with IL-3 and EPO. The results show that TGF-β1 inhibits greater than 50% of the total colony formation, which includes all of the multipotential progenitors, CFU-GEMM and CFU-GM, while colonies and clusters containing single lineages of granulocytes and macrophages are unaffected. As summarized in Figure 1, TGF-β1 inhibits the induction of Thy-1 antigen on

TABLE III. Effect of TGF-β1 on IL-3-Induced Thy-1 Expression*

Stimulator	TGF-β1	% Thy-1 expressed	% Inhibition
None	+ or −	0	0
IL-3	−	28	−
IL-3	20 ng/ml	6	79
IL-3	2 ng/ml	7	75
IL-3	0.2 ng/ml	21	25
IL-3	0.02 ng/ml	27	4

*Bone marrow cells were depleted of Thy-1+ cells by complement-mediated cytotoxicity and then plated in medium containing 100 U/ml IL-3 with the indicated concentrations of TGF-β1. Thy-1 expression was determined by FACS analysis after a 7-day incubation period.

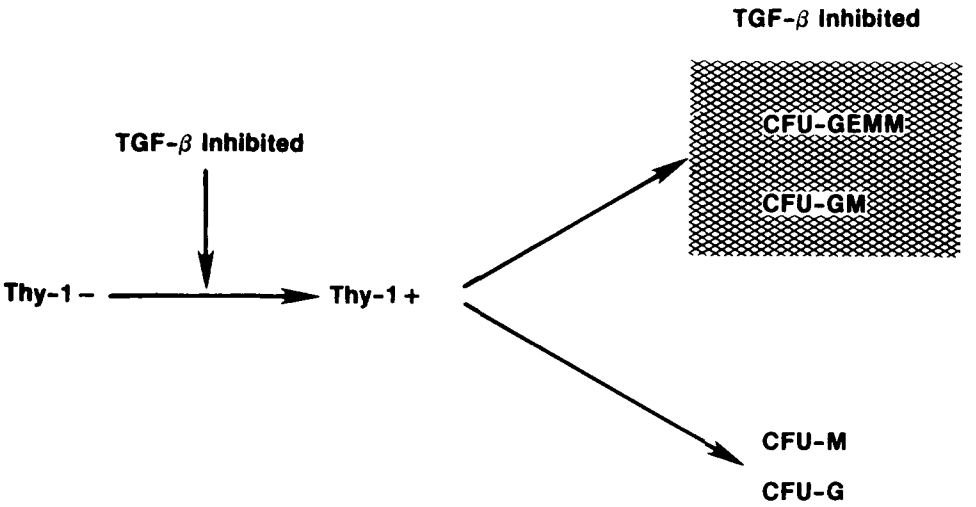

Fig 1. Effect of TGF-β on Thy-1 expression and on the proliferation of IL-3-induced Thy-1-positive cells.

hematopoietic progenitors and can directly act on isolated Thy-1 progenitors selectively to inhibit multipotential cell growth and differentiation.

To determine at what stage in hematopoietic development progenitor cells acquire the ability to respond to TGF-β, bone marrow cells were obtained from the femurs of mice injected with 5-fluorouracil (5-FU), a compound that enriches for noncycling primitive hematopoietic progenitors [13]. One class of hematopoietic progenitor cell in post 5-FU bone marrow is the highly proliferative potential colony-forming cell (HPP-CFC) that proliferates in vitro to generate large macroscopic colonies (greater than 0.5 mm). Therefore, we examined the effect of TGF-β1 on the growth of the three classes of HPP-CFC which have been defined. The first class of HPP, HPP-CFC-1, which can be induced to proliferate in response to interleukin 1 [IL-1 (previously known as hematopoietin-1)] and CSF-1, represents the most primitive HPP progenitor capable of reconstituting the hematopoietic system [14]. It can be inhibited by TGF-β1 in a dose-dependent manner, with an ED_{50} of 10–30 pM. The second class of HPP, HPP-CFC-2, which has been shown to be derived from HPP-CFC-1 [15] and is induced to proliferate by IL-3 and CSF-1, was also inhibited by TGF-β1 with similar dose-dependent kinetics. Finally, a third class of HPP, HPP-CFC-HLGF-1, induced to proliferate from normal bone marrow cells in response to hemato-lymphopoietic growth factor (HLGF-1) and CSF-1 [16], was also inhibited. Thus, TGF-β1 can inhibit the growth of the most primitive hematopoietic progenitors detectable in vitro. Since the HPP progenitors are quiescent cells, the mechanism of negative regulation by TGF-β probably involves maintaining the progenitor cells in a noncycling state. A summary of those progenitors whose growth can be inhibited by TGF-β is presented in Figure 2.

Effect of TGF-β1 on Leukemic Myeloid Cell Growth

Since the results obtained with normal hematopoietic progenitors suggest that TGF-β1 plays a role in the regulation of hematopoietic cell growth, experiments were designed to determine whether TGF-β1 also inhibits the growth of leukemic cell lines. Thus, we examined a variety of murine cell lines, including growth factor-dependent "preleukemic" progenitor cell lines blocked in early stages of differentiation as shown by phenotype, function and morphology and factor independent myeloid leukemic cells [17–19] (Table IV). TGF-β1 inhibits the proliferation of all the IL-3-dependent murine progenitor cell lines tested to date, regardless of their derivation. In addition, the growth of NFS-60 cells, which proliferate in response to IL-3, GM-CSF, G-CSF, CSF-1, IL-6, and IL-4, was inhibited by TGF-β1 in a dose-dependent manner with an ED_{50} of 5–10 pM regardless of the growth factor employed. TGF-β1 did not induce the differentiation of those lines that were inhibited. The inhibitory effects of TGF-β1 on the proliferation of factor dependent cell lines could be specifically neutralized with a polyclonal antiserum to TGF-β1 [5].

Examination of factor-independent murine leukemic cell lines revealed that cell lines with an early blastic phenotype were inhibited by TGF-β, but those with a more mature phenotype were not (Table IV). WEHI-3B (myelomonocytic) and GG2EE (promonocytic) were inhibited while the macrophage cell lines P388D1 and J774, the erythroid cell lines TP-3 and DS-19 and the mastocytoma P815 were insensitive to the effects of TGF-β1.

We next explored the question of whether factor dependence or independence plays a role in TGF-β sensitivity. To address this question two IL-3-dependent cell

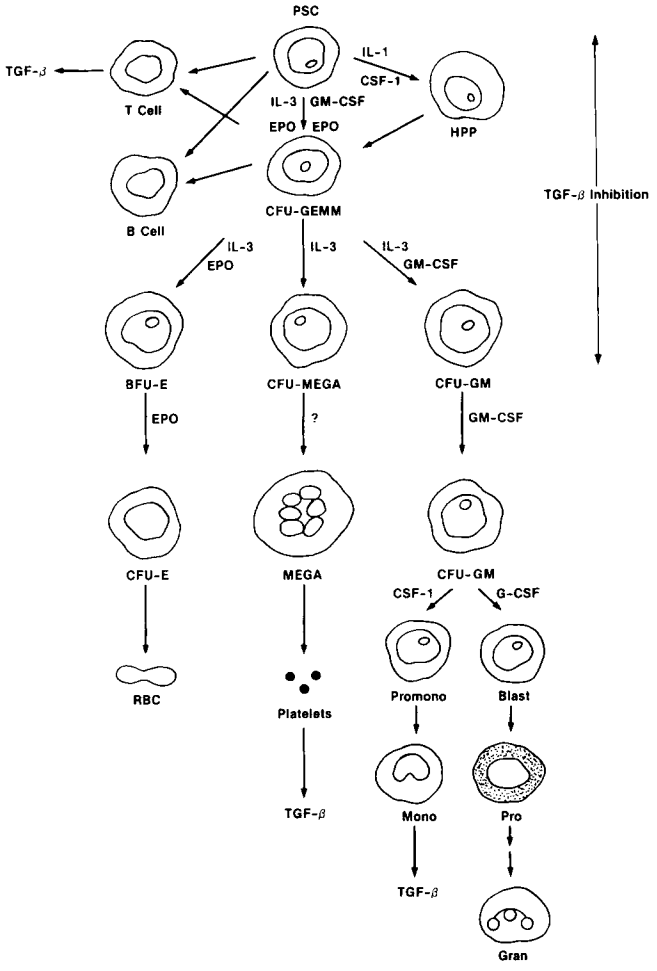

Fig 2. Scheme of TGF-β inhibition.

lines, NFS-60 and 32D-cl23, were infected with oncogene-containing retroviruses to abrogate their requirement for factor dependence [previously demonstated, 19]. In separate experiments, retroviruses containing v-abl, v-src, and v-fms were used to make factor-indepenent variants NFS-60 and 32D-cl23. In all cases, the factor-independent cell lines obtained retained the ability to be inhibited by TGF-β, suggesting that the response to TGF-β was not related to factor dependence.

TGF-β Receptor Differences on Human Leukemic Cells

A study of the effect of TGF-β on the growth of human myeloid and lymphoid cell lines revealed that all myelomonocytic cell lines except the promyelocytic HL-60 cell line were inhibited by TGF-β (Table V). In contrast to our data with myeloid leukemic cells, four out of four mature B-lymphoid leukemic cell lines and four out of four mature T-lymphoid leukemic cell lines were not inhibited by TGF-β (Table V), while their normal counterparts were sensitive to TGF-β [20,21]. To determine whether the differential response of these cell lines to TGF-β could be at the level of

TABLE IV. Effect of TGF-β1 On Leukemic Cell Lines*

Cell line	Lineage	Factor	% TGF-β1 inhibition
FDC-P1	Myeloid	IL-3	80–90
32D-c123	Myeloid	IL-3	70–80
NFS-60	Myeloid	IL-3	60–70
NFS-60	Myeloid	GM-CSF	60–70
NFS-60	Myeloid	G-CSF	60–70
NFS-60	Myeloid	CSF-1	60–70
NFS-60	Myeloid	IL-4	60–70
WEHI-3	Myelomonocytic	—	80–90
P388D1	Macrophage	—	0
J774A.1	Macrophage	—	0
TP-3	Erythroid	—	0
DS-19	Erythroid	—	0
P815	Mastocytoma	—	0

*TGF-β1 was diluted into cell proliferation assays to generate a dose-response curve starting at a concentration of 40 ng/ml. The range represents the maximum percent inhibition obtained from the dose-response curves from three separate experiments.

TABLE V. Effects of TGF-β1 in the Proliferation of Human Leukemia Cells*

		TGF-β inhibition		
Cell line	Cell type	ED-50 (pM)	Maximal (%)	TGF-β1 receptors
U937	Promonocyte	24	60	+++
THP-1	Monocyte	24	45	+++
KG-1	Myeloblast	14	70	+++
HL-60	Promyelocyte	–	0	0
RL	B-cell lymphoma	–	0	0
DB	B-cell lymphoma	–	0	0
HT	B-cell lymphoma	–	0	0
SR	Lymphoma	–	0	0
Hut 78	T-cell lymphoma	–	0	±
Hut 102	T-cell lymphoma	–	0	±
MT-2	T-cell lymphoma	–	0	±
CM-235	T-cell lymphoma	–	0	0

*TGF-β1 was diluted into cell proliferation assays to generate a dose-response curve starting at a concentration of 40 ng/ml. The range represents the maximum percent inhibition obtained from the dose-response curves from three separate experiments.

receptor expression, ligand-binding and affinity-labeling studies were performed. Three structurally distinct cell surface glycoproteins—a 280-Kd, an 85-Kd and a 65-Kd species—have been previously described as being high affinity TGF-β receptors [22]. These receptor molecules were identified on all cell lines sensitive to TGF-β growth inhibition. When the TGF-β-insensitive cell lines were examined, six out of nine had no detectable TGF-β receptors, while the other three had reduced numbers of receptors. These results suggest that the loss of TGF-β receptor expression might play a role in the growth of some leukemias by allowing cells to escape negative growth regulation by TGF-β.

SUMMARY

We have found that TGF-β is a potent selective inhibitor of early murine [23,24] and human [25] hematopoietic progenitor cell growth. It inhibits CFU-GEMM,

BFU-E, and CFU-GM colony formation but has no effect on CFU-G, CFU-E, and CFU-M colony formation. Using purified IL-3-induced Thy-1+ progenitors, we have shown that multipotent but not unipotent cell growth is directly inhibited by TGF-β [26]. In addition, all three classes of the HPP progenitor cells, which are the earliest measurable cells in vitro, were inhibited by TGF-β. Since HPP-CFC-1 cells are quiescent and have to be induced to enter the cell cycle in vitro by IL-1, it seems likely that TGF-β acts by interfering with the ability of cells to enter the cell cycle. Two forms of TGF-β, TGF-β1, and TGF-β2 were found to have identical effects in all the assays employed.

In summarizing the effects of TGF-β on leukemic cell growth, it appears that sensitivity to TGF-β is determined by the state of cellular differentiation and not the growth factor responsiveness of a particular cell type. For example, while G-CSF- and GM-CSF-induced normal bone marrow proliferation and colony formation were not inhibited by TGF-β1, G-CSF- and GM-CSF-driven NFS-60 cell proliferation was inhibited. In addition, it was found that the ability to respond to TGF-β was not due to growth factor dependence or independence. The TGF-β1-resistant leukemic erythroid and macrophage cells may have been transformed at a stage in their maturation where they are insensitive to TGF-β1. On the other hand, the resistance to TGF-β inhibition of some leukemic T and B lymphocytes as well as HL-60 is due to the absence of detectable receptors for TGF-β. Thus, it appears that some leukemic cells can gain a growth advantage by escaping from the negative growth regulation of TGF-β.

The capacity to inhibit selectively early marrow progenitor cells as well as leukemic cell proliferation could have clinical application. A variety of hematopoietic tumors may be responsive in vivo to TGF-β inhibition, which could be a useful adjunct to cytoreductive chemotherapy. In addition, if growth-arrested, quiescent marrow stem cells prove to be less sensitive to the effects of cycle-active drugs, TGF-β could be used as a protective agent to ameliorate the dose-limiting toxicity of many chemotherapeutic agents.

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REFERENCES

1. Sporn MB, Roberts AB, Wakefield LM, de Crombrugghe B: J Cell Biol 105:1039, 1987.
2. Massagué J: Cell 49:437, 1987.
3. Sporn MB, Roberts AB: Nature 313:745, 1985.
4. Sporn MB, Roberts AB, Wakefield LM, Assoian RK: Science 233:532, 1986.
5. Ellingsworth LR, Brennan JE, Fok K, Rosen DM, Bentz H, Piez KA, Seyedin SM: J Biol Chem 261:12362, 1986.

6. Metcalf D: Science 229:16, 1985.
7. Ohta M, Greenberger JS, Anklesaria P, Bassols A, Massagué J: Nature 329:539, 1987.
8. Ottman OG, Pelus LM: J Immunol 140:2661, 1988.
9. Ruscetti SK: JNCI 77:241, 1986.
10. Burgess AW, Metcalf D: Blood 56:947, 1980.
11. Keller JR, Ihle JN: J Immunol 135:1864, 1985.
12. Ihle JN, Keller J, Oroszlan S, Henderson LE, Copeland TD, Fitch F, Prystowsky MB, Goldwasser E, Schrader JW, Palaszynski E, Dy M, Lebel B: J Immunol 131:282, 1983.
13. Bradley TR, Hodgson GS: Blood 54:1446, 1979.
14. McNiece IK, Williams NT, Johnson GR, Kriegler AB, Bradley TR, Hodgson GS: Exp Hematol 15:972, 1987.
15. McNiece IK, Bradley TR, Kriegler AB, Hodgson GS: Exp Hematol 14:856, 1986.
16. Quesenberry P, Zenqxuan S, McGrath E, McNiece I, Shadduck R, Waheed A, Baber G, Kleeman E, Kaiser D: Blood 69:827, 1987.
17. Greenberger JS, Eckner RJ, Sakakeeny M, Marks P, Reid D, Nabel G, Hapel A, Ihle JN, Humphries KC: Fed Proc 42:2672, 1983.
18. Dexter TM, Garland J, Scott D, Scolnick E, Metcalf D: J Exp Med 152:1036, 1980.
19. Ihle JN, Morse HC, Keller J, Holmes K: Curr Top Microbiol Immunol 113:85, 1984.
20. Kehrl JH, Wakefield LM, Roberts AB, Jakowlew S, Alvarez-Mon M, Derynck R, Sporn MB, Fauci AS: J Exp Med 163:1037, 1986.
21. Kerhl JH, Roberts AB, Wakefield LM, Jakowlew S, Sporn MB, Fauci AS: J Immunol 137:3855, 1986.
22. Cheifetz S, Weatherbee JA, Tsang ML-S, Andersen JK, Mole JE, Lucas R, Massagúe J: Cell 48:409, 1987.
23. Ishibeshi T, Millee SL, Burnstein SA: Blood 69:1937, 1987.
24. Keller JR, Mantel C, Sing GK, Ellingsworth LR, Ruscetti SK, Ruscetti FW: J Exp Med 168:737, 1988.
25. Sing GK, Keller JR, Ellingsworth LR, Ruscetti FW: Blood In press, 1988.
26. Keller JR, Ellingsworth LR, McNiece IK, Quesenberry PJ, Sing GK, Ruscetti FW: Submitted, 1988.