[CANCER RESEARCH 47, 6576–6579, December15, 1987]

Modulation of Human Hemopoietic Progenitor Cell Growth *in Vitro* by Recombinant Human β-Interferon[1]

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ABSTRACT

Interferons are known to have modulatory effects on hemopoiesis. Human bone marrow mononuclear cells were employed to test the effects of human recombinant β-interferon on myeloid and erythroid hemopoietic stem cell growth. Results demonstrated that 1,000 U/ml of β-interferon significantly inhibited myeloid growth [colony-forming unit (CFU)-granulocyte macrophage] by 40–50%, whereas a higher concentration (10,000 U/ml) abolished CFU-granulocyte macrophage growth by 80–100%. The inhibitory effects of β-interferon were partially reversible by increasing the concentrations of colony stimulating activity in the culture and could not be abrogated by addition of toxic oxygen radical scavengers such as superoxide dismutase and catalase. The inhibitory effect of interferon was found to be partially dependent on the presence of accessory cells, since less inhibition was seen using T-cell and monocyte depleted bone marrow cells. Lower concentrations of β-interferon (10–100 units/ml) were without effect. In contrast to myeloid cells, the human erythroid progenitors (CFU-erythroid, burst-forming unit-erythroid) appear to be more sensitive to the inhibitory effects of β-interferon. In this regard it was found that 100 U/ml of β-interferon suppressed erythroid growth by 40–50%. These results suggest that human recombinant β-interferon is capable of suppressing hemopoietic colony growth.

INTRODUCTION

Interferons have been used as therapeutic agents for solid tumors and hematological malignancies for several years (1–4). Pancytopenia and in particular granulocytopenia are common toxic effects associated with interferon administration (4–6). Aplasia has occurred on occasion, even when the interferon dose used was well within tolerated limits (7). Interferons have been shown to affect hemopoietic progenitors *in vitro*, and in general they have a suppressive effect on these blood cell progenitors (8–16). Early studies utilized nonpurified forms of interferons and therefore results may not have reflected the true action of interferon itself.

Although the antiviral effects of interferons are well understood, the mechanisms involved in hemopoietic suppression and possible differentiation effects remain obscure. With the availability of recombinant forms of various biological response modifiers it is now possible to more clearly define the role of agents such as α- and β-interferons. In this respect, little experimental data is available concerning the effects of recombinant β-IF[4] on erythroid and myeloid cell lineages. In the present study we used *in vitro* culture assays for erythroid and myeloid progenitors in order to determine the effect of recombinant human β-interferon on these committed stem cells.

Received 2/3/87; revised 8/27/87; accepted 9/21/87.

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[1] Presented in part at The Annual Meeting of the American Association for Cancer Research, May 1986 (27).

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[4] The abbreviations used are: IF, interferon; BMNC, mononuclear cells; FCS, fetal calf serum; CSF, colony stimulating factor; BPA, burst promoting activity; CFU-GM, colony-forming unit-granulocyte macrophage; CFU-E, colony-forming unit-erythroid; BFU-E, burst forming unit-erythroid.

MATERIALS AND METHODS

Preparation of Mononuclear Cells from Human Bone Marrow

Heparinized bone marrow was aspirated from healthy adult individuals after appropriate informed consent was obtained. The marrow was diluted 1:3 with Iscove's modified Dulbecco's medium (GIBCO), layered over a Ficoll-Hypaque ($d = 1.077$) gradient and centrifuged at 400 × g for 30 min at room temperature (20–24°C). The cells were then washed twice, counted, and concentration adjusted to 5×10^6 cells/ml in Iscove's modified Dulbecco's medium with 20% FCS (Hyclone). The cells were applied to FCS-coated dishes and incubated for 60 min, 37°C, 5% CO_2. Nonadherent cells were removed, washed twice, and counted. Less than 3% monocytes (nonspecific esterase positive cells) were present in the nonadherent population. T-Cell depleted fractions were obtained from the monocyte-depleted population by the use of the 2-aminoethylisothiouronium-treated sheep red blood cells rosetting method described by Kaplan and Clark (17). 0–2% contaminating T-cells were found after depletion. Standard hemopoietic progenitor assays were performed using the same cell populations.

Hemopoietic Colony Assays

CFU-GM Assay. Nonadherent light density human marrow cells were plated in 0.5 ml triplicate cultures in 16-mm dishes (NUNC) at 5×10^4 cells/dish in 0.3% agar, Iscove's medium, 20% FCS, with a source of CSF-GCT-CM (GIBCO), 1–20% (v/v) with or without β-interferon. The cells were incubated for 14 days at 37°C, 7.5% CO_2, in humidified air; colonies with more than 40 cells were enumerated using a dissection microscope. Colony morphology was determined *in situ* by staining with chloracetate and nonspecific esterases as previously described (8). The CSF values used were partially purified and had an activity of approximately 1.4×10^3 U/ml (the latter a kind gift from Dr. Camille Abboud).

BFU-E/CFU-E Assay. Erythroid progenitors were assayed in plasma clot cultures as described by Tepperman *et al.* (18). BMNC (2×10^5 cells/1 ml) were cultured in the presence or absence of β-interferon with 0.5–2 U of human erythropoietin (Toyobo) for 7 and 15 days at 37°C, 3% CO_2, in humidified air. BFU-E were also assayed in a methylcellulose assay. Marrow cells at concentration of 1×10^5 cells/ml were cultured in triplicate 0.5 ml methylcellulose cultures containing 0.5–2 U erythropoietin, 30% FCS, 5×10^{-5} M mercaptoethanol with or without β-interferon and with or without a source of BPA. Medium conditioned by passaged human endothelial cells was heat inactivated (100°C, 5 min) and used as a source of BPA. It contained no CSF, no interferons; when used at concentrations of 5% (v/v) a significant increase (50–100%) in the number, size, and degree of hemoglobinization was seen in cultures containing BPA. After 15 days incubation at 37°C, 5% CO_2, 100% humidified air, colonies were counted and analyzed for constituent cells using a dissection microscope.

Interferon Preparation

Recombinant human β-interferon (pyrogen free) was kindly provided by Triton Biosciences. This preparation contained 1.8×10^8 U/mg protein, was reconstituted in saline, diluted to appropriate concentrations, aliquoted, and frozen at −70°C until used. Thawed specimens were discarded once used.

Time Course Studies

The interferon added to BMNC (at a concentration of 4×10^6 cell/ml) for periods of 1, 3, and 16 h at 37°C, 3% CO_2 in humidified air. The cells were washed three times, counted, and viability determined

by Trypan blue exclusion. They were resuspended and plated assuming original cell concentration. Control cultures consisted of cells incubated in media alone.

RESULTS

The addition of β-interferon to BMNC resulted in a dose dependent inhibition of CFU-GM colony growth. Results from seven experiments showed a 40–50% inhibition at a concentration of 1,000 U/ml of β-interferon and 90–100% at a concentration of 10,000 U/ml. Little or no inhibition could be demonstrated at lower doses. The inhibitory effect was seen in the presence or absence of T-cells or monocytes (Fig. 1), although accessory cells appeared to have an effect. In most experiments, there was considerably less suppression of colony growth in the accessory depleted cultures when compared to nondepleted BMNC cultures. Since IF has an inhibitory effect on CFU-GM formation, we were interested in determining if the inhibitory effect could be overcome by increasing the levels of exogenous CSF. Results depicted in Table 1 demonstrate that increasing the concentration of CSF did diminish the inhibitory effect of β-IF. Note that in this table inclusion of 5–20% CSF reduced the degree of colony inhibition in the presence of 100–1,000 U/ml β-interferon by 60–80%. Other sources of CSF such as recombinant-GM-CSF gave similar results (data not shown). In order to evaluate the possible requirement for direct cell contact with the interferon, we therefore examined the growth of precursor cells that were exposed to interferon for various time periods, and then removed from the interferon before culture. It was found that maximal inhibition occurred only when the cells were in constant exposure to interferon. Coincubation for periods of 1, 3, and 16 h had a lesser effect on the inhibition of hemopoietic progenitor cell growth (Table 2). Note that in this table in several cases much of the inhibitory effect was reduced after 1–3 h removal from exposure. Analysis of the types of colonies seen in control or β-IF treated cultures (Table 3) indicated that the interferon appeared to have no differential inhibitory effects on either granulocytic or monocytic components; inhibition of both lineages occurred to the same degree.

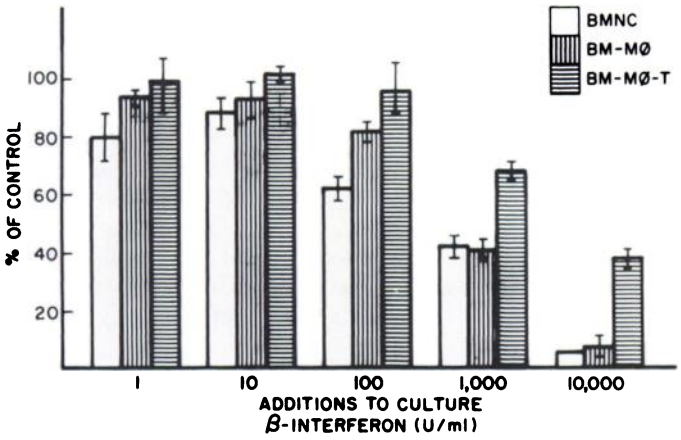

Fig. 1. Modulation of myeloid colony growth (CFU-GM) *in vitro* by β-interferon. BMNC was compared with monocyte (BM-MO) and T-cell depleted marrow cells (BM-MO-T).

Table 1 *Effect of β-interferon on myeloid colony growth (CFU-GM) in the presence of different concentrations of CSF*

Results presented as percentage of control (CSF without β-IF) colonies.

CSF (%)	β-IF (U/ml)				
	1	10	100	1,000	10,000
1	129.5	104	54.5	35.5	25
2.5	84.5	86	81.5	57.5	22.5
5	98.5	92.5	93.5	65.5	40
10	ND[a]	ND	98.5	51.5	44
20	ND	ND	98.5	74	48.5

[a] ND, not done.

Addition of 100 to 10,000 units of β-interferon to bone marrow erythroid cultures resulted in a significant dose dependent inhibition of erythroid colony (CFU-E) and burst forming (BFU-E) units (Fig. 2). Note in Fig. 2 that 100 U/ml interferon suppressed erythroid progenitor growth by 40–60%, whereas 1,000 U/ml interferon suppressed growth by 70–90%. In addition, the size of the individual colonies for either CFU-E or BFU-E were found to be reduced in size when compared with controls. Addition of increasing doses of erythropoietin (1–2 units/ml) did not overcome the inhibitory effect of interferon on colony growth. In a preliminary study, addition of BPA and recombinant erythropoietin were found to have no sparing effects on interferon exposed CFU-E and BFU-E cultures.

Fig. 3 represents results from experiments where depleted and nondepleted erythroid marrow cultures were grown in the presence or absence of β-interferon. As noted in the CFU-GM cultures described previously, depletion of accessory cells ameliorated the suppressive effect of interferon in some cultures. Removal of monocytes (BM-MO) appeared to reduce the inhibiting effects of 10–1,000 U of β-IF, whereas removal of both monocytes and T-cells (BM-MO-T) appeared to produce a biphasic effect at the same concentrations of β-IF. In this context, cultures containing β-IF, 100 U/ml, demonstrated a consistent sparing effect of IF induced inhibition in the absence of accessory cells.

DISCUSSION

Results from these studies further confirm that recombinant human β-interferon has a suppressive effect on human hemopoietic progenitors *in vitro*. Addition of β-IF to human marrow cultures resulted in a significant inhibition of both erythroid and myeloid progenitor growth. Addition of increasing concentrations of CSF was able to partially overcome some of the inhibitory effects of β-interferon on myeloid colony growth similar to that described by others using murine cells (15). In contrast, preincubation or addition of elevated concentrations of erythropoitein did not overcome the interferon mediated suppression of the erythroid progenitors, suggesting that different mechanisms of inhibition may be involved for different hemopoietic progenitors.

Previous studies have demonstrated considerable heterogeneity in response to interferons with the granulocyte-macrophage lineage (10, 16, 19). In fact, Mazur *et al.* (16) reported that CFU-GM colony growth from two out of four normal donors was unaffected by 200 U/ml of α-IF. Early studies in this laboratory demonstrated marked differences in human erythroid colony responses to leukocyte and fibroblast interferons, depending upon the hematological state of the bone marrow (9).

Experiments with accessory cell depleted bone marrow cultures yielded different responsiveness to IF than the nondepleted bone marrow cultures. In this respect, others have demonstrated that macrophage colony stimulating factor (CSF-1) is able to stimulate a murine bone marrow cellular population to generate α- and β-interferons. This effect required the presence of marrow adherent cells and it was therefore suggested that CSF-1 may act on the macrophage to produce interferons

Table 2 *Influence of β-IF on myeloid colony growth (CFU-GM): Time exposure, CFU-GM/10⁵ cells*[a]

β-IF	Constant	Exposure to β-IF (h)		
		1 h	3 h	16 h
Control	90.3 ± 2.5	85.3 ± 0.7[b]	53.3 ± 1.5	67 ± 9.4
10 U	92.3 ± 7.7 (102%)	84.3 ± 2.7 (99%)	70 ± 4.5 (131%)	55.3 ± 2.7 (83%)
100 U	74.7 ± 1.7 (85%)	82.3 ± 1.6 (96%)	56.3 ± 2.7 (105%)	55 ± 7.6 (82%)
1,000 U	60 ± 9.1 (66%)	57.7 ± 3.2 (68%)	56.7 ± 2.3 (106%)	53 ± 4 (79%)
10,000 U	12.3 ± 1.9 (14%)	73.7 ± 2.7 (86%)	52.7 ± 1.6 (99%)	46.3 ± 3.2 (69%)

[a] Cells were exposed to 0–10,000 U IF for 0–16 h after which the cells were washed and plated in semisolid media with CSF.
[b] Mean ± SEM of triplicate determinations from one of two representative experiments.

Table 3 *Analysis of colony types seen with β-IF (1,000 U/ml) treated myeloid cultures*

Data represent number of CFU-GM[a]/10⁵ cells.

Colony morphology, additions to culture	Granulocytic	Monocytic	Mix
CSF	51.3 ± 9.4 (79%)[b]	9.8 ± 1.1 (15%)	3.9 ± 1.1 (6%)
CSF and BIF	34.7 ± 2.0 (82%)	5.3 ± 2.2 (12%)	2.7 ± 1.0 (6%)

[a] Mean ± SEM of three experiments.
[b] Numbers in parentheses, percentage of total.

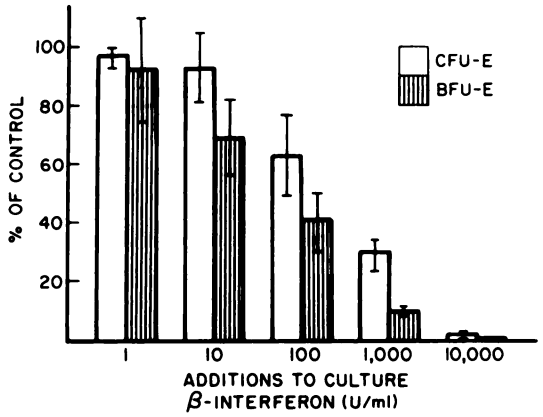

Fig. 2. Effect of β-interferon on erythroid colony formation *in vitro*. Results, mean ± SEM of three experiments.

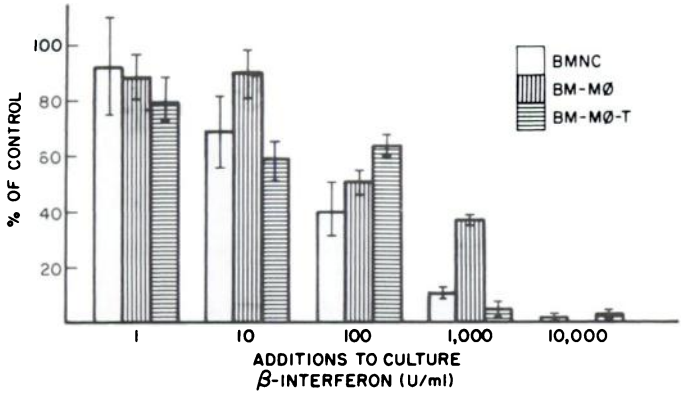

Fig. 3. Effect of β-IF on erythroid progenitor growth (CFU-E) in the presence or absence of monocyte (BM-MO) and T-cell depleted fractions (BM-MO-T).

(20). However, adherent cells contain several cell types and it remains possible that cells other than macrophages may contribute to these results. In view of the above mentioned results our observations indicated that in some cases accessory cell depleted bone marrows were less sensitive to inhibition by IF than were cultures using whole bone marrow populations. Such differences in part could be attributable to the presence of endogenous interferons and other biological response modifiers. In this regard, tumor necrosis factor has recently been shown to stimulate production of granulocyte CSF and could be of significance in our observations (21). Furthermore, observed bimodal inhibitory effects by IF may be ascribed to different cell populations coming into play.

Results from our studies demonstrated that there was also a reduced inhibitory activity seen in accessory cell depleted cultures of erythroid progenitors. In particular, 100 U IF/ml appeared to have less of a suppressive effect on depleted erythroid cultures in a manner similar to that for CFU-GM cultures. Certainly, the elaboration of endogenous interferons by lymphocytes and monocytes in the bone marrow depleted cultures may also contribute to our results. It remains possible that the mechanism(s) of hemopoietic inhibition by β-interferon may be mediated by direct cell contact, or indirectly via soluble factors released into the environment.

Interferons are known to mediate their antiviral effects primarily through induction of 2′,5′ oligonucleotides, however, the role of this mechanism in hemopoietic suppression remains unclear (22). More recently, it has been found that some interferon preparations may induce terminal differentiation in some types of leukemia cells (23). In other systems, continuous cellular contact was required in order for interferon to mediate its antiproliferative activity (24). These studies were not able to exclude the presence of diffusible factors mediated by cell to cell interactions. It is known that activation of immunocompetent cells by interferons can result in production/release of toxic oxygen radicals which in turn can affect hemopoietic progenitors (25). Studies by Grasset and Blanchet (25) demonstrated that 10 U/ml of catalase or superoxide dismutase were sufficient to overcome the toxic effects of H_2O_2 and OH radicals on hemopoietic progenitor cells. In preliminary experiments with these free radical scavengers, we found that addition of 10 U/ml of either catalase or superoxide dismutase to our cultures had no protective effect on CFU-GM inhibition by 1,000 U/ml β-IF. It appears that production of toxic O_2 intermediates may not be a major mechanism of inhibition by IF, in this culture system.

Results in this study demonstrate that the early erythroid progenitors (BFU-E) were consistently more sensitive to the cytotoxic effects of β-interferon than the later committed erythroid CFU-E. Furthermore, in order to obtain maximal inhibitory activity, it was necessary to maintain the IF preparations within the cell culture during the entire incubation period. This is in contrast to studies using γ-IF which may be explained in part by the activation of accessory cells by γ-IF. It is thought that the accessory cells are then capable of generating inhibitory interferons or other molecules (11, 26). As mentioned previously, variations in interferon effects have been reported using different types and preparations of interferons. Early studies by Broxmeyer *et al.* found that 1,000 U/ml β-interferon had little suppressive effect on day 14 CFU-GM growth (10). Their preparation of interferon had only a specific activity of 10^6 U/ml, compared to 1.8×10^8 U/mg protein in our recombinant

derived preparation. More recently these authors used β-interferon from a different source and found inhibition at much lower doses (10 and 100 U/ml). However, these results were obtained with a day 7 CFU-GM growth with less FCS in the medium. Seven day CFU-GM grown under these conditions are known to be much more sensitive to the interferons. Similar changes in culture conditions may account for the differences seen in the erythroid compartments. Results in the present study revealed a competition between the interferon and CSF, and this may be significant in the interpretation of our data (27). The inhibitory effect of interferon is likely to depend on the concentration of various components of the culture media which may account for the differences reported between several laboratories.

Our experiments support a role for β-interferon in modulating human hemopoiesis *in vitro* and that the antiproliferative effect of β-IF may not be limited to abnormal cells but may lead to hematological toxicity.

ACKNOWLEDGMENTS

We thank Rosemarie Ambrose and Kerry Donegan for help in the preparation of this manuscript.

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