lymphoma of MRL/lpr mice (*16*). A different virus, lactic dehydrogenase virus (LDV), can abort the antinuclear antibody production and immune complex disease of the lupus-prone New Zealand mouse (*17*). LDV is believed to bind to the I-A receptor and replicate in macrophages, hence presumably interfering with antigen processing (*18–20*). Recently, LDV was found to alter significantly the incidence of autoimmune allergic encephalomyelitis in Lewis rats (*21*). Thus, viruses, like bacteria and fungi, or their products, may be used for benefit, and perhaps to treat human illnesses. In addition, viruses may also be used as probes to dissect the molecular basis of various nonvirally caused disorders.

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Monocyte-Derived Human B-Cell Growth Factor Identified as Interferon-β_2 (BSF-2, IL-6)

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Soluble products of either Epstein-Barr virus (EBV)–infected B cells or activated monocytes promote the proliferation of EBV-infected B cells and permit their growth at low cell densities. This suggests that growth factors are important for B-cell immortalization by EBV. In this study, a monocyte-derived factor that promotes the growth of EBV-infected B cells was purified and identified as interferon-β_2 (IFN-β_2), which is also known as 26-kilodalton protein, B-cell differentiation factor (BSF-2), and interleukin-6 (IL-6). The purified protein has a specific activity of approximately 4×10^7 units per milligram of protein in assays of B-cell growth. Thus, IFN-β_2/BSF-2 is a B-cell growth factor that promotes the proliferation of human B cells infected with EBV.

THE MECHANISMS OF B-CELL PROliferation, immunoglobulin (Ig) production, and immortalization triggered by Epstein-Barr virus (EBV) are largely unknown. A role for autocrine or paracrine growth factors in these virus-induced processes is suggested by the observation that continuous proliferation of EBV-immortalized human B cells cultured at low cell densities requires the addition of either autologous "conditioned medium" (*1*) or supernatants of activated monocytes (*2*). Autocrine growth factors derived from EBV-infected lymphoblastoid cell lines appear to have functional similarities with T cell–derived "B-cell growth factors" (*3*) or with interleukin-1 (IL-1) (*4*). In contrast, paracrine growth factors derived from activated monocytes appear to be distinct from IL-1 and a variety of other monocyte-derived growth factors (*2*). We sought to identify the monocyte-derived growth factor or factors that permit growth of EBV-immortalized B cells at low cell density. We now report the purification of one such growth factor that we have identified as interferon-β_2 (IFN-β_2). This molecule is also known as 26-kD protein, B-cell differentiation factor (BSF-2), and interleukin-6 (IL-6).

The starting material for this purification was the culture medium of human peripheral blood monocytes stimulated with lipopolysaccharide (LPS) and phytohemagglutinin (PHA) (*5*). In a representative experiment we obtained a final purification of 4×10^5 times the original sample with recovery of approximately 10% of the original biological activity (Table 1).

The purified material was analyzed in reduced conditions by electrophoresis through a 12% polyacrylamide gel (*6*) followed by silver staining (*7*). Two major protein bands were identified with relative mass of 19 and 21 kD (Fig. 1A). This purified material enhanced the proliferation of an indicator lymphoblastoid cell line in a dose-dependent manner and revealed a spe-

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Table 1. Representative purification of B-cell growth factor from activated monocyte supernatants. Protein concentration in monocyte supernatant pool, CM-Sephadex pool, and DEAE-Sephacel pool was determined by the method of Smith *et al.* (*18*), whereas the protein content of the Synchropak RP-P pool was determined after silver staining (*7*) by a comparison with a 20-kD protein standard (soybean trypsin inhibitor). One unit of activity is arbitrarily defined as the activity inducing one-half maximal proliferation of an indicator lymphoblastoid cell line (TI) obtained by EBV (B95-8) immortalization of normal peripheral blood B cells. This cell line (in exponential growth phase) was cultured for 2 days in RPMI 1640 medium supplemented with 10% FCS, 2 m*M* L-glutamine, and 5 μg of gentamicin per milliliter at a cell density of 25×10^3 to 50×10^3 cells per milliliter. At higher cell densities little or no induction of proliferation was observed.

Fraction	Total proteins (mg)	Total activity (units $\times 10^4$)	Specific activity (U/mg)
Monocyte supernatant pool	84	2.4	2.86×10^2
CM-Sephadex pool	46	28.2	6.0×10^3
DEAE-Sephacel pool	1.8	8.96	4.87×10^4
Synchropak RP-P pool	6×10^{-4}	2.4	4.0×10^7

cific activity of approximately 4×10^7 U/mg of protein (Fig. 2). Enhanced [^{3}H]thymidine incorporation was associated with increases in cell numbers.

Because of the size similarities between the material we had purified and IFN-β_2 (*8*) and BSF-2 (*9*), we attempted to determine whether it might be IFN-β_2/BSF-2. A rabbit antiserum to highly purified *Escherichia coli*–derived IFN-β_2 (*10*) recognized both the 19- and 21-kD components of the purified monocyte-derived B-cell growth factor in a blot of the protein gel (Fig. 1B). Additional evidence of the identity of the monocyte-derived B-cell growth factor to IFN-β_2/BSF-2 was obtained in neutralization assays. As shown in Fig. 3, the antiserum to IFN-β_2/BSF-2 that recognized the purified protein in Western blots also neutralized its B-cell growth–enhancing activity in a dose-dependent manner. Similar results were obtained with a calf antiserum to a partially purified preparation of IFN-β that recognizes both IFN-β_1 and IFN-β_2/BSF-2 (*11*). Finally, recombinant BSF-2 enhanced the proliferation of each of six EBV-induced lymphoblastoid cell lines tested (Table 2), and these enhancements were neutralized by the antiserum to IFN-β_2/BSF-2 that neutralized the monocyte-derived growth factor.

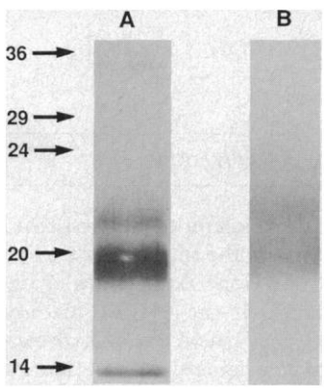

Fig. 1. Polyacrylamide gel electrophoresis and Western blotting of purified monocyte-derived B-cell growth factor. Growth factor purified as described in Table 1 was analyzed by electrophoresis on a 1% SDS–12% polyacrylamide gel (*6*). After electrophoresis, one lane (**A**) was silver-stained (*7*) and another lane (**B**) was transferred to nitrocellulose paper and incubated overnight with a rabbit antiserum to IFN-β_2/BSF-2 (1:200 dilution). This antiserum was obtained after five immunizations with 0.1 to 1 mg of *E. coli*–derived purified IFN-β_2/BSF-2 (*10*). Antibody bound to the nitrocellulose paper was detected with a biotinylated goat antiserum to rabbit immunoglobulin G and then with an avidin–biotin–horseradish peroxidase complex reagent (Vector).

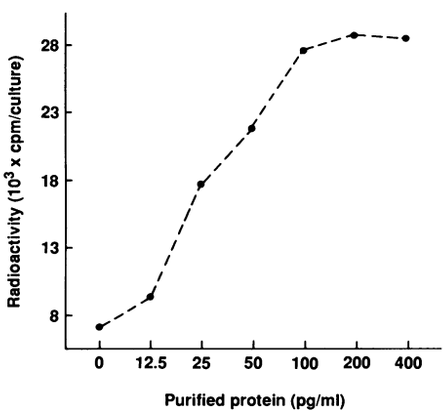

Fig. 2. Induction of proliferation by purified monocyte-derived B-cell growth factor. Lymphoblastoid cells (TI) in exponential growth phase (5×10^3 cells per 0.2-ml flat-bottom microwell) were cultured for 2 days in RPMI 1640 medium supplemented with fetal calf serum (FCS) (10%), L-glutamine (2 m*M*), and gentamicin (5 mg/ml) either alone or with the addition of purified protein at the indicated concentrations. [^{3}H]Thymidine (0.5 μCi per well) was added during the last 4.5 hours of culture. The results represent the mean radioactivity of triplicate cultures. Standard deviations were within 10% of the mean.

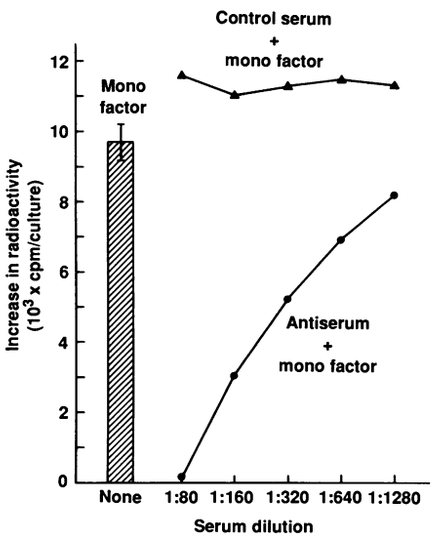

Fig. 3. Neutralization of monocyte-derived B-cell growth factor activity by a rabbit antiserum to *E. coli*–derived IFN-β_2/BSF-2. Lymphoblastoid cells in exponential growth phase (TI cell line, 10^3 cells per 0.2-ml flat-bottom microwell) were cultured for 48 hours without or with the addition of monocyte-derived B-cell growth factor (10 U/ml) either alone or in the presence of serial dilutions of either a control rabbit serum or a rabbit antiserum to IFN-β_2/BSF-2. This antiserum was obtained after five immunizations with of *E. coli*–derived IFN-β_2/BSF-2 purified by sequential anion-exchange chromatography, immunoaffinity chromatography, and gel electrophoresis (*10*). Appropriately diluted rabbit sera (control and antiserum) were incubated with either medium alone or growth factor for 2 hours at 37°C prior to the addition of the B cells. Proliferation was measured by [^{3}H]thymidine incorporation during the last 4.5 hours of culture, and the results are expressed as mean increase in radioactivity of triplicate cultures. Mean background proliferation was 7252 cpm per culture. The error bar identifies the standard deviation (nine cultures). The remaining data points represent the mean of triplicate cultures (standard deviations within 10% of the mean).

We therefore conclude that the monocyte-derived B-cell growth factor is IFN-β_2/26-kD protein/BSF-2/IL-6.

IFN-β_2/IL-6, a glycoprotein of 184 amino acids, was originally identified in human fibroblasts induced by poly(I)·poly(C) to produce IFN-β (*8*). Subsequently, a number of other factors identified on the basis of defined biological activities were found to be the same substance (*12*). These factors include the 26-kD protein (*13*), BSF-2 (*9*), the "hybridoma/plasmacytoma" growth factor (HPGF) (*14*), and a hepatocyte-stimulating factor (HSF) (*15*). There is evidence that IFN-β_2/BSF-2/IL-6 can be produced by a variety of cell types either constitutively or upon stimulation (*8–17*). IFN-β_2/BSF-2/IL-6 appears to have a number of biological functions, including antiviral activity (*8*). It is also a growth inhibitor for human fibroblasts (*11*), a growth factor for certain mouse-rat hybridomas and mouse plasmacytomas (*14*), a differentiation factor for human B cells (*9*), and an inducer of acute-phase proteins in hepatocytes (*15*). However, IFN-β_2/BSF-2/IL-6 has not been previously found to act as a growth factor for human B cells.

The stimulatory effects of IFN-β_2/BSF-2/IL-6 are observed only when the target B cells are cultured at low cell densities (*2*). This may be due to factors produced by EBV-immortalized B cells that can provide

Table 2. Enhanced proliferation of lymphoblastoid cell lines in response to recombinant IFN-β_2/BSF-2. Six lymphoblastoid cell lines obtained by EBV (B95-8 strain) immortalization of normal peripheral blood B cells that had been kept in continuous culture for 6 months to 4 years were cultured (5×10^3 or 10×10^3 cells per 0.2-ml microwell) either in medium alone (RPMI 1640 supplemented with 10% FCS) or with the addition of either recombinant IFN-β_2/BSF-2 (100 U/ml) or monocyte-derived IFN-β_2/BSF-2 (10 U/ml). Potency of the recombinant BSF-2 was determined in immunoglobulin production assays prior to shipment (*9*); potency of the natural product was determined by a comparison with a laboratory standard (*2*). At the end of a 2-day culture period proliferation was measured by [^{3}H]thymidine uptake during the last 4.5 hours of culture. Results are expressed as mean radioactivity (cpm) of triplicate cultures. Standard deviations were within 15% of the mean.

Cell line	Proliferation (cpm/culture)		
	Medium	Recombinant BSF-2	Monocyte-derived IFN-β_2/BSF-2
VDS-O	15,441	34,142	36,304
RY	8,897	15,577	13,147
FR	4,209	16,303	19,473
AVM	1,117	7,943	7,467
JR	4,683	36,850	34,758
TI	8,036	18,402	21,125

autocrine growth stimulation (*1, 3*). When EBV-immortalized cells are cultured at high densities, there are high concentrations of such factors, and cell growth cannot be enhanced further. However, when they are cultured at low cell densities, cell growth becomes dependent on exogenous factors, including IFN-β_2/BSF-2. This requirement that the cells be cultured at low density for the growth-promoting effects of IFN-β_2/BSF-2 to be observed may explain why this effect has not been documented previously (*9*).

We do not know whether this growth factor is B cell lineage–specific, whether it is selective for B cells activated by EBV, or whether it is part of a network of cytokine interactions. We report here that IFN-β_2/BSF-2/IL-6 is a potent growth factor for human B cells infected with EBV. This newly described property of the molecule emphasizes its role as an important mediator of the immune response in humans.

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The Effect of Eurasian Snow Cover on Global Climate

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Numerical simulations with a global atmospheric circulation model suggest that large-scale variations in the amount of snowfall over Eurasia in the springtime are linked to the subsequent strength of the Asian summer monsoon. Large-scale changes in Eurasian snow cover are coupled to larger scale changes in the global climate system. There is a large, strong teleconnection to the atmospheric field over North America. The model results also show snow cover effects to subsequently alter other climatic fields known to be intimately associated with the El Niño–Southern Oscillation (ENSO) phenomenon. Thus the model results seem to challenge the current dogma that the ENSO phenomenon is solely the result of close coupling between the atmosphere and ocean by suggesting that processes over continental land masses may also have to be considered.

OVER 100 YEARS AGO, HENRY Blanford (*1*) hypothesized that unusually heavy snow in the Himalayas preceded a failure of the Indian summer monsoon, and that this regional effect might be part of a "larger scale" climatic change associated with large-scale changes in snow cover over Eurasia. Recently, other researchers have argued also for the potential importance of the possible role of Eurasian snow cover in global climate dynamics (*2*), but only in the last decade has a serious effort been made to check such hypotheses (*3–6*). Unfortunately, studies conducted to date have been largely empirical and have yielded results that, while supportive of the original ideas, are largely unconvincing because of data problems or other limitations.

We have conducted simulations with a global general circulation model (GCM) in which the snow depth over the Eurasian continent was varied from its climatological norm and the subsequent climatic changes in the model noted. In simulations where the snow amount is increased, the model's summer monsoon is characterized by less rainfall, higher surface pressure over Southeast Asia, and reduced winds over the Arabian Sea (Fig. 1). These climatic changes are generally associated with a poor monsoon. The model simulations also suggest that the failure of the Asian monsoon is, as Blanford guessed, part of a far larger modulation of the global climate system. Specifically, there appear to be important teleconnections between the large convection region of Southeast Asia and the atmospheric fields over the tropical Pacific and North America (Figs. 2 and 3). These results all strongly support the original hypothesis that the amount of snow on the Eurasian continent in the spring has an important subsequent impact on both regional and global climate variations.

The physics responsible for the above results in the GCM are generally complex. The regional effects include all elements of the surface heat budget and the soil hydrology. The presence of the snow, its melting, and evaporation of its melt water retard and diminish warming of the Asian land mass and subsequent establishment of the land-sea temperature contrast that drives the monsoon circulation. The reason for the remote teleconnection to North America involves large-scale thermal forcing over the Asian land mass and subsequent adjustment, via Rossby wave dynamics, of the ultralong wave structure of the atmosphere. The tropical response is due to direct thermal forcing associated with the latent heat release during monsoon precipitation anomalies.

The details of our experiments were as follows. The model we used was a version of

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