Perspective

Human β_2 Interferon and B-Cell Differentiation Factor BSF-2 Are Identical

PRAVINKUMAR B. SEHGAL,*
LESTER T. MAY, IGOR TAMM,
JAN VILČEK

IT IS NOT UNCOMMON THAT BIOLOGICAL FACTORS ORIGINALLY detected on the basis of individual activities are subsequently shown to have the same structures. The structure of human β_2 interferon (IFN-β_2) (*1–3*), a protein first detected in poly(I) · poly(C)–induced human fibroblasts on the basis of its antiviral activity (*4*), is identical to that of human B-cell differentiation factor BSF-2 (*5*), a T-cell product that enhances immunoglobulin secretion in antigen-stimulated B cells without inducing cell proliferation (*6, 7*). A recently discovered protein secreted by poly(I) · poly(C)– or interleukin-1–induced human fibroblasts that stimulates the growth of certain murine hybridoma and plasmacytoma cell lines (HGF or "hybridoma growth factor") has also been recognized as being identical to IFN-β_2 (*8*).

IFN-β_2 stands apart from the rest of the interferons in that its constitutive expression in human diploid fibroblasts is enhanced by other cytokines such as tumor necrosis factor (TNF), interleukin-1α and -β (IL-1α and -β), and platelet-derived growth factor (PDGF) (*2, 3, 9–11*). It appears that IFN-β_2 functions as part of a complex cytokine network with respect to its antiviral and cell-growth regulatory activities, and the net biological effects observed are cell-type dependent (*9–11*). For example, recent data suggest that in TNF-treated human diploid fibroblasts (FS-4 strain) IFN-β_2 mediates the development of an antiviral state (*10, 11*) and enhances the expression of cell surface histocompatibility antigens (*3*). In these same cells, however, IFN-β_2 appears to inhibit the mitogenic effect of TNF (*10*).

Although PDGF and IL-1 also induce IFN-β_2 in human fibroblasts, an antiviral state does not become established in FS-4 cells exposed to PDGF or IL-1 (*11*). Moreover, PDGF and IL-1 can override the antiviral state induced by TNF as well as that induced by recombinant IFN-β_1 in human fibroblasts (*11*). However, IL-1 readily elicits an antiviral state in human osteosarcoma MG-63 cells (*9*). We anticipate that the biological role of IFN-β_2 in the immune system will also be best defined in the context of a network of tissue-specific cytokine interactions.

The existence of distinct T-cell–derived helper factors that promote B-cell proliferation, differentiation, or antibody secretion was recognized in the mid-1970s (*6, 12–14*). The human B-cell differentiation factor BSF-2 was characterized in activated T cells as well as in human T-cell tumor lines that secrete this factor constitutively (*7, 14*). Human BSF-2 can induce the following: (i) an increase in biosynthesis of secretory-type heavy chains of immunoglobulins (Ig) as well as their messenger RNA (mRNA); (ii) IgM and IgG secretion in *Staphylococcus aureus* Cowan I–activated normal B cells; and (iii) IgG or IgM secretion in Epstein-Barr virus–transformed human B-cell lines in the absence of an effect on cell growth (*7*).

Until this point, the histories of IFN-β_2 and BSF-2 have been separate; we will now consider them as one molecule. Mature IFN-β_2/BSF-2 is a 21-kD glycoprotein; it consists of 184 amino acid residues that are derived from a precursor peptide of 212 amino acids. The amino acid sequence of IFN-β_2/BSF-2 shares similarities with that of human IFN-β_1 (*2, 3*) and with that of human granulocyte–colony-stimulating factor (G-CSF) (*5*). It is striking that the closest similarity between IFN-β_2/BSF-2 and IFN-β_1 lies in the carboxyl-terminal region of IFN-β_2/BSF-2 (*3*), whereas the closest similarity between this cytokine and G-CSF lies in the amino-terminal region of IFN-β_2/BSF-2 (*5*). Could it be that different regions of this molecule serve different biological functions? That different monoclonal and polyclonal antibodies to IFN-β neutralize the antiviral activity of both recombinant IFN-β_1 and recombinant IFN-β_2/BSF-2 (*2, 15*) is consistent with the similarities in the amino acid sequences of the two proteins.

The gene for human IFN-β_2/BSF-2 contains at least four exons (*2*) and is located on chromosome 7 (*16*). The immediate 5′-flanking region of this gene shares distinctive nucleotide sequence similarities (*17*) with the serum-responsive enhancer element in the human c-*fos* proto-oncogene (*18*). A second human gene that is distinct from the original IFN-β_2/BSF-2 gene, but which shares at least one exon (carboxyl terminal) with it, has also been detected in DNA from several individuals and has been isolated from two different human genomic DNA libraries (*2, 16, 19*). It has been suggested that this second gene, which yields biologically active human interferon when transfected into rodent cells (*3*), be designated IFN-β_2b and the previously characterized gene be designated IFN-β_2a (*2*).

It is already clear that IFN-β_2/BSF-2 is expressed in a variety of lymphoid and nonlymphoid tissues both constitutively and in response to several different stimuli. The 1.3-kb IFN-β_2/BSF-2 mRNA is expressed constitutively in human fibroblasts (*10, 11, 20*), human monocytes (*21*), in certain T-cell lines (*5*), in T24 bladder carcinoma cells (*5, 22*), and in cardiac myxoma cells (*5*). Its expression in fibroblasts is enhanced by TNF, IL-1, PDGF, bovine serum, other interferons, and poly(I) · poly(C) (*2, 3, 9–11*). 1,2-Dioctanoylglycerol, 1-oleoyl-2-acetylglycerol, and the calcium ionophore A23187 also strongly enhance IFN-β_2/BSF-2 gene expression in human fibroblasts (*23*). An enhancement of IFN-β_2/BSF-2 mRNA levels is also observed in several human carcinoma cell lines in response to TNF and lymphotoxin (TNF-β) (*22*). Its expression in human lymphocytes can be enhanced by phytohemagglutinin (*5, 24*), concanavalin A (*8*), and tetradecanoyl phorbol 13-acetate (*5*). However, the human B lymphoblastoid cell line (Namalwa) cannot be induced to express IFN-β_2/BSF-2 mRNA under conditions that lead to the induction of large amounts of IFN-α and IFN-β_1 (*25*).

IL-1 and TNF increase IFN-β_2/BSF-2 gene transcription in human fibroblasts by different mechanisms (*17*). The enhancing effect of IL-1 on IFN-β_2/BSF-2 transcription, but not that of TNF, is decreased by cycloheximide, suggesting that newly synthesized protein mediates most of the increase in transcription in response to IL-1 but not that in response to TNF. The IFN-β_2/BSF-2 gene is an "interferon-inducible" gene; its transcription in human FS-4 fibroblasts is enhanced by recombinant IFN-β_1 in the presence of cycloheximide (*11, 17*).

P. B. Sehgal, L. T. May, and I. Tamm are associated with the Rockefeller University, New York, NY 10021, and J. Vilček is associated with the Department of Microbiology and Kaplan Cancer Center, New York University Medical Center, New York, NY 10016.

*To whom correspondence should be addressed.

The recognition that IFN-β_2/BSF-2 mediates biological functions as diverse as antiviral activity, enhancement of immunoglobulin secretion, and stimulation of growth of hybridoma cells is unexpected, albeit not unprecedented. IFN-γ, a protein with profound effects on the immune system, was discovered as an acid-labile antiviral substance secreted by phytohemagglutinin-activated human leukocytes (*26*). It later became apparent that IFN-γ and "macrophage activating factor" are one and the same molecule (*27*). IFN-γ is secreted by antigen-stimulated T cells and modulates antibody production by B cells, macrophage functions, effector T-cell functions, and natural killer cell activity (*27*). IFN-α_2, -β_1, and -γ induce blast transformation and plasmacytoid differentiation with intracellular Ig expression in leukemic B cells from a high proportion of patients with chronic B-lymphocytic leukemia (*28*). Many other cytokines, such as TNF or IL-1, that were originally believed to have a narrow spectrum of biological activities, upon closer scrutiny were found to have diverse actions and to lack tissue specificity. Nor is it unprecedented that IFN-β_2/BSF-2 can apparently act as a growth inhibitor in human fibroblasts (*10*) and a growth factor in murine hybridoma/plasmacytoma lines (*8*). A case in point is TNF, which is cytotoxic/cytostatic for many transformed cells but is a growth factor for fibroblasts (*29*). Another example is transforming growth factor–β, which is a potent inhibitor of the growth of many types of anchorage-dependent cells but a stimulator of anchorage-independent cell growth (*30*).

The relation between IFN-β_2/BSF-2 and colony-stimulating factors (CSFs) appears worthy of further study as there is a similarity between sections of the amino acid sequences of IFN-β_2/BSF-2 and G-CSF (*5*). IL-1 and TNF induce the synthesis of granulocyte-monocyte CSF (GM-CSF) (*31*); it is also possible that the demonstrated stimulation of B-cell differentiation by IL-1 (*32*) might be mediated through the induction of IFN-β_2/BSF-2. Thus, IL-1– and TNF-induced production of IFN-β_2/BSF-2 in connective tissue cells during inflammation may promote local immunoglobulin production, while production of GM-CSF (and perhaps of other CSFs) would stimulate the influx and proliferation of mononuclear and polymorphonuclear phagocytes.

Much remains to be learned about the functions of IFN-β_2/BSF-2. The molecular mechanisms by which this cytokine exerts its multiple effects on gene expression are unknown. The fact that IFN-β_2/BSF-2 is readily produced by normal and transformed cells of both nonlymphoid and lymphoid origin suggests that it can act in many different cell types, in addition to the already demonstrated effects on fibroblasts, B cells, and B-cell hybridomas. IFN-β_2/BSF-2 has emerged as a new means of bidirectional communication between cells of the immune system and those outside it.

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