The immunomodulatory effects of interferon-gamma on mature B-lymphocyte responses

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Summary. Interferon-gamma (IFN-γ) exerts a broad spectrum of activities which affect the responses of mature B-cells. It strongly inhibits B-cell activation, acts as a B-cell growth factor (BCGF), and also induces final differentiation to immunoglobulin (Ig) production. IFN-γ is deeply involved in the differential control of isotype expression, as it enhances IgG_{2a} production and suppresses both IgG_1 and IgE production. Although it is now possible to draw a general scheme of the effects of IFN-γ on B-cells, a number of paradoxical results still exist in the field. In this manuscript, different experimental systems are analyzed in an attempt to explain these apparent paradoxes.
Key words. IFN-γ; B-lymphocytes; lymphokines.

Introduction

Interferon-gamma (IFN-γ) mediates a number of modulatory signals at several points in the pathway of the progression of B-lymphocyte responses. Although it was originally proposed as an enhancer factor for antibody production by B-cells, further studies revealed a complex spectrum of activities. Thus it was found that, depending on the experimental conditions, IFN-γ could antagonize B-cell activating signals[18, 19, 28], exert BCGF activity, induce maturation[33] or act as a modulator of isotype expression[8, 36, 38].

The action of IFN-γ on proliferating B-cells yields opposing results depending on the bioassay used. Today, it is generally accepted that IFN-γ is a strong inhibitor of anti-Ig plus IL-4-mediated costimulatory B-cell activation, provided it is present with these stimuli from the onset of culture[18, 19]. In the case of LPS-induced proliferating B-cells, IFN-γ markedly suppresses growth, in contrast to its BCGF effect in both human[6, 30] and mouse (this paper).

At the stage of final B-cell maturation, IFN-γ has been reported to induce both Ig synthesis and secretion by normal and transformed B-cells[33]. However, no such maturation activity has been found in other experimental systems[6, 13]. Finally, in vivo experiments demonstrate that IFN-γ can also act as a modulator in the processes involved in the expression of specific Ig isotypes[9]. Hence, IFN-γ was shown to enhance IgG_{2a} and inhibit IgG_1 and IgE expression in the mouse[36–38].

IFN-γ sources

The assignment of IFN-γ action to different points in the progression pathway of B-cell responses correlates with the evolution of technology in lymphokine research and cellular immunology. In the early days, IFN-γ was produced and used as an activity present in supernatants of mitogen-/or antigen-stimulated bulk spleen cultures, helper T-cell lines and helper T-cell clones[22, 35]. The cytokine content in these supernatants varied according to the homogeneity and origin of the cells used. Therefore, it has been common to find IFN-γ activity associated with some other factors[16, 35]. As shown in figure 1, rat spleen cell cultures stimulated by concanavalin A (Con A) can produce at least 3 different activities. Fractions from a gel filtration system were tested for IFN activity T-cell replacing factor activity (TRF) and B-cell helper factor activity (BHF) using different functional biological assays. It can be seen that fractions 100 to 110 contain factors active in all three assay systems. In addition to these, two other activities, namely T-cell growth factor (TCGF) and B-cell maturation factor (BMF), comigrate with the TRF peak (data not shown). Hence, multiple activites can appear in the same fractions in biochemical separation procedures. These have been called TRF[31], IFN[35], IL-X[16] etc. depending on the assay.

Obviously, the extrapolation from a given activity in a biological assay to the existence of a single factor has brought confusion to nomenclature and function. As the knowledge of the helper T-cell network evolved, it was found that at least two helper T-cell subsets exist. These

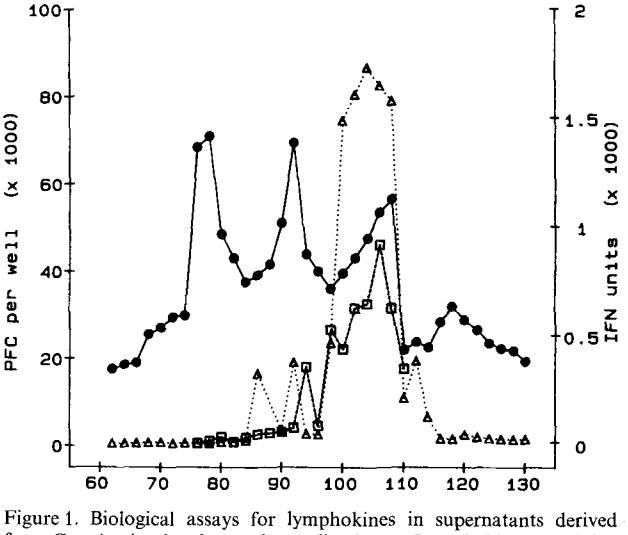

Figure 1. Biological assays for lymphokines in supernatants derived from Con A-stimulated rat spleen cell cultures. Lymphokine containing supernatants were induced by Con A in splenocyte cultures. The secreted proteins were precipitated, dialyzed and loaded into a Sephadex G-100 column. Fractions (62 to 130) were analyzed for IFN-γ (solid circles), BHF (open triangles) and TRF (open squares).

have been named Th-1 and Th-2 and differ substantially in the spectrum of lymphokines they secrete. The Th-1 subset has been found to secrete IL-2 and IFN-γ, whereas the Th-2 subset selectively secretes IL-4 and IL-5[5,32]. With modern molecular techniques, it has been possible to obtain relatively pure and well-defined recombinant sources of interleukins and cytokines. It is now important to define biological assays which discriminate reliably between the effects of these various mediators.

IFN-γ actions on B-cell activation

B-cells with rearranged variable regions leave the bone marrow and are distributed into the peripheral immunocompetent organs. At this level, they are resting cells waiting for contact with the specific antigen which, in conjunction with the so-called helper signals from other cells, will make them progress to activation, growth and maturation to antibody-secreting cells.

Experimentally isolated resting B-cells can be stimulated by antigen, anti-Ig[1,15] or mitogens. Transition to the activated state is accompanied by a host of metabolic events including a shift in the calcium influx[7,42], catalysis of phosphatidyl inositol[2], cellular enlargement, protein, RNA and DNA synthesis[23]. However, in the cases of anti-Ig and T-dependent antigens, the contact of the specific ligand is known to be insufficient for transit through the entire cell cycle. Strong B-cell activation characterized by increased IA expression, volume increase and progression to cellular replication is possible only when specific cytokines such as IL-1 or IL-4[1,4,5,12,23,25] (fig. 2) are present.

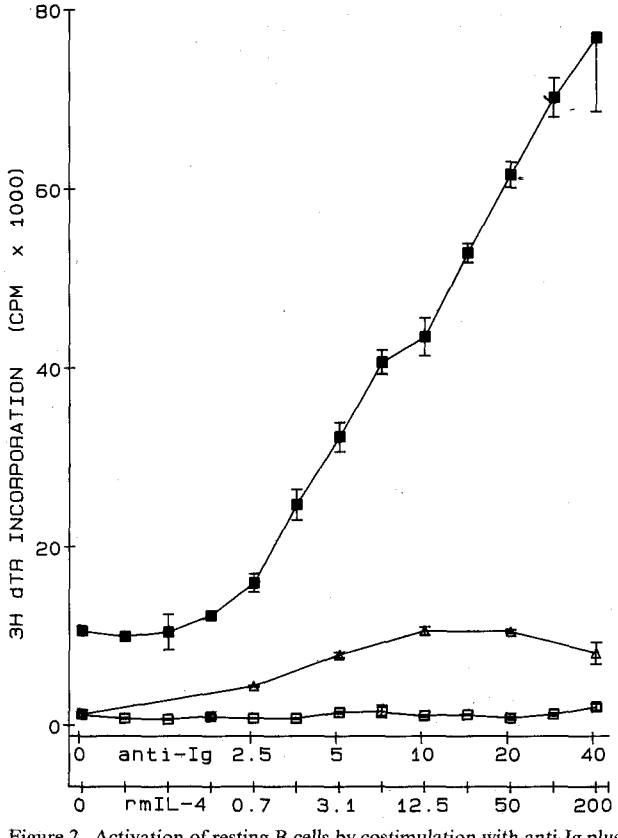

Figure 2. Activation of resting B-cells by costimulation with anti-Ig plus r-m-IL-4. Small, resting B-cells (5×10^4/well) were incubated with graded amounts of anti-IgM shown as µg/ml (open triangles), r-m-IL-4 given in U/ml (open squares), and a combination of anti-IgM (10 µg/ml) with increasing quantities of r-m-IL-4 (filled squares).

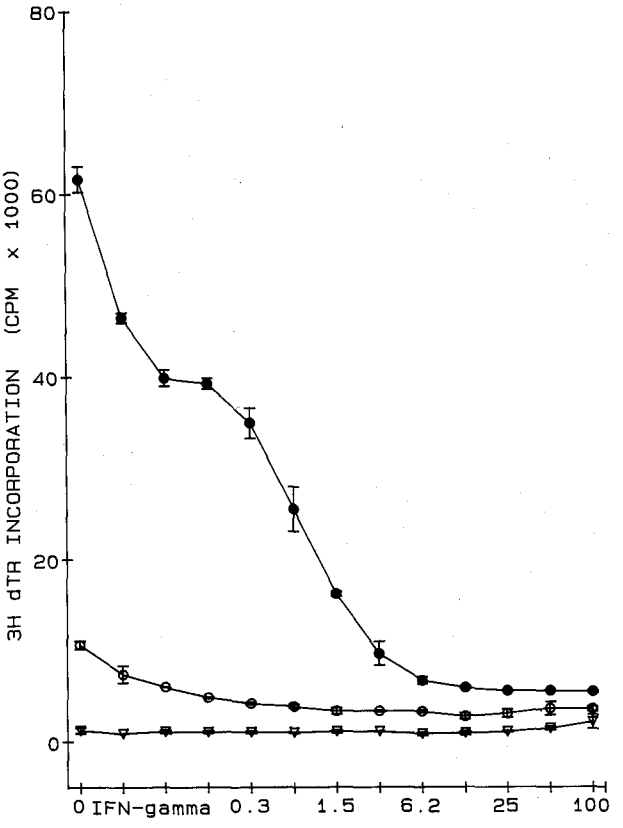

Figure 3. IFN-γ inhibits B-cell activation by anti-IgM plus r-m-IL-4. A suboptimal B-cell response induced by anti-IgM (10 µg/ml) plus r-m-IL-4 (50 U/ml) is inhibited by co-cultivation with different amounts (U/ml) of IFN-γ (filled circles) kindly provided by Drs Paul Trotta, Shering Corp. and Robert Coffman, DNAX, Palo Alto. Controls with anti-IgM (10 µg/ml) plus r-m-IL-4 or IFN-γ alone are shown by the open circles and the open inverted triangles, respectively.

The effects of IFN-γ on anti-Ig plus IL-4 B-cell activation have been investigated in both the mouse and human yielding a spectrum of experimental results. Reports in the literature[18,19,28] and our own results (fig. 3) show inhibition of B-cell activation. Nevertheless, the apparent discrepancy with previous reports, where IFN-γ was found to augment the antibody response[16,22,30,33] and to act as a BCGF[6,30], prompted us to investigate in which circumstances this lymphokine could mediate such an enhancing effect. We have performed the kinetic studies shown in figure 4. Here IFN-γ played an inhibitory role when present at the time of activation, thereby blocking the transit to the proliferation phase, as seen in other systems[17]. However, when this lymphokine is added later, it progressively loses its inhibitory capacity and finally mediates enhancement of proliferation. Since inhibitory or enhancing effects could be observed at both extremes of this kinetic experiment, it is unlikely that the

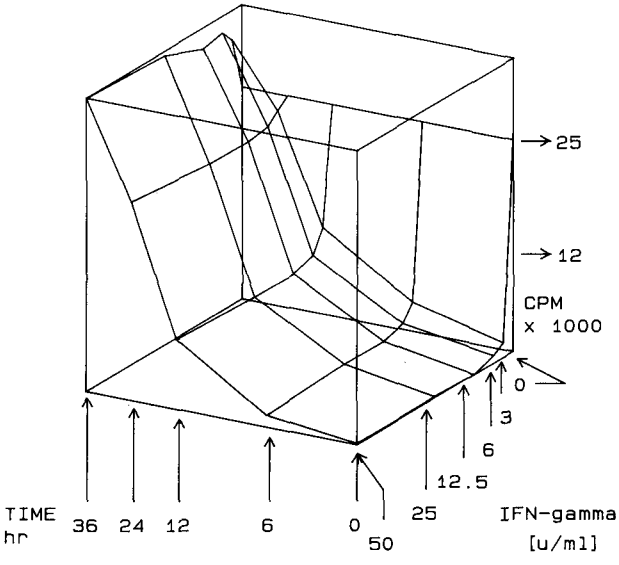

Figure 4. Time-dose kinetics of inhibition of B-cell activation. Cultures were suboptimally stimulated by anti-IgM (10 μg/ml) plus r-m-IL-4 (25 U/ml) in the absence of IFN-γ and incorporated about 25 000 cpm of tritiated thymidine. These were taken as positive controls and plotted as a straight line representing the level of B-cell response (vertical axis) at zero IFN-γ. This line is a constant along the time axis. A series of parallel independent cultures were pulsed with graded amounts of IFN-γ at different times. At 48 h, all cultures were pulsed with tritiated thymidine and harvested 12 h later.

insensitivity to inhibition is mediated by loss of specific receptors for IFN.

Overall, there are two important points to be made about this experiment. First, IFN must be present early in order to exert inhibition on anti-Ig activation of B-cells. Second, IFN enhances this type of B-cell activation if it is added to the system after the first 24 h. Together, these studies resolve the apparent paradox that IFN can act both as a strong negative modulator of B-cell activation and as a B-cell growth factor. In addition to the presence of other factors, the time of addition of IFN is a critical parameter in determining the characteristics of the response pattern observed. This is a clear demonstration that a single, well-defined, chemical mediator can modulate a biological response in opposing ways depending on the pint in the activation process at which it is perceived. Hence, the expression of different cellular programs in response to the same immunomodulator may be determined by the stage of differentiation in which it is perceived by the B-cell.

IFN-γ and B-cell proliferation

IFN-γ has been reported to act as a BCGF when tonsillar B-cells were cultured with anti-Ig or anti-Ig plus IL-2[30]. Moreover, coincubation with anti-Ig plus IL-2 and IFN-γ showed a synergistic effect. A BCGF effect of IFN-γ on peripheral human B-cells has also been found when these cells were stimulated with suboptimal amounts of anti-Ig[6]. Interestingly, no such effect was found when *Staphylococcus aureus* (SAC) was used as a costimulant. Furthermore, others could detect neither BCGF nor maturation activity mediated by IFN-γ as a single factor in the SAC costimulation B-cell system[13,14]. Nakagawa et al. have proposed a model for the sequential action of IL-2 and IFN-γ on SAC-stimulated human B-cells[20] and in Epstein-Barr virus transformed cells[20,21]. In this model, IL-2 acts as a proliferation signal while IFN-γ acts as a maturational agent. Bich-Thuy has proposed that IL-2 is absolutely required for induction of B-cell sensitivity to IFN[3].

As a model for steady state proliferation, we used the system shown in figure 5. In this case, LPS-induced, rapidly proliferating cells are confronted with the presence of IFN-γ. The results show a strong dose-dependent inhibition of proliferation. Although this result may appear as a contradiction to our finding in the anti-Ig system, several explanations are possible. The results of figure 4 show that the effect of IFN-γ during the first two days of B-cell growth depends on its time of addition. Hence, as B-cells differentiate and progress along the activation pathway, several response patterns appear to be available. One of many possibilities is that at later stages of B-cell activation, these cells become sensitive to

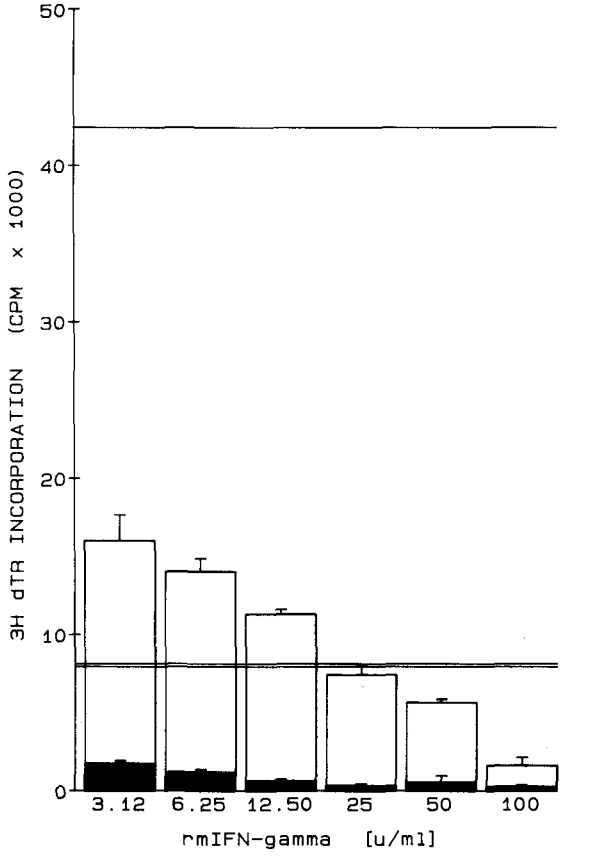

Figure 5. The effect of IFN-γ on LPS-induced proliferating B-cells. B-cell blasts from 48-h LPS cultures were washed and then recultured in the presence (upper straight line) or absence of fresh mitogen (lower double solid straight line). IFN-γ was then given to a series of independent parallel cultures of both types. Following a second 48-h culture period, thymidine incorporation was assessed as in figure 4. The results are shown as open bars for the first type of culture and dark bars for the second type.

differentiation induction by IFN. That is, as B-cells continue to proliferate under the influence of potent mitogens, they acquire responsiveness to agents which can induce antibody secretion. Alternatively, activation by LPS may differ qualitatively from activation by anti-Ig. Hence, this may result in qualitatively different responses to IFN in the two different model systems.

IFN as a maturation factor

Several activities, presumably mediated by single factors, have been proposed to drive B-cells into the maturation phase. Pioneering work detected such activities present in lymphokine-containing supernatants and the term BCDF (B-cell differentiation factor) was coined [39]. With further investigation, it became evident that the BCDF effect could be mediated by different agents, e.g. BSF-1 (today called IL-4) [26, 39, 40], TRF (IL-5), BMF [34, 35], IL-6 or BSF-2 [41] and IFN-γ [33]. In favor of IFN-γ acting as a maturation factor were the results obtained with the transformed B-cell line WEHI-279 and with resting murine splenic B-cell. In both systems, IFN-γ induced Ig secretion [33, 35]. While some investigators found similar effects with human IFN-γ [20], other investigators did not [6, 13].

The preceding sections have shown that some of the apparent contradictions in the literature concerning the effects of IFN-γ on B-cell proliferation can probably be attributed to different experimental methodologies. It is possible that a similar explanation may account for the apparent contradictions concerning the ability of IFN to induce B-cell maturation. Therefore, we have approached this problem by using purified, resting splenic B-cells cultured with IFN-γ and several different kinds of antigens, including thymus-independent types 1 and 2 and a soluble thymus-dependent protein. The antigens used were TNP-LPS, TNP-Ficoll and TNP-KLH, hence assay of PFCs to TNP could assess the influence of IFN on the same anti-hapten response using antigens with different carriers. The results are shown in the table.

Lack of B-cell maturational ability of IFN-γ

	Anti-TNP-SRBC PFC/10^6 cells Primary antigens					
Addition	1 μg/ml	TNP-LPS	10 μg/ml	TNP-Ficoll	1 μg/ml	TNP-KLH
Medium	420	(20)	1	(0)	2	(2)
rIL-2	325	(75)	0	(0)	0	(0)
rIL-5	985	(100)	5	(2)	3	(1)
rIFN-γ	435	(80)	0	(0)	1	(1)

Averages of triplicate determinations are shown with their standard deviations in parentheses.

With none of these antigens was IFN able to function as a TRF or a B-cell maturation factor whereas rIL-5 could when TNP-LPS was used. These results suggest that TRF may be a complex activity consisting of several activities acting at several different points in the response. In any case, it is clear that IFN alone cannot serve as a factor inducing terminal antibody secretion in these systems. These results also highlight the uniqueness of using SRBC as an antigen since responses to this antigen (fig. 1) appear to differ from responses to antigens of thymus-independent types 1 and 2 and to soluble proteins.

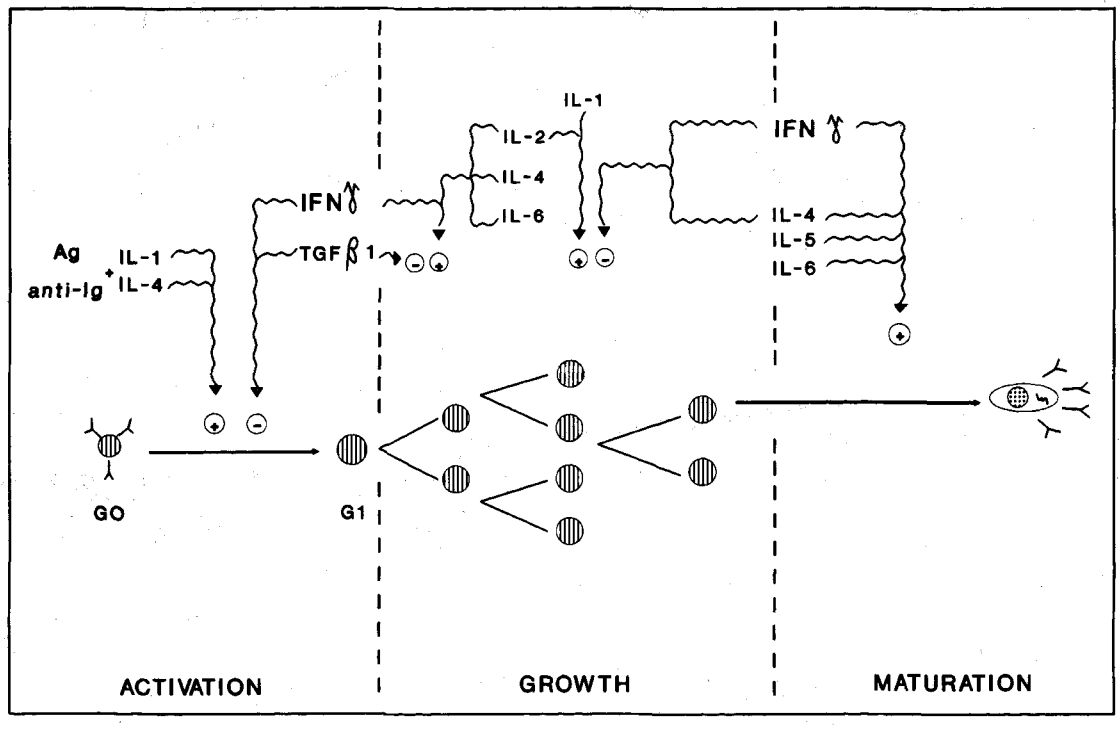

Figure 6. Modulation of the B-cell progression pathways by cytokines. The phases of B-cell activation, growth and maturation are schematized and the points of positive and negative modulation are indicated by the + and − symbols, respectively.

Concluding remarks

A model for the B-cell progression pathway is given in figure 6 where small resting B-cells are activated by specific antigen or anti-Ig. IL-1 and IL-4 are positive modulators of the transition to the G 1 state. A negative form of control is exerted by IFN-γ or by transforming growth factor-beta-1 (TGF beta-1)[27] at this stage. Once the B-cells are in the early proliferative phase, they become sensitive to IFN-gamma, IL-2, IL-4 or IL-6 acting as positive modulators for proliferation. Further growth may then be mediated by IL-1 or IL-2. At this point, i.e. in the later rounds of replication, IFN-γ, IL-4, IL-5 and IL-6 appear to both inhibit proliferation and induce maturation into Ig production and secretion.

The resulting pattern of isotype expression may be conditioned by the presence of one or more factors. Thus IFN-γ, when present alone, induces IgG_{2a}. On the other hand, it inhibits the positive effect of IL-4 on IgG_1 and IgE induction[5, 9, 37, 38]. IL-5 seems to selectively enhance IgA secretion while IL-6 may positively regulate IgM or IgG isotypes.

It is apparent that IFN-γ has activity in many immunological assays in addition to its function as an antiviral reagent. That this mediator is secreted by the TH 1 T-helper subset[5] underlines its importance in immunity and immune responses.

We have shown that IFN-γ can enhance proliferation of the immunologically relevant B-cells when it is added late to in vitro cultures. This, and the concomitant demonstration of inhibition of proliferation when added at culture onset show the multiplicity of effects that this cytokine can have. Perhaps the more important point is that these two observations may explain some of the conflicts between previous reports as being due to different experimental approaches. What remains is to understand the regulation of IFN expression in vivo during an immune response. It will be necessary to elucidate what determines when a responding B-cell is exposed to IFN-γ, and how the architecture of the microenvironment of an immune response is involved. In short, we must try to bridge the gap between our knowledge of in vitro responses and our understanding of responses in vivo.

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Expression of the genes of interferons and other cytokines in normal and diseased tissues of man

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Summary. Specific interferon genes are transcribed at low levels in the spleen, liver, and peripheral blood leukocytes of normal individuals in the apparent absence of virus infection while other interferon genes remain unexpressed in the same tissues. In contrast, the genes of cytokines such as IL-1, IL-6 and TNF are expressed at relatively high levels in the organs of normal individuals. The level of expression of the IL-1, IL-6 and TNF genes is markedly reduced in the livers of patients with autoimmune liver disease compared to the level of expression in the liver of normal individuals, whereas the expression of interferon genes is similar in both normal and diseased liver, suggesting that a defect in the expression of specific cytokines is associated with severe liver disease.
Key words. Interferon; cytokines; interleukins; gene expression; transcription; autoimmune; disease.

Introduction

Mammalian cells produce and respond to a variety of secreted polypeptides or cytokines such as interferons (IFN), tumor necrosis factor (TNF), interleukins (IL), and growth factors which affect the proliferation, differentiation, and function of cells involved in numerous physiological processes[19, 44, 65, 67, 109, 123]. I have suggested previously that such intercellular messengers occupy a central position in a putative network of cytokine interactions which act to maintain homeostasis in normal tissues[126]. In this article I shall review the current evidence in support of this concept and suggest a model for the organization of the cytokine network which may help us to understand cytokine interactions in vivo. I shall also examine the situations in which uncontrolled production of a specific cytokine could lead to the development of disease.

If we are to understand how cytokines regulate cell physiology and maintain homeostasis in vivo we must first determine how the expression of specific cytokine genes is regulated in normal tissues. It is important to establish, for example, how cytokines such as interferons, TNF, and interleukins, which are induced proteins, are able to function as endogenous regulators of cell function in vivo when their production is usually subject to stringent control.

I shall not discuss the production of cytokines by cells in culture, except to illustrate interactions which may exist in vivo. Although in vitro systems are of undoubted value for the study of cytokines, caution is required when extrapolating from such simplified and by definition artificial systems to the complexity of the whole animal. Although there are, for example, a number of reports of