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The interferons: a biological system with therapeutic potential in viral infections

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Abstract

Successful medical use of interferon for chronic viral infections is increasingly dependent on understanding the biologic and molecular mechanisms of the interferon system. Interferon (IFN) is one of the body's natural defenses. Production of IFN is a defensive response to foreign components of microbes, tumors and antigens. This IFN response begins with the production of the IFN proteins (α, β and γ) which then induce antiviral, antimicrobial, antitumor, and immunomodulatory actions. Thus, the initial production or administration of IFN(s) does not protect directly but instead reacts with specific receptors on cell surfaces to activate cytoplasmic transduction signals that then enter the nucleus to stimulate cellular genes encoding a number of effector proteins which lead to the defensive actions. The known molecular, humoral and cellular mechanisms by which these effector proteins exert their antiviral activities are presented. In addition, the pathogenesis of chronic infections is overviewed in the context of the interferon defenses.

Key words: Interferon; Viral infection; Interferon biological system; Natural defense

1. Introduction

Interestingly the majority of viral infections are asymptomatic and even when symptomatic the host usually recovers. This resistance to viral infections is attribu-

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table to an array of nonspecific and immune-specific host defenses (Dianzani et al., 1991; Klimpel, 1991). These defenses also moderate chronic viral infections. The interferon system is one of the nonspecific defenses against viruses. To understand the rationale for medical application to viruses we will overview the types of viral infection and then the interferon system. Citations may be to review articles from which the original publication may be identified.

2. Type of infection

Several types of viral infections occur and are illustrated in Fig. 1 (Boldogh et al., 1991). Acute infections are of short duration and the virus is eliminated. Persistent infections are those in which the virus is not cleared from the host following primary infection, and may remain associated with specific cells. Persistent infections include latent, chronic and slow infections. Latent persistent infection is characterized by the lack of demonstrable infectious virus between episodes of recurrent disease. Chronic persistent infection is characterized by the continued presence of virus following the primary infection and may cause chronic or recurrent disease. Slow persistent infection is characterized by a prolonged incubation period followed by progressive disease.

Diseases caused by persistent virus infections include acquired immune deficiency syndrome (AIDS), chronic hepatitis B and C, subacute sclerosing panencephalitis

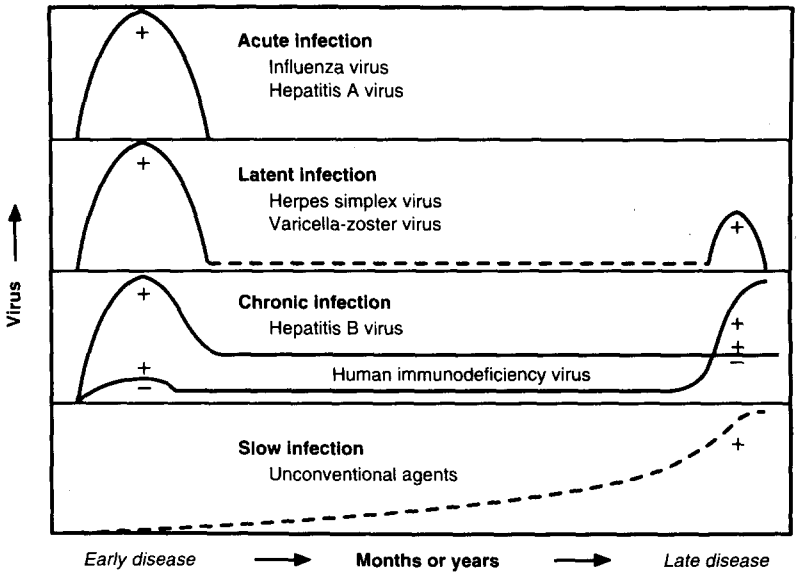

Fig. 1. Natural history of acute and persistent human infections. Solid line, shedding of infectious virus; dashed line, virus not readily demonstrable; +, disease episode. Reprinted (Boldogh, 1991) with permission.

(chronic measles encephalitis), persistent rubella virus infections, chronic papovavirus encephalitis (progressive multifocal leukoencephalopathy), spongioform encephalopathies (caused by unconventional agents), several herpesvirus-induced diseases, and some retrovirus-induced neoplasias.

3. Interferon

Interferon (IFN) was discovered over 35 years ago by Isaacs and Lindenmann (Issacs et al., 1957), who observed that fluids from virus-infected cell cultures contained a cell-specified protein that could react with cells to render them resistant to infection by many viruses. We now know that IFN is really a family of molecules which can be divided into three groups: IFN α, IFN β, and IFN γ. These IFNs differ in the agents which induce them and in the cell types which produce them. The IFN proteins have been purified. The IFN genes have been cloned, expressed and large quantities of the IFN proteins produced by genetically engineered microbes and also from cell cultures for clinical use (Baron et al., 1992). Although IFNs were first recognized for their potent antiviral properties, it has now been established that they may profoundly affect other vital cellular and body functions, including cell metabolism and growth, immunity, and tumors. Clinically, government licensing agencies have approved IFN for a number of medical uses including chronic hepatitis B and C. A wide variety of IFN activities including antiviral, antiproliferative, antitumor, immunomodulatory and hormonal have been described and partly characterized (Table 1) (Baron et al., 1987; Dianzani et al., 1989; Nelson et al., 1989; Borecky, 1989; Taylor et al., 1990). To induce these activities, medically or naturally, the IFN proteins must activate cells to produce effector proteins (Taylor et al., 1990).

4. The biological role of IFN mechanisms during viral infections

Most viral infections in vivo are controlled initially by nonspecific defenses that: (a) restrict the initial virus multiplication to manageable levels; (b) begin the elimination of viruses from peak amounts of virus that, if presented as the infecting dose, could be lethal; and (c) are joined later by the specific immune defenses (Baron et al., 1963). The nonspecific defenses, such as inflammation, IFN, and fever are produced

Table 1
Functional effects of interferon

Antiviral action	Enhancement of cytotoxicity of lymphocytes
Antitumor action	Influence on subsequent production of IFN
Cell growth inhibition	Hormonal interactions
Alteration of cell membranes	Oncogene regulation
Immunoregulatory action	Cellular differentiation
Macrophage activation	

by the host in response to infection. These nonspecific defenses are initiated early-several days before the specific immune defense responses.

The important role played by IFN as a natural defense against viruses is documented by three types of experimental and clinical observations: (a) in many viral infections a strong correlation has been established between IFN production and natural recovery; (b) inhibition of IFN production or action enhances the severity of infection; and (c) treatment with IFN protects against viral infection (Baron et al., 1987). As noted above, the IFN system is one of the earliest-appearing of the known host defenses, becoming operative within hours of infection. Fig. 2 compares the early production of IFN with the specific antibody response during experimental infection of humans with influenza virus. Clinical studies of IFN and its inducers have shown protection against a number of viruses, including hepatitis B and C viruses, papillomaviruses, rhinoviruses, and herpesviruses (Tyring, 1992; Greenberg, 1992).

5. IFN production and types

Production of IFNs (α, β and γ) occurs de novo by cellular protein synthesis. The three types of IFN proteins differ both structurally and antigenically and the natural IFNs have molecular weights ranging from 16 000–45 000 daltons. IFNs are secreted by the cell into the extracellular fluids. Usually, viral-induced IFN is produced at

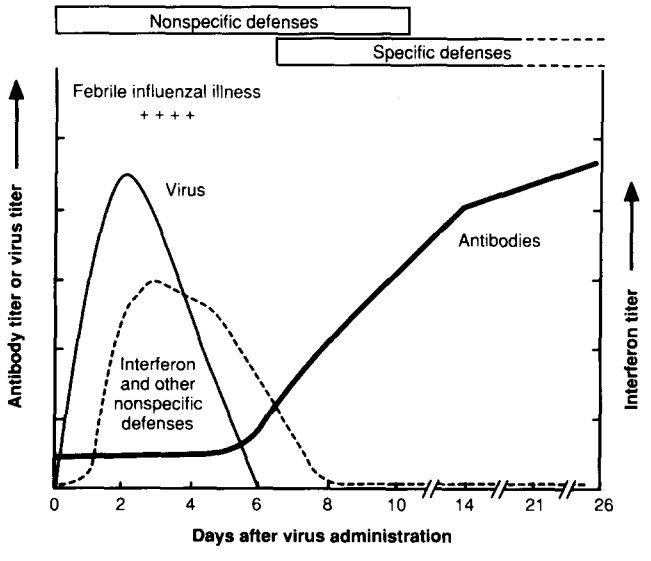

Fig. 2. Production of virus, IFN, and antibody during experimental infection of humans with influenza wild-type virus. From a study by Drs. B. Murphy et al., National Institutes of Health. Non-specific defenses include (1) anatomic barriers, (2) inhibitors, (3) phagocytosis, (4) fever, (5) inflammation, and (6) IFN. Specific defenses include (1) antibody and (2) cell-mediated immunity.

about the same time or even before the viral progeny are released from the infected cell. In this way the IFN may protect neighboring cells from the spreading virus.

The three known types of IFN are induced by different stimuli. Human IFN β is induced by viral and other foreign nucleic acids in many body cells (fibroblasts, epithelial cells, and macrophages). This induction mechanism is illustrated in Fig. 3, top. As shown in the middle portion of the figure, the second type of IFN (IFN α) can be induced by foreign cells, virus-infected cells, tumor cells, bacterial cells, and viral envelopes that stimulate B lymphocytes, null lymphocytes, and macrophages to produce IFN α protein. Mitogens for B cells may mimic this induction. An unusual, acid labile IFN α may occur during AIDS and also is found in patients with immune perturbations such as lupus erythematosus, rheumatoid arthritis, and pemphigus. A recent report indicates that this acid labile IFN may actually be a synergistic combination of acid labile IFN γ and acid stable IFN α (Capobianchi et al., 1992).

The third type, IFN γ, is produced (along with other lymphokines) by T lymphocytes induced in an immune-specific fashion by foreign antigens for which the T lymphocytes have specific receptors (Fig. 3, bottom) (Wheelock, 1965; Green et al., 1969; Youngner et al., 1973). Mitogens for T cells may mimic this induction. Under some conditions natural killer lymphocytes also may produce IFN γ (Baron et al., 1992). IFN γ has several unusual properties (Baron et al., 1992): (a) it generally exerts relatively greater immunomodulatory activity, including greater activation of macrophages than the other IFNs; (b) it exerts relatively greater cell lytic effects than the other IFNs; (c) it may potentiate the actions of other IFNs; (d) it activates

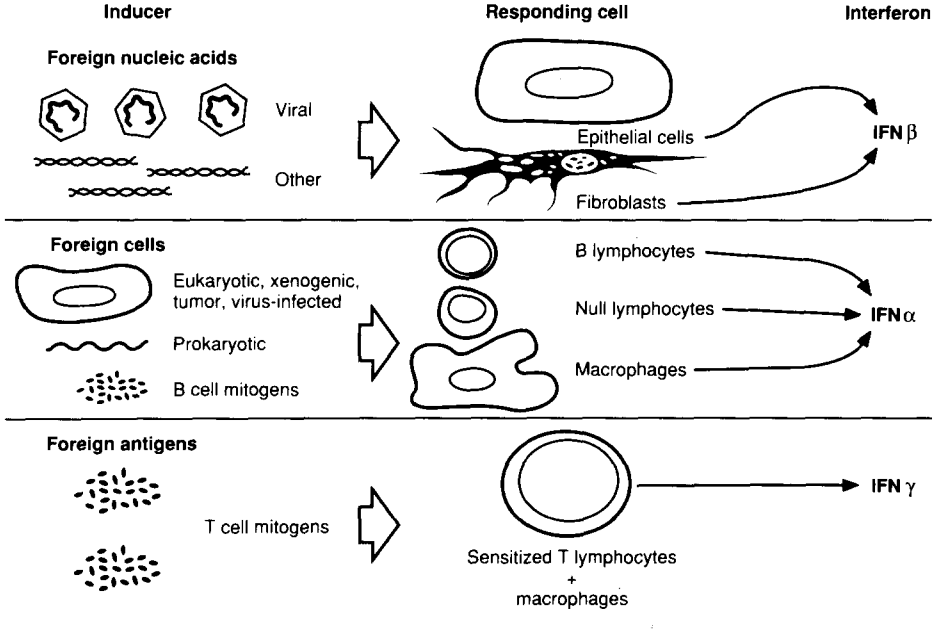

Fig. 3. Induction of IFN β, IFN α, or IFN γ, respectively, by foreign nucleic acids, foreign cells, or foreign antigens.

cells by a mechanism different from that of the other IFNs; and (e) it, more effectively than the other IFNs, inhibits infection by microorganisms other than viruses, e.g., some rickettsia, protozoa and bacteria.

6. Overview of antiviral actions of IFN

The IFN proteins (α, β, and γ), that are produced in response to foreign substances, do not protect cells directly. Instead, they activate surrounding cells by reacting with IFN-specific receptors on the surface of cell membranes which then activate cytoplasmic transduction signals that enter the nucleus to derepress cellular genes that encode intracellular effector proteins. These effector proteins must be synthesized before virus replication can be inhibited (Fig. 4). Similar genetic activation of cells by IFN appears to be required for most of its other biological actions, e.g., antitumor, immunomodulatory and antimicrobial. The underlying molecular mechanisms of action that are initiated by the effector proteins are specified in a later section.

Biologically, the IFN-induced antiviral state may be transferred from IFN-treated cells to adjacent untreated cells without the continued presence of IFN (Fig. 4);

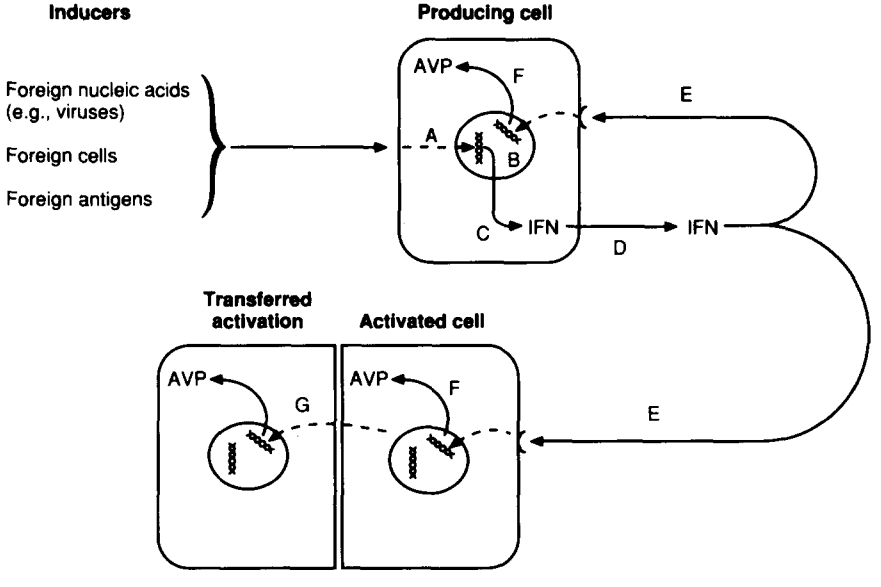

Fig. 4. Cellular events of the induction, production, and action of IFN. Inducers of IFN react with cells to derepress the IFN gene(s) (A). This leads to the production of mRNA for IFN (B). The mRNA is translated into the IFN protein (C) which is secreted into the extracellular fluid (D) where it reacts with the membrane receptors of cells (E). The IFN-stimulated cells derepress genes (F) for effector proteins (AVP) that establish antiviral resistance and other cell changes. The activated cells also stimulate contacted cells (G) to produce AVP by a still unknown mechanism.

this transfer mechanism may further amplify and spread the IFN system's activity (Blalock et al., 1978). Interestingly, IFN usually acts best on cells of the animal species in which it was induced (Sutton et al., 1961).

7. Antiviral mechanisms

7.1. IFN during natural virus infection

The importance of IFN during different virus infections varies. Much depends on the effectiveness of the virus in stimulating IFN production and on the susceptibility of the virus to the antiviral action of IFN. IFN is able to protect most body tissues at its local site of production during virus infection; IFN is also disseminated through the bloodstream during viremia, thereby protecting distant organs against the spreading infection (Baron et al., 1966). Cells protected by IFN against viral replication may eliminate large numbers of internalized virus by degrading the virus genome (Baron, 1966).

7.2. Mechanisms of the antiviral action of IFNs

Unlike specific antibodies which can inactivate viruses and other pathogens by binding to them, IFN does not act directly on viruses. Instead of binding, killing, or otherwise inactivating viruses, IFN acts through the virus-susceptible cells to produce its antiviral actions. In some senses IFN acts like a classical polypeptide hormone or cytokine (Baron, 1966). There is tight binding to a specific cell surface receptor (one receptor for both IFN α and β, and a second, distinct receptor for IFN γ), followed by transmembrane signalling and the induction of new proteins (Pestka et al., 1987; Samuel, 1988; Rubinstein et al., 1986; Fu et al., 1992). It is these induced proteins that actually effect the various biological actions of IFN. The mechanisms by which the binding of the IFNs to their receptors induce the synthesis of specific antiviral proteins is a subject of active research. There are pre-existing cytoplasmic proteins which are involved in maintaining the specificity of the cell's transducing response to IFN (Fu et al., 1992; Rutherford et al., 1988). IFN-induced proteins number over two dozen; however, the role and mechanisms of action have been determined for only a few (Pestka et al., 1987; Samuel, 1988; Samuel, 1987). Among the messenger RNAs and proteins which are known to be upregulated by the IFN system are a protein kinase, 2′,5′-oligo-A synthetase 2′,5′-phosphodiesterase, Mx protein, HLA antigens, β-microglobulin, the TNF receptor, and several enzymes. A number of other genes are repressed by IFN, including certain oncogenes, and the receptors for insulin, transferin, and epidermal growth factor (Samuel, 1988; Samuel, 1987; Faltynek et al., 1988).

The broad antiviral range of IFN activity seems to be due to the various biochemical pathways that are modulated by the IFN system. These different pathways have different antiviral effects, often acting on different parts of the various viral replication cycles (Pestka et al., 1987; Samuel, 1987; Samuel, 1988; Jacobsen, 1986). A schematic representation of the antiviral actions of IFN during virus replication, is shown in Fig. 5.

The virus replication cycle begins with contact of virus with the target cell and ends with the release of mature virus particles. Early replicative events consist of viral attachment to the cell, penetration of the cell membrane, and uncoating of the viral nucleic acid. Next is the replication of the viral proteins and nucleic acids. Finally the assembly, packaging, and release of mature virions occurs. IFN can inhibit each of these groups of events, depending on the virus family (Jacobsen, 1986). The major, and best studied, antiviral actions appear to affect the translation

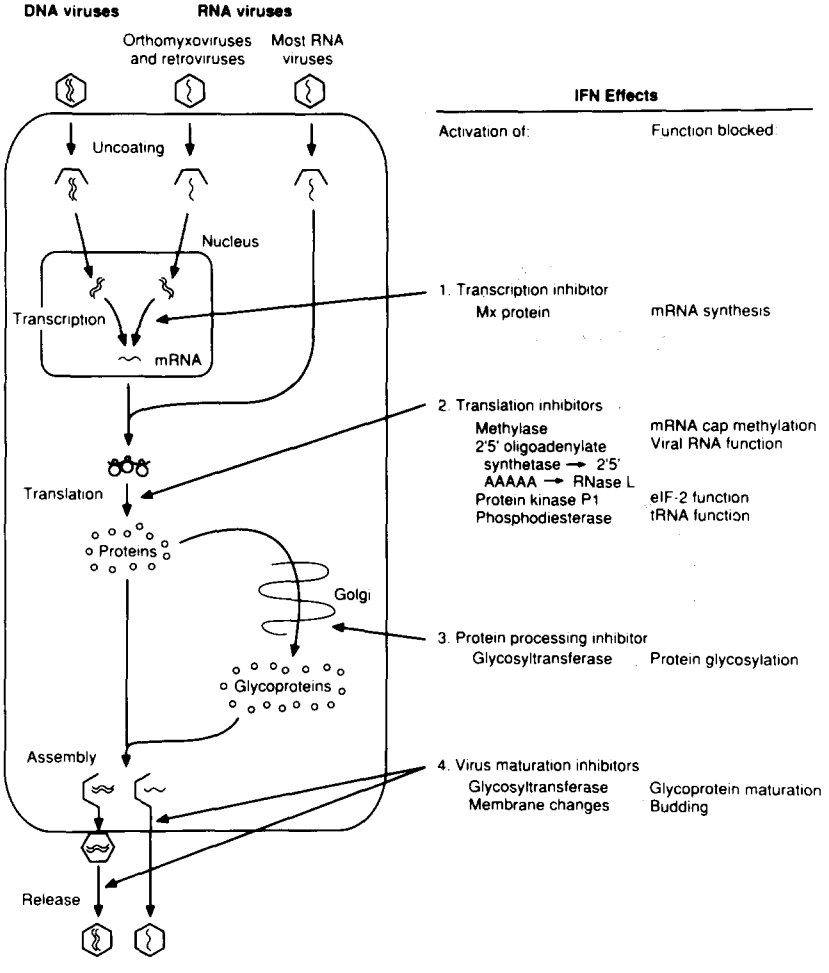

Fig. 5. Mechanisms of antiviral action of IFNs. After binding of IFN to specific cell surface receptor molecules, the cell is signalled to upregulate a series of antiviral proteins. The stage of viral replication which is inhibited by various IFN-induced antiviral proteins is shown. Most of these act to inhibit the translation of viral proteins (mechanism 2), but other steps in viral replication and maturation are also affected by IFN-induced mechanisms (mechanisms 1, 3, and 4). Not all of the antiviral mechanisms are effective against all viruses (e.g., Mx protein, (mechanism 1), may act mainly against influenza (orthomyxoviruses)). The roles of these mechanisms in the other actions of IFNs are under study.

of the viral genome. The important actions of three of the most fully understood antiviral pathways: the eIF-2α protein kinase, the 2′,5′-oligo A synthetase, and Mx protein are summarized below.

7.3. Protein kinase

The eIF-2α protein kinase system which is induced by IFN reduces the translation of viral proteins by the normal host cell translational machinery, including translation initiation factors (Pestka, 1987). The IFN-induced protein kinase system interferes with viral protein synthesis by phosphorylating the α subunit of initiation factor 2, thereby decreasing the efficiency of initiation of protein synthesis (Fig. 5, mechanism 2). The protein kinase is activated by the presence of double-stranded RNA (dsRNA) (Jacobsen, 1986; Jagus et al., 1980; Laurent et al., 1980; Gupta et al., 1982). This requirement for the presence of dsRNA to activate the protein kinase may confer the antiviral specificity for viruses which produce dsRNA (Pestka et al., 1987; Jacobsen, 1986).

7.4. 2′,5′-Oligo A synthetase

The 2′,5′-oligo A synthetase system exerts its antiviral effect by enzymatically degrading viral RNA (Fig. 5, mechanism 2) (Samuel, 1988; Faltynek et al., 1988; Jacobsen, 1986). The synthetase is upregulated by IFN, and is activated by dsRNA to convert ATP into a series of small oligoadenylates with an unusual 2′,5′ linkage. These oligoadenylates bind to and activate a cellular endoribonuclease, which then degrades single stranded RNA, preferentially viral RNA due to the proximity of the viral ssRNA to ds viral RNA (Faltynek et al., 1988; Jacobsen, 1986; Baglioni et al., 1985).

7.5. Mx protein

The Mx protein is a 75 kDa type IFN α- or β-induced protein that inhibits influenza and only a few other viruses (Haller et al., 1980; Staeheli et al., 1985). The exact mechanism by which the Mx protein acts to block influenza virus replication may involve an inhibition of transcription (Fig. 5, mechanism 1).

7.6. Other antiviral effects

There are a number of enzymes that are regulated by IFN which may affect virus replication. IFN's modulation of HLA as well as most types of leukocytes probably influences virus multiplication and spread (Peters, 1990). The effects of IFN on the cell membranes may be the cause of the inhibition of maturation and release of mature retroviruses (Fig. 5, mechanism 4) (Samuel, 1988; Chang et al., 1977; Wong et al., 1977). IFN also effects the glycosylation of viral proteins through an IFN-induced glycosyltransferase which could affect virus assembly and release (Fig. 5, mechanisms 3 and 4) (Maheshwari et al., 1980; Jacobsen, 1986). Different aspects of these IFN-induced antiviral effects are important against different viruses, and even in different cells.

7.7. IFN as an intercellular signaling substance

The interactions of the IFNs with other intercellular signaling substances (cytokines and hormones) is just beginning to be understood. The initial production of IFN often coincides with production by lymphocytes and macrophages of other hormones and cytokines. IFN's actions can be modulated by these hormones and cytokines. For example, a portion of IFN-γ's antiviral action is due to induction of IFN-α or -β (Hughes et al., 1987; Le et al., 1986). Also, IFN-γ activates macrophages by inducing their production of the cytokine TNF (Philip et al., 1986). Enhancement of natural killer cell activity by interleukin-2 (IL-2), apparently is partly due to its induction of IFN-γ in T lymphocytes (Weigent et al., 1983; Dianzani et al., 1987). Induction of IFN-γ by IL-2 in T lymphocytes is enhanced by monocytes (Weigent et al., 1983). Macrophage-produced IL-1 can induce IL-2, which in turn induces IFN-γ or IFN-β (Philip et al., 1988). Tumor necrosis factor can have an antiviral effect through induction of IFN-β (Hughes et al., 1988; Van Damme et al., 1987). This antiviral activity is potentiated by IFN-γ's interactions with the TNF-induced IFN-β (Stone-Wolff et al., 1984). Interferon γ also can potentiate TNF's general cytolytic activity. As our understanding of these complex cascades and interactions increases, opportunities for medical intervention in patients with infections, cancer, and immune diseases are likely to occur.

7.8. IFN during persistent infections

Persistent infections can occur with various viruses and by different mechanisms (Fig. 6). Some of the mechanisms involved in persistent infection have been identified and include interferon (Boldogh et al., 1991; Baron, 1973). The evidence includes IFN detection at a very early stage in persistent infections of mouse L cells with NDV, human amnion and KB cells with poliovirus, calf kidney cells with the WS strain of influenza virus and with foot-and-mouth disease virus, KB cells with parainfluenza 3 virus, mouse embryo cells with vaccinia virus, human amnion and

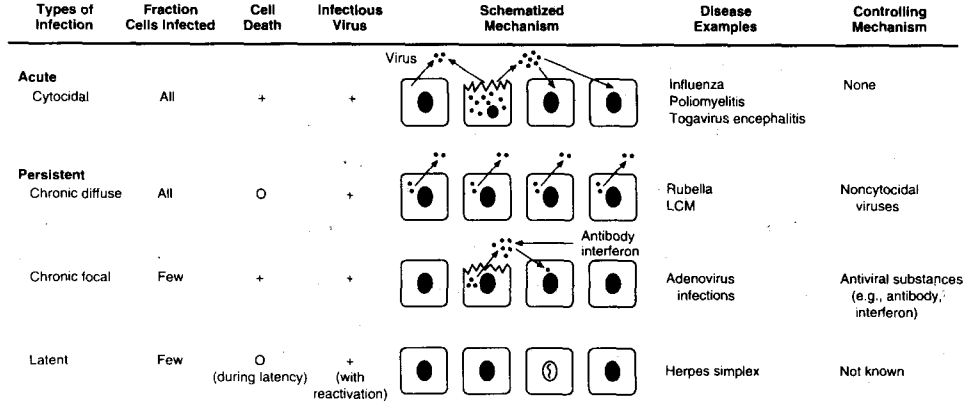

Fig. 6. Virus-cell interactions in vivo (Boldogh, 1991 with permission.)

mouse L cells with tick-borne encephalitis virus, mouse 23 P cells with polyoma virus and with herpes simplex virus, and monkey cells with rubella virus. In mice, similar results have been observed during the early stages of infection with lactic dehydrogenase virus. In comparison, neither interferon nor significant interference was detected in mouse L cell cultures persistently infected with polyoma virus, or in chicken cells infected with RAV leukosis virus, suggesting that the interferon system did not participate in the maintenance of these carrier cultures. However other evidence suggests that IFN, although undetectable, may be protective during herpesvirus infections of mice (Stanton et al., 1987).

Further evidence linking the interferon system to persistent infections come from in vitro studies in which the effects of the interferon system were enhanced or inhibited. Enhancement of the interferon mechanism during persistent infections in mouse cell cultures retarded multiplication of several viruses (Baron, 1973). Endogenous IFN production during persistent rubella virus infection of cell cultures inhibited virus production up to a thousand fold (Wang et al., 1967). Conversely, inhibition of the interferon mechanism by several techniques was followed by enhanced virus growth and increased cell destruction. Similarly, in mice, stimulation of the interferon system inhibited the growth of persistent lactic dehydrogenase virus 5–10-fold (duBuy, 1970). In general, the resistance of persistently infected cultures to virus infections was non-specific, a property coinciding with that of the interferon system. The quantity of interferon found during persistent infection of mouse cell cultures with herpes simplex virus was shown to be sufficient to account for the observed inhibition of herpes simplex virus.

The natural role of IFN during chronic hepatitis and HIV infections has not been determined fully. Chronic hepatitis B virus infections induce little IFN. Clinically persistent hepatitis B and C viruses can be inhibited significantly by exogenous IFN (Hoofnagle, 1992). In comparison, HIV infection is relatively resistant to IFN in vitro and in vivo although the associated Kaposis' sarcoma may be beneficially affected in some patients (de Wit, 1992). The sensitivity of HIV to inhibition by IFN in vitro is usually low during infection of lymphocytes and only somewhat higher during infection of macrophages (Dolei et al., 1986). Induction of IFN by HIV is generally weak, although interferon appears in the serum during the later stages of AIDS (Capobianchi et al., 1992). Thus, chronic hepatitis B and C infections often respond to IFN treatment but HIV appears to be less responsive.

Can we predict from in vitro or animal model studies, the efficacy of interferon treatment of chronic infections of humans? It may be possible to predict that IFN will not be effective clinically if the virus is highly resistant to IFN, e.g., arenaviruses and HIV. However, virus susceptibility to IFN in vitro or animal models does not necessarily predict clinical efficacy because of the many variables governing endogenous IFN production and action in vivo relative to treatment. Known IFN variables include: (a) the time of production of endogenous IFN relative to the time of exogenous treatment; (b) the site of endogenous IFN production and distribution (Bocci, 1992) relative to the pathogenic sites of infection; (c) the concentration of endogenous IFN at the critical sites; (d) virus susceptibility to inhibition by IFN in the actual target cells; (e) the ability of virus to modulate IFN production or action;

(f) the fraction of virus that is phenotypically resistant to IFN (Takemato et al., 1966); and (g) the side effects of exogenous or chemically induced IFN (Quesada, 1992). Thus, even with IFN-sensitive viruses the complexity of the interactions of the host defenses, virus and IFN eventually require testing in patients to determine efficacy and safety.

Taken together, the available evidence favors the view that the interferon system can be an important determinant of many viral infections in vitro and in vivo.

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