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The Role of Interferon in Viral Infections

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Summary. Interferon, a product of mammalian tissues, was originally described as an antiviral agent over twenty years ago. Only in the past few years has evidence started to accumulate that interferon actually played a role in vivo in natural virus infections.

Initially, evidence was accumulated showing that interferon could inhibit the replication of many viruses in vitro. The interferon, through induction of a second antiviral protein, could inhibit in vitro viral transcription or translation. Later, indirect evidence for an effect of interferon on in vivo viral infections was obtained by showing that (a) a temporal relationship existed between the appearance of interferon in viral infections and the progress of the infection and (b) treatment of virally infected animals with exogenous interferon or interferon inducer often resulted in less severe infections.

The most recent and direct evidence for a role for interferon in natural viral infections involves the use of an anti-interferon globulin. In several cases, injection of the anti-interferon globulin into animals infected with a wide variety of viruses resulted in a severely altered course of infection. These studies suggest that interferon is directly involved in the progress of viral infections. The involvement of the interferon in the viral infections could be a direct effect of the interferon on viral replication, or an interaction of the interferon with other host defenses, such as the immune system.

I. Introduction

Interferon was originally described over twenty years ago when Isaacs and Lindenmann observed an antiviral activity in media in which were suspended

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fragments of chicken chorio-allantoic membrane inoculated with inactivated influenza virus [109]. Since that initial observation, studies of interferon by many workers have demonstrated that interferons are a heterogenous, complex group of small proteins that have several antiviral and non-antiviral actions [81]. Recent studies have clearly demonstrated a role for interferon in viral infections, and the examination of these studies will be the main focus of this review.

A. Mechanism of Production and Subclasses of Interferon

For most early studies, the production of interferon involves the exposure of an animal or cell culture to a virus, such as Newcastle disease virus (17, 98). The interferon antiviral activity is then detected in the culture supernatant or in the serum of the animal. Criteria for differentiating the material produced in this manner as interferon are established and enumerated below [152]:

a) The antiviral material must be a protein.
b) The antiviral action should not be due to a general toxic effect on cells.
c) Unrelated RNA and DNA viruses must be affected by the antiviral material.
d) The action of the antiviral material should require cellular RNA and protein synthesis to produce inhibition of viral replication.
e) The interferon is generally species specific, *however* recent studies suggested that cells treated with the homologous interferon can transfer antiviral resistance to co-cultivated cells of another species that are normally resistant to that interferon [28].
f) Antiviral activity is acid (pH 2) stable and heat (56° C) labile. Interferon appears to be a glycoprotein with a molecular weight of between 15 000 and 100 000 daltons [152].

Later studies indicated that interferon could also be induced by a wide variety of non-antiviral inducers [161] including bacterial products such as lipopolysaccharide [103, 219] and extracts of *Brucella abortus* [219, 248], polynucleotides such as polyriboinosinic acid-polyribocytidylic acid [63], and other synthetic inducers such as the poly-carboxylate, pyran copolymer [191]. These interferons induced by viruses and by non-specific inducers have been classified Type I or 'classical' interferon [249].

Type I interferons have recently been sub-classified according to their antigenic nature [97]. Human studies have indicated that most of the interferon produced by fibroblast cell cultures in response to virus challenge is antigenically different from interferon produced by leukocyte cell cultures [97]. Similar antigenic differences among murine Type I interferons have also been reported [156]. Therefore, the classification Type I interferon applies to a heterogenous population of interferons induced in a similar manner under different conditions.

Recent studies have indicated the existence of a new kind of interferon produced as a lymphokine in a cell-mediated immune response, i.e., Type II or 'immune induced' interferon [201, 249]. Type II interferon is produced in response to challenge of lymphocytes with a mitogen such as phytohemagglutinin, concanavalin A, or staphylococcal enterotoxin A [56, 117, 242]. In addition, Type II interferon can be produced by sensitized animals or lymphocytes of such an animal after rechallenge with specific antigen [13, 57, 127, 128, 201, 249]. Type II interferon

differs from Type I interferon with regards to several physical, chemical, biologic, and antigenic properties [249]. Murine Type II interferon is pH 2 labile and heat stabile, highly species specific, and not neutralizable by an antibody directed against Type I interferon [249]. The molecular weight of Type II interferon range between 30 000 and 100 000 daltons [249]. Human Type II interferon is both pH 2 and heat labile [56, 57, 235]. Therefore, the designation Type II interferon, applies to a heterogenous populations of interferons produced as part of an immune response.

Several different assays have been developed to detect the antiviral activity of interferon. The most widely used assay for interferon is a plaque reduction assay. This assay involves protection of monolayers of fibroblasts from infection with viruses by pre-treatment with interferon [250]. Other assays include a microcytotoxicity assay [7] and a hemagglutinin-inhibition assay [172]. The titers (reciprocal of the greatest dilution of interferon able to cause a 50% reduction of virus activity) are then normalized to an international reference standard. All of these assays have been utilized for the study of the mechanism of antiviral action of interferon. The mechanism of action of interferon has been recently extensively reviewed elsewhere [68] and will only be briefly covered here.

B. Mechanism of Action of Interferon and its Relationship to the Spread of Viral Infection

Interferon appears to exert its antiviral action through a series of complex interactions with host cell functions, which may vary depending on the type of virus being inhibited. The interferon appears to have to bind to the intact cell membrane, and disruption of membrane ATPase function with ouabain also inhibits antiviral activity [141]. A specific membrane receptor, probably a ganglioside, apparently interacts with the interferon, since preincubation of cells with ganglioside inhibits the development of the antiviral state [37, 183, 230]. Exposure of cells to phytohemagglutinin and other mammalian lectins also inhibits interferon's binding to gangliosides as well as the antiviral action [21, 22]. Cholera toxin and thyrotropin, which also bind to ganglioside receptors, compete with interferon for membrane binding sites and therefore inhibit the antiviral activity [71, 132].

Interferon does have to interact with the cell membrane, and appears to become rapidly bound to the membrane as cells washed after 30 min of incubation still became resistant to virus infection [133]. Apparently very little if any interferon must enter the cell as Sepharose-bound interferon still has an antiviral activity [5, 129].

After interacting with the cells, interferon triggers the synthesis of new cellular proteins including a protein kinase and a low molecular weight protein synthesis inhibitor [125] which mediate the antiviral state and such cellular RNA and protein synthesis as are required for antiviral activity [73, 229]. This leads to inhibition of translation or transcription of viral RNA.

Studies with vesicular stomatitis virus and vaccinia, both of which carry their own transcribing enzymes, have shown that viral transcription is inhibited in interferon treated cells that had later been treated with cycloheximide and actinomycin D [155]. However, uncoating of vaccinia virus is inhibited in interferon treated cells, and early mRNA translation is required for uncoating [114],

indicating an effect of interferon on translation. The molecular mechanisms of action of Type I interferon therefore probably are multi-faceted and require further study. The mechanism of action of Type II interferon has not been studied to date.

C. New Aspects of Interferon Research

Interferon has recently been shown to have a wide variety of nonantiviral functions [81]. These include regulation of antibody and cell-mediated immune responses [30, 44, 45, 115, 149, 150, 210], regulation of the expression of lymphocyte cell surface antigens [126, 147, 148, 237], and several other anti-cellular activities including anti-tumor actions [80, 162]. These non-antiviral actions of interferon will be discussed in more detail in the last section of the review. However, it is important to note here that interferon preparations used for most of the above studies have been crude unpurified preparations that contain other activities, e. g., murine Type II interferon preparations contain a concomitantly induced macrophage migration inhibitory factor activity [201, 249].

Interferon has been extremely difficult to purify and it has only been very recent developments in antibody affinity chromatography [170] and lectin and nucleotide chromatography [46, 113] that have allowed advances in the purification of human [131] and murine [47, 130] interferons. One recent study has demonstrated purification to homogeneity of murine Type I interferon by sequential polynucleotide and antibody affinity chromatography [47]. It is only studies of such purified Type I interferons or purified Type II interferon preparations that will allow establishment of the identity or non-identity of the molecules responsible for the various antiviral and non-antiviral actions of interferon.

Purification of interferon also is a key to the understanding of interferon's antiviral role. Partial purification has permited studies that will be described later, especially those studies that show that treatment of mice with anti-interferon globulin resulted in aggravated virus infections [58, 89, 91, 194], which indicate a probable role for interferon in resistance to viral infection.

D. Focus of This Review Article – Role of Interferon in Mediating Viral Diseases

The effects of interferon on RNA and DNA virus replication in vitro and in vivo have been extensively studied [68] and were reviewed by DeClercq and Stewart in 1973 [42]. This review will be focused on recent developments (since 1973) in the field that demonstrate that interferon, by directly affecting viral replication, plays a role in mediating the progress of in vivo viral infections. In addition, we will examine how interferon, by interaction with various biologic system, e. g., stimulation of the antibody response by interferon treatment, can influence the containment of viral infections.

II. In vitro Model for the Containment of Viral Infections by Interferon

Over the past twenty years it has become very apparent that interferon can inhibit the replication of many viruses in vitro. These include cytopathic and tumoregenic RNA and DNA viruses [42]. We will now discuss some of the more recent in vitro studies.

A. Cytopathic RNA Viruses Inhibited by in vitro Application of Interferon

The range of cytopathic RNA viruses inhibited by interferon is very extensive. The viruses inhibited include:

1) Togaviruses – Sindbis virus [217], Semliki forest virus [66], Eastern equine, Western equine, Japanese, and St. Louis encephalitis viruses [92, 153, 238].
2) Picornaviruses – ECHO virus [104], poliovirus [31], rhinovirus [62], encephalomyocarditis virus [176].
3) Myxoviruses – Influenza [32], parainfluenza [196], Newcastle disease virus [110, 251].
4) Rhabdoviruses – Rabies virus [218], vesicular stomatitis virus [42].
5) Reoviruses – [243].

The replication of all of these viruses is inhibited by interferon treatment of cells prior to infection. The extent of inhibition varies among viruses, and is also affected by the species of origin of the interferon and the cells utilized for assay [42].

Recent in vitro studies have centered on the mechanism of interferon's inhibition of the replication of RNA viruses. Working with reovirus, Wiebe and Joklik [243] demonstrated that the most sensitive function of reovirus replication that were most affected by interferon treatment was translation of mRNA that coded for polypeptide λ 1, a structural component of reovirus [243]. These data suggest that the primary action of interferon on RNA viruses is on translation [243]. Further support for the primary inhibitory action of interferon on translation comes from the work of Baxt et al., who showed that if interferon treated cells were challenged with vesicular stomatitis virus (VSV), viral protein synthesis stopped while viral RNA, particularly mRNA was produced in normal amounts [19]. Currently, there is good evidence for a phosphoprotein, perhaps a ribosomally associated initiation factor and an oligonucleotide activated ribonucleotide as the critical intermediate in interferon's inhibition of messenger RNA function [16].

However, Young et al. have shown that if BSC cells are treated with interferon and then enucleated and challenged with VSV, the cells were protected against infection [247]. If the cells were enucleated before interferon treatment, then no protection was observed, suggesting that transcription of a host mRNA from nuclear DNA was required for interferon action [247]. Evidence is accumulating suggesting that interferon's action is pleiotropic and multifacted, since such a large number of virus classes are affected. The exact mechanism of viral inhibition may vary with each viral genus sub-type [111] and also with the host and interferon species and conditions of infection. Further evidence for this was obtained by Came et al., who determined the effects of human fibroblast interferon on replication of 25 different serotypes of rhinoviruses in HeLa cells and found wide variation in the ability of the interferon to induce viral resistance [33]. However, when human foreskin fibroblats were used as the target cells, no difference in the ability of interferon to induce resistance to several rhinoviruses strains was observed [33].

B. Cytopathic DNA Viruses Inhibited in vitro by Application of Interferon

As with RNA viruses, interferon has been shown to inhibit the replication of a wide range of DNA viruses in vitro [42]. These include:

1) Poxviruses – vaccinia [108]; fowlpox [11].
2) Herpesviruses – herpes simplex [11, 75], varicella zoster [8], cytomegalovirus [78], and pseudorabies [238].
3) Adenoviruses [76].

Interferon effectively inhibited the replication of all these viruses but again the degree of inhibition varied with each virus, interferon, and the cell culture system used [42].

Some recent in vitro work on the effect of interferon on DNA viruses has been focused on the herpesviruses. Herpesviruses were originally thought to be relatively resistant to the antiviral actions of interferon although some inducers of interferon were effective in inhibiting herpesviruses [123]. However, Rasmussen and Farley were able to show, using single-cycle infection, that herpes simplex Type I could be as sensitive to the anti-viral action of interferon as vesicular stomatitis virus when appropriate dosages of interferon were used [189]. Murine cytomegalovirus was shown to be able to induce interferon and to be sensitive to the antiviral action of interferon [173]. However, some of the virus-infected cells used in that study were shown to be resistant to the action of interferon, supporting the hypothesis that differences in conditions of infection affect the effectiveness of interferon in inhibiting viral replication.

The effect of differences in virus strains on the ability of interferon to express its antiviral effect were examined by Lerner and Bailey [142]. They showed that herpes simplex virus Type I was five to ten times more sensitive to the antiviral action of human interferon than was herpes simplex Type II. In addition, interferon has a greater inhibitory effect on infections with varicella-zoster virus and cytomegalovirus where cell free virus preparations are used for inoculum, instead of infected cells [106, 190]. In addition, when interferon was jointly applied with the antiviral agent 9-B-D-arabinofuranosyl-adenine (Ara-A), the combined drugs had a synergistic effect against herpes simplex Type I and only an additive effect against herpes simplex Type II [142]. Therefore the extent of the antiviral action of interferon on DNA viruses appears to be very dependent on the cells and viruses used.

C. Oncogenic Viruses Inhibited in vitro by Application of Interferon

Much attention has been focused on in vitro effects of interferon on oncogenic viruses and oncogenic virus-infected cells [42]. Interferon effects a range of RNA and DNA tumor viruses including:

1) Murine leukemia viruses – Friend [204], Rauscher [204], and Feline leukemia [195] viruses.
2) Sarcoma viruses – Rous [14, 222] and Maloney sarcoma viruses [180, 204].
3) Polyoma virus [3, 179].
4) SV 40 [177, 179, 230].
5) Adenovirus [178].

Much of the recent work on the effect of interferon on oncogenic viruses has centered on the mechanism of the effect on murine leukemia viruses. Billiau, et al. treated two different chronically infected oncornavirus infected cell lines, MO-P (produces Kirsten-MSV virus) and JLSV5 (produces Raucher MLV virus), with interferon and showed a decrease in extracellular C-type virus formation, but

intracellular virus production was not affected [25, 26]. After interferon treatment was discontinued, virus release resumed. These data suggested that the primary effect of interferon on tumor viruses is on virus release. Similar results were reported by Friedman and Ramsier working with AKR cells that spontaneously release murine leukemia virus, but they also reported an increase in viral group specific antigens suggesting some effect on late virus morphogenesis as well [35, 69, 72]. However, only release of C type viruses is inhibited by interferon treatment while A and B type virus particle production and release were much less affected by interferon treatment [23, 24]. Friedman and his co-workers have also shown that when AKR cells were treated with interferon, the viral genome could not be completely eliminated, while when L cells infected with cytopathic herpes simplex or vesicular stomatitis viruses were treated with interferon, all evidence of the viral genome was eliminated [70]. These data again support the hypothesis that the effect of interferon on cells chronically infected with tumor viruses is on late virus assembly or release [27]. These findings were further supported by Pitha et al. who found that interferon treatment of chronically infected AKR cells did not result in a generalized shut down of viral protein synthesis as is seen with cytopathic viruses [181]. This effect was reversible.

Further evidence for the effect of interferon on oncornaviruses being a late effect was also obtained by examining the effect of interferon on acute oncornavirus infections. Pitha et al. noted that in acute exogenous infections with AKR virus, interferon treatment decreased virus production, but did not eliminate the virus genome, since the process was reversible [181]. They also observed that the block occurred after transcription of viral mRNA and synthesis of virus-specific gs antigen and the major viral glycoprotein but before assembly [182]. Wong et al. [245] and Chang et al. [36] using temperature sensitive mutants showed that the inhibitory action of inteferon preceded the defect in assembly of the temperature sensitive mutants, and that interferon treatment at non-permissive temperatures resulted in release of non-infectious virus particles. Therefore the effect of interferon on most murine leukemia viruses appears to primarily be on an early stage of morphogenesis [68]. However, in a Maloney murine leukemia virus system, Aboud et al. showed an effect of interferon on early viral RNA synthesis [1]. This difference from the results of other workers may be due to differences in the virus cell line, or culture system used.

As with non-oncogenic viruses, different viruses, cells, and conditions of infection appear to mediate the extent and manner in which interferon affects leukemia virus replication. Allen et al. found that C type virus replication in two different Rauscher leukemia virus cell lines were differentially inhibited by interferon treatment [4]. However, when leukemia virus produced by those cell lines was transferred to a third cell line, both viruses were equally inhibited by interferon, suggesting that the differential effect was a result of differences in the cells and not the virus involved. Pitha et al. [181] also noted no build up in the amount of intracellular viral porteins accumulated in AKR cell lines treated with interferon, in contrast with the data reported by other workers [72] and suggested that these differences might be due to the frequency that the AKR virus has been passaged. These differences also probably play a role in chronically infected AKR cells that had been induced to produce virus by treatment with 5-iododeoxyuridine, where

Ramseur and Friedman [187] noted an effect on induction of virus from the host genome, while Pitha et al., noted an effect only on virus replication [181]. Tomita and Kuwata [232] showed that the anti-murine leukemia virus effects of interferon were not-blocked by 0.6 mM ouabain while the antivesicular stomatitis virus interferon effects were blocked, suggesting that the mechanism of antiviral action of interferon may be different for oncornaviruses then for cytopathic RNA viruses.

Work on the effects of interferon on oncogenic DNA virus has been much more limited. Pre-treatment of Epstein-Barr virus (EBV) challenged lymphocytes with interferon reduced the fraction of cells producing EBV induced nuclear antigen, but had no effect on EBV induced lymphocyte transformation [160]. However, pre-treatment of leukocytes with interferon resulted in inhibition in EBV-induced transformation and EBV induced super-infection of target cells [132]. High concentrations of interferon could also inhibit the replication of other oncogenic herpesviruses [140]. Interferon also inhibits the accumulation of virus specific RNA in nuclei from cells infected with SV 40 virus [165]. In addition, exposure of SV 40 infected BSC-1 African green monkey cells to homologous interferon after viral DNA replication had begun resulted in decreased subsequent viral DNA replication and virus yields [246]. All de novo synthesis of viral proteins was inhibited, but early viral RNA synthesis was not affected. Therefore, the effects of interferon on SV 40 virus replication may vary depending on the time of interferon administration.

III. Indirect and Direct Evidence for an in vivo Effect on Viral Infections by Interferon – Treatment of Hosts or Interferon Induction in Hosts

The in vitro studies described above have shown that interferon can inhibit the replication of a wide range of viruses. However, in order to determine the role of interferon in mediating viral infections, in vivo studies are necessary. To date, interferon has been shown to effect in vivo infections by many different types of viruses. The earlier studies have been reviewed by DeClercq and Stewart [42] and have involved studies of the following viruses:

1) RNA Viruses
   A) Togaviruses – Sindbis [48], Semliki forest [64], and yellow fever [65] viruses.
   B) Picornaviruses – Encephalomyocarditis virus [83].
   C) Myxoviruses – Newcastle disease virus [138].
   D) Rhabdoviruses – Rabies-virus [184] and vesicular stomatitis virus [18].
2) DNA Viruses
   A) Poxviruses – Vaccinia [18, 34, 108].
3) Oncogenic Viruses
   A) Oncornaviruses – Friend [85], Rauscher [82], Radiation [146], and Gross [84] leukemia viruses, Rous [138] and Maloney [20] sarcoma viruses.
   B) Polyoma virus [12].

More recent studies have also been directed towards demonstrating an effect of exogenous interferon or an interferon inducer in modification of viral infections. It is

only the recent studies involving the use of anti-interferon globulin in vivo [89, 91, 93, 194] that have demonstrated a role for endogenous interferon in natural virus infections. We will now review recent studies showing that interferon can mediate in vivo virus infections.

It is important to note that when interferon plays a role in limiting natural virus infection, it is probably acting in conjunction with other host defenses, such as the antibody or cell-mediated immune response to the virus [81].

A. In vivo Inhibition of Togavirus Infections by Interferon

Rinaldo et al. [193] have been able to demonstrate that moderate amounts of interferon were produced by adult and fetal cows that had been infected with bovine diarrhea virus. Some interferon was produced as part of a natural infection; it is possible that interferon could have played a role in mediating the infection. Treatment of animals with interferon inducers or directly with interferon often resulted in a change in the progress of the infection. Treatment of mice with tilerone hydrochloride and its analogues, inducers of interferon, after prior infection with Venezuelan equine encephalitis virus resulted in increased survival of the mice if the drugs were orally administered [135]. Intraperitoneal injection of the drugs had no effect.

Levy et al. [143] developed a new interferon inducer, polyriboinosinic acid-polyribocytidylic acid complexed with poly-L-lysine (poly (ICLC)), which is resistant to hydrolytic enzymes found in primate serum [143, 202]. Treatment of rhesus monkeys with poly (ICLC) eight hours prior to infection with simian hemorrhagic virus followed by repeated treatment after infection resulted in total inhibition of viremia and prevention of mortality [144]. In addition, treatment of rhesus monkeys eight hours before infection with virulent Asabi strain yellow fever virus also prevented mortality [215].

Johnson and Dubuy [118] reported a transient reduction of viremia in lactic dehydrogenase virus infected mice treated with interferon. Therefore, although interferon is produced as a result of togavirus infections and exogenous application of interferon or interferon inducers can influence the progress of the infections, no definitive information exists on the natural role of interferon in togavirus infections.

B. In vivo Inhibition of Picornavirus Infections by Interferon

There has been much interest in studying the antiviral effects of interferon on picornaviruses, particularly the rhinoviruses. When human volunteers received large doses of interferon (1.4×10^7 units) by the intranasal route (i.e., topical application) in a series of sprays starting previous to infection with rhinovirus 4 and continuing throughout the period of infection, a significant decrease in symptoms, virus shedding, and antibody response was noted in the interferon treated individuals as compared to placebo treated controls [164]. When interferon has been induced by intranasal administration of N,N-dioctadecyl-N'-N'bis (2 hydroxyethyl) propanediamine (CP20, 961) in human volunteers before infection with rhinovirus, only partial prevention of symptoms was observed with no effect on virus shedding [51, 214]. When interferon was induced with the fungal inducer BRL 5907, only minimal and non-significant reductions in disease severity and viral

shedding were noted [6]. These studies suggest that exogenously applied interferon may be more effective in limiting rhinovirus infections than induced interferon or that there are different sensitivities to interferon of different serotypes of rhinovirus.

Studies with encephalomyocarditis virus (EMC) have indicated the interferon can have an in vivo antiviral effect against these picornaviruses. Stringfellow and his colleagues [223, 224] were able to show that single or multiple doses of the interferon inducers polyriboinosinic-polyribocytidylic acid and tilerone were effective in limiting the mortality from EMC infection in mice. The inducers had to be applied early enough in infection to prevent viremia and seeding of the virus to the central nervous system. Olsen et al. [174] noted that treatment of EMC infected mice with the polyriboinosinic-polyribocytidylic acid-poly-L-lysine was even more effective, and was even effective if initiated 48 h after virus inoculation, or late in the infection.

The most convincing evidence for an endogenous effect of interferon in picornavirus infections involves use of an anti-interferon globulin [89], which will be described later in this review.

C. In vivo Inhibition of Myxovirus and Paramyxovirus Infections by Interferon

The most intensive study of the in vivo antiviral effect of interferon on myxoviruses has been directed against the most potentially pandemic agent of respiratory infections, influenza. Early studies suggested that low dosages of topically applied interferon could be effective in the prophylaxis or reduction of severity of influenza infections in humans [208, 209], but these studies have never been confirmed or extended. Prophylactic intranasal treatment of humans with 8×10^5 units of interferon 24 h before challenge with influenza B virus had no effect on the progress of infection or shedding of virus [164]. Topical intranasal treatment of humans with the interferon inducer CP-20, 961 also had no prophylactic or therapeutic effect on influenza A infections [52]. However, Richman et al. have shown that several strains of influenza A virus are sensitive to interferon in vitro and that those strains could stimulate interferon production in humans in vivo [192]. The time of appearance of symptoms was correlated with the time of interferon production, suggesting that interferon might be effective as a prophylactic agent [192].

The most promising recent evidence for a positive in vivo antiviral effect for interferon on influenza virus is the murine system of Suzuki and his workers [227]. This study showed that intraperitoneal injection of the interferon inducer dextran phosphate caused a decrease in viral symptoms and an increase in the survival rate of mice intranasally inoculated with influenza A virus after interferon induction. Interferon was implicated since there was no direct viracidal effect of the inducer and the production of antiviral antibody was decreased in mice given dextran phosphate. However, the possible role of macrophages, which could be activated by the polyanion, was not studied. The greatest titer of interferon was in the lung, suggesting that systemic induction of interferon may be more effective against influenza than local induction or application. The effect of interferon on influenza virus replication in mice may not be a direct effect against the virus, but may involve an interaction with the immune system [112] as will be described later in the review.

McIntosh [159] was not able to correlate the presence of interferon in nasal secretions with shedding of or recovery from respiratory syncytial virus infections in infants. This lack of correlation of interferon levels with virus shedding suggested that interferon did not play a role in controlling the progress of respiratory syncytial virus infections, or that only very small amounts of interferon were required for a significant effect.

D. In vivo Inhibition of Rhabdovirus Infections by Interferon

Interferon has also been shown to have an antiviral effect against rhabdoviruses. Direct injection of interferon into the brain of mice four days after intranasal inoculation of vesicular stomatitis virus resulted in increased mouse survival [90]. Interferon therefore appears to be able to have an antiviral effect even when applied well into the period of infection with the virus.

Several studies have been carried out examining the in vivo antiviral action of interferon against rabies virus. Ho and his co-workers noted that intrathecal administration of interferon to rabbits after they had been inoculated in the thigh with rabies virus resulted in a prolonged period of incubation but did not prevent development of encephalitis [105]. Combined intrathecal and intravenous injections of interferon were much more effective in preventing paralysis. Harmon et al. [96] reported that injection of the interferon inducer polyriboinosinic acid-polyribocytidylic acid into the same site previously inoculated with rabies virus resulted in protection of mice against rabies infection. Cynomolgus monkeys that were inoculated intramuscularly with rabies virus were also protected from encephalitis by repeated injections of human leukocyte interferon beginning 24 h after infection [100].

Harmon et al. [95] were also able to show that combined intramuscular injection of polyriboinosinic-polyribocytidylic acid and rabies vaccine yielded enhanced protection of mice previously infected with street rabies virus. These data suggest that interferon could interact with the immune response to control the spread of rabies virus. Similar results were observed by Wiktor et al. in monkeys using polyriboinosinic-polycytidylic acid or Newcastle disease virus to induce interferon, and rabies virus vaccine [244]. Injection of exogenous interferon and rabies virus vaccine was also successful in protecting mice and rhesus monkeys from the lethal consequences of rabies virus infection when injected after virus infection [15]. In this case, even when high titer rabies virus was given to the monkeys, a prophylactic effect of the interferon and vaccine could be observed when treatment was provided very rapidly (6 h) after virus inoculation [15].

E. In vivo Inhibition of Poxvirus Infections by Interferon

Recent studies of the in vivo antiviral effect of interferon on poxviruses have been limited to a few experiments done with vaccinia. Neumann-Haeffelin et al. [168] were able to show the prophylactic and simultaneous administration of human leukocyte interferon to corneas of rhesus monkey which were inoculated with vaccinia resulted in a decreased occurrence of keratitis. Therapeutic or postinfection administration of interferon resulted only in decreased severity of keratitis and shortened the length of time of virus shedding. Topical application of the interferon

inducer poly (ICLC) was also effective in stopping the development of vaccinia virus infection in rabbit skin [145]. The inducer was effective both prophylactically and therapeutically. Neumann-Haefelin and co-workers [167] also noted that rhesus monkeys that were immunosuppressed after receiving anti-lymphocyte globulin and that were infected with vaccinia virus developed both primary and secondary vaccinia lesions. Prophylactic intramuscular treatment or therapeutic intramuscular treatment with human leukocyte interferon of the monkeys at the first sign of primary lesions prevented the development of secondary lesions. The results of this study suggested that interferon might be helpful in preventing the dissemination of vaccinia in the immunosuppressed host.

F. In vivo Inhibition of Herpesvirus Infections by Interferon

One of the most studied in vivo antiviral effects of interferon is the effect of interferon on herpesviruses. This study has taken on new significance in recent years because infections with herpesviruses have become a problem of increasing severity in immunodeficient, immunosuppressed, or immunocompromised hosts such as transplant recipients, cancer patients on chemotherapy, and the newborn [216]. Interferon has been known to have antiviral effects when used to treat local herpes keratitis. Prophylactic or simultaneous administration of human leukocyte interferon was effective in preventing the development of herpes simplex keratitis in experimentally infected rhesus monkeys, but therapeutic treatment only resulted in decreased severity of the keratitis and shortened the duration of virus shedding [168].

Direct application of human leukocyte interferon to the lesion has shown to be efficacious in promoting the healing of lesions of ulcerative acute herpes keratitis [134]. Human leukocyte and fibroblast interferon were found to be equally effective in a monkey keratitis model [119, 122, 169, 226]. A single large daily dose of interferon directly applied to the lesion may prove to be the most effective antiviral protocol for primary keratitis [158], and recent results are quite encouraging [120, 225].

Interferon has also proved to be efficacious in systemic herpes simplex infections. Application of the interferon inducer, pyran copolymer, in adult mice [166] or polyriboinosinic acid in newborn mice [124] decreased the severity of systemic herpes infectious in those animals. In addition, immunosuppressed rhesus monkeys were protected from systemic infection with Medical Lake macaque herpesvirus by human leukocyte interferon treatment [167]. In one human case, intrathecal application of human leukocyte interferon to an infant with neonatal systemic herpesvirus infections did not prevent the death of the infant [41], suggesting that as with rabies [105], intrathecal administration of interferon is not effective if disease in the CNS is advanced.

Preliminary studies with cytomegalovirus-infected infants have indicated that human leukocyte interferon treatment causes a decrease in viruria, suggesting that interferon may be controlling the replication of the virus [10, 54, 175],

Interferon has also been shown to have an antiviral effect against varicella zoster. Preliminary studies suggested that interferon administration could be safely tolerated by cancer patients with varicella zoster infections [67, 121]. Treatment of

cancer patients with topical application of the interferon inducer polyriboinosinic-polyribocytidylic acid at the site of local infections did not prevent the spread of herpes zoster [61]. However, the course of herpes zoster infections in cancer patients can be moderated by treatment with human leukocyte interferon [55, 163, 220]. Treatment of children with various leukemias with high doses of intramuscular leukocyte interferon prevented the spread of varicella zoster to the viscera from primary skin lesions, suggesting that interferon does indeed inhibit the replication of varicella zoster [9].

G. In vivo Inhibition of Hepatitis Infections by Interferon

Several studies have shown an in vivo antiviral effect of interferon directed against hepatitis B virus. Greenberg et al. [79] treated humans with chronic hepatitis B infection with large dosages of human leukocyte interferon for a prolonged period of time. Dane particle DNA polymerase levels, HBeAg and HBsAg markers of hepatitis B virus infection all dropped considerably in several patients, indicating an antiviral effect of interferon against hepatitis B virus. Short-term treatment of patients with fibroblast interferon resulted in a drop in staining of the indicator HBcAg in the liver, suggesting that fibroblast interferon as well had an anti-hepatitis B effect [49]. Treatment of chronically infected chimpanzees with the interferon inducer poly-ICLC) also greatly reduced the level of various virus markers of hepatitis B virus [185].

Human (hepatitis B) [241] and murine (murine hepatitis virus) [231] studies have suggested that leukocytes from infected patients release less interferon than normal leukocytes. Initial hepatitis virus infection may be inhibiting leukocyte interferon production, allowing for further spreading and persistance of the infection. Therefore, an interaction between interferon produced by immunocompetent cells and virus replication may exist.

H. In vivo Oncogenic Virus Infections Inhibited by Induction or Application of Interferon

Several experiments have been carried out to determine the in vivo antiviral effects of interferon on oncogenic viruses. Several studies have shown that the development of Friend virus induced leukemia was inhibited by treatment of mice with the interferon inducers, tilerone [188] or pyran copolymer [205], or direct application of exogenous interferon [86]. Interferon also can delay the development of leukemias in AKR mice [87]. Similar results were seen with the interferon inducer, polyriboinosinic-polyribocytidylic acid, and the murine Moloney sarcoma virus induced tumors [43]. When interferon treatment was combined with use of an antitumor drug such as BCNU [38] or cyclophosphamide [88], to reduce tumor load, much more dramatic decreases in leukemia progression and lymphoma growth respectively were noted. However, inhibition of Friend leukemia virus replication in mice by interferon did not correlate with the inhibition of growth of Friend-virus leukemia cells [198]. These data suggest that the inhibitory effect of interferon on tumors may not be mediated directly by interferon's antiviral action but may mediated by interferon's ability to regulate cell division or differentiation, or immune function. These interferon activities will be discussed later in this review.

I. Other in vivo Virus Infections Inhibited by Interferon

A few other interesting studies have been carried out to determine the antiviral effects of interferon on other viruses. A child cogenitally infected with rubella virus was treated with large doses of interferon for two weeks at 14 months of age [139]. Chronic cutaneous vasculitis caused by the virus and viremia disappeared but viruria persisted.

A person accidently infected with Ebola virus was treated with large amounts of human leukocyte interferon for two weeks after virus inoculation [53]. The patient also received two units of hyperimmune plasma. Therapy resulted in a dramatic decrease of viruria, but because of the combined therapy with hyperimmune plasma, the extent of the interferon's antiviral action could not be definitely determined.

J. Studies Directly Demonstrating a Role for Interferon in Regulating Viral Infections by Utilization of Anti-Interferon Globulin

To this point, all in vivo evidence for interferon's role in viral infections relate to observations temporally relating interferon's presence to recovery during natural infections, or the interferon can improve the course of infections. This has been indirect evidence, as it has involved correlations of interferon titers with disease states or exogenous application of interferon.

The most conclusive evidence for a role for endogenous interferon in mediating viral infections has come from murine studies utilizing an antibody directed against interferon. In this type of study, mice are injected with anti-interferon globulin and then subjected to infections with various viruses. The system was developed after in vitro observations had shown that the yield of Semliki forest virus [60], and later, vesicular stomatitis virus [239], could be increased when cell cultures were treated with anti-interferon serum. The use of anti-interferon globulin allows development of direct evidence that interferon mediates natural viral infections.

Fauconnier [58, 59] first showed that injection of anti-interferon serum into mice several minutes after intramuscular injection of Semliki forest virus (SFV) increased mortality and virus replication in the brain. When high dosages of virus were used (100 LD_{50}) no significant effect of anti-interferon serum was observed. However, when lower multiplicities of infection were used, a viral inoculum that was not normally lethal 20 days post-infection (0.1 LD_{50}) killed all the anti-interferon treated mice within five days. Higher titers of virus were also demonstrated in the brains of anti-interferon treated mice early (48 h) after infection. These data suggested that the endogenous production of interferon was important for controlling the initial spread of Semliki forest virus.

Gresser and his colleagues [89] demonstrated that encephalomyocarditis virus (EMC) infection progressed much more rapidly in anti-interferon globulin treated mice. EMC was present in low titers in serum and visceral organs (spleen, liver, kidney, and heart) of control non-anti-interferon globulin treated mice, but did not attain high titers in the brain until the 4th–5th day post-infection at which time the control mice died of central nervous system disease. When mice were inoculated intraperitoneally with 100 LD_{50} of EMC and then immediately given 0.1 ml of anti-mouse interferon globulin, EMC was present in high titers in visceral organs 24–36 h post-infection and most mice were dead within 48 h. Anti-human interferon

globulin or normal sheep globulin had no effect on the course of disease, indicating that the anti-mouse interferon globulin was inactivating the endogenous mouse interferon. These data suggested that the anti-mouse interferon globulin was inactivating interferon produced by virus infected cells, allowing the virus to spread to other cells, and thereby allowing rapid and extensive viral replication in visceral organs where it did not normally occur, resulting in rapid death. Therefore, from these data, it appears that interferon is important in host resistance early in the infection cycle of EMC.

Gresser et al. later extended these studies to other viruses [91]. When mice, which were infected with Type I herpes simplex virus (HSV), were treated with anti-murine interferon immunoglobulin immediately after infection, the latent period was shortened and the LD_{50} was increased over 100 times compared to control infected mice. In addition, subcutaneous injection of HSV killed only 5% of control mice but 100% of anti-interferon globulin treated mice [93]. Treatment of mice with anti-interferon globulin also resulted in an earlier onset of Maloney sarcoma virus induced tumors, as well as in a greater percentage of inoculated mice actually developing tumors, an increase in tumor size, and an increase in length of duration of tumors. Vesicular stomatitis virus and Newcastle disease virus infections of adult and newborn mice respectively were accelerated with greater mortality in anti-interferon treated mice. However, the course of influenza infection in mice was not affected by anti-interferon globulin treatment, which may have been related to the dose, route of administration, or time of administration of anti-interferon globulin treatment.

In addition, anti-interferon globulin studies have shown that interferon exerts an effect on mouse hepatitis virus type 3 (MHV-3) infections [240]. Pre-treatment of mouse strains normally sensitive to MHV-3 infections accelerated the disease process. Anti-interferon globulin treatment of mice which are semi- or totally resistant to MHV-3 infections caused death from disease in circumstances where it did not normally occur. Therefore, interferon appears to be an important initial defense against MHV-3 infections. The interferon could have a direct anti-MHV-3 effect, or could interact with the immune system in inhibiting viral replication.

The above data suggest that interferon is very much involved in controlling the early spread of several different virus infections. However, additional studies by Reviere and Gresser et al. [91, 94] have suggested that interferon could mediate viral infections in a detramental manner. When newborn mice were inoculated subcutaneously with large doses of anti-interferon globulin before inoculation of lymphocytic choromenigitis virus (LCM), and then received an additional dose of anti-interferon immunoglobulin three days post-infection, there was decreased weight gain, liver cell necrosis, and death within three weeks after infection. The anti-interferon globulin treated mice had 100-fold more LCM in their serum, suggesting that interferon could be responsible for the acute manifestations of LCM disease in newborns. In addition, when mice that survived past three weeks were examined for chronic renal lesion, it was found that glomerulonephritis development was inhibited in anti-interferon globulin treated mice.

The results of the anti-interferon globulin studies strongly suggest that endogenous interferon is important in mediating the course of viral infections. The results also indicate that it is important to consider each virus individually because,

although in most cases interferon appears to decrease the pathogenic effects of the virus, in some it appears to increase them. The action of the interferon may be directly on viral replication, or, especially in the case of LCM disease, may involve interaction of the interferon with other host homeostatic systems, such as those which regulate cell growth and division, or the immune system. These interactions will be discussed in the next section of this review.

IV. Actions of Interferon not Directly Antiviral that could Influence the Progress of Viral Infections

Interferon has been shown to have several actions that do not involve a direct antiviral action and those actions have recently been reviewed [81]. These include inhibition of cell growth and division, enhancement of the expression of lymphocyte surface antigens, and regulation of the immune response. It is possible that interferon could inhibit viral replication indirectly by means of these actions, and we will now briefly discuss these actions.

A. Inhibition of Cell Division and Growth

Interferon can inhibit the growth and division of both normal and neoplastic cells, but neoplastic cells appear to be more severely inhibited [80]. Dose dependent reversible growth inhibition of several cell lines have been reported [2, 136, 157, 221]. In general, interferon appears to affect more rapidly growing cells (e. g., viral transformed cells) [40, 171], but differences in sensitivity with different cell lines have been noted [39].

Interferon can also inhibit the replication of Friend leukemia virus infected cells in mice [198]. It is possible that the spread of tumor virus infections is controlled by the cell inhibitory properties of interferon.

B. Inhibition of Differentiated Cell Function

Interferon has been shown to affect the dimethylsulfoxide-dependent erythropoietic induction of Friend virus leukemia cells [154, 197, 199, 228]. The effect is dose dependent with low dosages having a slight enhancing effect or no effect at all [154, 228] and large doses having an inhibitory effect [197, 199]. It is possible that interferon controls the dissemination of tumors caused by tumor viruses by regulating the differentiation of tumor virus infected cells.

C. Modification of Cell Membrane

The expression of antigens on cell surfaces is affected by treatment of the cells with interferon. Treatment of mouse thymocytes or of mouse L1210 tumor in culture with interferon results in increased expression of H-2D and H-2K histocompatibility antigens on the cell surface [147, 149, 150, 237]. This increased expression of cell surface antigen does not appear to be dependent on the position of the cells in the cell cycle [48]. In vivo treatment of mice with large doses of partially purified interferon also results in an increase in histocompatibility antigen expression [148].

The enhancement of cell surface antigen expression by interferon could indirectly inhibit the replication of viruses. A change in cell surface antigen expression could make it difficult for viruses to bind to and penetrate the cell surface. In addition, for those viruses that incorporate part of the cell membrane when budding, such as leukemia virus, a change in the surface antigen expression of a lymphocyte could change the viral coat and subsequent infectivity.

D. Interactions with the Immune System

Interferon has been shown to be able to interact with and regulate the immune system [115]. Interferon can inhibit blastogenesis of mouse lymphocytes stimulated by mitogen or by allogeneic cells [151]. The primary in vitro antibody response of mouse spleen cells to T dependent and T independent antigens is also inhibited by addtition of Type I interferon to cell culture [77, 116]. In addition, intravenous injection of Type I interferon can also cause the inhibition of the in vivo primary and secondary response of mice to sheep erythrocytes, a T dependent antigen, and to lipopolysaccharide, a T independent antigen [29]. In the sheep erythrocyte studies, the immunoregulatory effect of interferon in vivo was time and dose dependent. Murine interferon (1.5×10^5 units) given between 4 and 48 h before antigeneic stimulation produced maximum suppression of the antibody response [30]. However, if interferon treatment was delayed until 48 to 72 h after antigen administration, an immunoenhancing effect was observed [30].

Interferon also has a significant effect on the development of cell mediated immune responses. Administration of interferon caused inhibition of a graft versus host reaction [101] and prolongation of allograft survival in mice [102]. In addition, interferon has also been shown to influence the delayed hypersensitivity response to sheep erythrocytes in mice [44, 45]. In the latter experiment, the use of inbred animal strains with diminished capacity for interferon production has allowed use of inducers to examine interferon's action in both sensitization and elicitation of delayed hypersensitivity.

Type II immune induced interferon also has been shown to have immunoregulatory activities. Preliminary studies showed that inducers of Type II interferon such as concanavalin A, phytohemagglutinin, and staphylococcal enterotoxin A added to mouse spleen cell cultures can inhibit the in vitro plaque forming cell response to sheep exrythrocytes [117]. Antigen specific murine Type II interferon, which appears to be a product of B lymphocytes or macrophages in conjunction with suppressor or cytotoxic T lymphocytes [200, 211, 213] is 250 times more potent in immunosuppression than Type I interferon [210] when added to spleen cell cultures 24 h before antigen. The immunoregulatory action of Type II interferon is also time and dosage dependent; if added to spleen cell cultures 48 h after addition of antigen, Type II interferon will cause enhancement of the plaque-forming cell response [212]. The primary function of Type II interferon, which is a lymphokine produced as part of an immune response, may be immunoregulation.

Macrophages apparently were activated and can spread after parenteral treatment of donor mice with interferon inducers or interferon [50, 93, 107, 186]. As a result of activation, enhanced phagocytosis of a wide variety of antigens [50, 94], occurred. In addition, when macrophages were treated in vitro with purified mouse

fibroblast interferon, enhanced phagocytosis of leukemia cells was observed [206]. Therefore, interferon, by activating macrophages, could be limiting viral infections indirectly by causing phagocytosis of virus infected lost cells with their unique viral-induced membrane antigens.

Another parameter of the immune response recently shown to be affected by interferon are cytotoxic lymphocytes, both specific T cells [207] and natural killer cells [203, 233, 234]. When mouse L cells were infected with herpes simplex virus, histocompatibility-2 antigen specific lysis of the infected cells by T cells was enhanced by pretreatment of the L cells with interferon [207]. Treatment of human lymphocytes with interferon or interferon inducers dramatically increased non-specific natural killer activity [203, 233, 234]. However, at the same time, target cells could be protected from natural killer activity by preincubation of the target cells with interferon [203, 233, 234]. Therefore, interferon could limit viral infections indirectly by stimulating lymphocyte-mediated destruction of virus infected cells, but the interferon could also protect other non-infected cells from non-specific destruction.

Interferon has also been shown to enhance certain disease processes. New Zealand Black/New Zealand White F hybrid mice, which develop an autoimmune disease of possible viral etiology similar to human systemic lupus erythematosis, (SLE), showed accelerated and aggrevated disease symptomes after prolonged interferon treatment [99]. Also, addition of interferon to white blood cell cultures of asthmatic individuals resulted in increased release of histamine [74]. Therefore, interferon, as a result of its ability to interact with the immune response, could, in some immunologic diseases such as SLE, asthma, and the LCM infections we have previously described, regulate the immune response in a manner deleterious to the host.

Therefore, interferon could control the spread of virus infections indirectly by regulating the immune response to the virus. In addition, interferon might also control virus dissemination by enhancing the amount of phagocytosis of viruses or virus infected cells. Only further studies will tell how significant these non-antiviral actions are in the role interferon plays as a host defense to viral infection. Obviously, it must be remembered that a large number of other humoral and cellular response are at play in recovery from viral infection, and it can be difficult, if not at times impossible, to assess the role of each in disease pathogenesis.

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