# INTERFERONS AND THEIR ROLES IN VIRUS INFECTIONS

William E. Stewart II

Department of Medical Microbiology and Immunology
University of South Florida College of Medicine
Tampa, Florida

## INTRODUCTION

Interferons (IFNs) were originally identified by virologists who were looking for a virus-induced virus-inhibitory factor (1) and this induction-action relationship seemed to suggest that interferon's reason for being was to inhibit viruses. This simple relationship was quite comforting for several years, but it then started to get more complex by the observations that IFNs could induce a number of alterations in cells besides inhibition of virus replication (2). Such "non-antiviral activities" of IFNs (3) were for several years dismissed as attributable to impurities in the usually relatively crude IFN preparations, but eventually it was substantiated that IFNs are potent inducers of a number of seemingly unrelated "pleotypic alterations" in various cells (4).

Thus, as illustrated in Table 1, depending on the particular inducer-action relationship one is studying, one could really wonder about IFN's true role or purpose. If one were looking for a virus-induced factor that inhibited viruses, or a mitogen-induced factor that inhibited cell division, or an immune recognition-induced factor that modulated immune responses, each factor could be given an ethnocentrically appropriate name and still be an interferon by definition (5). Indeed, certain lymphokines that have been assigned immunomodulatorily appropriate names have been shown to be IFNs, e.g., macrophage activation factor = IFN gamma (6).

So much recent emphasis has stressed IFNs as antitumor agents and so much work in the last three or four years has concerned IFNs' immunomodulatory activities, that I have even encountered comments by immunologists to the effect that IFNs are actually immunoregulatory substances that just happen to have antiviral activities. Therefore, I shall here briefly and selectively review some information on IFNs as antiviral agents and shall emphasize their contributions to both virus resistance and pathogenesis. It should become clear from this discussion that IFNs are important in resistance to and recovery from virus infections, but they also contribute significantly to the production of viral diseases.

## INDUCTION OF INTERFERONS BY VIRUSES

IFNs were originally induced by viruses, but a wide variety of other substances are equally effective at triggering their production by cells.

A. Szentivanyi et al. (eds.), *Viruses, Immunity, and Immunodeficiency*

Table 1. Interferons as Viewed by Induction-Action Relations

| Inducer | Activity |
|---|---|
| Viruses | Antiviral |
| Mitogens | Cell growth inhibition |
| Immune responses | Immunomodulations |

Indeed, it is probably a shorter list of agents that do not induce IFNs than those that do so. IFNs are induced by an extensive list of viruses in all vertebrates that have been tested; thus, IFNs have been induced in dozens of species of fish, amphibians, reptiles, birds and mammals (2).

In the human system, literally dozens of different IFN forms have been identified: two beta IFNs; three gamma IFNs and 20 or more alpha IFNs, including both non-glycosylated and glycosylated native forms (7). In most cases, these virus induced IFNs are stimulated by the virus genome or its replicative forms, giving rise to alpha and/or beta IFNs. In some cases, however, such as in sensitized cells, the viral proteins alone can serve as IFN inducers, giving rise to the production of gamma IFNs. Thus, the character of the IFNs produced early and late in a virus infection, as well as those produced during primary and secondary infections are different, changing from alpha/beta to gamma types of IFNs.

## ROLES OF IFNS IN PATHOGENESIS OF VIRUS INFECTIONS

IFNs can be produced locally very early in virus infections, as in rhinovirus and coronavirus infections of the nasal mucosa (8), or they can be produced locally very late in virus infections, as in rabies or St. Louis encephalitis virus infections of the CNS (9,10). Also, IFNs can be produced systemically in generalized virus infection such as measles, mumps, etc., with interferonemia coincident with the secondary viremia. Therefore the possible involvements of the IFNs must be considered at many stages of virus infections, from the portal of entry, the secondary foci, the circulatory system and in the terminal target tissues.

Quite often, detectable amounts of IFNs are not produced in local or systemic virus infections, but this does not eliminate their roles in the virus resistance of the organism. Indeed, Gresser and his associates (11) have shown that both the pathogenicity and the pathogenesis of many virus infections can be drastically altered by pretreatment of animals with anti-IFN antiserum prior to virus infection (Table 2). Obviously, therefore, even if undetectable levels of IFNs are produced in virus infections, they can significantly augment resistance mechanisms to virus infections.

## MECHANISMS OF IFN-INDUCED VIRUS RESISTANCE

The mechanisms of antiviral activities induced by IFNs must be considered at both the cellular and the organism levels.

At the cellular level, IFNs action against viruses are myriad. Depending on the particular virus examined, the amounts of IFNs, the types of IFNs and the stages of replication studied, IFNs can:

Table 2. Endogenous IFN Restriction of Virus Infections: Demonstration with Anti-IFN Antibodies

| Virus Infection | Effect of Anti-IFN Pretreatment |
|---|---|
| Encephalomyocarditis | Increased fatality; altered pathogenesis (visceral lesions) |
| Vesicular stomatitis | Shortened intranasal to CNS incubation period |
| Semliki forest | Shortened incubation period; increased fatality |
| Herpes simplex | Increased infectivity (several $logs_{10}$) |
| Molony sarcoma | Earlier, larger, longer-lasting tumors; several $logs_{10}$ increase in tumor-inducing potency |

1. Reduce the efficiency of virus attachment/penetration

2. Inhibit uncoating of virus within cells

3. Block primary transcription

4. Inhibit virus messenger RNA translation through induction of enzymes (protein kinase and 2'-5' oligoadenylate synthetase)

5. Interfere with virus progeny assembly/maturation

6. Prevent the release of mature virus progeny from cells

Additionally, IFNs can inhibit virus infections via the many "non-antiviral activities" they induce. Thus, IFNs can, at the organism level:

1. Induce febrile responses which can inhibit virus replication by several mechanisms (e.g., elevation of body temperature above virus optimum; activate endonucleases)

2. Enhance phagocytosis, thus promoting clearance of viremia

3. Activate immune killer cell elements to lyse virus infected cells

4. Sensitize infected cells to antibody-dependent immunolysis

5. Induce other lymphokines (IL-2, TNF, etc.) which can facilitate immuno-removal of virus-infected cells, either alone or in synergy with IFNs.

Thus, in terms of resistance to virus infections, IFNs' mechanisms must be considered both at the molecular level and at the organism level (12,13).

## CONTRIBUTIONS TO IFNs TO VIRUS PATHOGENESIS: IFN SIDE-EFFECTS

It is now clear that IFNs can contribute more than beneficial effects to virus infections. It was demonstrated several years ago (11) that IFNs

Table 3. IFN-Induced Disease: Chronic LCM Virus

| | | |
|---|---|---|
| Newborn mice + LCM | = | Chronic low levels of LCM virus |
| | = | Chronic low levels of IFN |
| | = | Liver necrosis |
| | = | Glomerulonephritis |
| | = | Runting syndrome |
| Newborn mice + LCM | = | High levels of LCM virus |
| | = | No detectable IFN |
| + anti-IFN | = | No liver necrosis |
| | = | No glomeruloenphritis |
| | = | No runting |

could induce damage and death in newborn mice. IFNs also apparently contribute to the production of virus disease and play a causal role in chronic LCM virus infection (Table 3). Thus, chronic IFN production causes the LCM-induced runting syndrome, and neutralization of the IFN induced by the virus prevents this disease (11).

Thus, IFNs presence in virus infections is not uniformly beneficial. Indeed, there was considerable early data showing that crude IFN preparations induced "side effects" in man (14) and recent studies with the various forms of essentially pure natural or recombinant-derived IFNs have shown that IFNs administered systemically can produce several side effects (15,16), some of which can be dose-limiting (Table 4).

Not surprisingly, many of the common prodromal symptoms and circulating IFN levels seen during viremic stages of acute generalized virus infections are similar to the side effects and IFN levels seen at maximum-tolerated doses of patients on IFN therapy.

Even in terms of local utility (as against the common cold), the side effects of IFNs have presented a commercially disturbing situation: the

Table 4. "Side Effects" of Interferons

| Route of Administration | Symptoms |
|---|---|
| Systemic | Flu-like syndrome (fever, malaise, fatigue, headache, nausea, chills, backache) |
| (intramuscular; intravenous) | Leukopenia (transient) |
| | CNS toxicity (depression, drowsiness, confusion, loss of smell and taste) |
| Topical | Nasal stuffiness |
| | Thickened mucus |
| (intranasal) | Local inflammation and irritation |
| | Headache |

side effects of intranasally administered IFNs reflect the symptoms of the common cold (Table 4), likely caused in colds by the IFNs induced locally by the viruses.

In terms of antiviral therapy with IFNs late in virus infections, augmentation of IFN levels could be a mixed blessing: eradication of virus from target tissues such as the CNS could be accomplished by the conventional intracellular antiviral mechanisms induced by IFNs; this should be beneficial. However, elimination of virus-infected cells by IFN-induced augmentation of cell-mediated immunolysis of infected brain cells could be detrimental. The best way to sort out the contributions of these various resistance mechanisms induced by IFNs will be to employ various genetically-engineered fused protein hybrid IFN forms that have constant antiviral levels but low or high immunomodulatory potentials. Then it will be possible to better assess the roles of IFNs in virus infections.

REFERENCES


1. A. Isaacs and J. Lindenmann, Virus interference. I. The interferon, Proc. Royal Soc. B 147:258 (1957).
2. W. E. Stewart II, "The Interferon System," Springer-Verlag, Vienna, Austria (1981).
3. W. E. Stewart II, L. B. Gosser, and R. Z. Lockart, Priming: a nonantiviral function of interferon, J. Virol. 7:792 (1971).
4. W. E. Stewart II, E. DeClercq, P. DeSomer, K. Berg, C. A. Ogburn, and K. Paucker, Antiviral and non-antiviral activity of highly purified interferon, Nature 246:141 (1973).
5. W. E. Stewart II, J. E. Blalock, D. C. Burke, C. Chany, J. Dunnick, E. Falcoff, R. M. Friedman, G. J. Galasso, W. K. Joklik, J. Vilcek, J. S. Youngner, and K. C. Zoon, Interferon nomenclature, Nature 286:110 (1980).
6. W. E. Stewart II and D. K. Blanchard, Interferons: cytostatic and immunomodulatory effects, in: "Immunity to Cancer," A. Reif and M. Mitchell, eds., Academic Press, New York (1985).
7. W. E. Stewart II, Heterogeneities of human interferons, in: "Biological Responses in Cancer," E. Mihich, ed., Plenum Publishing Corporation, New York (1984).
8. S. B. Greenberg and Harmon, Clinical use of interferons: localized application in viral diseases, in: "Interferons and Their Applications," P. E. Came and W. A. Carter, eds., Springer-Verlag, Berlin (1984).
9. W. E. Stewart II and S. E. Sulkin, Interferon production in hamsters experimentally infected with rabies virus, Proc. Soc. Exp. Biol. Med. 123:650 (1966).
10. J. P. Luby, W. E. Stewart II, S. E. Sulkin, and J. P. Sanford, Interferon in human infections with St. Louis encephalitis, Ann. Int. Med. 71:703 (1969).
11. I. Gresser, Can interferon induce disease?, in: "Interferon 4," I. Gresser, ed., Academic Press, London (1982).
12. B. Lebleu and J. Content, Mechanisms of interferon action: biochemical and genetic approaches, in: "Interferon 4," I. Gresser, ed., Academic Press, London (1982).
13. W. E. Stewart II, The natural recovery process from acute virus infection, in: "Selective Inhibitors of Viral Functions," W. A. Carter, ed., CRC Press, Cleveland (1973).
14. H. Strander, K. Cantell, G. Carlstrom, S. Ingimarsson, P. A. Jakobsson, U. Nilsonne, Acute infections in interferon-treated patients with osteosarcoma: a preliminary report of a comparative study, J. Infect. Dis. 133:A245 (1976).

15. G. M. Scott, W. E. Stewart II, D. A. J. Tyrrell, K. Cantell, T. Cartwright, and V. G. Edy, Skin reactions to interferon inoculations are reduced but not abolished by purification, J. Interferon Res. 1:79 (1980).
16. D. A. J. Tyrrell, Some thoughts on the clinical exploitation of interferon in infectious diseases, in: "Interferon 4," I. Gresser, ed., Academic Press, London (1982).