View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Elsevier - Publisher Connector

Immunity 25, 343–348, September 2006 ©2006 Elsevier Inc. DOI 10.1016/j.immuni.2006.08.008

Fifty Years of Interferon Research: Aiming at a Moving Target

Commentary

Jan Vilcek[1,*]
[1] Department of Microbiology
New York University School of Medicine
New York, New York 10016

Summary

Nearly half a century has passed since the first published description of interferons (IFNs). This commentary introduces the four accompanying review articles on type I IFN research and attempts to relate how the field of IFN research has been changing during its history.

Interferon (IFN) was first described as a product of influenza virus-infected chick embryo cells, capable of inducing resistance to infection with homologous or heterologous viruses (Isaacs and Lindenmann, 1957). Some years later, a functionally related protein (now called IFN-γ or type II IFN) was described as an IFN-like virus-inhibitory protein produced by mitogen-activated human T lymphocytes (Wheelock, 1965). Type I IFNs include numerous subtypes, of which IFN-α and IFN-β are the predominant forms (see review by van Boxel-Dezaire et al., 2006 in this issue of *Immunity*). Twelve separate functional IFN-α genes and proteins and a single IFN-β gene exist in humans.

Touted as a potentially useful antiviral drug, the study of IFN from the very beginning attracted wide attention. In the 1960s, Flash Gordon magazine featured a comic strip in which doctors in a space ship used IFN to cure a patient afflicted with a mysterious virus infection. Nevertheless, because efforts to purify and molecularly define IFN proteins remained fruitless for about 20 years, many scientists had been openly skeptical about properties ascribed to IFN, including its very existence. It was only after the successful cloning of IFN cDNAs and identification of IFN genes that IFN research joined the mainstream of the scientific enterprise (Gray and Goeddel, 1982; Nagata et al., 1980; Taniguchi et al., 1979). This commentary serves as a brief introduction to a group of accompanying reviews summarizing the current state of knowledge in some of the most active areas of IFN research within the context of innate immunity and autoimmunity. My comments will focus on how views of the field of IFN research (especially of type I IFN) have been evolving over the nearly 50 year period since the first publications describing IFN (Table 1).

From Selective Antiviral Inhibitor to Multifunctional Cytokine

Isaacs, Lindenmann, and other pioneers of IFN research had not anticipated that the significance of IFN would extend beyond the field of virology. In fact, an article in a leading textbook on IFN published more than 15 years after the original description of IFN proposed that the "probable lack of other (than antiviral) cellular effects of interferons" be part of a definition of IFNs (Lockart, 1973). Yet, as early as 1962, some investigators argued that murine IFN inhibited the growth of mouse cells in culture and that this activity could not be separated from the antiviral action of IFN (Paucker et al., 1962). Almost concurrently, IFN was shown to inhibit the appearance of intracellular inclusions formed by *Chlamydia psittaci,* an obligate intracellular bacterium (Sueltenfuss and Pollard, 1962). The latter finding was followed by demonstrations that type I IFN inhibits intracellular multiplication of protozoa, rickettsia, and other intracellular bacteria (reviewed in Stewart, 1979; Vilcek and Jahiel, 1970). Among other early recognized pleiotropic activities of type I IFNs were also enhancement of the lytic action of cytotoxic T cells for tumor target cells (Lindahl et al., 1972) and enhancement of MHC antigen expression (Lindahl et al., 1976). Other studies revealed that treatment with IFN can inhibit tumor growth in animals, an activity now known to be attributable to multiple mechanisms (Gresser et al., 1969).

Naturally, today no one doubts that type I IFNs have multiple functions in addition to their well-known ability to inhibit virus replication. This is also true of IFN-γ, which functions primarily as an immunomodulatory cytokine. It is useful, however, to remind ourselves that IFN was discovered by virologists who found what they had been looking for: an antiviral product of virus-infected cells responsible for viral interference. It took many years to change the ingrained concept of IFN as a specific and selective antiviral protein devoid of any other "side effects."

The real breakthrough in the understanding of the molecular mechanisms of IFN actions had to await the definition of IFN receptors and elucidation of signal transduction pathways triggered by the ligand-receptor interactions. During the first decade of IFN research, the prevailing view was that the IFN molecule itself—upon entering the cell and perhaps undergoing some metabolic changes—was the actual inhibitor of virus replication. Indirect evidence for IFN binding to the cell surface was first reported in the late 1960s (Friedman, 1967). By the early 1980s, binding studies with radiolabeled IFN proteins had led to the conclusion that there are specific high-affinity cell-surface receptors for IFNs, that different subspecies of type I IFN (IFN-α and IFN-β) share a common receptor, and that receptors for type I and type II IFN are distinct (Aguet et al., 1982; Branca and Baglioni, 1981). Molecular cloning and characterization of components of type I IFN receptors were largely completed by the mid-1990s (Domanski and Colamonici, 1996; Novick et al., 1994). It is now clear that all type I IFNs bind to the same dimeric receptor, but different type I IFNs elicit somewhat different biological responses (van Boxel-Dezaire et al., 2006).

Another important chapter in the annals of IFN research concerns the identification of signaling pathways responsible for IFN actions. Gradual elucidation of the details of the JAK-STAT signaling pathway activated by IFNs helped to clarify not only the molecular mechanisms responsible for IFN actions, but also laid the

*Correspondence: jan.vilcek@med.nyu.edu

Table 1. Selected Milestones in Interferon Research

Year	Accomplishment or Demonstration[a]	References[b]
1957	Description of IFN as virus-inhibitory protein from chick embryo cells exposed to inactivated flu virus	Isaacs and Lindenmann, 1957
1962	IFN inhibits growth of cultured cells	Paucker et al., 1962
	IFN inhibits growth of intracellular bacteria	Sueltenfuss and Pollard, 1962
1964	IFN induced in animals by bacteria and endotoxin	Ho, 1964; Stinebring and Youngner, 1964
1965	Description of IFN-γ (type II IFN)	Wheelock, 1965
1967	Double-stranded RNA induces IFN	Field et al., 1967
1969	IFN inhibits tumor growth in animals	Gresser et al., 1969
1972–1976	Immunoregulatory actions of IFN are recognized	Lindahl et al., 1976, 1972
1974–1976	IFN-induced proteins mediating antiviral action are described	Kerr et al., 1974; Lebleu et al., 1976
1975	Identification of distinct subtypes of type I IFN proteins (IFN-α and -β)	Havell et al., 1975
	Description of elevated levels of IFN in patients with systemic lupus	Skurkovich and Eremkina, 1975
1975–1977	Recognition of IFN's adverse effects in animals	Gresser et al., 1975; Riviere et al., 1977
1979	Isolation and sequencing of human IFN-β cDNA	Taniguchi et al., 1979
1980	Isolation, sequencing, and expression of human IFN-α cDNA	Nagata et al., 1980
	Purification and partial sequencing of human IFN-α and IFN-β proteins	Knight et al., 1980; Zoon et al., 1980
1982	Isolation and sequencing of human IFN-γ cDNA	Gray and Goeddel, 1982
	Elevated IFN concentrations described in HIV-infected patients, correlating with severity of disease	DeStefano et al., 1982
1985	ISRE recognition element identified in upstream region of IFN-inducible genes	Friedman and Stark, 1985
1988	Discovery of IRF transcription factor family	Miyamoto et al., 1988
1990	Identification of ISGF-3 protein complex mediating activation of IFN-inducible genes	Fu et al., 1990
1990–1996	Identification and characterization of type I IFN receptor components	Novick et al., 1994; Domanski and Colamonici, 1996
1992–1994	JAK-STAT signaling pathway identified as major pathway for IFN-induced gene expression	Velazquez et al., 1992; Darnell et al., 1994
1995–1998	IRF-3 and IRF-7 found to play key roles in type I IFN induction	Juang et al., 1998; Marie et al., 1998; Sato et al., 1998
1999	Plasmacytoid dendritic cells are robust producers of type I IFN	Siegal et al., 1999
2001	Toll-like receptor 3 shown to recognize double-stranded RNA	Alexopoulou et al., 2001
2004–2005	Cytosolic helicases RIG-I and MDA5 can trigger IFN production in response to double-stranded RNA or RNA viruses	Yoneyama et al., 2004

[a] Unless otherwise indicated, milestones refer only to research accomplishments in the field of type I IFN research.
[b] Not all references pertaining to the listed accomplishments or demonstrations could be included.

groundwork for understanding the actions of many other cytokines (Darnell et al., 1994). The nuances and complexities of the multifaceted biology of type I IFN actions are reviewed in an accompanying review article (van Boxel-Dezaire et al., 2006).

Multiple Agents and Multiple Pathways Can Lead to IFN Induction

Although the recognition that IFN is a pleiotropic cytokine was slow, it had taken less time to learn that many different stimuli, in addition to viruses, can trigger IFN production. Thus, IFN production was demonstrated in chickens, mice, and rabbits injected with a variety of bacteria or bacterial lipopolysaccharide (LPS) (Ho, 1964; Stinebring and Youngner, 1964). IFN-γ owes its discovery to the finding that the addition of phytohemagglutinin, a mitogenic lectin, to a suspension of human leucocytes elicited IFN production (Wheelock, 1965). Crude filtrates from cultures of the fungus *Penicillium stoloniferum* were shown to induce IFN in mice and in tissue culture (Kleinschmidt et al., 1964). (The filtrate was called "statolon" and shown earlier to have antiviral activity.) Of special significance was the demonstration that the active principle of "statolon," and a similar fungal extract called "helenine," was double-stranded RNA—likely originating from a polyhedral virus infecting the fungal cells. Double-stranded RNA from statolon or helenine, and also synthetic double-stranded RNA, poly (I).poly(C), readily triggered IFN production in intact animals or in cell cultures (Field et al., 1967). Although hopes of using double-stranded RNA as a therapeutic agent for virus infections have not materialized, identification of double-stranded RNA as a potent IFN inducer provided researchers with a precious tool for the study of IFN induction pathways. In addition, it soon became apparent that double-stranded RNA plays a key role not only in IFN induction, but also in IFN action. Two of the IFN-induced proteins central to IFN's antiviral actions, 2′-5′ oligoadenylate synthetase and double-stranded RNA-dependent protein kinase (PKR), were shown to require double-stranded RNA for their activation (Kerr et al., 1974; Lebleu et al., 1976).

It was expected that identification of double-stranded RNA as a potent IFN inducer in the late 1960s would rapidly provide clues to the mechanism of IFN induction by viruses. After all, double-stranded RNA was known to be a byproduct of replication of many viruses, so wouldn't exposure of cells to double-stranded RNA simply mimic the process of IFN induction by viruses? In reality, the situation proved to be more complicated. Molecular pathways mediating cellular responses to double-stranded RNA remained largely unknown until the demonstration that toll-like receptor 3 (TLR3) recognizes double-stranded RNA (Alexopoulou et al., 2001). As explained in more detail in the accompanying review (Stetson and Medzhitov, 2006), this cytosolic pathway is functional mainly in specialized cells, namely dendritic

cells (DCs). It is now apparent that the main pathway of type I IFN induction by double-stranded RNA and various RNA-containing viruses, which can be activated in a variety of cell types, is triggered by the cytosolic caspase-recruitment domain (CARD)-containing helicases RIG-I or MDA5 (Kato et al., 2006; Yoneyama et al., 2004). In addition to double-stranded RNA, other microbial components or products have been shown to trigger type I IFN production through other pathways, including single-stranded viral RNA (acting on TLR7 and TLR8) and viral or bacterial DNA (via TLR9). Although nucleic acids are arguably the most important activators of type I IFN production, bacterial LPS is now known to trigger IFN production in macrophages and DCs via TLR4 (Kawai and Akira, 2006; Stetson and Medzhitov, 2006). Molecular pathways used by other stimuli known to trigger type I IFN production, e.g., some viral glycoproteins and other microbial components, have not yet been fully elucidated (Malmgaard, 2004).

Another shot in the arm for the study of molecular mechanisms of IFN induction was provided by the discovery of the new family of transcription factors, the IFN regulatory factors (IRFs), by Taniguchi and colleagues (Miyamoto et al., 1988). The earliest-discovered members of this family, IRF-1 and IRF-2, were shown to be important in a variety of innate and adaptive immune responses, including T helper 1 responses and natural killer (NK) cell differentiation (Taniguchi et al., 2001). Two other members of the IRF family, IRF-3 and IRF-7, have been found to play key roles in type I IFN gene activation (Juang et al., 1998; Marie et al., 1998; Sato et al., 1998).

It has also become apparent that several IRF family members, including IRF-3, -5, and -7, are important in TLR signaling (Honda and Taniguchi, 2006; Kawai and Akira, 2006). IRF family transcription factors play broader roles in TLR signaling that are not limited to IFN gene activation. For example, MyD88-dependent activation of IRF-5 is essential for the TLR-mediated induction of the proinflammatory cytokines TNF-α, IL-6, and IL-12, but not for IFN-α and IFN-β induction (Takaoka et al., 2005). The molecular pathways of the complex processes of type I IFN induction are reviewed in the accompanying articles (Honda et al., 2006; Stetson and Medzhitov, 2006).

Good Interferon versus Bad Interferon

In the early days, IFN was believed to be a highly selective and specific antiviral agent devoid of any actions in uninfected cells and assumed to be completely nontoxic in the intact organism. The presumed lack of IFN toxicity served as an important argument in the effort to develop IFNs as therapeutic agents for the treatment of viral infections and cancer in the 1970s and early 1980s. And yet, results suggesting adverse actions of IFNs in the body were already at hand in the mid-1970s. Thus, injection of large doses of type I mouse IFN to newborn mice caused growth retardation and, eventually, death (Gresser et al., 1975). The major histopathological finding was steatosis and necrosis of the liver. Mice given sublethal doses of IFN developed glomerulonephritis later in life. The biological relevance of these findings was recently corroborated by a study demonstrating that embryonic lethality seen in DNase II-deficient mice is due to the animals' inability to degrade DNA derived from erythroid precursors, which in turn triggers IFN-β production that induces expression of a specific set of IFN-responsive genes leading to embryonic lethality (Yoshida et al., 2005).

Another surprising development was the gradual realization that endogenous IFN, produced in the body in the course of an infection, can be harmful—first clearly demonstrated in the model of lymphocytic choriomeningitis virus (LCMV) infection in newborn mice (Riviere et al., 1977). Most of LCMV-infected animals died within 2–3 weeks, and surviving mice developed glomerulonephritis later in life. However, LCMV-infected newborn mice treated with a potent neutralizing antibody to type I mouse IFN survived and had a lower incidence of glomerulonephritis later in life.

Gradually, other evidence became available suggesting that IFN produced in the course of common virus infections, while serving as an inhibitor of virus replication, may also contribute to morbidity. Some of this evidence was gleaned from early clinical studies with natural or recombinant IFNs revealing that administration of IFN-α or IFN-β to patients produced fever, fatigue, malaise, myalgia, and anemia (Vilcek, 1984). It became apparent that similar "flu-like" symptoms seen in many common acute virus infections are due, at least in part, to the production of endogenous IFN. Thus, administration of IFN-α by intranasal spray protected volunteers from rhinovirus infection. However, intranasal IFN administration also produced a local inflammatory reaction, not unlike that seen in patients suffering from naturally acquired rhinovirus infection (Merigan et al., 1973; Vilcek, 1984).

Another indication of possible adverse effects of IFN came from studies showing that sera of many patients with autoimmune diseases, especially patients with systemic lupus erythematosus (SLE), have elevated amounts of type I IFN (Hooks et al., 1982; Preble et al., 1982; Skurkovich and Eremkina, 1975). Although the exact significance of these observations was not understood at the time, the fact that the presence of IFN seemed to correlate with disease activity suggested a pathogenetic, rather than protective, activity. Further support for the role of type I IFN in autoimmunity was gained when it had became apparent that IFN therapy may sometimes cause or aggravate autoimmune disorders, including thyroiditis, diabetes, arthritis, and vasculitis (Banchereau and Pascual, 2006).

Much more information about the source and role of IFN in SLE and some other autoimmune disorders is available today, as reviewed in the accompanying article (Banchereau and Pascual, 2006). A central hypothesis proposed by these authors is that overproduction of type I IFN in SLE causes activation of immature myeloid DCs, which in turn leads to the activation and expansion of autoreactive T cells and B cells. Further amplification of autoimmune responses then occurs through additional interactions involving, among others, TLR7- or TLR9-mediated activation of plasmacytoid DCs by nucleic acid containing immune complexes.

An interesting concept concerns the crossregulation of IFN and tumor necrosis factor (TNF) in autoimmunity (Banchereau and Pascual, 2006; Palucka et al., 2005). It has been known for a while that some patients treated with anti-TNF agents may develop anti-nuclear antibodies, antibodies to double-stranded DNA, and in

rare occasions, SLE (Feldmann and Maini, 2001). The latter findings in patients treated with anti-TNF agents correlate with enhanced IFN production by plasmacytoid DCs, suggesting that TNF inhibits type I IFN generation. Conversely, IFN-β was found to inhibit TNF production by microglia, which might partially explain the beneficial effect of IFN-β in multiple sclerosis (Teige et al., 2003).

Elevated amounts of type I IFN with properties similar to the IFN found in the sera of SLE patients were also demonstrated in a high percentage of AIDS patients (DeStefano et al., 1982). The presence and the amounts of IFN in the AIDS patients' sera generally correlated with the severity of disease, suggesting that IFN may contribute to immune dysfunction. However, the possible mechanisms whereby IFN may contribute to AIDS pathogenesis remained mysterious for a long time. We now appreciate the fact that type I IFNs can sensitize cells to apoptotic signals, especially to virus-induced apoptosis (see review by Stetson and Medzhitov, 2006 in this issue of *Immunity*). As far as I know, there exists no direct evidence that IFN sensitizes $CD4^+$ T cells to HIV-induced cell death, but such action is a plausible possibility. It is also possible that depletion of $CD4^+$ T cells may be an indirect consequence of IFN action. A recently proposed hypothesis links the depletion of $CD4^+$ T cells in HIV-infected patients to IFN's ability to enhance the generation of TNF-related apoptosis-inducing ligand (TRAIL) and its receptor DR5 (Herbeuval et al., 2005).

Studies in animals indicate that in certain situations IFN may promote, rather than inhibit, the multiplication of an infectious agent. Type I IFN receptor-deficient mice were shown to be markedly more *resistant* to infection with a high dose *Listeria monocytogenes* (Auerbuch et al., 2004). At 3 days after inoculation, wild-type mice contained a thousand times more bacteria in their spleens than IFN receptor-deficient mice. Resistance to *Listeria* infection correlated with elevated amounts of interleukin 12 in the blood and increased numbers of spleen macrophages producing TNF. A similar enhanced resistance to *Listeria* was seen in IRF-3-deficient mice (O'Connell et al., 2004). The results of these studies suggest that *Listeria monocytogenes* is exploiting an IFN-driven innate immune mechanism to promote its pathogenesis.

Conclusion

Our understanding of the nature and roles of type I IFNs is very different today from what it was during the "romantic period" when nearly supernatural properties had been attributed to IFN. We now appreciate the fact that IFNs play important roles in host defenses, but we understand that they can also be harmful when produced at the wrong time or wrong place. On the positive side, although the clinical utility of IFNs has not met the rosy expectations of some of its most enthusiastic promoters, several recombinant type I IFN products have earned a solid foothold in the pharmaceutical armamentarium. One viral infection in which IFN-α is widely used (frequently in combination with the nucleoside analog Ribavirin) is chronic hepatitis C. Other currently approved clinical applications of IFN-α are for the treatment of some neoplasias, including certain forms of chronic myelogenous leukemia and malignant melanoma. Recombinant IFN-β is being used for the treatment of relapsing forms of multiple sclerosis. As is frequently the case with other therapeutics, a thorough understanding of the mechanism of IFN's beneficial actions in malignancies and in multiple sclerosis has lagged behind its therapeutic utility.

We have made enormous strides in the understanding of the molecular mechanisms of regulation of IFN induction and synthesis and in the elucidation of the mechanisms of IFN action. The most recent advances in these areas are highlighted in the four accompanying reviews published in this issue (Banchereau and Pascual, 2006; Honda et al., 2006; Stetson and Medzhitov, 2006; van Boxel-Dezaire et al., 2006).

References

Aguet, M., Belardelli, F., Blanchard, B., Marcucci, F., and Gresser, I. (1982). High-affinity binding of 125I-labeled mouse interferon to a specific cell surface receptor. IV. Mouse gamma interferon and cholera toxin do not compete for the common receptor site of alpha/beta interferon. Virology *117*, 541–544.

Alexopoulou, L., Holt, A.C., Medzhitov, R., and Flavell, R.A. (2001). Recognition of double-stranded RNA and activation of NF-kappaB by Toll-like receptor 3. Nature *413*, 732–738.

Auerbuch, V., Brockstedt, D.G., Meyer-Morse, N., O'Riordan, M., and Portnoy, D.A. (2004). Mice lacking the type I interferon receptor are resistant to *Listeria monocytogenes*. J. Exp. Med. *200*, 527–533.

Banchereau, J., and Pascual, V. (2006). Type I interferon in systemic lupus erythematosus and other autoimmune diseases. Immunity *25*, this issue, 383–392.

Branca, A.A., and Baglioni, C. (1981). Evidence that types I and II interferons have different receptors. Nature *294*, 768–770.

Darnell, J.E., Jr., Kerr, I.M., and Stark, G.R. (1994). Jak-STAT pathways and transcriptional activation in response to IFNs and other extracellular signaling proteins. Science *264*, 1415–1421.

DeStefano, E., Friedman, R.M., Friedman-Kien, A.E., Goedert, J.J., Henriksen, D., Preble, O.T., Sonnabend, J.A., and Vilcek, J. (1982). Acid-labile human leukocyte interferon in homosexual men with Kaposi's sarcoma and lymphadenopathy. J. Infect. Dis. *146*, 451–459.

Domanski, P., and Colamonici, O.R. (1996). The type-I interferon receptor. The long and short of it. Cytokine Growth Factor Rev. *7*, 143–151.

Feldmann, M., and Maini, R.N. (2001). Anti-TNF alpha therapy of rheumatoid arthritis: what have we learned? Annu. Rev. Immunol. *19*, 163–196.

Field, A.K., Tytell, A.A., Lampson, G.P., and Hilleman, M.R. (1967). Inducers of interferon and host resistance. II. Multistranded synthetic polynucleotide complexes. Proc. Natl. Acad. Sci. USA *58*, 1004–1010.

Friedman, R.M. (1967). Interferon binding: the first step in establishment of antiviral activity. Science *156*, 1760–1761.

Friedman, R.L., and Stark, G.R. (1985). alpha-Interferon-induced transcription of HLA and metallothionein genes containing homologous upstream sequences. Nature *314*, 637–639.

Fu, X.Y., Kessler, D.S., Veals, S.A., Levy, D.E., and Darnell, J.E., Jr. (1990). ISGF3, the transcriptional activator induced by interferon alpha, consists of multiple interacting polypeptide chains. Proc. Natl. Acad. Sci. USA *87*, 8555–8559.

Gray, P.W., and Goeddel, D.V. (1982). Structure of the human immune interferon gene. Nature *298*, 859–863.

Gresser, I., Bourali, C., Levy, J.P., Fontaine-Brouty-Boye, D., and Thomas, M.T. (1969). Increased survival in mice inoculated with tumor cells and treated with interferon preparations. Proc. Natl. Acad. Sci. USA *63*, 51–57.

Gresser, I., Tovey, M.G., Maury, C., and Chouroulinkov, I. (1975). Lethality of interferon preparations for newborn mice. Nature *258*, 76–78.

Havell, E.A., Berman, B., Ogburn, C.A., Berg, K., Paucker, K., and Vilcek, J. (1975). Two antigenically distinct species of human interferon. Proc. Natl. Acad. Sci. USA *72*, 2185–2187.

Herbeuval, J.P., Grivel, J.C., Boasso, A., Hardy, A.W., Chougnet, C., Dolan, M.J., Yagita, H., Lifson, J.D., and Shearer, G.M. (2005). CD4+ T-cell death induced by infectious and noninfectious HIV-1: role of type 1 interferon-dependent, TRAIL/DR5-mediated apoptosis. Blood *106*, 3524–3531.

Ho, M. (1964). Interferon-like viral inhibitor in rabbits after intravenous administration of endotoxin. Science *146*, 1472–1474.

Honda, K., and Taniguchi, T. (2006). IRFs: master regulators of signalling by Toll-like receptors and cytosolic receptors. Nat. Rev. Immunol. *6*, 644–658.

Honda, K., Takaoka, A., and Taniguchi, T. (2006). Type I interferon gene induction by the interferon regulatory factor family of transcription factors. Immunity *25*, this issue, 349–360.

Hooks, J.J., Jordan, G.W., Cupps, T., Moutsopoulos, H.M., Fauci, A.S., and Notkins, A.L. (1982). Multiple interferons in the circulation of patients with systemic lupus erythematosus and vasculitis. Arthritis Rheum. *25*, 396–400.

Isaacs, A., and Lindenmann, J. (1957). Virus interference. 1. The interferon. Proc. R. Soc. Lond. B. Biol. Sci. *147*, 258–267.

Juang, Y.T., Lowther, W., Kellum, M., Au, W.C., Lin, R., Hiscott, J., and Pitha, P.M. (1998). Primary activation of interferon A and interferon B gene transcription by interferon regulatory factor 3. Proc. Natl. Acad. Sci. USA *95*, 9837–9842.

Kato, H., Takeuchi, O., Sato, S., Yoneyama, M., Yamamoto, M., Matsui, K., Uematsu, S., Jung, A., Kawai, T., Ishii, K.J., et al. (2006). Differential roles of MDA5 and RIG-I helicases in the recognition of RNA viruses. Nature *441*, 101–105.

Kawai, T., and Akira, S. (2006). TLR signaling. Cell Death Differ. *13*, 816–825.

Kerr, I.M., Brown, R.E., and Ball, L.A. (1974). Increased sensitivity of cell-free protein synthesis to double-stranded RNA after interferon treatment. Nature *250*, 57–59.

Kleinschmidt, W.J., Cline, J.C., and Murphy, E.B. (1964). Interferon production induced by statolon. Proc. Natl. Acad. Sci. USA *52*, 741–744.

Knight, E., Jr., Hunkapiller, M.W., Korant, B.D., Hardy, R.W., and Hood, L.E. (1980). Human fibroblast interferon: amino acid analysis and amino terminal amino acid sequence. Science *207*, 525–526.

Lebleu, B., Sen, G.C., Shaila, S., Cabrer, B., and Lengyel, P. (1976). Interferon, double-stranded RNA, and protein phosphorylation. Proc. Natl. Acad. Sci. USA *73*, 3107–3111.

Lindahl, P., Leary, P., and Gresser, I. (1972). Enhancement by interferon of the specific cytotoxicity of sensitized lymphocytes. Proc. Natl. Acad. Sci. USA *69*, 721–725.

Lindahl, P., Gresser, I., Leary, P., and Tovey, M. (1976). Interferon treatment of mice: enhanced expression of histocompatibility antigens on lymphoid cells. Proc. Natl. Acad. Sci. USA *73*, 1284–1287.

Lockart, R.Z., Jr. (1973). Criteria for acceptance of a viral inhibitor as an interferon and a general description of the biological properties of known interferons. In Interferons and Interferon Inducers, N.B. Finter, ed. (Amsterdam: North-Holland Publishing Company), pp. 11–27.

Malmgaard, L. (2004). Induction and regulation of IFNs during viral infections. J. Interferon Cytokine Res. *24*, 439–454.

Marie, I., Durbin, J.E., and Levy, D.E. (1998). Differential viral induction of distinct interferon-alpha genes by positive feedback through interferon regulatory factor-7. EMBO J. *17*, 6660–6669.

Merigan, T.C., Reed, S.E., Hall, T.S., and Tyrrell, D.A. (1973). Inhibition of respiratory virus infection by locally applied interferon. Lancet *1*, 563–567.

Miyamoto, M., Fujita, T., Kimura, Y., Maruyama, M., Harada, H., Sudo, Y., Miyata, T., and Taniguchi, T. (1988). Regulated expression of a gene encoding a nuclear factor, IRF-1, that specifically binds to IFN-β gene regulatory elements. Cell *54*, 903–913.

Nagata, S., Taira, H., Hall, A., Johnsrud, L., Streuli, M., Ecsodi, J., Boll, W., Cantell, K., and Weissmann, C. (1980). Synthesis in *E. coli* of a polypeptide with human leukocyte interferon activity. Nature *284*, 316–320.

Novick, D., Cohen, B., and Rubinstein, M. (1994). The human interferon α/β receptor: characterization and molecular cloning. Cell *77*, 391–400.

O'Connell, R.M., Saha, S.K., Vaidya, S.A., Bruhn, K.W., Miranda, G.A., Zarnegar, B., Perry, A.K., Nguyen, B.O., Lane, T.F., Taniguchi, T., et al. (2004). Type I interferon production enhances susceptibility to *Listeria monocytogenes* infection. J. Exp. Med. *200*, 437–445.

Palucka, A.K., Blanck, J.P., Bennett, L., Pascual, V., and Banchereau, J. (2005). Cross-regulation of TNF and IFN-alpha in autoimmune diseases. Proc. Natl. Acad. Sci. USA *102*, 3372–3377.

Paucker, K., Cantell, K., and Henle, W. (1962). Quantitative studies on viral interference in suspended L cells. III. Effect of interfering viruses and interferon on the growth rate of cells. Virology *17*, 324–334.

Preble, O.T., Black, R.J., Friedman, R.M., Klippel, J.H., and Vilcek, J. (1982). Systemic lupus erythematosus: presence in human serum of an unusual acid-labile leukocyte interferon. Science *216*, 429–431.

Riviere, Y., Gresser, I., Guillon, J.-C., and Tovey, M.G. (1977). Inhibition by anti-interferon serum of lymphocytic choriomeningitis virus disease in suckling mice. Proc. Natl. Acad. Sci. USA *74*, 2135–2139.

Sato, M., Hata, N., Asagiri, M., Nakaya, T., Taniguchi, T., and Tanaka, N. (1998). Positive feedback regulation of type I IFN genes by the IFN-inducible transcription factor IRF-7. FEBS Lett. *441*, 106–110.

Siegal, F.P., Kadowaki, N., Shodell, M., Fitzgerald-Bocarsly, P.A., Shah, K., Ho, S., Antonenko, S., and Liu, Y.J. (1999). The nature of the principal type 1 interferon-producing cells in human blood. Science *284*, 1835–1837.

Skurkovich, S.V., and Eremkina, E.I. (1975). The probable role of interferon in allergy. Ann. Allergy *35*, 356–360.

Stetson, D.B., and Medzhitov, R. (2006). Type I interferons in host defense. Immunity *25*, this issue, 373–381.

Stewart, W.E., II. (1979). The Interferon System (New York: Springer Verlag).

Stinebring, W.R., and Youngner, J.S. (1964). Patterns of interferon appearance in mice infected with bacteria or bacterial endotoxin. Nature *204*, 712.

Sueltenfuss, E.A., and Pollard, M. (1962). Cytochemical assay of interferon produced by duck hepatitis virus. Science *139*, 595–596.

Takaoka, A., Yanai, H., Kondo, S., Duncan, G., Negishi, H., Mizutani, T., Kano, S., Honda, K., Ohba, Y., Mak, T.W., and Taniguchi, T. (2005). Integral role of IRF-5 in the gene induction programme activated by Toll-like receptors. Nature *434*, 243–249.

Taniguchi, T., Saka, M., Fujii-Kuriyama, Y., Muramatsu, M., Kobayashi, M., and Sudo, T. (1979). Construction and identification of a bacterial plasmid containing the human fibroblast interferon gene sequence. Proc. Jpn. Acad. *55B*, 464–469.

Taniguchi, T., Ogasawara, K., Takaoka, A., and Tanaka, N. (2001). IRF family of transcription factors as regulators of host defense. Annu. Rev. Immunol. *19*, 623–655.

Teige, I., Treschow, A., Teige, A., Mattsson, R., Navikas, V., Leanderson, T., Holmdahl, R., and Issazadeh-Navikas, S. (2003). IFN-beta gene deletion leads to augmented and chronic demyelinating experimental autoimmune encephalomyelitis. J. Immunol. *170*, 4776–4784.

van Boxel-Dezaire, A.H.H., Rani, M.R.S., and Stark, G.R. (2006). Complex modulation of cell type-specific signaling in response to type I interferons. Immunity *25*, this issue, 361–372.

Velazquez, L., Fellous, M., Stark, G.R., and Pellegrini, S. (1992). A protein tyrosine kinase in the interferon α/β signaling pathway. Cell *70*, 313–322.

Vilcek, J. (1984). Adverse effects of interferon in virus infections, autoimmune diseases and acquired immunodeficiency. Prog. Med. Virol. *30*, 62–77.

Vilcek, J., and Jahiel, R.I. (1970). Action of interferon and its inducers aginst nonviral infectious agents. Arch. Intern. Med. *126*, 69–77.

Wheelock, E.F. (1965). Interferon-like virus-inhibitor induced in human leukocytes by phytohemagglutinin. Science *149*, 310–311.

Yoneyama, M., Kikuchi, M., Natsukawa, T., Shinobu, N., Imaizumi, T., Miyagishi, M., Taira, K., Akira, S., and Fujita, T. (2004). The RNA helicase RIG-I has an essential function in double-stranded RNA-induced innate antiviral responses. Nat. Immunol. *5*, 730–737.

Yoshida, H., Okabe, Y., Kawane, K., Fukuyama, H., and Nagata, S. (2005). Lethal anemia caused by interferon-beta produced in mouse embryos carrying undigested DNA. Nat. Immunol. *6*, 49–56.

Zoon, K.C., Smith, M.E., Bridgen, P.J., Anfinsen, C.B., Hunkapiller, M.W., and Hood, L.E. (1980). Amino terminal sequence of the major component of human lymphoblastoid interferon. Science *207*, 527–528.