Antiviral Research, 6 (1986) 1–17
Elsevier

AVR 00181

Review article

The interferon system as an integral part of the defense system against infections

Holger Kirchner

Institute of Virus Research, German Cancer Research Center, Heidelberg, F.R.G.

(Received 25 February 1985; accepted 2 April 1985)

Contents

Introduction

Interferon, a protein with antiviral effects has been discovered by Isaacs and Lindenmann more than 25 years ago [39]. For the first 20 years, progress has been slow, mainly for the reason that purification, molecular characterization and production have met great difficulties. Rapid progress has been made during the past 5 years

Address for correspondence: Professor Dr. H. Kirchner, Institute of Virus Research, German Cancer Research Center, 280, Im Neuenheimer Feld, D-6900 Heidelberg, F.R.G.

and various interferons are now well characterized. Three aspects are noteworthy regarding the progress of recent years (for a review see refs. 48 and 67):

(1) There are numerous interferons, some of which are closely related, whereas others are quite different from each other.

(2) The interferons have a multitude of diverse biological effects [31], some of which are understood to a certain degree, whereas others are understood poorly, and perhaps others again that are as yet undiscovered.

(3) Interferons are the products of different cell types. Some of these are cellular components of the immune system such as T lymphocytes and macrophages [49]. The functions of the cells of the immune system are regulated and thus, presumably interferon production is also regulated. Also, the functions of these cells are well studied by immunologists, and in interferon research this knowledge should be used for a better understanding of the interferon system.

(4) Interferon production is genetically controlled [17].

Interferons are now being tested for their clinical effectiveness and it is obvious that they cause objective responses in tumor bearers or in individuals suffering from viral diseases [9,70]. Yet the number of situations in which this causes a clear-cut benefit for the patient is limited. It is hoped that it will be possible to identify additional clinical situations in which interferons represent a useful addition to already available drugs.

It is the purpose of this paper to stress another aspect of the interferon system, which is, as is my belief, that the interferon system represents an integral part of the body's defense system. Studying this system will allow deeper insight into the mechanisms by which the body defends itself against infections and perhaps tumors caused by infectious agents. The knowledge derived from these studies may then lead to better concepts of treatments or prevention.

Definition of interferons

Interferons are defined by their antiviral effect which is typical and different from antiviral effects of other compounds, for example antiviral drugs or antibodies. Pretreatment of cells by interferon causes protection against subsequent virus infection. Thus, this effect is in reality an effect on cells and requires intact cellular RNA synthesis. Interferons have a certain species restriction in that they usually protect cells of the species of which they are derived but not cells of other species. There are however exceptions to this rule. Since the antiviral effect of interferons indicates an effect on cells it is not surprising that interferons have multiple additional effects on cells.

The interferon system – multiple interferons

It is now recognized that there are a variety of different interferons, and probably there are others that have not yet been discovered. Currently, one distinguishes between three types of interferons. These have been identified in all animal species in which one has looked for them. They include: interferon alpha (IFN-α), interferon

beta (IFN-β), and interferon gamma (IFN-γ). It is well established that action of all three types of interferon commences by binding to cell surface sites which are of high affinity and selectivity [2]. One class of high affinity sites seems to be of broader specificity accommodating the various IFN-α subtypes and IFN-β, the other exclusively recognizes IFN-γ.

Interferon alpha

Interferons of the α-type are products of a multi-gene family sharing up to 80% homology with each other on the genomic level [87]. Whereas some of the genes are pseudogenes, several others are expressed. Whenever leucocytes (or lymphoblastoid cells) are induced to produce IFN-α, a number of these genes are expressed resulting in a preparation that contains a mixture of different IFN-α subtypes. It seems to be worthwhile to entertain the speculation that different types of white blood cells are producing different types of IFN-α. Perhaps the stage of differentiation is relevant in regard to the subtype of IFN-α produced. Alternatively, in the same cells several interferon genes are activated simultaneously and this may also differ between inducers.

Interferon beta

In contrast to the large number of IFN-α genes, the number of genes of IFN-β seems to be much smaller. Although data suggestive for the existence of two IFN-β genes in man have been presented, the current consensus is that there is only a single human IFN-β gene. In other animal species (bovine) there may be two. It is not known whether IFN-β is produced in vivo during viral infections. The genes coding for the human α-IFNs and for β-IFN show about 30% homology on the genomic level [87]. They are located on the same chromosome and are believed to be derived from a common ancestor gene [58,83]. In the mouse, the genes for IFN-α and IFN-β are usually expressed simultaneously thus resulting in preparations containing mixtures of both interferons. The term IFN-α/β is used to indicate this fact. However, we have recently found that a low molecular weight interferon inducer, CMA (10-carboxymethyl-9-acridanone) induces exclusively IFN-β in mouse macrophages [11].

Interferon gamma

By definition, IFN-γ is not only an interferon but also a lymphokine, since it is a product exclusively of lymphocytes. The gene coding for IFN-γ shows little if any homology with the genes for IFN-α and -β. In addition, it contains introns which are absent in the other interferon genes [30,88]. Recently, the gene of another lymphokine, interleukin-2, has been reported to share a certain degree of homology with the IFN-γ gene [26,57]. As stated above, the receptor for IFN-γ on the cell surface is distinct from the receptor common for IFN-α and -β [10]. Thus, at first glance, it appears surprising that IFN-γ shares so many biologic effects with IFN-α and -β and it makes one inclined to assume the existence of a second messenger common to all interferons. This however, is not validated by experimental data at the time of this writing.

All available evidence points to the conclusion that the production of IFN-γ is a specialized function of T-lymphocytes [56]. It has in addition been shown that the so-called 'large granular lymphocytes' are capable of producing IFN-γ (besides other lymphokines) [20]. These cells are known to act functionally as 'natural killer cells'. Their position within the lineages of the hemopoietic systems is still unclear.

It seems an interesting question why among the cells of the immune system only T-lymphocytes but not macrophages or B-cells express the IFN-γ gene. There has been a recent report that B-lymphoblastoid cell lines produce IFN-γ upon 'heat shock' [89]. This report still awaits confirmation.

Multiple interferon effects

Many of the effects of interferons have been discovered by adding interferon to tissue cultures or by injecting them into experimental animals (or more recently, into patients). It is assumed that the effects are identical when interferons are produced endogenously after infection with a virus or after injection of an inducer. From the acute side effects of interferon we have learned that they resemble the systemic symptoms of acute virus infections such as influenza (fever, chills, malaise, leukopenia, etc.) [80]. The symptoms of influenza are probably in part caused by the interferon induced and not exclusively by the virus itself.

It is now obvious that interferons have many effects on cells including effects on membranes, cytoskeleton and cellular metabolism. Some of these are still poorly understood. Others, particularly the induction of certain enzymes, have been analyzed to a considerable degree, as was competently reviewed in Ref. 4. Certain effects of interferon may influence the interaction between cells of the immune system, i.e., interferons activate macrophages for increased phagocytosis of bacteria [22] and cytotoxicity against tumor cells [62,79,92], to name but a few. Interferons also activate NK cell cytotoxicity [27]. Thus, one can imagine that interferon production by the primary effector cells leads to amplified effects on other cells. Even more importantly, interferons cause an increased expression of immunologically relevant membrane constituents such as products of the major histocompatibility locus [52,74]. Since the I-a antigens, for example, are considered to be crucial membrane molecules for interactions between immunocompetent cells, the conclusion is almost inevitable that interferons are immunoregulatory molecules of high potency.

Recently, it has been shown unequivocally that IFN-γ is one of the factors involved in driving the maturation of resting B-cells to active immunoglobulin synthesis [84]. Finally, there seems to be a differential effect of IFN-γ and the other interferons as far as the expression of histocompatibility antigens is concerned [74,95]. Whereas IFN-γ induces the expression of both class I and class II antigens in a variety of cells [97,98], the other interferons only cause expression of H-2 antigens and not of Ia-antigens [42]. Interferons have also been shown to act on the differentiation of cells, particularly on the cells of the white blood cell system [5].

Multiple producer cells of interferons

Leucocytes of various types are important interferon producers. Thus, T-lymphocytes are capable of producing IFN-α and IFN-γ [16]. They possibly also produce IFN-β, but this is established only for tumor cells of the T cell type but not for normal T cells [60]. Long-term cultures of T cells grown in the presence of (and dependent on) T cell growth factor (IL-2) are also potent producers of interferon [56,61]. As has repeatedly been shown, they produce IFN-γ. Recent studies of our laboratory have established that such lines are producing IFN-β when stimulated by CMA [85]. Resting T cells purified from spleen cell suspensions did not respond to CMA treatment with interferon production.

B lymphoblastoid cells transformed by EBV can be induced with viruses to produce IFN-α whereas this has not been established for normal B cells. Macrophages produce IFN-α when exposed to viruses [72,75]. Mouse macrophages produce IFN-β when stimulated with certain low molecular weight compounds such as CMA [11]. Probably, NK cells are also among the producer cells of interferons.

A question that has been debated for years is that concerning spontaneous ('constitutive') production of interferon. The transformed B cell lines appear to produce low levels of interferon spontaneously, whereas high titers are produced upon activation. There are only few additional examples of spontaneous interferon production in vitro [24]. There are certain diseases in which circulating interferon has been detected but this may merely indicate a yet undetected infection [19,23,36].

A variety of cells other than leucocytes can produce interferon in vitro, e.g. fibroblasts which produce IFN-β. It is not clear whether fibroblasts or other structural cells in the intact organism such as hepatocytes or muscle cells produce interferon. It may be rewarding to consider the possibility that different structural cells are capable of producing interferon and by doing so activate immune effector cells. In this sense one could envision a broad network of defense mechanisms involving not only immunocytes but other cells as well.

What evidence is there that endogenous interferon is important in defense

There has been a long-standing debate on whether endogenous interferon produced during the course of an infection is of relevance in this very infection. An argument often raised goes as follows: In some experimental infections high interferon titers are observed concomitantly with maximal virus titers, yet the fatal outcome of the infection is obvious. From these data it would appear that the interferon production associated with general virus spread is of little significance for the outcome of the infection.

However, the first indication contrary to this argument came from the experiments of Gresser [34] which documented that injection of anti-interferon serum was capable of breaking resistance of mice against virus infections. Recently, we have presented a series of experiments documenting that in at least one viral system the magnitude of the early interferon response correlated positively with resistance [99]. In this system

(herpes simplex virus, HSV), maximal local interferon titers are produced already within 2 h after infection, that is well ahead of the termination of the first round of viral replication requiring at least 8 h.

Genetic control of interferon production after virus infection

As first established by De Maeyer [17] the in vivo interferon response of mice towards virus injection is genetically controlled. There are high-producer and low-producer inbred mouse strains when for example Newcastle disease virus (NDV) is used as an in vivo inducer. However, the loci coding for high production are not generally responsible for high interferon production towards all viruses (or inducers) but they differ between viruses [18]. For example, high interferon production in response to herpes simplex virus (HSV) in mice is genetically controlled by loci different from those controlling high interferon production in response to NDV [100].

We found the situation with HSV quite interesting since, in contrast to NDV, which is apathogenic for mice, HSV is highly pathogenic for certain mouse strains whereas others are relatively resistant. There was a positive correlation between high interferon production and resistance and it is our hypothesis that resistance results from the capability to mount a high and early interferon response towards the infection. The data in the HSV system apply only to the early interferon titer. Thus, there are high titers in the resistant mice at 2 h after infection whereas at this time the titers in susceptible mouse strains are essentially zero. At later times, in fact, the differences may be the other way around, that is higher interferon titers are observed in the susceptible mouse strains eventually prone to acquire lethal encephalitis.

It is of interest to note that the interferon response of an organism is rapid. Thus, after intraperitoneal injection of virus, high interferon titers in the serum are observed already within 2 to 4 h [6] and this interferon will be cleared again within a few hours. It is an interesting problem to find out what the significance of the serum interferon is and where it is derived from. It may be simply an overspill product from other sites. Alternatively, it may be a product of circulating leukocytes. It remains a tantalizing problem to find out where the serum interferons come from and what their potential role could be. Perhaps, interferon is a molecule which is predominantly important at the local site.

Genetic control of interferon gamma production

Production of IFN-γ by T lymphocytes might also be genetically controlled. Certainly, the production of IFN-γ in mixed lymphocyte culture upon recognition of alloantigens is controlled immunogenetically [28,44]. Thus, differences both in the KD ends of H-2 as well as in the I region are capable of inducing IFN-γ production in the murine MLC [51]. Even differences in minor H-2 loci alone are sufficient to cause interferon production [78]. The human MLC is more difficult to study in regard to interferon production and most investigators have observed only low titers. Yet, the situation appears to be similar to that observed in the mouse [3,54].

Cole et al. [15] and Kirchner et al. [50] reported a novel mitogen derived from *Mycoplasma arthritidis* (MAS) that is a potent inducer of IFN-γ. This mitogen is a soluble protein obtained from the cell-free supernatant of cultured mycoplasmata and has a molecular weight of approximately 13 000. Thus far, *M. arthritidis* appears to be the only mycoplasma species elaborating the mitogen. Most excitingly, IFN-γ production in response to MAS is stringently controlled by the I-E subregion of the major histocompatibility locus of the mouse. Thus, spleen cell cultures of mouse strains unable of expressing I-E on the cell surface (e.g., C57BL/6) do not produce interferon after treatment with MAS. The response of T cells towards MAS is also dependent on accessory cells [53].

IFN-γ may be induced not only by immunologically specific stimulants but also by nonspecific mitogens. Usually, in the laboratory plant mitogens are used, such as lectins derived from beans (e.g., concanavalin A). However, as exemplified by the mycoplasma mitogen there may be mitogens in microorganisms capable of eliciting the production of IFN-γ in hosts not immune to them. The conclusion then is that IFN-γ may not only be important in specific immune reactions but also in the nonspecific primary defense. Recent concepts put major emphasis on the role of Ia-expression in the autoimmune reaction: One may then speculate that this increased expression is caused by IFN-γ which may be induced by mitogens present in certain microorganisms.

In vitro, IFN-γ is readily induced by mitogens such as PHA and Con A or by alloantigens. It has, however, been found extremely difficult to induce production of IFN-γ in the intact animal, at least in our laboratory. There has been only one exception, which is the protocol in which mice are prestimulated by BCG and subsequently injected by PPD [37,38]. One wonders whether it is at all possible to induce IFN-γ in vivo by injection of allogeneic cells. One also wonders why ten-thousands of units of IFN-α/β are found in the serum of mice after injection of an appropriate inducer, whereas it is very difficult to induce even small quantities of IFN-γ.

Cellular control of interferon production

Above, I have discussed the evidence that leucocytes may be the main producers of interferon in the intact organism. If this assumption is correct, interferon research will touch closely with immunology, i.e. the discipline that studies the biology of the white blood cells. We already know of many interactions between different types of leucocytes. Many T cell reactions are dependent on accessory cells, for example macrophages. In this context it is highly interesting that the induction of IFN-γ by MAS in T lymphocyte cultures is dependent on accessory cells [53]. Immune reactions are carefully regulated by many types of interaction and one expects to find this also for the production of interferon. Undoubtedly, many further studies will be required to delineate the immunological control of lymphokine production including interferon.

Molecular control of interferon production

We have already alluded to findings that certain types of leucocytes produce interferon. Different interferon subtypes seem to be produced by different subtypes of leucocytes. Also the inducers used in a given experimental set-up appear to be crucial. For example, at present it appears that T lymphocytes are the sole producers of IFN-γ. Since all nucleated cells of the body contain the interferon gene it will be of the greatest interest to find out what causes the interferon gene expression in certain cell types and what inhibits it in others. Interesting in this regard are leukemia cells representing 'frozen differentiation states'. It will be also interesting to find out which interferon genes are expressed in different leukemia cell lines, for example with regard to the different members of the IFN-α gene family, or IFN-γ.

Interferon as a general defense system

Interferons have been discovered initially because of their in vitro antiviral effect. It is obvious that this effect is a cellular effect in that the metabolism of the cell is changed in a way that the cell is incapable of supporting viral replication. It is, however, remarkable and speaks for the importance of the interferon system that quite a variety of different pathways exist for inhibiting the multiplication of different viruses by interferon. For example, for some viruses a correlation has been established between the enzyme cascade induced by interferons and inhibition of translation of viral proteins [4]. On the other hand, this does not apply to all viruses and for example certain RNA tumor viruses are inhibited by interferons at the stage of viral budding through the cell membrane [8]. In addition, a number of different types of antiviral mechanisms have been described, for example for bovine papilloma virus [91] and SV40 [12]. More recently, the effects of interferons on the replication of herpes simplex virus have been studied [21,29,65]. In contrast to earlier opinions replication of HSV may well be inhibited by interferon. It has been shown that the early HSV-coded β-proteins are inhibited in interferon-treated, HSV-infected tissue cultures.

Interferons have antiviral effects in vivo as well as in vitro and this effect appears to be caused in part by the activation of certain cellular defense elements [77], of which the macrophages are only one example. It is obvious, that these nonspecific defense elements are not involved exclusively in antiviral defense but in resistance against other pathogenic microorganisms. It is therefore my belief that interferons play a role in defense mechanisms of the body against a variety of different infections, including for example those caused by bacteria [46]. There has been a recent report documenting this for the infection of the mouse with intracellular bacteria [43].

Antitumor effects of interferons

Already in 1970 Gresser [32] has shown that interferon treatment inhibits tumor growth in mice. This was found not only for virus-induced tumors but also for tumors induced by chemical carcinogens. Since then, considerable efforts have been put into

the elucidation of the antitumor effects of interferons and yet they are poorly understood. Interferons have an antiproliferative effect on cells themselves [66]. Furthermore, it seems that the main contribution to the in vivo antitumor effects stems from the activation of relevant defense cells. More recently, two sets of data, that may be actually related have been presented concerning the antitumor effects of interferon. Brouty-Boyé [13] and Hicks et al. [35] have shown a reversion of the malignant phenotype upon prolonged cultivation of transformed cells in interferon-containing media. Several groups, on the other hand, have reported that the expression of oncogenes in tumor cells is reduced after interferon treatment [40,41,76]. Oncogene expression may be causing the malignant phenotype and thus, by reducing oncogene expression, interferon causes the reversion of the malignant phenotype.

The successful treatment of hairy cell leukemia with interferon [71] seems noteworthy and there are strong suggestions that the clear-cut beneficial effect is not caused by an antiproliferative effect on leukemic cells but rather by influencing differentiation by mechanisms that remain as yet unclear.

Surveillance against tumors

The issue of immune surveillance against tumors is controversial (see the competent review by Stutman [86]). Maybe, if surveillance mechanisms exist they may be represented by nonspecific aspects of the defense system and not by immunologically specific mechanisms. I have expressed the point of view that surveillance mechanisms may be operative against oncogenic DNA viruses [45]. Since interferons do have antiviral properties one may speculate that they may be operative against oncogenic DNA viruses for example human papillomaviruses [47]. There are certainly sufficient clinical data indicating that human papillomas are susceptible to in vivo treatment by exogenous interferon [63,81,96]. I would like to suggest that during immunosuppression papillomavirus infections occur with frequency because of a defect of the interferon system. The same may apply to other tumorigenic viruses.

Clinical implications

I believe that the interferon system represents a system of molecules produced mainly by white blood cells and consisting of a large number of different molecules. The activity of this system is genetically controlled by cellular interactions. I see two potential clinical implications:

(1) There may be defects in this system facilitating disease (mostly infections, perhaps tumors induced by oncogenic viruses).

(2) There may be diseases caused by dysregulation and overproduction (i.e. autoimmune disease).

Ad 1

The role of endogenous interferon in defense against infections (particularly viral)

has been argued about for years. I have been attracted by the importance of the early interferon production. This was obvious when studying infection by a virus with a long replication cycle such as HSV. In this situation peak interferon titers are observed before the first cycle of virus replication is completed [99]. Certainly, no one is assuming that interferon is an antiviral defense operating against all viruses yet there are points that are noteworthy.

From many clinical observations on the course of viral infections it has become obvious that there are differences between individual patients regarding the course of the infection even under conditions where there was identical exposure to the same virus strain. The infection may be peracute or chronic. Certain patients do not develop disease at all. Host defense elements appear to be critical for the eventual outcome of the infection and in our opinion interferon is a prime candidate among these. I speculated above that interferons are not only active against viruses but also against other types of infections. Macrophages can be activated by interferon against bacteria [46].

Furthermore, one may learn from the side effects of interferon therapy. The acute side effects have been termed the influenza-like syndrome including leukopenia, fever, chills, fatigue, etc. This has led to the suggestion that some of the symptoms of acute viral illness are not caused by the virus per se but by interferon induced in the patient. Also of high interest are the psychoneurological side effects of interferon therapy [1,55,73]. These consist of depression, apathy and similar symptoms and may in fact, be serious enough to cause interruption of the therapy. Objective changes of the EEG are also seen.

Ad 2

I have described above that interferons are potent immunoregulatory molecules and that they are in principle capable of causing autoimmune disease-like symptoms. Gresser et al. [33] have first shown that treatment of newborn mice with interferon causes glomerulonephritis similar to the one observed in autoimmune disease. Since then in a number of studies the interferon system has been linked with autoimmune diseases. Serum interferon which is not found in healthy individuals has been detected in some patients suffering from autoimmune disease [69]. There is as yet no evidence that autoimmune disease is caused by viruses but it is tempting to speculate that the interferon detected may be an indicator of a chronic viral infection.

The interferon in the serum of patients with autoimmune disease represents an unusual subtype of acid-labile IFN-α [68] (before this discovery it has been held that only IFN-γ is acid-labile). So far, to my knowledge no one has observed IFN-γ in vivo in man. In other patients one has detected (auto)antibodies against interferon in the serum [64]. Recent evidence suggests that some patients after treatment with interferon develop antibodies [90]. During routine screening one has also observed the existence of such antibodies in persons not having been treated by interferon. Finally, defects of interferon production have been observed in blood cell cultures derived from patients with certain diseases [93].

Recent theories of autoimmune disease put major emphasis on observations indicating a role of increased Ia-expression on cells early in autoimmune disease. Since it is

one of the selective effects of IFN-γ to cause an increment of Ia antigens expression, one has assumed a role of IFN-γ in the pathogenesis of autoimmune disease. One may then ask what causes the production of IFN-γ in such situations. I am intrigued noting that a mycoplasma-derived mitogen is a potent inducer of IFN-γ [15]. Maybe, similar mitogens are produced by a number of infectious agents and chronic infections by them may be causally involved in autoimmune disorders. Rheumatic diseases are particularly interesting in this respect. The hypothesis has been entertained for many years that mycoplasmata may be causally involved. Thus, *M. arthritidis* can cause arthritis in experimental animals [14]. It is therefore of particular interest that this mycoplasma contains an IFN-γ inducing mitogen.

Important among the diseases with unknown etiology are demyelinating diseases of the nervous system such as multiple sclerosis. Over and over it has been speculated that viruses are involved in their pathogenesis. Yet a solid association with a particular virus has never been found and new theories are focussing more on autoimmunity. Very intriguing concepts have been presented by Wekerle and his coworkers [25]. These are based in part on observations that IFN-γ causes Ia-expression on astrocytes, being the first cells of the brain surrounding the blood vessels. Specifically sensitized T cells may interact with the astrocytes causing Ia-expression via the production of IFN-γ. On the other hand, Vervliet et al. [93] have reported a defect of IFN-γ production in leucocyte cultures of MS patients, while the production of IFN-α was normal.

Finally, the group of psychiatric diseases, are worthy speculation in regard to the interferon system. It is now obvious, that high-dose interferon therapy after long treatment causes neurological and psychological side effects. It is tempting to speculate that in patients with psychiatric disease interferon is present and perhaps in part responsible for the symptoms. Again the detection of circulating interferon may be an indicator for an as yet undetectable chronic virus infection. So far proof is lacking for the presence of serum interferon in the patients. However, similarly as in the patients with multiple sclerosis studied by Vervliet et al. [93] we have observed a significant defect in interferon-producing ability of leucocytes from schizophrenic patients [59]. This was observed for both IFN-γ and IFN-α when a variety of interferon inducers were tested. Again, the situation appears to be complex and the data at the moment cannot be fitted in a satisfactory intellectual frame.

Conclusions

Interferons form a coherent system of molecules produced in vivo and in vitro in cell cultures. A number of interferons are now defined in molecular terms and probably besides these, others exist. The 'classical' interferons IFN-α and IFN-β are related to each other and probably derived from a common ancestor gene. The gene for IFN-γ is completely different from the latter two and so is the protein. IFN-γ is, however, related to at least one lymphokine, interleukin-2. Prominent among the interferon-producing cells are white blood cells and it has been shown that both T lymphocytes and macrophages are producers of interferons. B cells transformed by EBV are also

producing multiple subtypes of IFN-α, yet it is not known if normal B cells are capable of interferon production. The production of interferons by leucocytes puts interferon in perspective with immunological regulation and one has to assume the production of interferons to be subjected to immunoregulation. It is not known if, in addition to leucocytes, structural cells of the body such as muscle cells, liver cells, etc. do produce interferon.

Interferons have a multitude of biological effects, for example, antitumor and immunoregulatory effects. The latter include activity on B cells, and activation of macrophages and NK cells. Most importantly, interferon treatment causes enhanced expression of the products of the major histocompatibility locus. In this respect, IFN-γ is unique in that it affects class I as well as class II molecules whereas the classical interferons affect only class I molecules. Because of the central role of these molecules in immunoregulation the conclusion becomes inevitable that interferons are molecules central in immunoregulation. Since interferons are produced by leucocytes (for example, IFN-γ by T lymphocytes) their production is controlled by regulatory influences such as is the production of other products of immunocompetent cells (i.e., lymphokines). The production of classical interferons is under genetic control and so is the production of IFN-γ at least with certain inducers.

Interferons have antitumor effects, which may result from various direct and indirect activities. Thus, interferons have antiproliferative effects on cells, and activate certain elements of the defense system such as macrophages and NK cells. Furthermore, interferon treatment has been shown to reverse the malignant phenotype of tumor cells and to act on the expression of oncogenes.

It is my belief that interferons may turn out not only to have effects on tumors and virus infections but also on infections by bacteria, since interferons activate macrophages and these are of central importance in antibacterial defense.

Clearly, the interferon system appears to be an integral part of the body's defense system. The possible clinical implications of this are twofold. There may be defects in the interferon system which cause or facilitate disease. For example, defective production of IFN-γ has been described to occur in multiple sclerosis. On the other hand, dysregulation in the interferon system or hyperproduction of interferon may play a key role in autoimmunity. Thus, in lupus erythematosus, circulating interferon as well as antibodies against interferon have been found. These clinical data as well as data from animal models suggest a role of interferon in autoimmunity, but a satisfying concept yet has to emerge.

Acknowledgements

I am grateful to Ion Gresser, Fons Billiau, and Huub Schellekens for critically reading this article. Excellent secretarial assistance was provided by Ms. M. Kasamasch.

References

1 Adams, F., Quesada, J.R. and Gutterman, J.U. (1984) Neuropsychiatric manifestations of human leukocyte interferon therapy in patients with cancer. J. Am. Med. Assoc. 252, 938–941.

2 Aguet, M. and Mogensen, K.E. (1983) Interferon receptors. In: Interferon 5. Ed.: Gresser, I. Academic Press, New York, pp. 1–18.

3 Andreotti, P.E. and Cresswell, P. (1981) HLA control of interferon production in the human mixed lymphocyte culture. Hum. Immunol. 3, 109.

4 Baglioni, C. (1979) Interferon-induced enzymatic activities and their role in the antiviral state. Cell 17, 255.

5 Ball, E.D., Guyre, P.M., Shen, L., Glynn, J.M., Maliszewski, C.R., Baker, P.E. and Fanger, M.W. (1984) Gamma interferon induces monocytoid differentiation in the HL-60 cell line. J. Clin. Invest. 73, 1072–1077.

6 Baron, S. and Buckler, C.E. (1963) Circulating interferon in mice after intravenous injection of virus. Science 141, 1063.

7 Berger, R., Knapp, W. and Kirchner, H. (1984) Interferon induction in human mixed leucocyte tumor cell reactions: evidence for restriction to a certain lineage expressing glycophorin A. Int. J. Cancer 34, 39–47.

8 Billiau, A., Heremans, H., Allen, P.T., Baron, S. and De Somer, P. (1978) Interferon inhibits C-type virus at a posttranscriptional, prerelease step. Arch. Virol. 57, 205.

9 Bonnem, E.M. and Spiegel, R.J. (1984) Interferon-α: Current status and future promise. J. Biol. Responde Mod. 3, 580–598.

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

11 Brehm, G., Storch, E. and Kirchner, H. (1985) Purification and characterization of interferons induced by 10-carboxymethyl-9-acridanone in murine macrophage cultures. Nat. Immun. Cell Growth Regul., in press.

12 Brennan, M.B. and Stark, G.R. (1983) Interferon pretreatment inhibits simian virus 40 infections by blocking the onset of early transcription. Cell 33, 811.

13 Brouty-Boyé, D. (1980) Inhibitory effects of interferons on cell multiplication. In: Lymphokines. Ed.: Pick, E. Academic Press, New York, p. 99.

14 Cole, B.C. and Casell, G.H. (1979) Mycoplasma infections as models of chronic joint inflammation. Arthritis Rheum. 22, 1375.

15 Cole, B.C. and Thorpe, R.N. (1983) Induction of human γ interferons by a mitogen derived from mycoplasma arthritidis and by phytohemagglutinin: differential inhibition with monoclonal anti-HLA.DR antibodies. J. Immunol. 131, 2392.

16 Conta, B.S., Powell, M.B. and Ruddle, N.H. (1983) Production of lymphotoxin, IFN-γ, and IFN-α,β by murine T cell lines and clones. J. Immunol. 130, 2231.

17 De Maeyer, E. and De Maeyer-Guignard, J. (1968) Influence of animal genotype and age on the amount of circulating interferon induced by Newcastle disease virus. J. Gen. Virol. 2, 445.

18 De Maeyer, E., De Maeyer-Guignard, J., Hall, W.T. and Bailey, D.W. (1974) A locus affecting circulating interferon levels induced by mouse mammary tumor virus. J. Gen. Virol. 23, 209–211.

19 De Stefano, E., Friedman, R.M., Friedman-Kien, A.E., Goedert, J.J., Henriksen, D., Preble, O.T., Sonnabend, J.A. and Vilček, J. (1982) Acid-labile human leucocyte interferon in homosexual men with Kaposi's sarcoma and lymphadenopathy. J. Infect. Dis. 146, 451.

20 Djeu, J.Y., Stocks, N., Zoon, K., Stanton, G.J., Timonen, T. and Herberman, R.B. (1982) Positive self regulation of cytotoxicity in human natural killer cells by production of interferon upon exposure to influenza and herpes viruses. J. Exp. Med. 156, 1222.

21 Domke, I., Panet, A., Straub, P., Jacobsen, H. and Kirchner, H. (1985) Inhibition of replication of herpes simplex virus in mouse macrophages by interferons. J. Gen. Virol., in press.

22 Donahoe, R.M. and Huang, K.-Y. (1976) Interferon preparations enhance phagocytosis in vivo. Infect. Immun. 13, 1250.

23 Eyster, M.E., Goedert, J.J., Poon, M.-C. and Preble, O. (1983) A possible preclinical marker for the acquired immunodeficiency syndrome in hemophilia. N. Engl. J. Med. 309, 583.

24 Fischer, D.G. and Rubinstein, M. (1983) Spontaneous production of interferon-γ and acid-labile interferon-γ by subpopulations of human mononuclear cells. Cell. Immunol. 81, 426.
25 Fontana, A., Fierz, W. and Wekerle, H. (1984) Astrocytes present myelin basic protein to encephalitogenic T-cell lines. Nature 307, 273–276.
26 Fujita, T., Takaoka, C., Matsui, H. and Taniguchi, T. (1983) Structure of the human interleukin 2 gene. Proc. Natl. Acad. Sci. USA 80, 7437–7441.
27 Gidlund, M.A., Örn, A., Wigzell, H., Senik, A. and Gresser, I. (1978) Enhanced NK cell activity in mice injected with interferon and interferon inducers. Nature 273, 759–761.
28 Gifford, G.E., Tibor, A. and Peavy, D.L. (1971) Interferon production in mixed lymphocyte cell cultures. Infect. Immun. 3, 164.
29 Gloger, I. and Panet, A. (1984) Synthesis of herpes simplex virus proteins in interferon-treated human cells. J. Gen. Virol. 65, 1107–1111.
30 Gray, P.W. and Goeddel, D.V. (1982) Structure of the human immune interferon gene. Nature 298, 859.
31 Gresser, I. (1977) On the varied biologic effects of interferon. Cell. Immunol. 34, 406.
32 Gresser, I. and Bourali, C. (1970) Antitumor effects of interferon preparations in mice. J. Natl. Cancer Inst. 45, 365.
33 Gresser, I., Maury, C. and Tovey, M. (1976) Progressive glomerulonephritis in mice treated with interferon preparations at birth. Nature 263, 420.
34 Gresser, I., Tovey, M.G., Maury, C. and Bandu, M.-T. (1976) Role of interferon in the pathogenesis of virus diseases in mice as demonstrated by the use of anti-interferon serum. II. Studies with herpes simplex, Moloney sarcoma, vesicular stomatitis, Newcastle disease, and influenza viruses. J. Exp. Med. 144, 1316.
35 Hicks, N.J., Morris, A.G. and Burke, D.C. (1981) Partial reversion of the transformed phenotype of murine sarcoma virus-transformed cells in the presence of interferon: a possible mechanism for the antitumor effect of interferon. J. Cell Sci. 49, 225.
36 Hooks, J.J., Moutsopoulos, H.M., Geis, S.A., Stahl, N.I., Decker, J.L. and Notkins, A.L. (1979) Immune interferon in the circulation of patients with autoimmune disease. N. Engl. J. Med. 301, 5.
37 Huygen, K. and Palfliet, K. (1983) Strain variation in interferon γ production of BCG-sensitized mice challenged with PPD. I. CBA/Ca mice are low producers in vivo but high producers in vitro. Cell. Immunol. 80, 329–334.
38 Huygen, K. and Palfliet, K. (1984) Strain variation in interferon γ production of BCG-sensitized mice challenged with PPD. II. Importance of one major autosomal locus and additional sexual influences. Cell. Immunol. 85, 75–81.
39 Isaacs, A. and Lindenmann, J. (1957) Virus interference. I. The interferon. Proc. R. Soc. Lond. Biol. 147, 258.
40 Jonak, G.J. and Knight, E., Jr. (1984) Selective reduction of c-myc mRNA in Daudi cells by human β interferon. Proc. Natl. Acad. Sci. USA 81, 1747–1750.
41 Jonak, G.J., Anton, E.D., Fahey, D., Friedland, B.K., Cheng, Y.-S.E. and Knight, E., Jr. (1984) Interferon-mediated regulation of the c-myc oncogene expression in human cells and its relation to the inhibition of cell growth. In: The biology of the interferon system. 3rd TNO/ISIR Congr. Biol. Interferon System, Heidelberg, October 1984. Antiviral Res., Abstr. 1 No. 3, 24.
42 Kelley, V.C., Fiers, W. and Strom, T.B. (1984) Cloned human interferon-γ, but not interferon-β or -α, induces expression of HLA-DR determinants by fetal monocytes and myeloid leukemia cell lines. J. Immunol. 132, 240–245.
43 Kiderlen, A.F., Kaufmann, S.H.E. and Lohmann-Matthes, M.-L. (1984) Protection of mice against the intracellular bacterium *Listeria monocytogenes* by recombinant immune interferon. Eur. J. Immunol. 14, 964–967.
44 Kirchner, H., Zawatzky, R. and Schirrmacher, V. (1979) Interferon production in the murine mixed lymphocyte reaction. I. Interferon production caused by differences in the H-2K and H-2D region but not by differences in the I region of the M locus. Eur. J. Immunol. 9, 97.
45 Kirchner, H. (1982) Editorial: Logistics of tumor immunology. Klin. Wochenschr. 60, 37–47.
46 Kirchner, H., Digel, W. and Storch, E. (1982) Interferons and bacterial infections. Klin. Wochenschr. 60, 740–742.

47 Kirchner, H. (1984) Immunologic surveillance and human papillomaviruses. Immunol. Today 5, 272–276.
48 Kirchner, H. (1984) Interferons, a group of multiple lymphokines. Springer Sem. Immunopathol. 7, 347–374.
49 Kirchner, H. and Marcucci, F. (1984) The producer cells of interferon in leucocyte cultures. In: Interferon, Volume 2; Interferon and the Immune System. Eds.: Vilcek, J. and De Maeyer, E. Elsevier Science Publishers B.V., Amsterdam, pp. 8–34.
50 Kirchner, H., Nicklas, W., Giebler, D., Keyssner, K., Berger, R. and Storch, E. (1984) Induction of interferon gamma in mouse spleen cells by culture supernatants of mycoplasma arthritidis. J. Interferon Res. 4, 389–397.
51 Landolfo, S., Marcucci, F., Schirrmacher, V. and Kirchner, H. (1981) Characteristics of alloantigens and cellular mechanisms responsible for γ IFN production in primary murine MLC. J. Interferon Res. 1, 339.
52 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 78, 1284.
53 Lynch, D.H., Gurish, M.F., Cole, B.C. and Daynes, R.A. (1983) T cell proliferative responses to a mitogen derived from mycoplasma arthritidis are controlled by the accessory cells. J. Immunol. 131, 1702.
54 Manger, B., Zawatzky, R., Kirchner, H. and Kalden, J.R. (1981) Interferon production in the human mixed lymphocyte culture. Transplantation 32, 149.
55 Mattson, K., Niiranen, A., Iivanainen, M. and Farkkila, M. (1983) Neurotoxicity of interferon. Cancer Treatment Rep. 67, 958.
56 Marcucci, F., Waller, M., Kirchner, H. and Krammer, P. (1981) Production of immune interferon (IFN-γ) by murine T cell clones from long-term cultures. Nature 291, 79.
57 Mita, S., Maeda, S., Obaru, K., Nishino, N., Shimada, K., Hirano, T., Onoue, K., Ogawa, T. and Ogawa, H. (1983) Isolation and characterization of a human interleukin 2 gene. Biochem. Biophys. Res. Commun. 117, 114–121.
58 Miyata, T. and Hayashida, H. (1982) Recent divergence from a common ancestor of human IFN-α genes. Nature 295, 165.
59 Moises, H.W., Schindler, L., Leroux, M. and Kirchner, H. (1985) Defect of interferon production in leucocyte cultures of schizophrenic patients. Acta Psych. Scand., 72, 45.
60 Morris, A.G., Morser, J. and Meager, A. (1982) Spontaneous production of gamma interferon and induced production of beta interferon by human T-lymphoblastoid cell lines. Infect. Immun. 35, 533.
61 Nathan, I., Groopman, J.E., Quan, S.G., Bersch, N. and Goide, D.W. (1981) Immune (γ) interferon produced by a human T-lymphoblast cell line. Nature 292, 842.
62 Nathan, C.F., Prendergast, T.J., Wiebe, M.E., Stanley, E.R., Platzer, E., Remold, H.G., Welte, K., Rubin, B.Y. and Murray, H.W. (1984) Activation of human macrophages. Comparison of other cytokines with interferon-γ. J. Exp. Med. 160, 600–605.
63 Niimura, M. (1983) Intralesional human fibroblast interferon in common warts. J. Dermatol. 10, 217–220.
64 Panem, S., Check, I.J., Henriksen, D. and Vilček, J. (1982) Antibodies to gamma-interferon in a patient with systemic lupus erythematosus. J. Immunol. 129, 1.
65 Panet, A. and Falk, H. (1983) Inhibition by interferon of herpes simplex virus thymidine kinase and DNA polymerase in infected and biochemically transformed cells. J. Gen. Virol. 64, 1999–2006.
66 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.
67 Pestka, S. (1983) The human interferons – from protein purification and sequence to cloning and expression in bacteria: before, between, and beyond. Arch. Biochem. Biophys. 221, 1.
68 Preble, O.T., Black, R.J., Friedman, R.M., Klippel, J.H. and Vilček, J. (1982) Systemic lupus erythematosus: presence in human serum of an unusual acid-labile leukocyte interferon. Science 216, 429.
69 Preble, O.T. and Friedman, R.M. (1983) Interferon-induced alterations in cells: relevance to viral and nonviral diseases. Lab. Invest. 49, 4.
70 Quesada, J.R. (1983) Interferons in cancer research – an update. Cancer Bull. 35, 30.

71 Quesada, J.R., Hersh, E.M. and Gutterman, J.U. (1984) Therapy of hairy cell leukemia with alpha-interferon. In: Biology of the Interferon System. 3rd TNO/ISIR Congr. Biol. Interferon System, Heidelberg, October 1984. Antiviral Res., Abstr. 1 No. 3, 34.
72 Roberts, N.J., Douglas, R.G., Simons, R.M. and Diamond, M.E. (1979) Virus-induced interferon production by human macrophages. J. Immunol. 123, 365.
73 Rohatiner, A.Z.S., Prior, P.R., Burton, A.C., Smith, A.T., Balkwill, F.R. and Lister, T.A. (1983) Central nervous system toxicity of interferon. Br. J. Cancer 47, 419.
74 Rosa, F. and Fellous, M. (1984) The effect of gamma-interferon on MHC antigens. Immunol. Today 5, 261–262.
75 Saksela, E., Virtanen, I., Hovi, T., Secher, D.S. and Cantell, K. (1983) Monocyte is the main producer of human alpha interferons following Sendai virus induction. Proc. Med. Virol. 30, 3.
76 Samid, D., Chang, E.H. and Friedman, R.M. (1984) Biochemical correlates of phenotypic reversion in interferon-treated mouse cells transformed by a human oncogene. Biochem. Biophys. Res. Commun. 119, 21–28.
77 Schellekens, H., Weimar, W., Cantell, K. and Stein, R. (1979) Antiviral effect of interferon in vivo may be mediated by the host. Nature 270, 742.
78 Schirrmacher, V., Landolfo, S., Zawatzky, R. and Kirchner, H. (1981) Immunogenetic studies on the resistance of mice to highly metastatic DBA/2 tumor cell variants. Invasion Metastasis 1, 175.
79 Schreiber, R.D. (1980) Identification of gamma-interferon as a murine macrophage-activating factor for tumor cytotoxicity.
80 Scott, M., Secher, D.S., Flowers, D., Bate, J., Cantell, K. and Tyrrell, D.A. (1981) Toxicity of interferons. Br. Med. J. 282, 1345.
81 Scott, G.M. (1983) Papillomas. In: Interferon and Cancer. Ed.: Sikora, E. Plenum Press, New York, pp. 153–168.
82 Seghal, P.B. and Sagar, A.D (1980) Heterogeneity of poly (I) poly (C)-induced human fibroblast mRNA species. Nature 288, 95.
83 Shows, T.B., Sakaguchi, A.Y., Naylor, S.L., Goeddel, D.V. and Lawn, R.M. (1982) Clustering of leucocytes and fibroblast interferon clones on human chromosome 9. Science 218, 373.
84 Sidman, C.L., Marshall, J.D., Schultz, L.D., Gray, P.W. and Johnson, H.M. (1984) γ-interferon is one of several direct B cell-maturing lymphokines. Nature 309, 801–803.
85 Storch, E., Kirchner, H., Brehm, G., Hüller, K. and Marcucci, F. Production of interferon beta by murine T cell lines induced by 10-carboxymethyl-9-acridanone, Scand. J. Immunol., in press.
86 Stutman, O. (1977) Immunologic surveillance. In: Origins of Human Cancer. Eds.: Hiatt, H.H., Watson, J.D. and Winsten, J.E. Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, pp. 729–750.
87 Taniguchi, T., Mantei, N., Schwarzstein, M., Nagata, S., Muramatsu, M. and Weissmann, C. (1980) Human leucocyte and fibroblast interferons are structurally related. Nature 285, 547.
88 Taniguchi, T., Matsui, H., Fujita, T., Takaoka, C., Kashima, N., Yoshimoto, R. and Hamuro, J. (1983) Structure and expression of a cloned cDNA for human interleukin-2. Nature 285, 547.
89 Taylor, M.W., Long, T., Martinez-Valdez, H., Downing, J. and Zeige, D. (1984) Induction of γ-interferon activity by elevated temperatures in human B-lymphoblastoid cell lines. Proc. Natl. Acad. Sci. USA 81, 4033–4036.
90 Trown, P.W., Kramer, M.J., Dennin, R.A. Jr., Connell, E.V. and Palleroni, A.V. (1983) Antibodies to human leucocyte interferon in cancer patients. Lancet 1, 81.
91 Turek, J.P., Byrne, J.C., Lowy, D.R., Dvoretzky, I., Friedman, H.M. and Howley, P.M. (1982) Interferon induces morphologic reversion with elimination of extrachromosomal viral genomes in bovine papillomavirus-transformed mouse cells. Proc. Natl. Acad. Sci. USA 79, 7914–7918.
92 Varesio, L., Blasi, E., Thurman, G.B., Talmadge, J.E., Wiltrout, R.H. and Herberman, R.B. (1984) Potent activation of mouse macrophages by recombinant interferon-γ. Cancer Res. 44, 4465–4469.
93 Vervliet, G., Carton, H., Meulepas, E. and Billiau, A. (1984) Interferon production by cultured peripheral leucocytes of MS patients. Clin. Exp. Immunol. 58, 116–126.
94 Vilček, J., Henriksen-Destefano, D., Robb, R.J. and Le, J. (1985) Interleukin-2 as the inducing signal for interferon-gamma in peripheral blood leukocytes stimulated with mitogen or antigen. In: The Biology of the Interferon System, 1984. Eds.: Kirchner, H. and Schellekens, E. Elsevier Science Publishers, Amsterdam, pp. 385–396.

95 Wallach, D., Fellous, M. and Revel, M. (1982) Preferential effect of γ interferon on the synthesis of HLA antigens and their mRNAs in human cells. Nature 299, 833.

96 Whisnant, J. (1985) Interferon treatment of juvenile laryngeal papillomas: analysis of risk/benefit for future trials. In: Biology of the Interferon System 1985. Eds.: Kirchner, H. and Schellekens, H. Elsevier Biomedical Publishers B.V., Amsterdam, in press.

97 Wong, G.H.W., Clark-Lewis, I., McKimm-Breschkin, J.L., Harris, A.W. and Schrader, J.W. (1983) Interferon-γ induces enhanced expression of Ia and H-2 antigens on B lymphoid, macrophage and myeloid cell lines. J. Immunol. 131, 788.

98 Wong, G.H.W., Clark-Lewis, I., Harris, A.W. and Schrader, J.W. (1984) Effect of cloned interferon-γ on expression of H-2 and Ia antigens on cell lines of hemopoietic, lymphoid, epithelial, fibroblastic and neuronal origin. Eur. J. Immunol. 14, 52–56.

99 Zawatzky, R., Hilfenhaus, J., Marcucci, F. and Kirchner, H. (1981) Experimental infection of inbred mice with herpes simplex virus. I. Investigation of humoral and cellular immunity and of interferon induction. J. Gen. Virol. 53, 31.

100 Zawatzky, R., Kirchner, H., DeMaeyer-Guignard, J. and DeMaeyer, E. (1982) An X-linked locus influences the amount of circulating interferon by herpes simplex virus type 1 (HSV-1) induced in the mouse. J. Gen. Virol. 63, 325.