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How Does Interferon Inhibit Tumour Growth? [and Discussion]

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How does interferon inhibit tumour growth?

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Interferon can inhibit tumour growth in experimental animals and in some patients with benign and malignant tumours. There is experimental evidence to suggest that several mechanisms may be involved: a direct effect on the tumour or an indirect effect via the host, or both. Thus, interferon may slow the rate of tumour cell multiplication and this may lead to cell death. Interferon may induce changes in the cell surface rendering tumour cells more sensitive to host defence mechanisms. Interferon may induce reversion in the phenotype of tumour cells. Interferon may stimulate specific and non-specific humoral and cellular host mechanisms. The relative importance of these different effects of interferon may vary depending on the host and the particular tumour.

The title of my talk is phrased as a question. It is perhaps an unfair title because I am assuming that you do accept that interferon does indeed inhibit tumour growth. I shall try first to trace the origin of the observation that interferon inhibits tumour growth, and then touch on the evolution of our understanding of interferon's biologic role. Lastly, I shall try to give some answers – all incomplete – to the question posed: How does interferon inhibit tumour growth?

In 1965 we began a series of experiments to determine whether interferon could inhibit viral-induced leukaemias in mice. It was thought at the time that the increase in the number of leukaemic cells in mice was related to the continued multiplication of the leukaemia-inducing viruses (Friend and Rauscher viruses). Our reasoning was simple. These leukaemias resembled subacute or chronic viral infections. Interferon was an antiviral substance. If we injected enough interferon repeatedly throughout the course of the disease, we might diminish viral multiplication and thus diminish the evolution of the leukaemic process. There were, however, two seemingly good reasons not to do the experiment. First, it was believed that interferon would only act prophylactically – i.e. before the virus was injected into the mouse. Secondly, extrapolating from the amounts of interferon necessary to protect cells in culture, it was deemed technically difficult at the time to prepare enough interferon to affect the course of a subacute or a chronic viral infection. We disregarded these pessimistic considerations, and using a technique described by Finter (1964) we prepared large quantities of mouse brain interferon. We became a mouse brain interferon factory. After tenfold concentration, the interferon-containing brain of one mouse provided a single dose for one leukaemic mouse. We were able to show that the daily administration of these concentrated mouse brain interferon preparations, but not the concentrated normal brain preparations, inhibited all the different manifestations of the Friend and Rauscher leukaemias in mice and increased mouse survival (Gresser *et al.* 1966, 1967*a*, *b*, *c*, *d*, 1968). Interferon treatment could even be initiated 1 week after viral inoculation (at a time when the spleens were already enlarged) and still significantly inhibit the evolution of the leukaemic process (Gresser *et al.* 1967*d*). There was a one-hundredth the amount of virus in the spleens of interferon treated mice than in untreated mice (Gresser *et al.*

1967*c*, *d*). It seemed probable therefore that continued repression of viral multiplication by the repeated administration of interferon was related to the reduction in the size and number of foci of Friend cells observed in the spleens of mice treated with interferon (Gresser *et al.* 1967*c*, *d*). Nevertheless, in a CIBA Symposium on Interferon in 1967 we stated, 'Although it seems likely to us that interferon acted by repressing viral multiplication and thus cellular transformation, it should be emphasized that a direct action of interferon on virus-infected transformed cells has not been excluded' (Gresser *et al.* 1967*c*).

To test this possibility, we decided to determine whether interferon could exert an antitumour effect in mice injected with a transplantable tumour rather than with an oncogenic virus. When mice are injected with a transplantable tumour, the tumour cells multiply in the peritoneal cavity or subcutaneously and kill the mice. No virus is involved. Half of the tumour-inoculated mice were to be treated daily with mouse brain interferon, and the other half with the control brain preparation. We undertook this experiment with a bias. We expected interferon to prove ineffective. The absence of an inhibitory effect of interferon on the growth of a transplantable tumour would support our contention that interferon acted in the viral leukaemias by inhibiting viral multiplication. Lampson *et al.* (1963) had in fact shown that chick interferon could inhibit Rous virus-induced sarcomas when injected before viral inoculation, but was ineffective when injected even 6 h after viral inoculation. Contrary to our predictions, interferon very effectively inhibited the growth of a transplantable tumour in mice (Gresser *et al.* 1969). We then showed in the ensuing years that concentrated brain interferon preparations, and then, later, semi-purified cell culture interferon preparations markedly inhibited the growth of a wide variety of transplantable tumours of different origins – viral, chemical carcinogen induced, or spontaneously appearing; tumours injected intraperitoneally in an ascitic form or subcutaneously as a solid tumour (Gresser & Bourali 1969, 1970; Gresser *et al.* 1970*a*). Antitumour effects were observed in syngeneic tumour mouse systems and in all strains of mice. Interferon inhibited the growth of the primary tumour and the formation of pulmonary metastases (Gresser & Bourali 1972). Again it was necessary to inject interferon repeatedly. A few injections of interferon at the time of tumour inoculation did not suffice. Optimal effects were obtained when contact between interferon and tumour cells was maximal.

In our early experiments we were of course aware that our interferon preparations were crude and that it was incumbent upon us to show that interferon itself was the responsible antitumour factor. Without listing the evidence, suffice it to say that over the years the accumulated evidence convinced us that interferon was indeed the active factor. Although we were convinced, others were not convinced, and for many years these antitumour effects of interferon were questioned. It was held by many that such antitumour activity as was present was due to non-interferon impurities in the preparations, and not to interferon. In 1969 we published our first article on the increased survival of tumour-inoculated mice treated with crude concentrated mouse brain interferon preparations (Gresser *et al.* 1969). Ten years later we published results showing that very highly purified interferon (homogeneous in polyacrylamide gels in SDS) prepared in collaboration with Edward & Jaqueline de Maeyer (1978) inhibited the growth of a transplantable tumour to the same extent as the semi-purified interferon of comparable antiviral titre (Gresser *et al.* 1979). I believe that we can now accept that interferon itself can exert an antitumour effect.

Since interferon inhibited the growth of transplantable tumours, we were obliged to consider the possibility that interferon was not exclusively an antiviral substance. I should therefore like

to review the development of the concept that interferon characterized initially as an antiviral substance does in fact exert other biological effects. It is necessary to stress this concept before we try to understand how interferon can inhibit tumour growth.

Probably the first indication that interferon exerted an activity other than inhibition of viral multiplication was the observation of Burke & Isaacs in 1958 that incubation of cells with interferon could increase the subsequent production of interferon, a phenomenon called 'priming'. But I believe it was only in 1971 that Stewart and his co-workers clearly showed that this activity could be distinguished from the antiviral activity of interferon (Stewart *et al.* 1971). In 1961 I showed that crude human interferon preparations altered the morphology of human amnion cells (Gresser 1961) and in 1962 Paucker, Cantell & Henle showed that crude mouse interferon preparations inhibited the multiplication of mouse L cells in suspension culture (Paucker *et al.* 1962). I am sorry to say that neither of these observations was immediately pursued to its logical conclusion, i.e. that interferon could affect cells in interesting and different ways. The moral is obvious. It is not sufficient to make a novel observation or have a good idea: one has to have the tenacity to hold on to the dragon's tail. Then, in the mid-1960s, several articles were published casting doubt on the validity of these observations and their interpretation (Baron *et al.* 1966; Levy & Merigan 1966). Most investigators were satisfied. Interferon was an antiviral substance, and it did not affect host cell metabolism. It somehow selectively inhibited the multiplication of DNA- and RNA-containing viruses. All other effects could be attributed to non-interferon contaminating substances. But for some of us this dogma was not convincing. It seemed to us unlikely that a cellular protein that inhibited such a wide range of viruses should not affect the host cell in some other manner. In investigating the inhibitory effect of interferon on the growth of transplantable tumours, we were forced to consider the possibility that interferon could in fact inhibit the multiplication of tumour and normal cells in culture. Again, it took almost 10 years of effort from our laboratory, and from the laboratories of an increasing band of 'believers', to demonstrate to the satisfaction of the majority that interferon can inhibit cell division *in vitro* and *in vivo*. There are now over 100 articles reporting that interferons α, β and γ inhibit the division of both malignant and normal cells (Brouty-Boyé 1980). Mouse and human interferon purified to homogeneity have been shown to exert this effect as well as human leucocyte interferon produced in bacteria.

Interferon can also inhibit or enhance the synthesis of specific substances and it can modify the expression of surface antigens (Gresser 1977*a*, *b*). In short, the interferon-treated cell is an altered cell, altered in its structure and in its behaviour. Inhibition of viral multiplication appears to be only one manifestation of the effect of interferon on cells. Space does not permit me to list all the different effects of interferon on cells *in vitro* and *in vivo* but these have been reviewed elsewhere (Gresser 1977*a*; Gresser & Tovey 1978; Stewart 1979).

From these observations, I think we can predict that the antitumour effects of interferon may also be multiple. On the one hand interferon may act in some manner directly on the tumour cell and on the other it may also affect the host's ability to inhibit the growing tumour (table 1).

I do not wish to minimize the possibility that some of the antitumour effects of interferon may be mediated by inhibition of viral multiplication. In man the most striking antitumour effect of interferon described so far has been in patients with laryngeal papilloma (Haglund *et al.* 1981). Under interferon treatment even voluminous tumour masses regress and tumour regrowth can be prevented. Is this because the laryngeal papilloma is inherently benign or because it is of viral origin? Animal tumours harbour viruses, and tumour growth may be

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Table 1. Possible mechanisms of the antitumour effects of interferon

(*a*) direct effects of interferon on tumour cells	(*b*) effects of interferon on the host
(1) inhibition of tumour cell multiplication	(1) effector cells
(2) interferon-induced alterations in cells, which may affect their behaviour	(2) antibody formation
(3) effect of interferon on the production of factors by tumour cells	(3) non-specific mechanisms
(4) reversion of the transformed and malignant phenotype by interferon	(4) interaction between stroma and tumour

dependent on some viral function that is interferon sensitive. I shall assume, however, that there are instances in which tumour growth is independent of any viral activity and that inhibition of tumour growth by interferon is mediated by mechanisms other than its antiviral activity.

Let us consider first that interferon may act directly on the tumour cell. This effect may be manifested in different ways. First, as I have just indicated, interferon may inhibit tumour cell division. In most systems, interferon does not block cells in a given phase of the cycle, but slows the growth rate by prolonging the overall generation time (Collyn d'Hooghe *et al.* 1977). Although interferon is usually not directly cytocidal, inhibition of cell multiplication can be associated with cell death. The results of experiments with tumour cells adapted to grow in chemostat culture suggested that cell death may result from a reduction of the growth rate to a level incompatible with cell viability (Tovey & Brouty-Boyé 1979). It is important to emphasize that the inhibitory effect of interferon on tumour cell multiplication does not appear to be specific, since the division of normal cells is also inhibited (Lindahl *et al.* 1971).

The second point to stress is that interferon induces alterations in tumour (and normal) cells that may affect their behaviour (table 2). These cells may therefore respond differently to a variety of host humoral factors or effector cells as well as to a variety of foreign substances. Since the surface of these cells is altered, transport of vital substances may be modified (Brouty-Boyé & Tovey 1978).

Table 2. Different manifestations of interferon action on cells that may affect their behaviour

membrane structure	cytoskeleton
expression of cell-surface antigens	morphology
receptors for lectins	cell mobility
surface charge	cell division

Tumours secrete a variety of factors ('oncotrophins') (Gresser 1977*b*) that may be important in influencing the rate at which the tumour grows, by directly stimulating tumour cell multiplication, depressing the host immune response, inducing vascularization of the tumour, etc. Interferon may inhibit or enhance the production of a variety of substances by tumour cells.

I should now like to invoke a fourth possibility: that interferon treatment can induce a reversion of the transformed and malignant phenotype to a more normal phenotype. For the moment this possibility rests on the results of cell culture experiments. For example, X-ray transformed cells passaged with interferon showed a progressive reversion of the transformed phenotype, exemplified by changes in morphology, distribution of cytoskeletal structures, saturation density and a loss of tumorigenicity (Brouty-Boyé & Gresser 1981). It would seem of considerable interest to determine in appropriate experimental systems whether interferon treatment of a tumour-bearing animal is also associated with an attenuation or reversion of the

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malignant phenotype. Reversion of the tumour phenotype is observed with plant tumours. The possibility of inducing the reversion of tumours in man warrants serious consideration.

I wish now to turn our attention to the possible effects of interferon on the host that may mediate the antitumour effects of interferon. Our interest in this possibility stemmed from experiments that showed that interferon clearly inhibited the growth of the L1210 lymphoma in mice (Gresser & Bourali 1970) and the multiplication of these lymphoma cells in culture (Gresser *et al.* 1970*b*). We selected a subline of these cells completely resistant to the biological effects of interferon (Gresser *et al.* 1974). We know now that these cells are resistant because labelled interferon does not bind *specifically* to receptors at the cell surface (Aguet 1980; Aguet & Blanchard 1981). To our surprise we found that interferon treatment protected mice injected with either the interferon-sensitive or the interferon-resistant cells (Gresser *et al.* 1972; Gresser & Bourali 1973). Again we had set out with a bias: to show that interferon would protect only those mice injected with interferon-sensitive cells, and not mice injected with the resistant cells. Such a result would permit us to conclude that interferon exerted an antitumour effect by acting directly on the tumour cell. Instead, we found that interferon also protected mice injected with the interferon-resistant cells. The experiments were repeated, varying a number of conditions. The results were the same: interferon could protect mice injected with L1210 lymphoma cells that were completely resistant to even 10^6 interferon units/ml. These results suggested to us that at least part of interferon's antitumour effect in this experimental systems was host-mediated.

How might interferon exert an antitumour effect via the host? I think it is a good prediction that there are mechanisms operative in a host bearing an autochthonous tumour that may restrain tumour growth. Both specific cellular and humoral mechanisms have been invoked as well as non-specific mechanisms, and the interaction of interferon with these mechanisms has received considerable attention.

Interferon has been shown to enhance the cytotoxicity of sensitized T lymphocytes (Lindahl *et al.* 1972) and Natural Killer (NK) cells for tumour target cells (Saksela 1981) and phagocytosis of tumour cells by macrophages. There are now several reports suggesting that interferon injected into a malignant melanoma or into a brain tumour of patients resulted in a marked lymphocytic infiltrate. The literature on the enhancing effect of interferon on NK cell activity *in vitro* and *in vivo* is already awesome (Saksela 1981). At the risk of going against the current fashion, I would doubt, however, that there is a given cell population destined to prevent autochthonous tumour growth, or that the antitumour effects of interferon can be explained by enhancement of NK activity.

I have listed production of antibody in table 1 as a possibility, but I am not aware of any work on the effect of interferon on the production of antibody to tumour-associated antigens.

Interferon can influence the production by host cells of prostaglandins, histamine and hormones. It has recently been shown that injection of normal volunteers with highly purified human interferon induces fever, leucopenia and a variety of unpleasant symptoms characteristic of acute viral disease (Scott *et al.* 1981). Some of these effects may be associated with the release of pharmacologically active substances. It is entirely possible that some of these effects also contribute to the antitumour action of interferon.

Lastly, I think the microenvironment of the tumour, the interaction of the growing tumour with the surrounding stroma is a virtually unexplored but a possibly important field for investigation. Histopathologists are well aware of the importance of the host's reaction to the tumour, but we have little information on how the direct contact of tumour cells with

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surrounding normal cells influences the growth of the tumour. For example, Diamandopoulos has presented evidence that the 'tissue environment that neoplastic lymphocytes encounter during circulation and/or proliferation regulates their subsequent behaviour in the intact host' (Diamandopoulos 1978). I think it is also a good possibility that interferon influences this interaction of tumour with the stroma.

I shall give one example from cell culture experiments. X-irradiation of normal C3H mouse cells results in the emergence of foci of transformed cells. It can be shown that the presence of normal C3H cells exerts an inhibitory effect on the emergence of these foci (Bertram 1977). When interferon was added to these X-irradiated cultures, it actually *enhanced* the emergence of foci of transformed cells (Brouty-Boyé & Little 1977). In investigating this phenomenon it appeared that interferon appeared to exert a greater inhibitory effect on the multiplication of normal cells than on the multiplication of transformed cells. Thus, the restraining effect of normal cells on tumour cell multiplication was diminished.

I should have liked to conclude the discussion of the mechanisms of the antitumour effects of interferon with a figure illustrating the perfect integration of all the different possible effects I have discussed. For the present, however, it is impossible to assess the relative importance of these different effects and to state with any assurance whether the antitumour effect of interferon is exerted predominantly on the tumour cells themselves or on the host. Perhaps the answer depends on the tumour, the host and a variety of factors, and both mechanisms are not mutually exclusive. Although there is evdence for a host-mediated component, experiments show that human IFN-α or β inhibits human tumours grafted into nude mice and this is evidence that there is a direct effect on the tumour.

I have traced some of the meanderings of experimental studies on the antitumour effects of interferon. I have not even touched on the main question that scientists and non-scientists must ask. How effective will interferon be as an antitumour substance, alone or in combination with other therapeutic regimens? The availability in the near future of large amounts of cloned interferon will permit testing of its efficacy in different patients with different benign and malignant tumours. If interferon proves of some benefit, it will then become evident to a larger group of scientists that it is worth while and necessary to understand the mechanisms of the antitumour effects of interferon. This is the way that most of us operate: 'necessity is the mother of invention'.

A speaker may not have the last word, but in closing he is usually permitted a prediction. It makes no difference, since whether right or wrong his predictions are often interred with his bones. I will predict that once more, man will behave even better than a mouse, and interferon will prove to exert a significant antitumour effect in some patients with some malignancies, and will prove a clinically useful drug.

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Discussion

Sir Michael Stoker, F.R.S., suggested that it could be that interferons kill malignant cells only by slowing growth, because normal cells do not die when their growth is retarded.

It was reported that F. Balkwill at I.C.R.F. was separating the effect of the direct and host-mediated effect on tumours by using nude mice bearing human breast tumours, and monitoring 2-5A and NK cells and tumour growth in response to cloned human and mouse interferons.

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