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ANTITUMOR EFFECTS OF INTERFERON

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Abstract

Both natural and recombinant interferons have shown definite antitumor activity in some patients with some malignancies. The history of the development of interferon as an antitumor agent is reviewed, with special attention to its use in mice bearing 'spontaneously' appearing tumors and in mice injected with tumorigenic viruses or transplantable tumor cells. Interferon can inhibit the growth of primary tumors as well as the development of metastases. These experimental results have provided some indications as to the probable optimal regimens of interferon administration in man. Although the mechanisms of interferon's antitumor activity are unknown, it seems likely that interferon can act directly on the tumor cells as well as on the tumor bearing host.

Key words: Interferons, antitumor effects, animal studies, review.

It is now generally accepted that interferons can exert some antitumor activity in some patients with some tumors (1). The extent of the antitumor effects of interferon has been variable: some patients have had a complete or partial remission, whereas therapy was apparently ineffective in other patients. We do not know whether this difference in response of patients with a given histologic type of tumor reflects differences in the biology of these tumors or differences in the responses of different individuals to interferon. Several common cancers do not yet appear to be amenable to interferon therapy alone; pulmonary, gastric, colonic, prostatic and breast cancer. We do not know why this is so.

How does interferon exert an antitumor effect? Most of our information comes from cell culture experiments or experiments in mice, and these may or may not be relevant to patients bearing autochthonous tumors. I will assume that these experimental results have some relevance and try to present the state of our current understanding of the various possible mechanisms responsible for the antitumor actions of interferon. I shall try first to trace the origin of the observation that interferon inhibits tumor 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 tumor growth?

In 1965 we began a series of experiments to determine whether interferon could inhibit viral-induced leukemias in mice (2–5). It was thought at the time that the increase in the number of leukemic cells in mice was related to the continued multiplication of the leukemia-inducing viruses (Friend and Rauscher viruses). Our reasoning was simple. These leukemias 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 leukemic 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. Nevertheless, using a technique described by Finter (6) we prepared large quantities of mouse brain interferon and were able to show that 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 leukemias in mice and increased mouse survival (2–5). There was one-hundredth the amount of virus in the spleens of interferon treated

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mice than in the spleens of untreated mice (4, 5). 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 (4). We also showed that daily administration of interferon for a year markedly retarded the development of the 'spontaneously appearing' lymphoma in AKR mice and increased survival time (7).

Although this paper concerns the results of experimental studies I should like here to introduce a comment on the clinical relevance of these early studies. Influenced by these results Hans Strander of the Karolinska Hospital in 1971 began a very important series of clinical studies on patients with different malignancies using leukocyte interferon prepared in the laboratory of Kari Cantell in Helsinki. He first chose to use interferon in patients with osteosarcoma (8) for several reasons: 1) at the time there was no effective treatment for this cancer; 2) the natural evolution of the disease was well known so that any effect could be compared to historical control groups; and 3) a viral etiology of this tumor was suspected and it was presumed that if interferon had any beneficial effect it would act as an antiviral agent. Although in retrospect there have been some criticisms of these seminal studies, in my opinion this criticism is not well founded. In view of our knowledge at the time and the great scepticism that was then prevalent that interferon therapy would be of any benefit it would not have been possible to randomize the patients in different treatment groups. There was no effective treatment of osteosarcoma. In fact it was because the initial results of these studies were so encouraging (compared to historical controls) that Strander, Cantell and their colleagues extended their clinical trials to include patients with Hodgkin's disease (9) and multiple myeloma (10). For many years their careful clinical results did not receive the attention and respect they deserved and virtually all clinical trials of interferon in patients with different malignancies were carried out in Sweden by Strander and his colleagues with interferon provided by Kari Cantell (11). If laboratory studies influenced clinicians, there is no question that the preliminary encouraging results of Strander and his colleagues strongly influenced and encouraged laboratory scientists. A few of us followed very closely the results of these early clinical trials and persisted in our research despite considerable criticism due to the clinical impression that interferon was of benefit to patients. I do not mean to imply that this was the only measure of interferon's interest to the scientific community, but it was an important one, and should not be underestimated.

To return to the mouse. Although at that time it seemed likely that interferon acted in the various viral leukemias of mice by inhibiting viral multiplication, we had not ruled out the possibility that interferon acted in some manner directly on the virus-induced transformed cells themselves. To test this possibility, we determined whether interferon could exert an antitumor effect in mice injected with a transplantable tumor rather than with an oncogenic virus. When mice are injected with a transplantable tumor, the tumor cells multiply in the peritoneal cavity or subcutaneously and kill the mice. No virus is involved. 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 tumor would support our contention that interferon acted in the viral leukemias by inhibiting viral multiplication. Lampson and his colleagues had in fact shown that chick interferon could inhibit Rous virus-induced sarcomas when injected before viral inoculaton, but was ineffective when injected even 6 h after viral inoculation (12). Contrary to our predictions, interferon very effectively inhibited the growth of transplantable tumors in mice (13–16). We then showed in the ensuing years that concentrated partially purified interferon preparations, and then, later, highly purified interferon α/β (17) markedly inhibited the growth of a wide variety of transplantable tumors of different origins—viral, chemical carcinogen induced, or spontaneously appearing tumors; tumors injected intraperitoneally in an ascitic form or subcutaneously as a solid tumor. Antitumor effects were observed in syngeneic and allogeneic tumor mouse systems and in all strains of mice as well as in athymic nu/nu mice. Interferon inhibited the growth of the primary tumor and also the formation of pulmonary metastases (18).

Since interferon inhibited the growth of transplantable tumors, we were obliged to consider the possibility that interferon was not exclusively an antiviral substance. I should therefore like to make a few comments on 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 tumor growth.

Probably the first indication that interferon exerted an activity other than inhibition of viral multiplication was the observation of Burke & Isaacs in 1958 (19) 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 co-workers clearly showed that this activity could be distinguished from the antiviral activity of interferon (20). In 1961 I showed that crude human interferon preparations altered the morphology of human amnion cells (21) and in 1962 Paucker, Cantell and Henle showed that crude mouse interferon preparations inhibited the multiplication of mouse L cells in suspension culture (22). 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. Then, in the mid 1960s, several articles were published casting doubt

on the validity of these observations and their interpretation (23, 24). 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 tumors, we were forced to consider the possibility that interferon could in fact inhibit the multiplication of tumor and normal cells in culture. We confirmed the original work of Paucker et al. (22) showing that interferon could inhibit the multiplication of cells in culture. Over a period of 10 years we analyzed the effect of mouse and human interferons on the multiplication of normal and transformed murine and human cells in culture (25–35). There are now several hundred articles reporting that interferon α, β and γ inhibit the division of both malignant and normal cells (reviewed in 36). Mouse and human interferon purified to homogeneity have been shown to exert this effect as well as recombinant interferons.

The finding that interferon itself could inhibit the multiplication of normal cells in culture led us to determine whether interferon could also inhibit the multiplication of normal cells in the mouse (37–39), and to suggest that interferon may be important in the regulation of cell division and function *in vivo*. In fact, in some instances excess interferon even resulted in disease of the liver (39, 40) kidney (41, 42) and lung (43). It also became quite clear that interferons exerted important effects on the immune system; both on the humoral and cell mediated immune response (reviewed in 44, 45), on the expression of histocompatibility antigens (46–49) and even on the circulation of lymphocytes (50).

It is now of course quite evident that interferon and in fact probably most if not all cytokines exert multiple biologic activities. Nevertheless, for more than 10 years most investigators in the interferon field were reluctant to abandon the notion that interferon was a selective viral inhibitor. The question now is how relevant are some of these effects to the antitumor action of interferon.

Most of the experimental work has been done in mice injected with different transplantable tumors. In all of our studies we used immunocompetent mice syngeneic with the tumor inoculated. The tumor was injected intraperitoneally (i.p.), subcutaneously (s.c.) or intravenously (i.v.). We tested the effect of mouse interferon α/β on the growth of the primary tumor and on the development of metastases. Other workers have in recent years tested the effect of interferon γ (51). With the availability of recombinant human interferons α, studies have been undertaken in nude mice injected s.c. with human tumors (52, 53). The finding that some hybrid recombinant human interferon α show biologic activity on mouse cells has permitted studies on the effect of this hybrid human interferon α on murine tumors in immunocompetent mice (54).

It became quite clear from our early studies that it was necessary to inject the interferon repeatedly to obtain optimal therapeutic results (13, 16, 55). Treatment confined to the period of tumor injection or treatment prior to tumor injection usually proved without effect especially if the mice were kept for long periods to determine the effect of interferon on survival time (16). In our experience the efficacy of interferon treatment was clearly proportional to the amount of interferon injected (55). We have never observed a 'prozone' effect, and in fact we have never achieved a plateau of efficacy. Mice appear to tolerate the injection of 10 million units of mouse interferon α/β for days without showing any ill effects. Unfortunately we have been limited in the amounts of interferon we can produce and so we have never been able to determine whether injection of 100 million units of interferon per day would prove far superior to the dose of 1 million units per day which is the standard amount we use in most of our experiments. It also seems that optimal effects are achieved when interferon is in close contact with the tumor cells (13, 55). Although interferon injected at a site distant from the tumor is still effective, a greater therapeutic effect is obtained when interferon is injected at the site of tumor growth (55).

In discussing how interferon acts, it may be necessary to consider a few experimental models since it may be the fact that different mechanisms of action are important depending on the site of tumor growth. In the ensuing paragraphs I will only consider the effect of interferon on transplantable tumors in syngeneic mice. In the first example, transplantable tumors are injected directly into the peritoneal cavity. After several hours mice are treated daily intraperitoneally with interferon or control preparations. Mice are either sacrificed in the ensuing days and the number of tumor cells in the peritoneum quantitated by very selective and accurate techniques, or the mice are left and the survival time scored. From a number of studies it can be shown that interferon treatment results in a drastic fall in the number of tumor cells in the peritoneum in the few days following tumor inoculation (56). This is an important observation, because in cell culture interferon can inhibit the multiplication of tumor cells (or normal cells) but usually does not kill the cells. In the mouse, however, interferon treatment leads to tumor cell loss. This effect is usually accompanied by a corresponding increase in the survival time or cure of the tumor inoculated mouse. Using tumor cell lines resistant to interferon α/β [L1210 (35) or Friend erythroleukemia (57)] we observed that interferon was as effective in mice injected with interferon resistant cells as in mice injected with the parental interferon sensitive cell lines (55, 56, 58). These results strongly suggested to us that in this particular experimental system interferon was not acting directly

on the tumor cells. We could even show that these tumor cells were resistant to several effects of interferon within the peritoneum (55, 59). We concluded that interferon was acting in some manner on the host and not on the tumor. What is the nature of the host mediated effect? Unfortunately we still do not know. Although we have accumulated considerable information on the different effects of interferon on the immune system (44) we have no evidence that the immune system is involved in the antitumor effects of interferon. Thus, interferon is effective in nude mice or in mice treated with antilymphocytic serum or in x-irradiated mice (60). The tumor cells used were resistant to NK cell lysis (56). Likewise, injection of silica particles which damage peritoneal macrophages did not abolish the antitumor activity of interferon (60, 61). Furthermore, we were never able to demonstrate the presence of a soluble toxic factor in the peritoneal washings of interferon treated mice (61). In fact, after so many years of studies, I am very disappointed and surprised that we still have not found the answer. Were the antitumor effects discrete it would not be surprising not to have discovered the mechanism, but the effects are on the contrary very marked. One week after inoculation of 100000 Friend erythroleukemia cells (FLC), for example, control mice have 10–100 million tumor cells in the peritoneum, whereas interferon treated mice may have only 1000 or less tumor cells (56). The mechanism of tumor cell destruction is thus very potent indeed which is of course why we persist in trying to understand the mechanisms involved.

When interferon resistant FLC are injected subcutaneously they form solid tumors which can be measured and weighed when the mice are sacrificed (62). If interferon is injected peritumorally shortly after tumor injection it will block completely the development of these s.c. tumors (depending on the dose of interferon and the number of tumor cells inoculated) (62). In some experiments we waited until the tumor nodules had developed and then injected the interferon peritumorally. We observed a regression of the established tumor and in some instances a complete regression of the tumor with cure of the mouse (62). As these cells were interferon resistant, again we concluded that the antitumor effect of interferon was not due to an effect of interferon on the tumor cell (either by inhibiting tumor cell multiplication or by affecting the tumor cell surface) but rather an effect on the host. Histologic examination of the interferon treated tumors showed large areas of ischaemic necrosis which suggested that interferon was in some manner affecting the blood supply of the established tumor (62). There was no histologic evidence that the tumor was infiltrated by lymphocytes or macrophages even in the early stages of tumor degeneration (62). Detailed and quantitative studies by Dvorak & Gresser showed that interferon treatment resulted in very early degeneration of the endothelial cells in the vessels of the tumor (unpublished data). The vessels in the surrounding normal tissue were spared. These results suggested the possibility that the mechanisms involved in the interferon induced regression of a solid subcutaneous tumor might well be different from those involved in the inhibition of a rapidly growing tumor in the peritoneum. Further evidence for this hypothesis stemmed from the following series of experiments. The ESb lymphoma is resistant to the antiproliferative effects of interferon in cell culture. In contrast to the effect of interferon in mice injected with the L1210 and FLC interferon resistant cells, interferon treatment proved ineffective in mice injected i.p. with the ESb lymphoma cells. However, when interferon was injected around established s.c. ESb tumors it also induced regression of these tumors and histologic examination showed the same pattern of ischemic necrosis as we observed with FLC tumors injected with interferon. We do not know how interferon damages the endothelium of tumor vessels; whether it is a direct effect on these cells or by the induction of other cytokines. It is noteworthy, for example, that tumor necrosis factor (TNF) induces very similar lesions (63, 64) and far more rapidly than interferon so that it is possible that interferon induces the local production of TNF. Unfortunately experiments using antibody to TNF were inconclusive. We were able, however, to show the converse, i.e. that TNF did not act by inducing interferon (63).

Of special interest was the finding that interferon can inhibit the development of experimental metastases. In the model in which FLC are injected s.c., for example, mice died in the weeks following tumor injection, not of the large s.c. tumors but of overwhelming liver and spleen metastases (62). Eight days after s.c. inoculation of FLC tumor cells had already implanted and multiplied in the liver and spleen (65). Nevertheless, if interferon treatment is initiated at this time (8 days after tumor inoculation), a marked increase in survival time was observed and some of the mice were considered cured (65). We extended these experiments and injected several million FLC i.v. All the control mice died 7 to 12 days thereafter with massive tumor involvement of the liver and spleen (66). Again we used interferon resistant FLC. Interferon treatment initiated hours or days after inoculation of the tumor cells resulted in a marked increase in survival time (mean 80 days) and cure of about 15% of the mice. The effect of interferon in this system was far superior to single agent chemotherapy (67). Although the tumor cells were interferon resistant, interferon treatment induced a clear cut inhibition of the multiplication of these tumor cells in the liver and spleen. Interferon treated mice died in the weeks or months following tumor inoculation despite the continued interferon treatment. In these interferon treated mice tumor was often observed in the kidneys, the meninges, the ovaries, and retroaortic lymph nodes. Often the liver and spleen appeared free of tumor. There was clearly some mechanism involved in the long-term suppression of the FLC tumor (66, 67). At present we do not know if the mechanisms involved in the early antitumor effect of in-

terferon in the inhibition of liver and splenic metastases is the same or different from the mechanism(s) involved in the long-term suppression of tumor development. In either case we have virtually no information on the possible mechanisms. Nevertheless, the potency of these mechanisms is such that it seems imperative to continue these sorts of studies.

If we are correct in suggesting that interferon is acting on the host, it does not mean that interferon can not also act on the tumor. We have deliberately used interferon resistant cells only to try to limit the possibilities. It is clear that in the patient, interferon may be acting on the tumor cell and even acting as an antiviral agent. Interferon treatment has proven very effective in patients with the laryngeal papilloma and here a virus may be directly involved. Interferon induced regression of these tumors may be due to interferon's antiviral effect. In the experimental models I have referred to, the antitumor effect of interferon on the host does not seem to be mediated by the classic antitumor activities of the host i.e. the immune or phagocytic systems. What then are the possible mechanisms? There are 3 very general possibilities. First, interferon might induce the production of some cytotoxic substance that acts locally on the tumor. This substance could either be released by host cells or would be present on the membranes of interferon treated host cells and would interact with the tumor cells. A second possibility would be that interferon induces a reduction in the availability of some necessary factor, a necessary growth factor, amino acid, vitamin, glucose or oxygen. A third possibility would be that interferon, directly or indirectly, enhances the differentiation of the tumor or changes the tumorigenic phenotype. There are examples from cell culture experiments that interferon can induce the production of cytostatic substances, that interferon increases the cells' needs in specific amino acids, growth factors or glucose and that interferon can inhibit or enhance differentiation. Unfortunately, there is no evidence that any of these different possibilities is applicable to the tumor models we have been investigating. Of course we know even less concerning the mode of action of interferon in the patient. Interferon is very active in patients with hairy cell leukemia, and relatively inactive or totally inactive in some other malignancies. We have far more questions than answers. The only consolation I can offer myself or others for our failure to come up with the correct answers is that the problem seems to me of great interest and importance and worth working at until we do understand how interferon does inhibit the growth of some tumors in experimental animals and in man.

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