Selected Abstracts
on

Interferon: Preclinical Studies of Anticellular, Antitumor and Immunomodulatory Activities

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INTRODUCTION

This ONCOLOGY OVERVIEW on preclinical studies of the anticellular, antitumor, and immunomodulatory effects of interferon consists primarily of abstracts selected from the CANCERLINE data base and covering the period from 1975 to 1981. In some cases, abstracts of papers published prior to 1975 are included for their historical value. The strategy used to retrieve these abstracts can be requested from the CIDAC and entered into any MEDLARS/MEDLINE terminal system to update references in this area.

The scope of this OVERVIEW includes preclinical studies on the antitumor activity of interferon as well as pharmacologic and toxicologic studies on interferon. It also includes studies on the effects of interferon on cellular growth and division, and on the synthesis of DNA, RNA, and proteins. In addition, it includes the effects of interferon on cell-mediated and humoral immunity, on phagocytosis, and on lymphocytic mitogenesis. Abstracts of reports pertaining to other areas of interferon research may be found in two previously published OVERVIEWS, entitled "Interferon: Induction, Production, and Physicochemical Properties," and "Interferon: Preclinical Studies of Antiviral Activity." An OVERVIEW on the clinical evaluation of interferon is in preparation.

This OVERVIEW was prepared by Gerald Sonnenfeld, Ph.D. (Editor), of the Microbiology Department of the University of Louisville, Louisville, Kentucky, and Deborah Liss-Suter, B.A., and Allan Fried, Ph.D., both of the CIDAC for Virology, Immunology, and Biology, The Franklin Research Center, Philadelphia, Pennsylvania.

EDITORIAL COMMENTARY

Interferon was originally described as an antiviral agent in 1957 (1). Since that time it has become apparent that interferon has several other activities, including regulation of cell growth and division (2), regulation of immune responses (2-4), and regulation of histocompatibility antigen expression (2,4). In addition, direct effects of interferon on tumor growth in animal models (2) have also been reported. These reports have initiated a great deal of interest in the possible use of interferon as an antitumor agent.

A question that has existed since the multiple biological effects of interferon were first described is: Are all of the biological effects of a given preparation due to interferon itself, or are some effects due to impurities in the preparation? Gresser and his associates (5) provided strong evidence that the multiple biological effects of an electrophoretically pure murine fibroblast type I preparation were indeed all attributable to interferon itself and that, within the limits of resolution of the electrophoretic procedure, the interferon consisted of only two distinct molecular species. Studies with alpha and beta interferon produced by bacteria that have the mammalian interferon genes inserted into their genomes have indicated, however, that there may be several closely related subclasses of each interferon. The importance of and the activities of those subclasses are now the subjects of further studies.

A question has also existed as to the possible mechanism of action of interferon on tumors and tumor cells. Although interferon has been shown to act prophylactically by protecting cells from virus infection (6), the manner in which interferon affects an already established tumor remains unclear. It is likely that interferon exerts multiple effects, including the inhibition of further virus replication, if a virus is involved in the growth of the tumor. This inhibition could either be a direct effect on virus RNA translation (6) or the result of interference with the budding of viruses by an interferon-induced change in membrane histocompatibility and other antigens (2,7). In addition, the interferon could be directly inhibiting the growth of rapidly growing tumor cells while not affecting normal cells (2). Finally, the interferon could be marshalling host immunologic defenses (4), including natural killer cells (8,9), antibody (4), and cell-mediated immunity (10). The possible multiple effects of interferon on tumor cells reemphasizes the importance of the finding of Gresser and his associates that pure interferon can exert all of these effects.

The possible role of an interferon that has been induced as a result of a cell-mediated immune response has also been the sub-

ject of much study. This interferon, which is a lymphokine, has been referred to as type II or immune-induced interferon. This interferon has been reported to be more potent than other interferons with regard to its immunoregulatory (11,12), cell regulatory (13) and tumor inhibitory (14,15) activities. In addition, type II interferon has been reported to potentiate the activities of other types of interferon. Therefore, great interest exists as to the possible use of type II interferon for tumor therapy. Unfortunately, type II interferon is the least available and least purified interferon. There is no strong evidence that the same molecule is responsible for all of the activities present in the type II interferon preparations. Therefore, many purification studies as well as techniques for production of greater amounts of type II interferon are necessary before type II interferon can be fully exploited as a potential antitumor agent.

The use of interferon in conjunction with chemotherapeutic drugs as a type of adjuvant therapy has also attracted much interest. This interest has developed partly as a result of antiviral studies in which interferon was combined with adenine arabinoside (an antiviral drug) in the treatment of chronic active hepatitis B in humans (16). Patients treated with both agents had a much better response than those treated with one agent. In addition, experimental studies have indicated that interferon or interferon-inducer treatment can slow hepatic drug metabolism (17,18). This could result in increased bioavailability of some chemotherapeutic agents, possibly leading to enhancement of the efficacy of the treatments. This area is also becoming the subject of extensive studies.

Experimental trials have yielded a great deal of evidence suggesting that interferon has some antitumor potential. However, several questions remain unanswered. Many more pre-clinical trials with interferon will be required to fully answer these questions and perhaps lead to new insights in the development of future clinical trials.

A final note on nomenclature. A new nomenclature for interferon has recently been adopted (19). Although the majority of the abstracts listed in this OVERVIEW utilize older nomenclatures, it is important that the reader be aware of the new nomenclature in order to be able to cross reference these abstracts with future publications. The new nomenclature is as follows: alpha interferon is equivalent to what was previously referred to as leukocyte type I interferon; beta interferon is equivalent to what was previously referred to as fibroblast type I interferon; and gamma interferon is equivalent to what was previously referred to as immune type II interferon.

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ABSTRACTS

I. EXPERIMENTAL STUDIES ON THE ANTITUMOR ACTIVITY OF INTERFERON

1. EFFECT OF HUMAN AND MOUSE INTERFERON AND OF POLYRIBOINOSINIC ACID.POLYRIBOCYTIDYLIC ACID ON THE GROWTH OF HUMAN FIBROSARCOMA AND MELANOMA TUMORS IN NUDE MICE.

De Clercq E, Georgiades J, Edy VG, Sobis H
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Eur J Cancer; 14(11):1273-1282 1978

Athymic nude mice with 1-day-old sc implants of two human tumors (HT-1080 fibrosarcoma or A-375 amelanotic melanoma) were treated ip with human WBC, human fibroblast, or mouse interferon (ITF: 5 x 10(5) to 5 x 10(6) units/kg) or polyinosinic:polycytidylic acid (poly(I):poly(C): about 5 mg/kg) every other day until day 9 or 23 after tumor inoculation. Poly(I):poly(C) was not toxic at this dose. In mice with HT-1080, a 5-dose course of poly(I):poly(C) reduced tumor size by about 50% (12 days after inoculation). In mice with A-375, a 12-dose course of poly(I):poly(C) reduced tumor size by about 33% (21 days after inoculation; both, p less than 0.001). None of the ITF preparations inhibited the growth of either tumor. In mice with HT-1080, serum ITF titers after treatment with poly(I):poly(C) or any ITF preparation were comparable (about 1,000 units/ml). The inactivity of human ITF was not attributable to its unusually rapid disappearance from the blood. Serum ITF activity after injection of human ITF had the species specificity of human ITF. After injection of mouse ITF or poly(I):poly(C), serum ITF activity was of the mouse type. Both human tumors were highly susceptible to the cytotoxic effects of poly(I):poly(C) and the antiproliferative effects of human ITF in vitro (no further details). Mouse ITF may have had little effect on host-mediated resistance to the tumor xenografts. These ITF doses were low, but they were comparable to the doses generally considered feasible in man and higher than the doses given to patients with osteogenic sarcoma. Both tumor xenografts formed encapsulated, non-metastasizing nodules. If the predominant action of ITF is the prevention of metastases, its potential antitumor activity would be unnoticed in a system in which the host itself prevents tumor dissemination. (46 Refs)

2. ANTITUMOR EFFECTS OF HUMAN LEUKOCYTE INTERFERON ON HUMAN OSTEOSARCOMAS TRANSPLANTED IN NUDE MICE.

Masuda S
Dept. Orthopedic Surgery, Kyushu Univ. Faculty Medicine, Fukuoka 812, Japan
Fukuoka Igaku Zasshi; 71(11):600-611 1980

Effects of human leukocyte interferon (HL-IF) were studied in athymic nude mice bearing serially transplanted human osteosarcomas (OS-SU or OS-OH). The mice were administered the HS-IF in doses of 5,000, 25,000, or 50,000 IU 24 hr or 2 wk after tumor inoculation. Only slight tumor inhibition was observed in the OS-SU mice, but marked inhibition was observed in the OS-OH mice after administration of 50,000 IU of the HL-IF. The inhibition was dose dependent, and total disappearance of the tumor was observed in some mice that were given daily injections. Concurrent use of adriamycin or vincristine and the HL-IF resulted in tumor regression similar to that observed when the HL-IF was administered singly. Kinetic responses of phytohemagglutinin-stimulated human lymphocytes to HL-IF was analyzed with pulse cytophotometry; reduction of the growth fraction of the cells was observed 72 hr after exposure to HL-IF. The Hl-IF was thought to possibly inhibit DNA synthesis or suppress cell transition from G1 to S phases of the cell cycle. (36 Refs)

3. THE ANTITUMOR EFFECT OF HUMAN LEUKOCYTE INTERFERON.

Fukuma H, Masuda S, Beppu Y
Dept. Orthopedic Surgery, Natl. Cancer Center Hosp., Chuo-ku, Tokyo 104, Japan
Gan To Kagaku Ryoho; 6(Suppl1):59-64 1979

The effect of human WBC interferon (HL-IF) was studied in two human osteosarcomas, transplanted and passed serially in athymic nude mice and in patients with osteosarcoma. Transplanted osteosarcomas included OS-SU tumor derived from an osteosarcoma of the right femur of an 8-yr-old female, and OS-OH derived from a pulmonary metastasis of osteosarcoma of the right femur of a 21-yr-old male. Histological appearance of OS-SU was different from the original tumor and was fibrosarcomatous, while that of OS-OH was identical to the original tumor and showed malignant osteoid and bone formation. Interferon treatment was initiated 24 hr after tumor inoculation or 2 wk later, when the tumor had grown to an appreciable size. HL-IF was administered ip in doses of 5,000, 25,000, or 50,000 IU/mouse, 2-3x/wk for 4 wk. Some inhibition of tumor growth was observed in the group of animals with OS-SU tumor administered HL-IF in a dose of 50,000 IU/mouse, 3x/wk for 4 wk. However, tumor size in the group treated with 5,000 or 25,000 IU was not significantly different from those of the control group. Tumor growth of OS-OH was markedly inhibited by 50,000 IU HL-IF, whether interferon treatment was initiated 24 hr or 2 wk after inoculation of tumor. Combination chemotherapy consisting of 50,000 IU of HL-IF and 0.2 ug/g vincristine or 2 mg/kg adriamycin was effective in the treatment of OS-OH tumor. The antitumor effect of HL-IF was found to be dose dependent. HL-IF was administered to 5 patients with pulmonary metastases and/or skeletal metastases from osteosarcoma in a Phase I clinical trial. Five patients received a single dose of 100-333 x 10(4) IU of HL-IF. Although toxic manifestation and hematological changes were not noted within the range of these doses for a single injection, chill and high fever were seen in all but one patient. They received HL-IF, total doses ranged from 400 to 5,000 x 10(4) IU, and the duration of the treatment ranged from 2 wk to 3 mo. Regression of tumor was not seen in any patients. HL-IF is an effective tumor agent. (11 Refs)

4. ISOPRINOSINE INCREASES THE ANTITUMOR ACTION OF INTERFERON.

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Cancer Treat Rep; 62(11):1971-1974 1978

Swiss mice were injected ip with Sarcoma 180/TG (resistant to purine antimetabolites; 10(6) cells) simultaneously with isoprinosine (IPR: 1 mg/g body wt). Treatment with mouse fibroblast interferon (IF: 5 x 10(4) units/mg protein) was begun 3 hr after tumor inoculation. When both agents were given, IF was given 3 hr after IPR. One dose of IPR, IF, or the combination increased the median survival time (MST) from 19 days (controls) to 21, 26.5, and 28 days, respectively. At 60 days, 1/20 mice given IPR, 3/20 given IF, and 3/20 given the combination survived; there were no 60-day survivors among the controls. Mice treated with 3-12 doses (3x/wk) were observed for 100 days, at which time 6/190 controls were alive. After three doses of IPR alone, IF alone, or the combination, the MSTs were 24, 30, and 31.6 days, respectively (controls, 25 days); there were 2/80, 5/80, and 7/80 survivors, respectively, at 100 days. After six doses of IPR alone, IF alone, or the combination, the MSTs were 39, 54, and 64 days, respectively (controls, 30 days); there were 7/60, 18/60, and 25/60 survivors, respectively, at 100 days. After 12 doses, the MST was 45 days (10/50 survivors) with IF alone, 23 days (1/50 survivors) with IPR alone, and 64 days (21/50 survivors) with the combination. The combination was significantly more effective than IF alone after 12 doses; in the other groups, the differences between IF and the combination were not significant. The combination was more effective than IF or IPR alone in inhibiting tumor growth at the inoculation site. Some tumors regressed in long-term survivors. (14 Refs)

5. POTENTIATION OF ANTITUMOR EFFECT OF VIRUS-INDUCED INTERFERON BY MOUSE IMMUNE INTERFERON PREPARATIONS.

Fleischmann WR, Kleyn KM, Baron S
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JNCI; 65(5):963-966 1980

In inbred DBA/2 mice, the antitumor activities of separate and combined preparations of mouse immune interferon and mouse virus-induced interferon on the development of P388 tumors were studied. Immune interferon alone (25 U/day) did not affect tumor development. Virus-induced interferon alone (25,000 U/day) delayed tumor development and increased survival time. The mouse immune interferon preparations significantly enhanced or potentiated the antitumor effects of mouse virus-induced interferon when the interferons were used in combined therapy. (Author abstract) (16 Refs)

6. ENHANCEMENT OF INTERFERON ANTITUMOR ACTION BY SODIUM BUTYRATE.

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Cancer Res; 39(11):4720-4723 1979

The effects of sodium butyrate (BU: 50 milliM, ip) on the antitumor action of mouse interferon (IFR: 20,000 IU) in sarcoma 180 TG (S-180TG) bearing Swiss mice (10(6) cells) or L1210 bearing DBA/2 mice (10(4) cells) are reported. BU was administered immediately after inoculation of the mice and 24 hr before IFR. BU and IFR were administered alternately every 24 hr for 3 wk. S-180TG tumors developed by day 10 in 40% of the mice treated with BU alone and maximal incidence (90%) was reached on day 18. The incidence of day-10 tumors in animals treated with IFR alone was 59%; the maximum incidence of 79% was reached between days 18-23. A highly significant delay in tumor development occurred (5% incidence on day 10) in animals treated with BU and IFR; the maximal tumor incidence was 42% on day 26. The 100-day survival rate of mice treated with BU and IFR (39/75) was significantly greater than that of mice treated with BU (5/75), IFR (11/75), or of controls (2/75). Similar results were obtained when treatment was delayed 5 days after tumor cell inoculation. BU was effective po at doses 5x higher than ip doses but was not effective iv. In L1210 bearing mice, the median survival time (MST) of mice treated with BU and IFR was 33-36 days compared with 29-30 days for IFR- or BU-treated mice and 22-28 days for controls. When L1210 cells were treated with IFR, BU, or both for 24 hr in vitro and then inoculated in mice ip, the MST of mice treated with IFR and BU was slightly but significantly delayed compared with that of controls (24 days vs 22 days, p less than 0.05). Simultaneous treatment of L1210 cells (10(5)) in culture with BU (0.5 milliM) and IFR (125 IU) resulted in inhibition of cell growth and of DNA synthesis. Possible mechanisms of BU-induced enhancement of IFR activity in these tumor systems is discussed. (13 Refs)

7. POTENTIATION OF INTERFERON ACTIVITY BY MIXED PREPARATIONS OF FIBROBLAST AND IMMUNE INTERFERONS.

Fleischmann WR, Georgiades JA, Osborne LC, Johnson HM

Infect Immun; 26:248-253 1979

8. EXPRESSION OF METASTATIC POTENTIAL OF TUMOR CELLS IN YOUNG NUDE MICE IS CORRELATED WITH LOW LEVELS OF NATURAL KILLER CELL-MEDIATED CYTOTOXICITY.

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Int J Cancer; 26(5):675-680 1980

Of 6-and 3-wk old nude mice given iv injections of murine tumor cells with well-defined metastatic properties, only the 3-wk-old mice developed lung tumor colonies in significant numbers. The quantitative differences in metastatic potential among tumor cell lines injected into syngeneic recipients were also maintained following iv injection into young nude mice. Successful metastasis in 3-wk-old nude mice is correlated with the low levels of natural killer cell activity detected in these young recipients. Boosting of the natural killer cell activity of 3-wk-old nude mice by the administration of bacterial adjuvants and interferon inducers significantly inhibited metastasis formation. The differences in metastasis development could not be attributed to differences in the initial arrest of tumor cells in the pulmonary vascular bed, but rather to a better survival of the arrested cells in the lungs of 3-wk-old nude mice as compared with 6-wk-old counterparts. We conclude that low levels of NK cell activity are associated with increased incidence of experimental metastasis. (Author abstract) (39 Refs)

9. INFLUENCE OF ANTI-MOUSE INTERFERON SERUM ON THE GROWTH AND METASTASIS OF TUMOR CELLS PERSISTENTLY INFECTED WITH VIRUS AND OF HUMAN PROSTATIC TUMORS IN ATHYMIC NUDE MICE.

Reid LM, Minato N, Gresser I, Holland J, Kadish A, Bloom BR
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Proc Natl Acad Sci USA; 78(2,part2):1171-1175 1981

Baby hamster kidney or HeLa cells form tumors in 100% of athymic nude mice. When such cells are persistently infected (PI) with RNA viruses, such as mumps or measles virus, the tumor cells either fail to grow or form circumscribed benign nodules. Neither the parental nor the virus PI tumor cells form invasive or metastatic lesions in nude mice. Previous studies have indicated a correlation between the susceptibility of virus-PI tumor cells in vitro and the cytolytic activity of natural killer (NK) cells and their failure to grow in vivo. Because interferon (IF) is the principal regulatory molecule governing the differentiation of NK cells, it was possible to test the relevance of the IF-NK cell system in vivo to restriction of tumor growth by treatment of nude mice with anti-IF globulin. This treatment was shown to reduce both IF production and NK activity in spleen cells. Both parental and virus-PI tumor cells grew and formed larger tumors in nude mice treated with anti-IF globulin than in control nude mice. The viral-PI tumor cells and the uninfected parental cells formed tumors in treated mice that were highly invasive and often metastatic. Some human tumor types have been notoriously difficult to establish as tumor lines in nude mice (eg, primary human prostatic carcinomas). When transplanted into nude mice treated either with IF globulin or anti-lymphocyte serum, two prostatic carcinomas grew and produced neoplasms with local invasiveness and some metastases. The results are consistent with the view that IF may be important in restricting the growth, invasiveness, and metastases of tumor cells by acting indirectly through components of the immune system, such as NK cells. (Author abstract) (34 Refs)

10. DISCREPANT EFFECTS OF INTERFERON ON MURINE SYNGENEIC ASCITES TUMORS AND THEIR SOLID METASTASIZING COUNTERPARTS.

Ryd W, Hagmar B, Lundgren E, Strannegard O
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Int J Cancer; 23(3):397-401 1979

The effects of interferon (IF) on CBA and C57BL/6J mice with transplanted nonviral ascites tumors were studied. IF (12,500 units/day ip for 10 days starting the day after tumor transplant) prolonged survival time in mice inoculated ip with one of two ascites tumors and caused one of the tumors to grow in predominantly solid rather than disseminated form. There was no effect on survival time following inoculation of a more virulent ascites tumor. In a second study, ascites tumors were inoculated sc, and IF was given for 11-15 days beginning with the onset of metastasis. When ascites tumors are transplanted sc, they grow as solid tumors. The mean tumor wts were higher in all IF-treated mice compared with untreated controls, and mean survival times were reduced. In mice receiving one of the less virulent tumors, the tumor-enhancing effect was highly significant and there was a highly significant increase in the development of lung metastases. The incidence and distribution of metastases were not affected by IF in the mice receiving the other two tumors. Animal models for analyzing IF effects should be developed before IF treatment is initiated in human cancer patients. (32 Refs)

11. INHIBITION OF GROWTH OF B16 MURINE MALIGNANT MELANOMA BY EXOGENOUS INTERFERON.

Bart RS, Porzio NR, Kopf AW, Vilcek JT, Cheng EH, Farcet Y
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Cancer Res; 40(3):614-619 1980

We previously reported that polyinosinic-polycytidylic acid, a potent interferon inducer, inhibits the growth of B16 malignant melanoma in the C57BL/6 mouse. Two experiments were done to evaluate the effectiveness of interferon in tumor inhibition in vivo. In the first, mice were implanted with melanoma and divided into four groups, according to treatment: interferon preparation; interferon control preparation ('breakthrough fraction'); phosphate-buffered saline control; and murine serum albumin control. Daily, each mouse was given ip injections of 200,000 NIH reference units (hereafter called units) of interferon or of one of the control substances. The second experiment was similar to the first, except that bovine serum albumin was an additional control. In both experiments, the av tumor vol in interferon-treated mice was statistically significantly smaller than that of each control group. Mouse interferon preparations also inhibited the multiplication of B16 malignant melanoma cells in culture. This inhibition was statistically significant from interferon levels as low as 5 to as high as 5,000 units/ml. The degree of inhibition markedly increased from 5 up to 500 units, the inhibition reaching its max at this concentration. The inhibitory effect of interferon was abrogated by anti-murine interferon serum produced in a rabbit. These findings suggest that the in vivo inhibition of the growth of B16 melanoma demonstrated with polyinosinic-polycytidylic acid and with exogenous interferon probably results, at least in part, from a direct effect of interferon on the tumor cells themselves. (Author abstract) (33 Refs)

12. ROLE OF INTERFERON IN THE ANTI-MELANOMA EFFECTS OF POLY(I).POLY(C) AND NEWCASTLE DISEASE VIRUS.

Bart RS, Kopf AW, Vilcek JT, Lam S
Dept. Dermatol., N.Y. Univ. Sch. Med., New York
Nature [New Biol]; 245(147):229-230 1973

The role of interferon in the inhibitory actions of synthetic RNA, polyinosinic:polycytidylic acid (poly I:C) and Newcastle disease virus (NDV) upon growth of B16 malignant melanoma was studied in 6-wk-old female C57BL/6 mice. Sixty mice received whole body irradiation (500 R); 6 hr after irradiation these mice and most of the non-irradiated mice received sc implants of B16 cell suspension (50 microl). On d. 3-7 and d. 10-14, 3 mice from each of the 8 groups were exsanguinated and the serum interferon titer determined by a modified semimicro technique using mouse L-cells and vesicular stomatitis virus. On d. 14 av tumor vol in irradiated and non-irradiated mice receiving allantoic fluid, and in untreated mice were similar (1.80, 1.69, and 1.70 ml, resp). Poly I:C inhibited tumor growth in irradiated and non-irradiated mice (0.50 and 0.51 ml, resp), while NDV produced a moderate inhibition in non-irradiated animals (1.28 ml) and a marked inhibition in irradiated animals (0.74 ml). Interferon titers 6 hr after the first inj were 10x greater in NDV- than in poly I:C-treated subjects among irradiated and non-irradiated mice; at later times there was a reversal of this effect, poly I:C stimulated higher interferon titers, with the highest values in irradiated mice. (12 refs)

13. TREATMENT OF NEOPLASIA IN MICE WITH INTERFERON PREPARATIONS.

Gresser I, Bourali C, Chouroulinkov I, Fontaine-Brouty-Boye D, Thomas MT
Sci. Res. Inst. Cancer, Villejuif, France
Ann NY Acad Sci; 173(1):694-705 1970

Mice with 1-d-old ascites RC19 tumors (originally induced by the Rauscher leukemia virus) were treated with exogenous interferon (0.25 ml/d ip), or with endogenous interferon induced by either Newcastle disease virus (0.25 ml/d ip) or by polyinosinic:polycytidylic acid (50 ug/d ip). All control mice died in 17-24 d (7/188 survived >22 d). Of the treated mice, 101/103 survived >22 d and 16/103 (15%) survived >60 d. Exogenous interferon was more effective in increasing the survival time than either of the endogenous methods. The 2 inducers of endogenous interferon were about equally effective. The long-term survivors were resistant to repeated inocn of the RC19 tumor, but their susceptibility to the Ehrlich ascites carcinoma was the same as that of untreated controls.

14. INHIBITORY EFFECT OF INTERFERON ON MULTIPLICATION OF FRIEND LEUKEMIA CELLS IN VIVO.

Rossi GB, Marchegiani M, Matarese GP, Gresser I
Virology Sect., Sanita Superior Inst., Rome, Italy
JNCI; 54(4):993-996 1975

The inhibitory effect of interferon on multiplication of Friend leukemia cells (FLC) in irradiated and non-irradiated DBA/2 mice is reported. Two groups of mice received 1.8 x 10 FLC i.v after 800 R whole body irradiation. One group received 20,000 U/d of mouse brain interferon i.p. The uptake of 125-iodo-2'-deoxyuridine (IUDR) in the spleen was increased in mice inoc with FLC compared to uninoc mice. However, it was significantly inhibited in mice inoc with FLC and treated with interferon. Non-irradiated mice given live FLC showed increased IUDR uptake in the spleen compared to mice given FLC which were frozen and thawed 3x. Daily treatment of mice with interferon markedly inhibited multiplication of FLC in either irradiated or non-irradiated mice. (28 refs)

15. CURE OF MURINE LEUKEMIA WITH DRUG AND INTERFERON TREATMENT.

Chirigos MA, Pearson JW
Viral Leuk. Lymph. Branch, Natl. Cancer Inst., Bethesda, Md.
JNCI; 51(4):1367-1368 1973

Male CDF(1) mice were inoc sc with LSTRA leukemia cells; on d. 7 after tumor inocn, a group of mice received 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU; 30 mg/kg); another group received 50,000 U interferon ip (derived from C243-3 cells), on d. 7 and continued daily until death; 3 groups received BCNU on d. 7 and interferon (50,000 U) was initiated at different intervals and continued thereafter once daily for 19 treatments; and 1 group served as the tumor control animals. Treatment with BCNU alone resulted in 130% increase in median survival time over controls, followed by relapse and death in 75% of the animals. Interferon alone did not prolong survival time. Mice receiving continuous daily treatment with interferon, initiated 2, 6, or 10 d after BCNU admin, survived for longer periods with a higher percentage of survivors. An overall cure rate of 72% was achieved with BCNU + interferon therapy, as compared with 25% obtained with BCNU alone. Survivors, killed after 90 d, showed no gross symptoms of leukemia, and the tissues showed no histological evidence of leukemic cells. Results indicate that residual cells surviving BCNU treatment are sensitive to interferon; furthermore, interferon is believed to be inhibitory to small numbers of leukemia cells. (13 refs)

16. TREATMENT OF SPONTANEOUS LEUKEMIA IN AKR MICE WITH CHEMOTHERAPY, IMMUNOTHERAPY, OR INTERFERON.

Bekesi JG, Roboz JP, Zimmerman E, Holland JF
Dept. Neoplastic Diseases, Mount Sinai Sch. Medicine, New York, NY 10029
Cancer Res; 36(2,Part2):631-639 1976

Treatment of spontaneous leukemia in AKR mice with a variety of modalities is reported. Both neuraminidase (NA)-treated syngeneic leukemic AKR thymocytes and allogeneic E2G leukemia cells were equally effective in delaying the appearance of primary lymphoma in AKR mice ($p < 0.05$). Immunization with NA-treated L1210 leukemic cells or normal AKR thymocytes was ineffective. Immunotherapy of established leukemia (beginning 14 days after diagnosis) with NA-treated spontaneous leukemic thymocytes or allogeneic E2G leukemic cells without prior cytoreductive therapy did not change the survival pattern. Chemotherapy with vincristine (VCR, 0.75 mg/kg on day 0), palmO-ara-C (130 mg/kg on day 3), and 1-(2-chloroethyl)-3-(trans-4-cyclohexyl)-1-nitrosourea (methyl-CCNU, 25 mg/kg on day 7) resulted in an ILS of 180%, but < 7% of animals survived > 100 days. Combination chemotherapy followed by immunization with 2 x 10(7) NA-treated allogeneic E2G leukemic cells injected on six occasions at multiple sites resulted in survival of 30% of treated animals > 120 days. Immunization alone was ineffective. Cytoreductive therapy alone did not significantly alter the viral titer, but chemotherapy and immunotherapy produced a noticeable decrease in the viral titer after the 13th day, and this was still demonstrable at 45 days. The antiviral agent Virazole alone (up to 800 mg/kg) had no demonstrable antitumor effect on established AKR leukemia. Chemotherapy with VCR + methyl-CCNU + cytoxan increased the life span 183%, but chemotherapy followed by Virazole (200 mg/kg x 3) produced an ILS of 280%. Chemotherapy + Virazole produced a decrease in the viral titer that was evident after the 13th day of treatment. Exogenous mouse *interferon* (5 x 10(4) or 5 x 10(5) units x 5 on days 0, 2, 4, 6, and 8) markedly reduced the virus titer from 2,000 to < 100, and this effect persisted for at least 85 days. Mouse interferon also delayed the onset of primary leukemia in AKR mice. At the highest concentration, treated animals died at the same rate as untreated animals, but only 6/20 died of leukemia; the others died with splenic or thymic atrophy. At 7 x 10(4) units x 5, interferon resulted in 45% of animals living at 52 wk, compared to a median life span of 34-38 wk for untreated animals. Only two animals showed signs of organ atrophy at this dose. (47 refs)

17. EFFECTIVENESS OF EXOGENOUS MOUSE INTERFERON IN AKR LEUKEMIA.

Roboz JP, Holland JF, Bekesi JG
Dept. Neoplastic Disease, Mount Sinai Sch. Medicine, New York, NY, 10029
Prog Cancer Res Ther; 2:369-379 1977

The effectiveness of exogenous mouse interferon in the prophylactic treatment of murine leukemia virus-infected preleukemic AKR mice and in the therapeutic treatment of AKR mice with spontaneous leukemia was investigated. In 3-mo-old preleukemic mice treated with multiple im injections of 5 x 10 or 5 x 10 units of interferon, there was a significant reduction in viral titers from 2,000 to less than 100. No changes in viral titers were observed in mice treat-

ed with saline or mock interferon. All mice treated with mock interferon developed spontaneous leukemia, and less than 10% remained alive at 12 mo of age. AKR mice receiving the highest concentration of interferon every 2nd day still died at the same rate as the control group, but only 5/40 died of leukemia. The remaining animals showed marked signs of organ atrophy and wasting. Changing the injection schedule from every 2nd day to 1x/wk while maintaining the same total dose produced no toxic side effects, reduced the viral titer, and significantly delayed the appearance of primary leukemia. Interferon at doses of 2 x 10 and 2 x 10 units injected im on days 1, 2, 3, 4, 7, 10, and 15 was also of therapeutic value in the treatment of spontaneous leukemia in AKR mice. The effect was dose related both in terms of reduction of leukemic organ wts and prolonged survival duration. The survival of mice receiving 2 x 10 units of interferon was 29.6 +- 5.2 days compared with 24.4 +- 3.8 days for mice receiving 2 x 10 units and 17.6 +- 2.4 days for controls receiving mock interferon. (23 Refs)

18. EFFICACY OF COMBINED INTERFERON CYCLOPHOSPHAMIDE THERAPY AFTER DIAGNOSIS OF LYMPHOMA IN AKR MICE (LETTER TO EDITOR).

Gresser I, Maury C, Tovey M
Lab. Viral Oncology, Institut de Recherches Scientifiques sur le Cancer, 94800 Villejuif, France
Eur J Cancer; 14(1):97-99 1978

Female AKR mice with spontaneous lymphomas (definite peripheral lymphadenopathy and splenomegaly, sometimes accompanied by respiratory distress caused by thymic enlargement) were treated ip with single doses of cyclophosphamide (CP: 150 mg/kg), alone or followed (3 days later) by mouse C-243 cell interferon (ITF: 0.25 ml/day, ip). The ITF preparation had a titer of 3.2 x 10(-6) and a specific activity of about 2.8 x 10(6) - 1.2 x 10(7) units/mg protein. The mean survival time after diagnosis was 17.0 days in untreated controls, 29.3 days with CP alone (p less than 0.01), 24.7 days with CP and ITF control preparation (the difference from CP alone was not significant), and 52.7 days with CP and ITF (p less than 0.001). In all groups, CP caused regression of lymphadenopathy, splenomegaly, and thymic enlargement after 1-3 days. Although the tumor burden was reduced, tumor cells were not eliminated; all mice eventually died of lymphoma. An ITF-treated group was not included in this experiment, but the results of a previous study showed that ITF alone and CP alone were about equally effective in increasing survival. In this study, ITF treatment following CP-induced reduction of the tumor burden increased the survival time by about 200%. The therapeutic effects of CP and ITF seemed to be additive.

19. INTERFERON AND MURINE LEUKEMIA. VII. THERAPEUTIC EFFECT OF INTERFERON PREPARATIONS AFTER DIAGNOSIS OF LYMPHOMA IN AKR MICE.

Gresser I, Maury C, Tovey M
Lab. Viral Oncology, Institut Recherches Scientifiques sur le Cancer, Villejuif, France
Int J Cancer; 17(5):647-651 1976

Treatment of female AKR mice with interferon (from suspension cultures of C-243 cells induced with Newcastle's disease virus), after the diagnosis of lymphoma, is reported. Mice were either untreated, treated with a control preparation, or with one of two concn of interferon (0.25 ml of a preparation titering 1.6 x 10 or 8 x 10 d., i.p.). There was no statistical difference in survival between the untreated mice and those treated with the control preparation (harmonic mean survival 14.4 and 11.9 d., resp.) but those treated with the higher interferon dose had a harmonic mean survival of 23.4 d. While the survival of those mice treated with the lower interferon dose (14.0 d.) was not significantly increased over untreated animals, 4/11 mice survived at least 33 d and one died on the 94th d.; none of the untreated mice survived beyond d. 22. It is suggested that the therapeutic effects reported may be due to a direct inhibitory effect of interferon on the multiplication of the lymphoma cells themselves, although this effect could be host-mediated. It is unlikely that the therapeutic effects of interferon are derived from its anti-viral activity. (29 refs)

20. EFFECT OF MOUSE INTERFERON AND POLYRIBOINOSINIC ACID-POLYRIBOCYTIDYLIC ACID ON L-CELL TUMOR GROWTH IN NUDE MICE.

De Clercq E
Rega Inst. Medical Res., Univ. Leuven, B-3000 Leuven, Belgium
Cancer Res; 37(5):1502-1506 1977

The possible role of interferon induction or thymus-dependent immunity in the inhibition of tumor growth by synthetic polyribonucleotide complexes was investigated. Tumors were induced in athymic nude mice of predominantly NMRI background by inoculation with 10(6) L-929 cells. Repeated injections of polyriboinosinic acid-polyribocytidylic acid (pI-pC) (100 ug/mouse, ip) or mouse interferon (10(3) IU/mouse, ip) beginning 21 days post-inoculation resulted in inhibition of tumor growth in pI-pC treated mice but not in interferon-treated mice. The interferon dosage was adjusted to mimic interferon blood levels induced endogenously by pI-pC. In a second experiment, treatment with three injections of pI-pC (1, 10, or 100 ug/mouse) or interferon (10(3), 10(4), or 10(5) IU/mouse)/wk for 5 wk began 1 day after L-929 inoculation. The inhibitory effect of pI-pC was found to be dose-dependent. Doses of 10(3) or 10(4) IU interferon/mouse did not affect tumor growth, while 10(5) IU interferon/mouse resulted in tumor growth inhibition similar to that obtained with 1 ug pI-pC/mouse. At these dosages, neither pI-pC nor interferon altered the life span of normal nude mice. Results of this study indicate that the inhibitory effect of pI-pC is not due to interferon production or stimulation of thymus-dependent immunity. (35 Refs)

21. ROLE OF ENDOGENOUS INTERFERON IN THE ANTI-TUMOR EFFECT OF POLY I-C AND STATOLON AS DEMONSTRATED BY THE USE OF ANTI-MOUSE INTERFERON SERUM.

Gresser I, Maury C, Bandu MT, Tovey M, Maunoury MT
Institut de Recherches Scientifiques sur le Cancer, Villejuif, France
Int J Cancer; 21(1):72-77 1978

The effect of sheep anti-mouse interferon globulin (2 mg/mouse, iv) on the antitumor effects of polyriboinosinic-polyribocytidylic acid (poly I-C) (100 ug, iv), statolon (5 mg, iv), tilorone (4 mg, po), pyran copolymer (0.6 mg, iv), and BCG vaccine (1 mg, iv) in mice (BALB/c and DBA/2) inoculated with Ehrlich ascites or L1210 lymphoma cells was investigated. The antitumor effects of poly I-C and statolon were nullified when mice were injected with the anti-interferon globulin, whereas the anti-tumor effects of pyran copolymer and BCG were not modified by this treatment. Tilorone showed no significant antitumor effect when injected alone or with the anti-interferon globulin. However, interferon was detected (1:160) in the sera of mice inoculated with tilorone but not in the sera of mice inoculated with tilorone and anti-interferon golbulin. It is concluded that interferon mediates the antitumor activity of poly I-C and statolon in these experimental systems, and it is suggested that

anti-interferon serum provides a direct method of determining whether other biological effects attributed to viruses, poly I-C, statolon, tilorone, pyran copolymer, and possibly other interferon inducers are mediated by interferon. (48 Refs)

22. RETINOIC ACID: ENHANCEMENT OF A TUMOR AND INHIBITION OF INTERFERON'S ANTITUMOR ACTION.

Baron S, Kleyn KM, Russell JK, Blaloc JE
Dept. Microbiology, Univ. Texas Medical Branch, Galveston, TX, 77550
JNCI; 67(1):95-97 1981

The effect of trans-retinoic acid on the growth of P388 lymphoid tumors in inbred female DBA/2 mice in the presence or absence of interferon (IFN) treatment was studied. This acid derivative of vitamin A enhanced local tumor growth. Trans-retinoic acid also partially reversed IFN protection against tumor growth and mortality. (Author abstract) (15 Refs)

23. ROLE OF HOST CELLS IN THE SUPPRESSION OF EHRLICH ASCITES CARCINOMA CELL PROLIFERATION IN VIVO BY VIRUS-INHIBITING FACTOR OR INTERFERON.

Nagano Y, Saito H, Kurashima S, Kumazawa Y
Hopital National de Sagamihara, Sagamihara, Japan
C R Soc Biol (Paris); 173(5):960-966 1979

The effect of activation or depression of peritoneal macrophages or lymphoid cells on the antitumoral action of interferon was studied in mice inoculated with Ehrlich ascites carcinoma (EAC) cells. EAC cells were implanted ip in male STD-ddy mice (aged 5-7 wk) previously irradiated (500 rads to the whole body) or treated with lymphocytosis-promoting factor, ip injections of silicium, trypan blue, or carrageenan lambda. Interferon was obtained from L929 cells infected with Newcastle's disease virus, and injected ip into the mice at the rate of 20,000 units/day for 3 days following inoculation. The results show no significant difference in the suppressive action of interferon on the proliferation of EAC cells between the various groups of mice, suggesting that host cells have no role in the mediation of the antitumoral action of interferon. (10 Refs)

24. ELECTROPHORETICALLY PURE MOUSE INTERFERON EXERTS MULTIPLE BIOLOGIC EFFECTS.

Gresser I, De Maeyer-Guignard J, Tovey MG, De Maeyer E
Institut de Recherches Scientifiques sur le Cancer, B. P. 8, 94800 Villejuif, France
Proc Natl Acad Sci USA; 76(10):5308-5312 1979

Partially purified (PP) and electrophoretically pure (EP) mouse interferon (IF) from C-243 cells had species-specific antiviral activity. EP-IF contained two proteins (mol wt 22,000 and 35,000). The specific activity of PP-IF was 1-2.9 x 10(7) reference units/mg protein, compared to 9.9 x 10(8) to 1.5 x 10(9) units/mg for EP-IF. EP-IF was stabilized by suspension in bovine serum albumin (BSA: 100 ug/ml in phosphate-buffered saline). PP-IF or EP-IF (9-day ip course) was given to BALB/c mice, beginning 2 hr after ip inoculation of Ehrlich carcinoma (1.6 x 10(4) cells). The mean survival time (MST) was 16.7 days in untreated controls, with no long-term survivors (LTS: greater than 160 days). BSA alone (0.25 ml/day) had no antitumor effect. Both IF preparations significantly increased the MST (34.2 days with EP-IF, 51.3 days with PP-IF) and the LTS rate (1/8 and 3/7 mice, respectively), and significantly reduced tumor cell counts (day 7 after tumor inoculation). There was no significant difference between the antitumor effects of PP-IF and EP-IF. EP-IF significantly inhibited the multiplication of IF-sensitive L1210 mouse leukemia cells, but not of an IF-resistant subline. L1210 cells exposed to EP-IF absorbed more mouse alloantiserum (C57BL/6 mouse anti-DBA/2 lymphocyte serum) than untreated or BSA-exposed L1210 cells. Both IF preparations also inhibited antibody formation (in vitro), sensitization to sheep RBC (in vitro), and the expression of delayed-type hypersensitivity (in mice). Both IF preparations enhanced natural killer cell activity (in vitro and in vivo), the sensitivity of mouse embryo fibroblasts to polyinosinic:polycytidylic acid (poly-I:poly-C) in vitro, and IF production induced by poly-I:poly-C. These results suggest that the molecules responsible for the antiviral activity of IF are also responsible for these other biologic effects. (60 Refs)

25. DIFFERENCES IN THE ANTIVIRAL AND ANTIONCOGENIC EFFECTS OF INTERFERONS PRODUCED IN PERITONEAL CELLS OF MICE AND IN KREBS-2 ASCITIC CARCINOMA CELLS.

Marchenko VI, Pokidysheva LN, Malinovskaia VV, Aliab'eva TI, Khesin IaE
N. F. Gamaleia Inst. Epidemiology and Microbiology, USSR Acad. Medical Sciences, Moscow, USSR
Vopr Virusol; (3):344-348 1977

Results of the comparative analysis of two murine interferon preparations are presented. Macrophage interferon was derived from mouse peritoneal cells; 'Krebs' interferon, from ascitic fluid of albino random bred mice with transplanted Krebs-2 carcinoma. Interferon synthesis was induced by incubation of the cell cultures with Newcastle disease virus. L cells treated with macrophage interferon developed resistance to vesicular stomatitis virus within 5-6 hr of exposure, while L cells treated with Krebs interferon developed resistance within 1-2 hr of expsoure. Activity of acid phosphatase was higher in L cells treated with Krebs interferon (40%, compared with 2% in cells treated with macrophage interferon). Both macrophage and Krebs interferon inhibited reproduction of Krebs-2 carcinoma cells in mice. (3 Refs)

26. TREATMENT OF MAMMARY CARCINOMA OF C3H MICE BY MEANS OF THYMIC FACTOR, MEASLES VACCINE AND L-DOPA.

Busse E, Rose H, Helmholz M
Abteilung fur Angewandte Tumorbiologie, Geschwulstklinik der Charite, Schumannstr. 20/21, DDR-1040 Berlin, E. Germany
Radiobiol Radiother (Berl); 22(1):63-68 1981

Effects of various combinations of thymic factor (TF), measles vaccine (MV), and L-dopa on mammary tumors in C3H mice were investigated. L-dopa was used to induce interferon and MV was used to induce cyclic AMP in the tumor-bearing mice. The mice were treated daily for 28 days with 0.3 ml TF, 300 mg L-dopa, or 0.3 ml of liver suspension, ip; MV (total dose of 2,000 TCD) was given 3x in a period of 2 days at the beginning of the experiment. The combination of L-dopa, TF, and MV produced tumor regression or tumor lysis in 12/19 mice. Omission of the TF from the protocol greatly reduced its efficacy; regression or lysis was induced in 3/15 mice treated with L-dopa and MV alone. No regressions or lysis were observed in the tumors of eight mice treated with the liver suspension or in the tumors of seven mice treated with the liver suspension and MV. It was concluded that the high rate of regression induced by the administration of all three antitumor agents resulted from synergism. (46 Refs)

27. ANTITUMOR AND ANTIMETASTATIC EFFECTS OF INTERFERON AND ITS INFLUENCE ON THE IMMUNE SYSTEM OF THE HOST.

Hiruma T
Dept. Microbiology, Nihon Univ., Sch. Medicine, Itabashi-ku, Tokyo 173, Japan
Nichidai Igaku Zasshi; 39(10):835-844 1980

The antitumor and antimetastatic effects of interferon were studied by using Lewis lung carcinoma which easily metastasizes spontaneously to the lungs from the inoculated site. The effect of interferon at the therapeutic dose on the immune system of the host was also investigated. When interferon was injected before inoculation of the tumor cells, it had neither an antitumor nor an antimetastatic effect. When interferon was injected repeatedly after the inoculation of tumor cells, a significant antimetastatic effect on pulmonary metastasis was observed but no antitumor effect on the primary tumor was evident. Surgical removal of the primary tumor resulted in a decrease in the number of metastatic foci in the lungs, and interferon treatment after surgical amputation of the limb into which the tumor had been inoculated was more effective in reducing the number of pulmonary metastases. The dose of interferon that was effective against metastasis to the lungs did not have any effect on the immune system of the host. (31 Refs)

28. INTERFERON MEDIATES ENHANCEMENT OF TUMOUR GROWTH AND VIRUS-INDUCED SARCOMAS IN MICE.

Gazdar AF, Sims H, Spahn GJ, Baron S
Natl. Cancer Inst., Bethesda, Md.
Nature [New Biol]; 245(142):77-78 1973

Although interferon and its inducers have been reported to inhibit the growth of tumors in vivo or tumorigenic and diploid embryonic cells in vitro, interferon inducers have also been reported to accelerate the growth of transplanted and virus-induced tumors and to enhance spontaneous and virus-induced transformation in vitro, particularly when there is pretreatment with the inducers. In the present work, weanling BALB/c mice and suckling Osborne-Mendel rats were used. The interferon used was prepared from Newcastle disease virus-infected Moloney sarcoma virus transformed S+L- cells. Pretreatment of mice with a single dose of interferon or poly (I) poly (C) 6-24 hr before infection with MSV enhanced tumor size and incidence. Simultaneous administration of virus and interferon or poly (I) poly (C) gave more variable and less significant results, while administration of interferon or poly (I) poly (C) 24 hr after virus had no significant effect. The tumor enhancing effect of both substances was strongly dose-dependent. Pretreatment of rats with interferon had no effect on tumor induction while poly (I) poly (C) pretreatment had a moderate effect. It was suggested that the paradoxical effects of interferon and its inducers on tumor growth may be associated with their effects on the immune system. Thus, under certain circumstances, interferon and poly(I) and poly (C) act as immunological adjuvants, while pretreatment may depress immunological responsiveness.

29. ANTITUMOR ACTIVITY OF INTERFERON AGAINST MURINE OSTEOGENIC SARCOMA IN VITRO AND IN VIVO.

Glasgow LA, Crane JL, Kern ER, Youngner JS
Dept. Pediatrics, Univ. Utah Coll. Medicine, Salt Lake City, UT, 84132
Cancer Treat Rep; 62(11):1881-1888 1978

In a line of osteogenic sarcoma (OGS) cells from a 239Pu-induced OGS of C57BL/6 mice, 3-7 days of exposure to mouse interferon (IF) inhibited cell growth at all concentrations tested (3-30,000 units/culture). Inhibition was almost complete at 3,000-30,000 units/culture. Inhibition of OGS cell growth was demonstrated by reduced clone formation in liquid medium, reduced tumor cell counts in monolayer cultures, suppression of colony formation in agar, and reduced DNA synthesis. IF did not inhibit the growth of mouse embryo fibroblasts at these concentrations. Rabbit anti-mouse IF antiserum blocked the growth-inhibitory effects of IF in OGS cells, showing that the active component of the preparation was IF rather than a contaminant. C57BL/6 mice inoculated sc with OGS (10(5) cells) were treated bid with IF for 7 days; IF injections (sc) at the site of tumor inoculation began immediately after tumor inoculation. All controls developed palpable tumors after 2-4 wk and died with tumors. All mice given 32,000 units/day of IF eventually developed tumors, but the latent period was prolonged by greater than 20 days and the mean survival time by 24 days. When a higher IF dose was given (60,000 units/day), the latent period was prolonged by 40 days, and 20% of the mice were tumor-free (NED) at 100 days. In mice treated with mouse IF Type I (induced by Newcastle disease virus in C-243-3 cells), all mice given a low dose (600 units/day) developed tumors within 16 days. At a higher dose (60,000 units/day), 80% of the mice were NED after 80 days. In mice treated with 600 mg/day of Type II IF (a serum IF of relatively low IF activity, containing other lymphokines), 90% were NED on day 80. Further studies are needed to determine the reasons for the markedly different antitumor activities of Types I and II IF. (18 Refs)

30. EFFECT OF INTERFERON ADMINISTRATION ON PULMONARY OSTEOGENIC SARCOMAS IN AN EXPERIMENTAL MURINE MODEL.

Glasgow LA, Kern ER
Dept. Pediatrics, Univ. Utah Coll. Medicine, Salt Lake City, UT, 84132
JNCI; 67(1):207-212 1981

The iv inoculation of a suspension of osteogenic sarcoma cells induced metastatic tumor nodules in the lungs of C57BL/6 mice. The administration of 50,000-100,000 U of interferon daily for 7 days strikingly reduced the tumor mass in the lung and the number of tumor nodules present in histopathologic sections when the interferon treatment was initiated immediately after tumor cell inoculation. In some animals the development of any detectable metastatic lesion was completely prevented. Extending the therapy from 7 days to 21 days failed to improve the protective effect. Interferon therapy delayed until 7 days after tumor cell inoculation had no effect. These findings indicate the effectiveness of exogenous interferon in this murine osteogenic sarcoma model when interferon treatment is initiated within 1 hr of tumor cell inoculation, but not when it is delayed until tumor nodules are established in the lungs. (Author abstract) (20 Refs)

31. INHIBITORY ACTION BY AN INTERFERON ANTAGONIST ON THE DEVELOPMENT OF THE CROCKER 180/TG TUMOR. A NEW MURINE LECTIN.

Chany-Fournier F, Pauloin A, Cerutti I, Chany C
Institut de Recherches scientifiques sur le Cancer, B.P. no 8, 94800 Villejuif, France
C R Acad Sci [D] (Paris); 286(21):1551-1553 1978

The effect of a costal cartilage extract from Swiss mice on the in vivo and in vitro growth of the 180/TG tumor (a mutant of the Crocker sarcoma) was investigated. Aqueous

extracts of the costal cartilage (TAI) were prepared both in crude and purified (filtration on Sephadex G 100 gel) forms. Previous tests showed the extract to be an antagonist to interferon. In vitro tests on the 180/TG cells revealed that the agglutination activity of the purified form was 4 x that of the crude form. In vivo tests were performed on Swiss mice inoculated ip simultaneously with 10 tumor cells and crude or purified TAI. The treatment with TAI was continued for 1 mo using three injections/wk at 48 hr intervals. The av duration of survival for mice treated with TAI was significantly (p less than 0.001) greater than that of mice inoculated with the tumor only. Furthermore, treatment with purified TAI caused complete tumor regression in 8/15 mice. (7 Refs)

32. TUMOR SUPPRESSION BY A LYMPHOKINE RELEASED INTO THE CIRCULATION OF MICE WITH DELAYED HYPERSENSITIVITY.

Salvin SB, Youngner JS, Nishio J, Neta R
Dept. Microbiol., Sch. Med., Univ. Pittsburgh, Pittsburgh, Pa.
JNCI; 35(5):1233-1236 1975

The effect of sera containing lymphokines such as migratory inhibitory factor and type II interferon on the growth of a transplanted 3-methylcholanthrene-induced sarcoma (MC-36) was studied in female CeHeB/FeJ mice. Sera containing the soluble mediators were obtained from Swiss Webster mice several wk after i.v. infection with viable Bacillus Calmette Guerin organisms. Treatment consisted of 0.2 ml of serum, it, daily beginning 24 hr after tumor transplant. Tumor growth was inhibited 96-99.8% in treated animals compared with mice treated with control sera. Histologic examination indicated a greater infiltration of mononuclear cells into the tumor sites. This demonstration of 'tumor inhibitoty factor' against a solid tumor in mice may suggest an approach to tumor immunotherapy in animals and man.

33. ANTITUMOR EFFECT OF INTERFERON PREPARATIONS ON MURINE TRANSPLANTABLE TUMORS.

Takeyama H, Kawashima K, Kobayashi M, Yamada K, Ito Y
First Dept. Internal Medicine, Nagoya Univ. Sch. Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466, Japan
Gan; 69(5):641-647 1978

Purified interferon (ITF) from Newcastle disease virus-infected mouse L-cell cultures was given to mice with 1-day-old ascites leukemias L1210, P388, or EL4, ascites lymphoma 6C3HED-OG, or solid (sc) transplants of a methylcholanthrene-induced fibrosarcoma (MCA tumor). In C57BL/6 mice with MCA, intratumoral injection of ITF (5 x 10 units/kg/day) significantly inhibited tumor growth. All treated mice survived 20 days, whereas 4/7 controls had died. This dose of ITF (given ip) had no antileukemic activity, but higher doses (10 units/kg/day) caused a significant increase in life span in mice with leukemias L1210 (39%) and P388 (100%). The antileukemic effects of ITF were dose-related. Ascites fluids from ITF-treated leukemic mice showed marked macrophage infiltration. The ED50 of mouse L-cell ITF in cultures of L1210 or MCA cells was 10 units/ml. The same titer of human WBC ITF was not cytotoxic to L1210 cells. Mouse L-cell ITF had little effect on L1210 or MCA cells at 10 units/ml. (21 Refs)

34. ANTITUMOR ACTIVITY OF INTERFERON PREPARATIONS INDUCED BY BACTERIAL ENDOTOXIN OR PURIFIED PROTEIN DERIVATIVE OF TUBERCULIN (PPD) IN BACILLUS CALMETTE-GUERIN (BCG)-INFECTED MICE.

Takeyama H, Kawashima K, Kobayashi M, Yamada K, Ito Y
First Dept. Internal Medicine, Nagoya Univ., Sch. Medicine, Showa-ku, Nagoya 466, Japan
Gan To Kagaku Ryoho; 6(3):537-543 1979

BCG-infected mice produced a large amount of interferon into circulation after iv injection of Escherichia coli endotoxin or purified protein derivative. Endotoxin-induced interferon (E-IF) and immune-induced interferon (I-IF) are different from virus-induced interferon (L cell IF) in physico-chemical properties. Both E-IF and I-IF were approx 100 x more potent on inhibitory activity of cell growth than cultured L cell IF. E-IF showed marked cytopathic effect on L cells. Daily intratumor injection of E-IF or I-IF into C57BL/6 mice inoculated with 3-methylcholanthrene-induced fibrosarcoma significantly suppressed tumor growth. (Author abstract) (21 Refs)

35. EFFECTS OF IMMUNOTHERAPY ON A RETICULOSARCOMA IN SWISS MICE INDUCED BY A VT4 VIRUS WITH RNA, ISOLATE OF THE TUMOR IN COMBINATION WITH INTERFERON, INDUCED IN VITRO BY THE SAME RNA.

Tran Ba Loc P
Lab. Zool. Parasitol., Fac. Med. Pharm., Besancon, France
C R Soc Biol (Paris); 166(2/3):343-345 1972

A transplantable reticulosarcoma tumor, ST4, was induced in Swiss mice by massive doses of chloramphenicol. The presence of an oncogenic virus VT4 in the cell-free filtrates of such tumors could be demonstrated by electron microscopy. A preparation of chemically modified RNA was obtained from spleen extracts of ST4-bearing animals by treatment with sodium formaldehyde sulfoxide and subsequent phenol extraction. Four-hr incubation of cultured L1210 cells with such RNA preparations (1 mg RNA 10(6) cells) led to the production of an interferon-like substance, named immunoferon by the author. The method of isolation of immunoferon from the L1210 cultures is given. Ip admin of immunoferon (in a dose corresponding to the amount extracted from 5 x 10(6) leukemia cells) to Swiss mice on 0 15, 17, or 19 after inocn with VT4 increased survival from 42 +/- 7 to 97 +/- 5 d. (7 refs)

36. HUMAN FIBROBLAST INTERFERON IN HUMAN NEOPLASIA: CLINICAL AND LABORATORY STUDY.

Horoszewicz JS, Leong SS, Ito M, Buffett RF, Karakousis C, Holyoke E, Job L, Dolen JG, Carter WA
Dept. Viral Oncology, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Cancer Treat Rep; 62(11):1899-1906 1978

The mass production and purification of human fibroblast interferon (HFIF) from 12 normal diploid cell lines is described. During a 6-mo period, greater than 850 x 10(6) international reference units (RU) of HFIF were purified to a specific activity of 2 x 10(7) RU/mg protein. Lyophilized purified HFIF (5 x 10(6) RU/vial) passed standard safety tests in rats, mice, and normal persons. In established human tumor cell lines 5959 (osteogenic sarcoma), RT-4 (transitional cell carcinoma), and DAUDI (Burkitt's lymphoma), HFIF inhibited cell growth by greater than 50% at 100 RU/ml. A higher concentration (greater than 1,000 RU/ml) was required for growth inhibition of cell lines A-204 (rhabdomyosarcoma), HT-29 (colonic adenocarcinoma), and

MeWo (melanoma), as well as normal human diploid fibroblasts. In athymic nude mice inoculated sc with DAUDI, MeWo, A-204, or RT-4 (5 x 10(6) cells), the effects of HFIF (20,000 RU/day x 6 wk) on tumor growth showed a good correlation with the in vitro results for all tumors but DAUDI. In tissue cultures of benign prostatic hyperplasia, HFIF (100-1,600 RU/ml, 48 hr) caused a dose-dependent reduction in DNA synthesis. Epithelial cells were 2-10x more sensitive to HFIF than fibroblastic cells. Two patients with disseminated cutaneous melanomas were injected intratumorally with HFIF (5 x 10(5) RU/day x 14-30). One patient's tumor disappeared clinically and histologically. The other patient showed 75% regression of the tumor, although viable cells persisted. Uninjected tumors did not regress. Both HFIF-injected tumors were heavily infiltrated by lymphocytes; this was not observed in uninjected tumors. There were no side effects. It is concluded that HFIF may soon be suitable for clinical trials. (8 Refs)

37. MECHANISM OF REJECTION BY NUDE MICE OF TUMORS PERSISTENTLY INFECTED WITH VIRUS. ROLE OF THE NATURAL KILLER (NK) CELL-INTERFERON (IF) SYSTEM (MEETING ABSTRACT).

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Jichi Medical Sch., Sch. Medicine, Minamikawachi-machi, Tochigi Pref. 329-04, Japan
Proceedings of the 10th Annual Meeting of the Japanese Society for Immunology held in Kumamoto, 4-6 December, 1980. The Japanese Society for Immunology, Kyoto 606, Japan, 750 pp., 1980.

Although HeLa or BHK cells (greater than 10(1) cells) killed Balb/c nude mice, producing tumors during 2-4 wk when injected sc, those cells infected with various RNA viruses (Virus PI cells) did not produce tumors in nude mice at all, even with more than 10(6) cells, in spite of their activity in vitro. When nude mice were given whole body x-irradiation with 600 R, Virus PI cells produced tumors and killed the mice. In in vitro experiments the spleen cells of nude mice showed strong cytotoxic activity against Virus PI cells, killing 20-50% of them, but they did not kill any HeLa or BHK cells. The effector cells responsible for the killing activity were identified as NK cells. The supernatants of mixed cultures of the spleen cells with Virus PI cells showed NK-enhancing activity and contained IF, whereas the supernatants of mixtures of spleen cells with HeLa or BHK cells did not have such activity or IF. The NK-enhancing activity was inactivated by anti-IF antiserum, but the addition of purified IF restored the activity. The cells selectively reacting with Virus PI cells in the production of IF were classified as members of a subset to which NK-effector cells belong. When Virus PI cells were transplanted sc into nude mice which were inoculated simultaneously with anti-IF gamma-globulin iv, tumors grew rapidly within 10-20 days and metastasis occurred. (no Refs)

38. EFFECT OF INTERFERON ON TUMOR-FORMING ABILITY OF WALKER CARCINOSARCOMA 256 CELLS and SECRETION OF EXOTOXIN BY THE BACILLUS, CLOSTRIDIUM WELCHII (TYPE C).

Babbar OP, Singh DP, Bajpai SK
Cent. Drug Res. Inst., Lucknow, India
Indian J Exp Biol; 11(3):199-206 1973

Both endogenous and exogenous interferon induced by Ranikhet disease virus specifically blocked tumor formation by Walker 256 carcinosarcoma cells in rats and markedly decreased the secretion of exotoxins by Clostridium welchii (type C), without altering their other potentialities. The blocking induced by endogenous interferon could be further prolonged by exogenous interferon; excessive doses of interferon were accompanied by decrease in tumor size (and in some cases complete remission), but 14 d after the end of interferon treatment there was no residual immunity. Results suggest two modes of action of interferon in rats: (1) the ability to inhibit the cellular mechanism by which Walker 256 cells form tumors; and (2) the ability to stimulate a tissue rejection mechanism in the host. (58 refs)

39. INTERFERON (IF) AND ITS IMPLICATION FOR MALIGNANT BRAIN TUMORS. (II) POLYINOSINIC-POLYCYTIDYLIC ACID (POLY(I)-POLY (C)) AND POLYINOSINIC-POLYCYTIDYLIC ACIDS STABILIZED WITH POLY-L-LYSINE AND CARBOXYMETHYL CELLULOSE (POLY(I;C-L.C.)) (MEETING ABSTRACT).

Shidara N, Nakamura O, Takakura K, Sano K, Machida H
Dept. Neurosurgery, Univ. Tokyo, Faculty Medicine, Bunkyo-ku, Tokyo 113, Japan
Program and Proceedings of the 38th Annual Meeting of the Japan Neurosurgical Society, held in Tokyo, Japan, October 3-5, 1979. Tokyo, Japan, 1979.

The inhibition of transplantation and the life prolongation effect of synthetic double-stranded RNA [(Poly(I)-Poly(C) and Poly(I;C-LC)] in an experimental brain tumor model in Wistar rats, and the interferon (IF) values in patients given Poly(I)-Poly(C) or Poly(I;C-LC), were determined. When 10(6) C6 cells were transplanted into the brains of rats 4 wk or more after birth, and Poly(I)-Poly(C) (10 mg/kg) was injected ip, 6 days after transplantation, the rate of transplantation was 10%, whereas that of the control was 66.6%. The av survival rate of rats with tumors after administration of 10 mg of Poly(I)-Poly(C) per kg 7 days after transplantation and two subsequent injections of 2.5 mg/kg was 22.3 +-1.3 days, which was significantly higher than the 16.7 +-0.9 days for the control group (p less than 0.005). When Poly(I)-Poly(C) was administered iv to four patients with neuroblastoglioma (1 mg/kg), the serum IF values were determined by the 50% plaque depression method. The IF value was markedly increased by iv injection of 1 mg of Poly(I;C-LC) per kg, [2,410 +-319 (4 hr), 3,100 +-84 (8 hr) and 232 +-26 (24 hr)], values 10-20x greater than those for Poly(I)-Poly(C), and the concentration was also continuous. Thus, both Poly(I)-Poly(C) and Poly(I;C-LC) were found effective in an experimental model and a significant IF value was obtained in clinical cases suggesting the possibility of using IF inducers clinically as maintenance therapy for malignant tumors. (no Refs)

II. CELLULAR AND SUBCELLULAR EFFECTS OF INTERFERON

A.
Effects of Interferon on DNA Synthesis

40. EFFECTS OF INTERFERON ON THE HUMAN CLONAL CELL LINE, RSA: INHIBITION OF MACROMOLECULAR SYNTHESIS.

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Dept. Microbiology, Sch. Medicine, Chiba Univ., Chiba 280, Japan
J Gen Virol; 33(1):17-24 1976

The inhibitory effect of human leukocyte interferon preparations on protein and DNA synthesis and on cell division was investigated in RSa cells and interferon-resistant (IFr)

cells. Growth of RSa cells was completely suppressed after 2 day treatment with interferon (500 units/ml), but the effect of interferon was less marked in IFr cells. Higher interferon concentration resulted in less incorporation of H-thymidine in RSa cells which were pulse-labelled with H-thymidine after 2 day treatment with interferon; max inhibition was 31% in the acid-soluble fraction and 625 in the acid-insoluble fraction after 3 days of interferon treatment. Incorporation of H-thymidine into the same fractions of IFr cells was inhibited slightly and at almost the same rate. Interferon treatment of RSa cells led to a slight increase in rate of H-uridine uptake, and the comparably increased rate of RNA synthesis presumably reflected this increase. A significant decrease in protein synthesis in interferon-treated RSa cells was observed; protein synthesis decreased to 58% of control cells when treated with 500 units/ml of interferon for 3 days. Histologic examination showed that the number of fibroblastic type cells decreased and the percentage of epithelial-type cells increased after treatment for 24 hr with interferon. The inhibitory effect of interferon is presumed to result from epithelial-type cells being prevented from entry into a particular phase of the cell cycle. This could be the result of inhibition of DNA synthesis, protein synthesis, or both. Preliminary results show that DNA synthesis in the S phase is completely inhibited when interferon is added late in the G1 phase, and cells remain in the G1/S boundary phase. (18 refs)

41. INHIBITION OF DNA SYNTHESIS OF SYNCHRONIZED RSA CELLS BY HUMAN LEUKOCYTE INTERFERON.

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JNCI; 58(4):891-896 1977

Monolayer cultures of synchronized RSa cells (obtained from double-transformed foci induced by Rous sarcoma virus and simian virus 40 in human embryonic fibroblasts) were prepared by double thymidine or thymidine-Colcemid block, and the action of interferon in the cell cycle was studied. After reversal of thymidine block, cell growth resumed in a synchronous manner with an increased rate of [H]thymidine incorporation followed by an abrupt increase in cell number. When interferon was added to synchronous cultures at G1/S boundary phase, a slightly reduced but not delayed DNA synthesis was noted, and subsequent cell mitosis was delayed and reduced. These results are consistent with those previously reported of no delay of DNA synthesis by the alkylating agent when exposed cells reached the first S phase. When RSa cells were treated with interferon preparations during late G1 phase, the peak of DNA synthesis in S phase disappeared, and subsequent mitosis, as measured by changes in cell number and cell morphology, was not seen. The depression in the rate of overall protein synthesis in asynchronous cultures was not so marked as that in synchronous culture of RSa cells, and the reduced rate of protein synthesis was not so marked as that of DNA synthesis in treated cultures. Results suggested that critical events leading to inhibition of DNA synthesis and mitosis by interferon take place in late G1 phase or S phase. It is also noted that anticellular activity present in interferon preparations may be ascribed to interferon molecules themselves. (25 refs)

42. INHIBITION OF DNA SYNTHESIS AND ALTERATION OF CYCLIC ADENOSINE 3',5'-MONOPHOSPHATE LEVELS IN RSA CELLS BY HUMAN LEUKOCYTE INTERFERON.

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Dept. Microbiology, Sch. Medicine, Chiba Univ., 1-8-1 Inohana, Chiba 280, Japan
JNCI; 60(6):1227-1232 1978

The effects of human WBC interferon (INF: 10-1,000 units/ml) on DNA synthesis and intracellular cyclic AMP (cAMP) levels were studied in the RSa line of doubly (SV40 and Rous sarcoma virus) transformed human embryonic fibroblasts and in an INF-resistant subline (INFr) of RSa. In RSa cells in G1 and early S-phase, INF inhibited proliferation, reduced H-thymidine (TdR) incorporation into an intracellular pool, and reduced TdR kinase activity. In asynchronously growing RSa cells, an INF concentration (1,000 units/ml) that reduced TdR incorporation by greater than 90% also caused a greater than 2x increase in intracellular cAMP. Lesser inhibition of DNA synthesis was associated with smaller increases in cAMP levels. INF had much less effect on DNA synthesis and cAMP levels in INFr cells. DNA polymerase levels remained constant in both cell lines and were not affected by INF. Addition of dibutyryl-cAMP (1.0 milliM), with or without theophylline (1.0 milliM), inhibited the growth of RSa and INFr cells to about the same extent. RSa cells were arrested by G1 by cultivation for 3 days in unchanged Eagle's minimal essential medium. The initiation of DNA synthesis and decrease in cAMP caused by addition of serum was prevented by INF pretreatment. It is concluded that intracellular cAMP may mediate the inhibitory effects of INF on DNA synthesis and cell growth. (35 Refs)

43. BLOCK OF A GLIOMA CELL LINE IN S BY INTERFERON.

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Int J Cancer; 27(6):749-754 1981

The human glioma cell line U-251 MG, with a well-characterized defect in growth control, was sensitive to the antiproliferative effects of human (fibroblast) interferon (IFN). IFN inhibited exponentially growing cells by increasing the number of cells in the S stage of the cell cycle. At the same time the number of cells in G0/G1 diminished. The rate of thymidine incorporation was decreased during the first cell cycle, with no prolongation of S. However, in synchronized cultures, the wave of cells with an S-phase content did not decrease over a time period several hr longer than the length of S measured by pulse labeling. Thus we conclude that, at a sufficient dose, the cells were unable to accomplish cell division as they prematurely stopped synthesizing DNA. (Author abstract) (28 Refs)

44. EFFECT OF BROMODEOXYURIDINE AND INTERFERON ON CELLULAR AND VIRAL FUNCTIONS IN HUMAN PROSTATIC CELLS.

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Dept. Medical Viral Oncology, Roswell Park Memorial Inst., Buffalo, NY
Oncology; 36(1):35-39 1979

Some of the human prostatic cells in culture apparently produce oncornavirus-like particles. Bromodeoxyuridine does not enhance the production of these particles. On the contrary, this drug depresses such production. This depression is likely to be due to the cytotoxic effects of bromodeoxyur-