Circulating Interferon Production in the Mouse

Origin and nature of cells involved and influence of animal genotype

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ABSTRACT A radiobiological study of circulating interferon production in the mouse was undertaken in the hope of elucidating the site(s) of circulating interferon production. After total body X-irradiation of the animals, different radiosensitivities of circulating interferon production were observed with different viral inducers. Myxovirus-induced circulating interferon production was especially radiosensitive. Moreover, a study of interferon production in syngeneic and xenogeneic radiochimeras demonstrated that cells producing NDV (Newcastle disease virus)-induced circulating interferon were derived from hematopoietic stem cells. In addition, treatment of mice with antilymphocyte serum significantly reduced NDV- and Sendai virus-induced circulating interferon, as opposed to other inducers. Taken together, these results strongly suggest that the lymphocyte is the major source of myxovirus-induced circulating interferon. A survey of interferon production in 12 inbred mouse strains, using NDV as inducer, revealed the existence of low and high producers. A Mendelian analysis carried out with low producing Balb/c and high producing C57BL indicated that the difference between low and high interferon producers was caused by a single, autosomal, codominant factor.

INTRODUCTION

Considerable amounts of interferon are released into the blood stream of animals a few hours following intravenous inoculation of an appropriate virus suspension (1). The interferon resulting from this artificially produced viremia is called "circulating" interferon, and its induction has been extensively used for in vivo studies. Interpretation of results, however, has been hindered by lack of information concerning the source(s) of circulating interferon. We were faced with this problem while studying the effect of chemical carcinogens on

interferon synthesis in vivo (2), and therefore, we decided to investigate the cellular origin of circulating interferon more thoroughly. In the course of this study, the influence of animal genotype on interferon production became evident (3), and this was also further explored (4, 5).

The present report is a review of our results up to date; most of the data has been published *in extenso* elsewhere, and the appropriate details and experimental procedures can be found in these papers (6–9).

ORIGIN AND NATURE OF CELLS INVOLVED IN CIRCULATING INTERFERON SYNTHESIS

A. *Effect of Whole-Body X-Irradiation on Circulating Interferon Production*

Circulating interferon production was studied in C3H mice after whole-body X-irradiation. The best way to obtain consistent results, as shown by preliminary experiments, was to expose different groups of mice, each group consisting of six animals, to different doses of whole-body X-irradiation, usually 125, 250, 500, and 1000 R. 4 days after irradiation, the animals were injected intravenously with a given virus suspension, and interferon was measured at times of peak levels in the blood which, in most cases, was 6–9 hr after inoculation. Using nine different viruses and the synthetic double-stranded nucleic acid polyriboinosinic–ribocytidylic acid (poly I:C) as inducers, three different types of interferon-producing systems were observed.

The first type was very radiosensitive, since already with 125 R interferon production was reduced to 25% or less of control values. This result has been obtained with the four myxoviruses tested as inducers, namely Newcastle disease virus (NDV), Influenza type A-Sing, Sendai, and mumps.

The second type of response was one of intermediate sensitivity, a dose of 250–500 R being required to bring down significantly the interferon production. This situation was observed with two arboviruses, Sindbis and Semliki Forest, and with VSV, as inducers.

The third type of response was characterized by a high radioresistance, since even after 1000 R there was hardly any detectable effect on interferon production. This was observed both with vaccinia and encephalomyocarditis virus (EMC), and also with poly I:C as inducers. The high radioresistance of interferon induction with EMC virus has also been reported by Glasgow (10).

The results obtained with the nine viral inducers are graphically represented in Fig. 1.

From these radiation studies, it became evident that myxovirus-induced circulating interferon production differed from the other systems by its high radiosensitivity, which suggested that cells derived from the hematopoietic system were involved in this production. Indeed, total body exposure of mice to X-irradiation of 125 or 250 R results in a marked decrease of the number of lymphocytes, due to a unique and very pronounced susceptibility of the latter

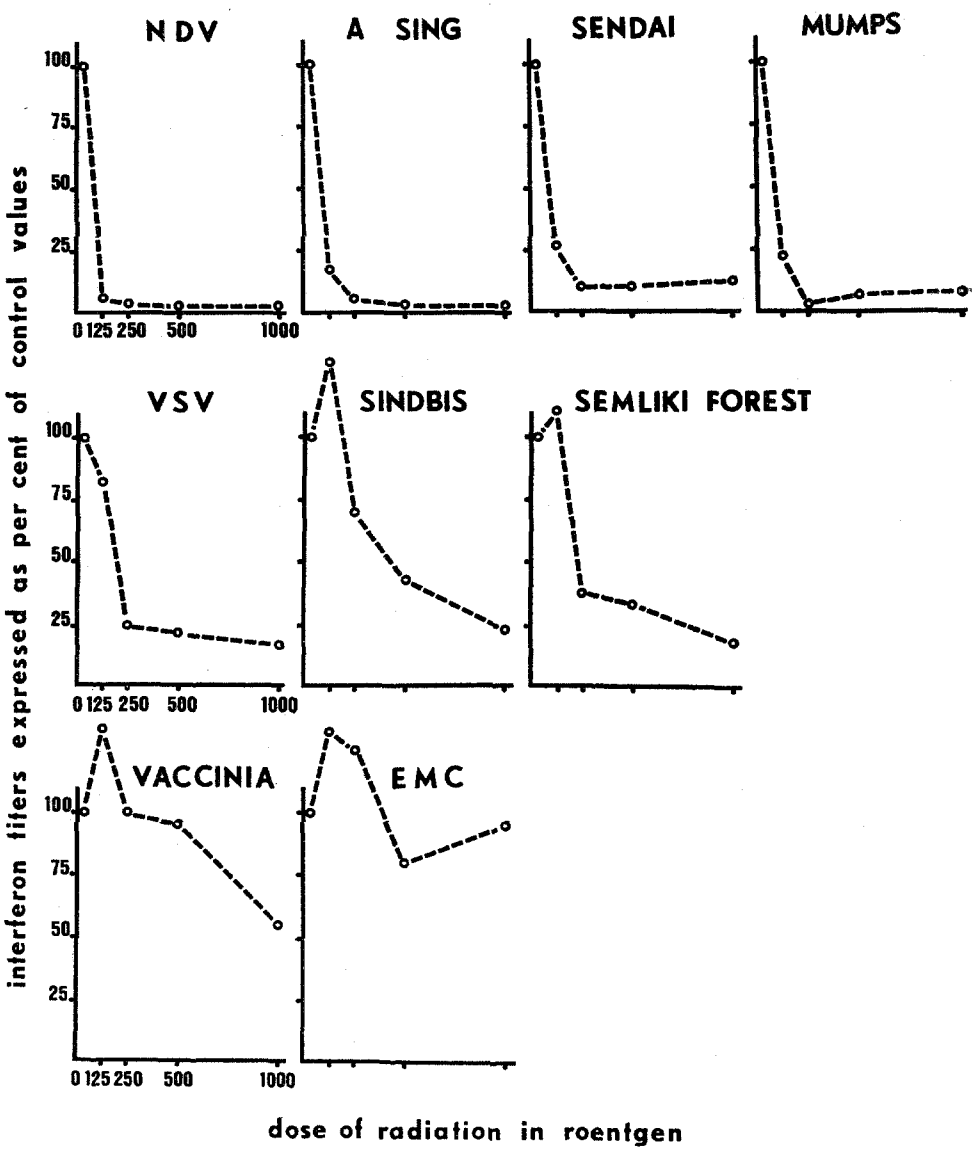

FIGURE 1. This figure represents the experiments concerning circulating interferon production with various viral inducers after total body exposure to different amounts of radiation. At each dose of exposure (plotted on the abscissa), circulating interferon levels are given as percentage of the control value obtained in unirradiated animals.

to a direct cell-killing effect of X-rays, a phenomenon known as "interphase death." In addition, X-irradiation results in a rapid decrease of granulocyte number, due to the combined effect of mitotic death of hematopoietic stem cells and the short half-life of the granulocyte (11, 12). The inhibition of myxovirus-induced interferon synthesis in irradiated animals therefore suggested a

causal relationship between the impairment of hematopoietic function and the decreased interferon levels observed in these animals. This hypothesis was investigated as follows.

B. *Restoration of Interferon Production in Lethally Irradiated Animals Grafted with Bone Marrow Cells*

C3H mice were exposed to 1000 R whole body X-irradiation, a dose which normally kills all animals about 9 days after irradiation mainly because of mitotic death of hematopoietic stem cells. However, the hematopoietic function of such lethally irradiated animals can be restored, and consequently the animals kept alive, if immediately after irradiation a sufficient amount of hematopoietic stem cells is administered. This can be achieved by inoculating bone marrow cells (13). In the experiments under discussion, some of the animals were grafted with a minimal amount of nucleated bone marrow cells (2×10^5) and the rest with an optimal amount (1×10^7). The marrow cells were obtained from syngeneic donors. Nonirradiated mice of the same age and sex were kept as controls. The NDV-induced interferon-producing capacity was then examined 11, 15, 21, and 30 days after irradiation and restoration, and each time grafted animals were compared with a control group of unirradiated mice. The results of this experiment are summarized in Fig. 2. It can be seen from the figure that in animals grafted with a minimal amount of marrow cells it took as long as 30 days for the interferon production to reach values close to normal levels, while in animals grafted with 10^7 cells, circulating interferon levels were back to normal already 15 days after irradiation and restoration. These results could be interpreted in the following two ways: either the interferon producing cells are derived from bone marrow cells, or the interferon producing system is not derived from bone marrow but depends

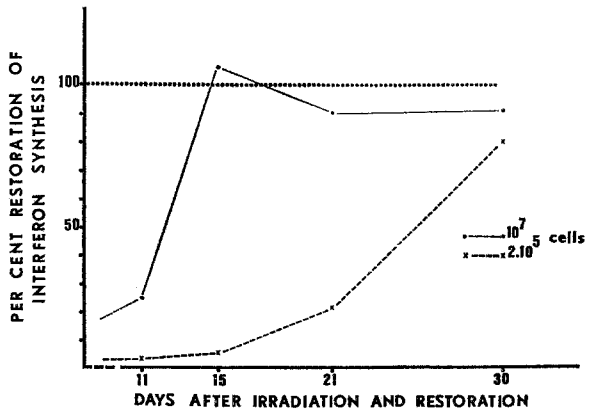

FIGURE 2. NDV interferon after irradiation (1000 R) and bone marrow restoration. *Figure reprinted from Int. J. Radiat. Biol. Related Stud. Phys. Chem. Med., 1967, 13:417, by permission of Taylor & Francis Ltd., London.*

somehow, yet indirectly, upon a normally functioning hematopoietic system for exerting its activity. To distinguish between these two possibilities, advantage was taken of the species specificity of interferon as will be shown in the next paragraph.

C. *Circulating Interefron Production in Rat-to-Mouse Chimeras*

It is now well established that, with a few interesting exceptions, interferon produced by cells of one species is unable to protect cells from a different species (14, 15). In related species some degree of cross-protection occurs, but in this case interferon usually is less active in heterologous cells. We have, therefore, attempted to restore the hematopoietic function of lethally irradiated C3H mice with rat marrow instead of syngeneic mouse marrow. This type of restoration has been reported by several investigators with varying results, the animals succumbing from a few weeks to several months after transplantation (16–18). In our experiments, the administration of Wistar rat cells to irradiated C3H/He mice proved successful, since those animals that were not used for experimentation survived at least 3 months. The fact that these animals were kept under specific pathogen-free conditions probably contributed to the successful establishment of the graft. As amply documented, rat-to-mouse chimera leukocytes are of rat type and make rat proteins (19–21). To study interferon production in xenogeneic chimeras, C3H mice were irradiated with 1000 R and grafted, thereafter, with 10^7 nucleated Wistar rat marrow cells. Some irradiated C3H mice were grafted with C3H mouse bone marrow to serve as controls. 30 days later, both kind of chimeras, together with unirradiated C3H mice and Wistar rats, were inoculated intravenously with NDV. Sera were obtained 6 hr later, pooled per experimental group, and interferon activity was measured in fibroblasts of rat and of mouse origin. Table I is a rather simplified summary of the whole experiment; it shows clearly that in rat-to-mouse radiation chimeras, circulating interferon induced

TABLE I

ACTIVITY IN RAT AND MOUSE CELLS OF NEWCASTLE DISEASE VIRUS INDUCED INTERFERON OBTAINED FROM RADIOCHIMERAS AND CONTROL ANIMALS

Origin of interferon	Titer in mouse embryo fibroblasts	Titer in rat WIRA* cells	Ratios of activity	
			mouse:rat	rat:mouse
Control C3H mice	15,500‡	2500	6.2	0.16
Mouse-to-mouse chimeras (syngeneic)	5000	1600	5.6	0.17
Wistar rats	200	2900	0.07	14.5
Rat-to-mouse chimeras (xenogeneic)	230	4600	0.05	20.0

* WIRA cells are a continuous line of rat cells isolated in our laboratory by C. Massenot.
‡ U/5 ml.

by NDV is mainly of rat type. Similar results were obtained in two comparable experiments, the first carried out 1 month, the second 2 months, after irradiation and bone marrow grafting; sera were titered individually instead of being titered as pools. As shown by the combined results of these experiments, cells producing circulating interferon in response to NDV are of donor type and are, therefore, most probably derived from hematopoietic stem cells present in the bone marrow graft. Additional evidence was obtained by comparing the molecular weights of the serum interferons in the four types of animals studied. This was done by gel filtration of sera on a column of Sephadex G-100, according to the method of Andrews (22), as applied to interferon by Merigan (23). Results are given in Table II.

TABLE II

MOLECULAR WEIGHTS OF CIRCULATING INTERFERON INDUCED BY NEWCASTLE DISEASE VIRUS IN RADIOCHIMERAS AND CONTROL ANIMALS

Source of interferon	Titration of effluent fractions on	
	Mouse L cells	Rat WIRA cells
Mouse	67,000 and 34,000	67,000 and 34,000
Mouse-to-mouse chimera	67,000 and 34,000	67,000 and 34,000
Rat	Too little activity for precise determinations	94,000 and 30,000
Rat-to-mouse chimera	Too little activity for precise determinations	94,000 and 30,000

As can be seen, when titrations of effluent fractions are carried out on mouse L cells, interferon activity is found in two peaks, corresponding respectively to molecular weights of 34,000 and 67,000 both for control mice and for syngeneic chimeras; this shows that irradiation and restoration per se have no effect on the molecular weight. Comparable molecular weights for NDV-induced mouse serum interferon have previously been observed by Hallum, Youngner, and Merigan (24). In contrast, rat interferon and rat-to-mouse chimera interferon show hardly any activity at all in the L cells, which is quite normal due to the low heterospecific activity and the dilution after gel filtration. However, there are two zones in which there is a suggestion of antiviral activity; one corresponds to a molecular weight of 30,000, the other to a molecular weight of 90,000. This impression is confirmed upon titration of the same fractions in rat embryo cells.

It was very fortunate that the heavy peak of rat interferon, with a molecular weight of 94,000, was located in a region different from that of the heavy mouse interferon (67,000); and therefore, it was possible to demonstrate that the molecular weight of NDV-induced interferon in rat-to-mouse chimeras has the characteristics of rat interferon.

D. *Effect of Antilymphocyte Serum on Circulating Interferon Production*

Up to this point, our experiments allow us to conclude that when NDV is inoculated into the blood stream, circulating interferon is to a great extent made by very radiosensitive, bone marrow-derived cells. Both lymphocytes and granulocytes fall into this category; however, the highly inhibitory effect of a dose of X-rays as low as 125 R suggests that lymphocytes, rather than granulocytes, are involved. This was borne out by an experiment in which C3H mice were inoculated intraperitoneally with antimouse lymphocyte serum during 3 consecutive days. On the 4th day circulating interferon production was induced with either NDV, Sendai, Sindbis, EMC, or poly I:C. At this time white cell counts from peripheral blood showed that the number of lymphocytes was decreased by 75%, while the number of granulocytes had not changed.

It can be seen from Table III that circulating interferon production is significantly decreased by antilymphocyte serum, only when NDV and Sendai are employed as inducers; this observation further strengthens the hypothesis that myxovirus-induced circulating interferon in the mouse is largely made by lymphocytes.

E. *Experiments with Encephalomyocarditis Virus as Inducer*

The situation is quite different in the case of the radioresistant system of interferon production induced with EMC or vaccinia virus. In this instance, we have no clue as to the origin of the cells responsible for circulating interferon synthesis; we can of course rule out a major contribution of very radiosensitive cells, such as lymphocytes or granulocytes. We have recently completed a series of experiments in which circulating interferon synthesis was studied after intravenous injection of EMC virus into unirradiated C3H mice, mouse-

TABLE III

EFFECT OF ANTILYMPHOCYTE SERUM ON CIRCULATING INTERFERON PRODUCTION IN C3H MICE*

Inducer	Interferon titers of mice treated with control serum	Interferon titers of mice treated with antilymphocyte serum
NDV	700‡	105 (15%)§
Sendai	765	83 (11%)
Sindbis	1050	555 (52%)
EMC	3000	2700 (90%)
Poly I:C	90	200 (220%)

* 7-month-old C3H mice received an intraperitoneal inoculation of 0.25 ml of antimouse lymphocyte horse serum (Microbiological Associates Inc., Bethesda, Md.) or of normal horse serum during 3 consecutive days. Circulating interferon was induced 16 hr after the last injection of serum.

‡ U/2 ml. Each value represents the titer of a serum pool from six mice.

§ Per cent of control value.

to-mouse chimeras, and rat-to-mouse chimeras. The relative species specificity of the EMC induced serum interferon was determined in these animals 14, 48, and 85 days after irradiation and restoration.

Table IV gives a rather simplified summary of the whole experiment. The ratios of interferon activity in mouse cells as compared with activity in rat cells represent the average value of ratios obtained for four to six individual sera per group. It is quite evident that, up to 85 days after irradiation and bone marrow grafting, EMC-induced circulating interferon is still of mouse type, even in rat-to-mouse chimeras. Just to make sure that the xenogeneic chimeras still harbored rat cells 85 days after grafting, NDV was injected into some of the animals; and we found that this virus still induced rat interferon. These results

TABLE IV

RATIOS OF ACTIVITY MOUSE CELLS:RAT CELLS OF EMC-INDUCED CIRCULATING INTERFERON OBTAINED FROM RADIOCHIMERAS AND CONTROL ANIMALS

Days after irradiation and bone marrow transfusion	Inducer	Control mice	Mouse-to-mouse chimeras	Rat-to-mouse chimeras
48	EMC Expt 1	20*	27	10
	Expt 2	35	30	26
85	EMC	70	76	40
	NDV	35	30	0.23

* Each value was obtained as follows. The interferon titer of each individual serum was determined on mouse embryo fibroblasts and on rat WIRA cells. The ratio of titer in mouse cells to titer in rat cells was then determined for each serum, and the average ratio was calculated for each experimental group, consisting of from four to six sera. A value of 20, for example, means that the interferon was on the average 20 times more active on mouse cells than on rat cells, or in other words, it retained only 5% of its activity in rat cells.

then are open to two interpretations: either EMC-induced interferon is not made in bone marrow derived cells, or it is made in bone marrow-derived cells characterized by a high radioresistance and a very slow turnover with a half-life exceeding 85 days. Macrophages are radioresistant, bone marrow-derived cells and, furthermore, as we have observed in vitro, they can go on making interferon even after exposure to 1000 R (8). However, as shown by Balner in radiation mouse-to-mouse chimeras, peritoneal macrophages are totally replaced by donor macrophages about 40 days after irradiation and bone marrow grafting (25). To check this in our animals, we have isolated peritoneal macrophages from our rat-to-mouse chimeras 45 and 85 days after irradiation and restoration, and we characterized the interferon produced by these cells upon stimulation in vitro with NDV. The obtained interferon had about equal activity in rat and in mouse fibroblasts when it was produced by macrophages derived from 45-day chimeras, suggesting that roughly one-half

of the macrophage population in these chimeras was derived from the graft. The macrophages derived from 85-day chimeras produced interferon which was about 3 times more active in rat cells than in mouse cells. The fact that circulating interferon induced by EMC virus in the rat-to-mouse chimeras had only a trace of activity in rat cells (see Table IV), therefore strongly suggests that macrophages play a minor role, if any at all, in circulating interferon synthesis triggered by this virus. Of course, we do not know how much the free peritoneal macrophages reflect the situation of, for example, fixed macrophages of spleen and liver.

F. *Conclusion*

At this stage of our experiments, we can conclude that, from a radiobiological point of view, there are three types of circulating interferon synthesis, depending upon the virus used as inducer. One system is very radiosensitive, bone marrow derived, and inhibited by antilymphocyte serum; this type of response was obtained with myxoviruses. Another system is radioresistant and probably not derived from hematopoietic cells; this type of response was obtained with EMC as inducer. And in between is a circulating interferon-producing system of intermediate radiosensitivity, slightly inhibited by antilymphocyte serum; this situation was observed with the two arboviruses studied and with vesicular stomatitis virus (VSV). We have not examined very extensively the origin of the interferon-producing cells of the intermediate system, but we have evidence suggesting that at least some of the cells are derived from hematopoietic stem cells (7).

INFLUENCE OF ANIMAL GENOTYPE ON CIRCULATING INTERFERON PRODUCTION

The contribution of interferon to the host defense mechanism is ill defined and even controversial. Interferon depressors also inhibit cellular or humoral immunity, and it would be difficult to single out interferon and to eliminate or increase its production during virus infection without changing other parameters as well. One approach to this problem would be to compare animals with already naturally significantly different interferon production upon infection with the same agent. Therefore, we though it worthwhile to follow up our fortuitous observation that mice of the C57BL strain had significantly higher serum interferon levels after inoculation with NDV than mice of either the Balb/c or C3H strain (3). Fig. 3 shows the kinetics of circulating interferon induction in 2-month-old Balb/c and C57BL mice. It can be seen that the average peak interferon titer obtained in Balb/c mice is about 3000 U/1.6 ml, 9 hr after inoculation of NDV, whereas the peak value of C57BL in this particular experiment is 15,000 U, 12 hr after inoculation of the virus. Later experiments have shown that usually peak values in C57BL are found between 8 and 9 hr after inoculation, and that they are situated around 20,000 U. If

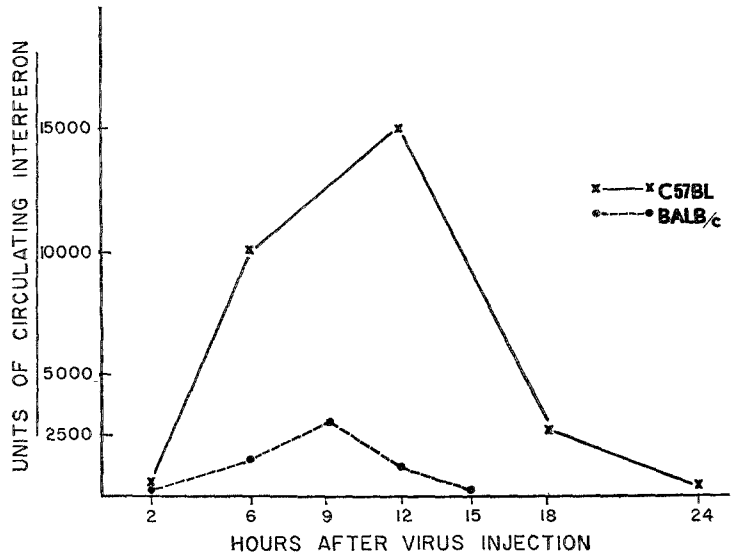

FIGURE 3. Kinetics of NDV-induced circulating interferon in C57BL and in Balb/c mice. 2-month-old Balb/c and C57BL mice were inoculated intravenously with a suspension of NDV. Blood was obtained from six animals at the intervals indicated, the sera were pooled, and the interferon content of the serum pools was measured. A different group of mice was used each time.

care is taken to measure interferon levels at their maximum value, no overlapping occurs between titers of Balb/c and C57BL mice. This enabled us to carry out a Mendelian analysis of the phenomenon by studying interferon synthesis in F_1 and F_2 hybrids and in different backcross generations. This analysis has shown that the difference in NDV-induced interferon production between both mouse strains is due to a single, autosomal, codominant factor, probably one gene or else a group of very closely linked genes (4) (Fig. 4).

The reason for the production of different amounts of interferon in both mouse strains is not clear at present; we have been able to rule out a number of possibilities, such as the presence of inactivators of interferon or of NDV in Balb/c serum or blood, or a difference in clearance rates of serum interferon between Balb/c and C57BL. Moreover, the different interferon levels probably do not merely reflect different degrees of virus replication in the animals, since UV-irradiated NDV also induces more interferon in C57BL mice, as does the synthetic polynucleotide poly I:C, although the difference in this case is not as pronounced as when NDV is used as inducer.

C57BL mice are generally quite resistant to infection with a number of agents, such as polyoma, mammary tumor virus, Friend or Rauscher leukemia virus, whereas Balb/c mice are susceptible to these agents; and the hypothesis that differences in interferon production contribute to this phenomenon

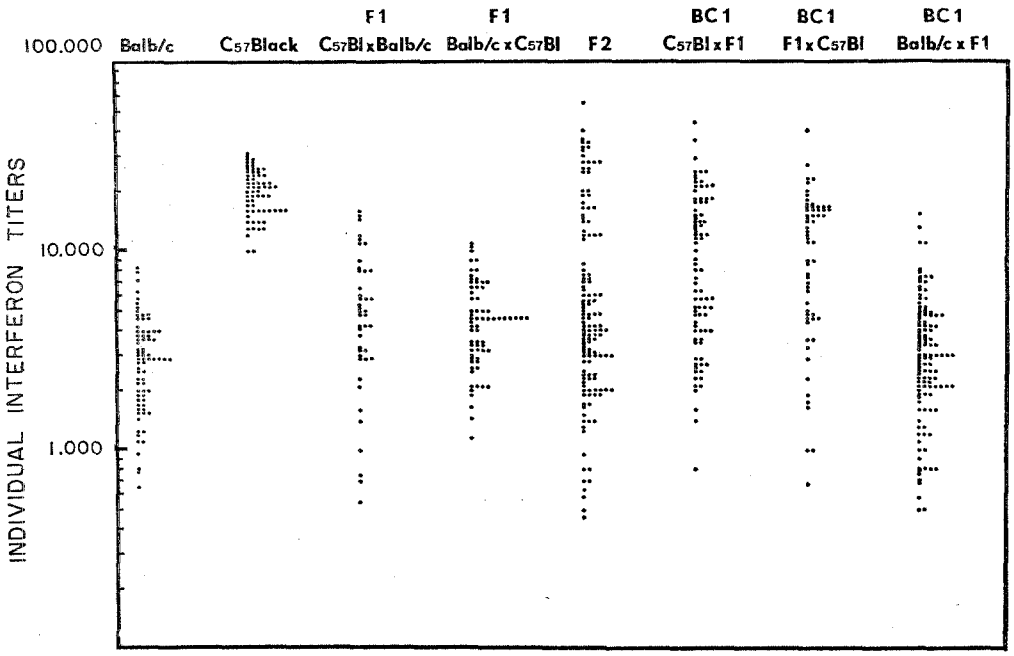

FIGURE 4. NDV-induced serum interferon titers from individual mice of both parent strains and different hybrid combinations. The titers are plotted on a log 10 scale. *BCI*, first backcross. *Figure reprinted from J. Virol., 1969, 3:506, by permission of the American Society for Microbiology.*

certainly merits further investigation. We are presently fully engaged in this study and will briefly summarize some of the information obtained at this stage. First of all, it was important to find out if the gene influencing interferon production with NDV also affected serum interferon induction by other agents. We have already mentioned that poly I:C induced more interferon in C57BL mice than in Balb/c mice; higher interferon levels in C57BL as compared to Balb/c were also found after inoculation of Sendai and Influenza virus (5). In addition, two oncogenic viruses have been tested. In collaboration with Dr. P. Hageman of the Netherlands Cancer Institute in Amsterdam, mammary tumor virus was inoculated intravenously into Balb/c and C57BL mice. In two out of three experiments, measurable circulating interferon was obtained, the titers being about 2.5 times higher in the C57BL mice. Similar experiments with Friend leukemia virus have shown that also with this agent interferon production was, on the average, 3 times higher in C57BL as compared with Balb/c, and this observation fits with Glasgow and Friedman's using Rauscher virus in C57BL and CDI mice (26).

While concentrating on the C57BL–Balb/c system, we have undertaken a survey of other inbred strains in order to examine the possibility of a correlation between the major histocompatibilility (H2) locus and the level of

circulating interferon production. This seemed relevant for two reasons. First, Lilly (27) and also Tennant and Snell (28) have shown an influence of the H2 allele on resistance to oncogenic viruses; and second, McDevitt and Chinitz have published very good evidence for linkage between the H2 locus and a gene having quantitative effect on antibody formation induced by synthetic polypeptides (29). Since myxovirus-induced interferon is primarily made in bone marrow-derived cells, the possibility that the gene influencing interferon levels was linked to the H2 locus seemed real. From a comparative study of 12 different mouse strains, it became evident however that there is no correlation between the H2 allele and high or low interferon production (Table V). This was further confirmed in a study of backcross mice, where we

TABLE V

CLASSIFICATION OF SOME INBRED MOUSE STRAINS ACCORDING TO THE AMOUNT OF CIRCULATING INTERFERON INDUCED BY NEWCASTLE DISEASE VIRUS

	Strain	H2 Allele
Low producers (average peak titers situated around 3000 U/2 ml)	A/J	a
	A/HeJ	a
	Balb/cJ	d
	C3H/HeJ	k
	DBA/1J	q
High producers (average peak titers situated around 20,000 U/2 ml)	AKR/J	k
	B10D2new/Sn	d
	B10D2old/Sn	d
	C57BL/10Sn	b
	C57BL/10J	b
	C57BL/6J	b
	C57BL/KS	d

found an independent segregation between the H2 allele and the gene influencing interferon levels. The H2 typing in this experiment was carried out by Peter Démant of the Institute of Experimental Genetics in Prague, and the results will be published in greater detail elsewhere.

GENERAL CONCLUSION

There are different sources of circulating interferon, depending on the virus inoculated into the animal. The major source of myxovirus-induced serum interferon in the mouse appears to be the lymphocyte. The amount of interferon released is under the control of a Mendelian factor, probably one gene segregating independently from the histocompatibility H2 allele. Whether this gene acts directly at the lymphocyte level or in some other way is a subject of current investigation.

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