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Interferon Structural Genes Do Not Participate in Quantitative Regulation of Interferon Production by *If* Loci as Shown in C57BL/6 Mice That Are Congenic with BALB/c Mice at the Alpha Interferon Gene Cluster

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Previous studies have shown that serum interferon (IFN) production in mice is quantitatively influenced by *If* loci, whose alleles determine high or low production. Although different loci influence IFN production in response to different inducers, such as Newcastle disease virus, Sendai virus, herpes simplex virus type 1, and polyriboinosinic-polyribocytidylic acid, BALB/c mice are in every instance low producers. It was therefore possible that, in addition to *If* loci, some feature of the BALB/c structural IFN genes contributed to low production. This was examined in the present work, in which IFN production was measured in two strains of C57BL/6 mice congenic with BALB/c at the murine alpha IFN (IFN-α) gene cluster on chromosome 4. One line, HW13 (B6.C-*H-15*^{c}-*H-16*^{c}-*H-20*^{c}-*H-21*^{c}/By) has a BALB/c fragment on chromosome 4 of at least 35 centimorgans which includes the BALB/c IFN-α gene cluster and four loci of the brown histocompatibility complex; the other line, HW13J (B6.C-*H-15*^{c}/By), has a much shorter fragment (about 15 centimorgans), but it also comprises the BALB/c IFN-α gene cluster. We show that these mice, carrying the BALB/c IFN-α structural genes on a C57BL/6 background, are high IFN producers when stimulated by Newcastle disease virus, Sendai virus, herpes simplex virus type 1, or polyriboinosinic-polyribocytidylic acid. Thus, the low IFN production of BALB/c mice is not directly due to some feature of the IFN-α structural genes but is mainly the result of different alleles at *If* loci.

Studies in humans and mice reveal widely divergent levels of alpha interferon (IFN-α) and IFN-β production during infection with the same virus in different individuals or in mice of different genotypes (1, 6, 15, 21, 33). A high level of IFN production is usually beneficial to the host since it enhances resistance to infection by limiting virus replication, and for example, high levels of IFN production have been correlated with resistance to infection with herpes simplex virus (HSV) or with murine cytomegalovirus (14, 32). However, high IFN production is not always a desirable feature, and it has been reported that whereas lymphocytic choriomeningitis virus multiplies to identical titers in C3H and BALB/c mice, the latter make less IFN and therefore do not develop the different manifestations of IFN-mediated disease caused by infection with this virus in C3H mice (13, 25). The quantitative control of IFN production is evidently an important parameter of host reaction during virus infection. In mice, IFN levels are genetically controlled, and for a given virus, mice of some genotypes are low IFN producers. In previous work we have analyzed the quantitative genetics of IFN production with BALB/c and C57BL/6 mice and the recombinant inbred strains and bilineal congenic lines derived from them by Bailey (2) and we have shown that many inducer-specific loci, designated as *If*, are involved in the quantitative control of IFN production (6). Table 1 represents the different loci influencing IFN production with five different inducers; none of the loci given in the table are closely linked. *If-1*, influencing IFN induction by Newcastle disease virus (NDV), has been mapped on chromosome 3 (22). The chromosomal assignment of the other *If* loci is presently unknown, except for one X-linked locus influencing early IFN production by NDV and HSV type 1 (HSV-1) (9, 34).

An intriguing aspect of the data summarized in Table 1 is the fact that although different loci are influencing IFN production in response to different inducers, mice of the BALB/c strain are low producers in every instance. This raises the possibility that, in addition to *If* loci, some feature of the BALB/c IFN structural genes contributes to low IFN production. For example, one could envisage that the IFN-encoding loci of the two mouse strains have different promoter or enhancer regions, resulting in a lower inducibility of BALB/c genes as opposed to the corresponding genes in C57BL/6. The murine IFN-α (MuIFN-α) genes have been mapped on chromosome 4, near the coat color locus called brown, or *b* (4). BALB/c and C57BL/6 DNA restricted with either *Eco*RI or *Hin*dIII and probed with an MuIFN-α cDNA show 13 and 15 bands, respectively, indicating the existence of multiple IFN-α genes (4). So far, nine different MuIFN-α structural genes have been sequenced (5, 17, 27, 35), which means that like in humans, the IFN-α locus in the mouse consists of a gene cluster. We have recently observed that the MuIFN-β gene, also assigned to chromosome 4 (31), is closely linked to the MuIFN-α gene cluster (3). Chromosome 4 of the mouse contains a number of histocompatibility loci, *H-15*, *H-16*, *H-18*, *H-20*, and *H-21*, all more or less near *b* and therefore referred to as the brown histocompatibility complex on chromosome 4 (2). Several bilineal congenic strains, carrying different fragments of the BALB/c chromosome 4 on a C57BL/6 background had been previously

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TABLE 1. Loci influencing IFN levels in serum in C57BL/6 and BALB/c mice

Inducer	Time of peak level (h)	Avg ratio of C57BL/6:BALB/c IFN levels at peak production[a]	*If* loci involved (reference)
NDV	7–9	10	*If-1* (7), some contribution of an X-linked locus on early production (9)
mMTV[b]	3	3	*If-2* (8)
Sendai virus	9–12	10	*If-3*, *If-4* (6)
HSV-1	2–4	10	At least three loci, different from the preceding, one of which is X-linked (34)
poly(rI·rC)	2–3	3	At least 2 loci not yet characterized

[a] The average ratio of IFN levels at the time of peak production is independent of the absolute level of production, which varies as a function of the amount of inducer inoculated into the animal; when more virus is inoculated, more IFN will be produced both by BALB/c and C57BL/6 mice, with the result that the ratio of production levels between both strains does not change.

[b] mMTV, Mouse mammary tumor virus.

constructed by one of us (D.W.B.) by selecting for the BALB/c alleles at the different loci of the brown histocompatibility complex (2). During the construction of some of these strains, the BALB/c IFN structural genes were introduced into the C57BL/6 background as "passenger" loci, and this has enabled us to test the hypothesis that the IFN structural genes are involved in the quantitative control of IFN production. In this paper we show that C57BL/6 mice congenic with BALB/c mice at the IFN-α structural loci produce as much IFN as parental C57BL/6 mice when tested with four different inducers, indicating that features of the structural loci are not responsible for the different levels of IFN production observed in these two strains.

MATERIALS AND METHODS

Mouse strains. BALB/c and C57BL/6 mice were originally from the Bailey colony at Jackson Laboratory, Bar Harbor, Maine, and have been maintained at Orsay for over 15 generations. Six bilineal congenic strains carrying BALB/c fragments of chromosome 4 on a C57BL/6 background had previously been examined for the allelism at the IFN-α locus. Southern blot analysis with an MuIFN-α probe of genomic DNA digested with *Eco*RI or *Hin*dIII revealed that two strains, HW13 (B6.C-*H-15*^{c}-*H-16*^{c}-*H-20*^{c}-*H-21*^{c}/By) and HW13J (B6.C-*H-15*^{c}/By), had the restriction fragment pattern of the BALB/c strains (4). Of the six congenic strains tested, only these two are congenic with BALB/c at *H-15*, which indicates that the IFN-α genes are more closely linked to *H-15* than to any other histocompatibility locus on chromosome 4. Besides having the BALB/c IFN-α and *H-15* locus, strain HW13 has also the BALB/c allele at *b* and at *Mup-1*, as well as at *H-16*, *H-20*, and *H-21*, indicating that it has a long chromosome fragment (at least 35 centimorgans [cM]) of BALB/c origin. Strain HW13J is a subline of HW13, derived by further backcrossing to C57BL/6. This strain also has the BALB/c allele at *Mup-1*, but it has the C57BL/6 allele at the *b* locus; like strain HW13, it has the BALB/c allele at the *H-15* locus, but unlike HW-13, it is not congenic with BALB/c at *H-16*, *H-20*, and *H-21*. The BALB/c chromosomal fragment of this strain can be estimated to be about 15 cM long (Fig. 1).

IFN titrations. IFN titers were determined by a 50% endpoint cytopathic assay in L cells with vesicular stomatitis virus (Indiana strain) as the challenge virus. All titers are expressed in units per 0.2 milliliters. One such unit corresponds to three international reference units, based on comparable titrations of a National Institutes of Health mouse IFN preparation (reference number, G-002-904-511).

Determination of the percentage of IFN-α and IFN-β in the serum. Percentages of IFN-α and IFN-β in serum were done by measuring the fraction of IFN activity that could be neutralized by an anti-MuIFN-β serum. The serum had been raised in rabbits against the 35-kilodalton component of polyriboinosinic-polyribocytidylic acid poly(rI-rC)-induced L-cell IFN and was a gift of L. Kronenberg (Lee Biomolecular, San Diego, Calif.).

IFN inducers. Stocks of NDV (Kumarov strain) were prepared in embryonated eggs. The titer of the virus was 2×10^7 PFU/0.2 ml as measured in Vero cells. Sendai virus (parainfluenza type 1) was also grown in eggs; its titer was $10^{7.5}$ 50% egg infective doses per 0.2 ml. HSV-1 had been prepared in monkey cells and was a gift of R. Zawatzky (German Cancer Center, Heidelberg, Federal Republic of Germany). The titer was 2×10^7 PFU/0.2 ml.

Poly(rI-rC) was purchased from P-L Biochemicals, Inc., Milwaukee, Wis., as lyophilized sodium salt. It was suspended in phosphate-buffered saline at a concentration of 25 μg/0.2 ml.

RESULTS

Since both the HW13 and HW13J strains carry the BALB/c IFN-α gene cluster on a C57BL/6 background, they offer a system of choice to test the hypothesis that some of the quantitative difference in circulating IFN production

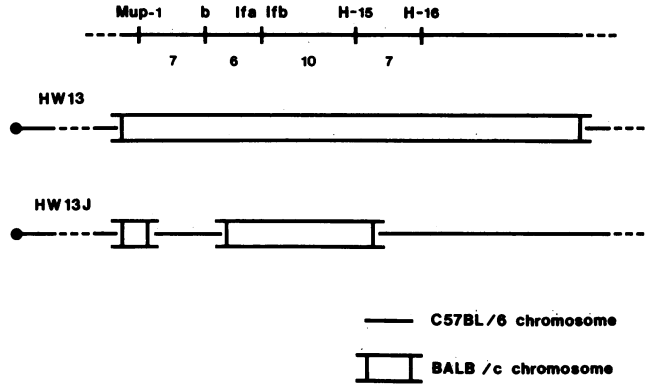

FIG. 1. The segment of chromosome 4 of BALB/c origin in HW13 and HW13J congenic mice. The upper part of the figure gives the gene order as recently determined (F. Dandoy, J. De Maeyer-Guignard, and E. De Maeyer, unpublished results) and the relative distance in centimorgans between the different loci. The IFN-α gene cluster is represented by the symbol "*Ifa*," in accordance with the nomenclature rules for mouse genetics. The IFN-β gene, represented as *Ifb*, is between 0 and 6 cM from *Ifa* (3). The estimated minimal size of the fragment of BALB/c origin, deduced from the alleles at the different loci, is 35 cM for the HW13 strain and 15 cM for the HW13J strain. The latter has the C57BL/6 allele at *b* but the BALB/c allele at *Mup-1*; it cannot be decided presently whether this is due to a double crossover or to an inversion of the segment between *b* and *Mup-1*. *Mup-1* alleles were determined electrophoretically (19, 29).

TABLE 2. NDV-induced IFN levels in parental and congenic strains[a]

Time after inoculation (h)	Major antigenic component (%)	Sex	NDV-induced IFN levels (IFN units/0.2 ml) in strain (range)[b]:				
			BALB/c	C57BL/6	HW13	HW13J	HW81
2	IFN-β (60–80)	F	1,800 (960–1,920)	9,900 (7,600–15,300)	9,900 (7,600–15,300)	15,300	ND[c]
2	IFN-β (60–80)	M	360 (240–480)	4,600 (3,800–7,600)	5,400 3,800–7,680	6,900 (3,800–7,680)	ND
7	IFN-α (>95)	F	3,400 (1,900–3,800)	24,000 (15,400–30,700)	24,600 (15,400–30,700)	24,600 (15,400–30,700)	2,600 (1,900–3,800)
7	IFN-α (>95)	M	1,400 (960–1,920)	24,500 (15,300–30,700)	20,050 (15,300–30,700)	25,500 (15,300–30,700)	1,450 (960–1,920)

[a] Mice 2 to 3 months old each received an intravenous injection of 0.2 ml of NDV (Kumarov strain), corresponding to 2×10^7 PFU as measured in Vero cells.
[b] Each value is the mean of the IFN titer of five mice.
[c] ND, Not determined.

between BALB/c and C57BL/6 mice is due to differences in the structural IFN genes. We do not actually know whether the structural genes of BALB/c and C57BL/6 are different, since the restriction-fragment-length polymorphism observed (4) is not necessarily due to a difference in gene structure and may be related to DNA merely linked to the gene. This point however was not important for the question we wanted to examine. We reasoned that if the quantitative difference in IFN production between BALB/c and C57BL/6 mice was somehow related to the IFN structural genes, then the HW13 and the HW13J mice would have a BALB/c-type production; if, on the contrary, the difference was not related to the IFN structural genes or genes closely linked to them, the two congenic strains would behave like C57BL/6.

Circulating IFN production was measured in BALB/c, C57BL/6, HW13, and HW13J mice after intravenous inoculation of NDV, Sendai virus, HSV-1, or poly(rI-rC). For the NDV study, we also included mice of the HW81 strain (B6.C-*H-28*^{c}-*If-1*^{l}) which carry the BALB/c allele at *If-1* on chromosome 3 on a C57BL/6 background (7, 22). For each IFN inducer, serum was obtained at the time corresponding to peak levels of IFN in the serum. In addition, for the study with NDV and HSV-1, early IFN production was also examined. Each time, male and female mice were used in view of the X-linked quantitative effect on IFN synthesis (9, 34). The IFN-α-IFN-β composition of the different IFNs was determined as described in Materials and Methods. It can be seen from Tables 2 to 5 that this composition depends on the inducer and, for the same inducer, varies with the time after onset of induction. At 2 h after inoculation of NDV, IFN consists of 60 to 80% IFN-β, whereas at 7 h after inoculation, it is over 95% IFN-α (Table 2). The major component of HSV-induced IFN at 3 h after induction is IFN-α, whereas at 6 h there is an equal amount of IFN-α and IFN-β (Table 4). This composition is not influenced by either the sex or the genotype of the mouse.

From the results shown in Tables 2 through 5, it is clear that in spite of the presence of the BALB/c structural genes, the congenic HW13 and HW13J strains have a C57BL/6 type IFN production since, like C57BL/6, these strains are high responders. This is the case regardless of whether the major component of the IFN is IFN-α or IFN-β, as can be seen for example with NDV at 2 and 7 h.

TABLE 3. Sendai virus-induced IFN levels in parental and congenic strains[a]

Sex	IFN (IFN units/0.2 ml) induced by Sendai virus in the following strain at 7 h after inoculation (range)[b]:			
	BALB/c	C57BL/6	HW13	HW13J
F	960	7,680	12,800 (7,680–15,360)	5,760 (3,840–7,680)
M	530 (240–960)	3,450 (1,920–7,680)	9,980 (3,840–15,360)	4,430 (3,840–7,680)

[a] Mice 2 to 3 months old each received an intravenous inoculation of 0.2 ml of Sendai virus (parainfluenza type 1), corresponding to $10^{7.5}$ 50% egg infective doses.
[b] Each value is the mean of five mice. The major antigenic component was >95% IFN-α.

DISCUSSION

The size of the IFN-α gene cluster in the mouse has not yet been determined, but from the analysis of genomic clones containing IFN-α structural genes, it can be estimated that the total size does not exceed 120 kilobases, corresponding to 15 structural genes separated by an average distance of 7 kilobases (17, 35). That the murine IFN-α gene cluster is on chromosome 4 has been determined by a variety of approaches, all giving concordant results. Southern blot hybridization of hamster-mouse somatic cell hybrid DNAs probed with MuIFN-α_2 DNA showed correlation of three *Bam*HI and seven *Hin*dIII fragments with mouse chromosome 4 (16, 20). With an MuIFN-α_1 probe Van der Korput et al. (31) showed that four *Eco*RI fragments coincided with the presence of murine chromosome 4 in DNA of a panel of somatic hamster-mouse cell hybrids. A more precise localization of the MuIFN-α genes was achieved by following segregation of restriction fragment length polymorphism (RFLP) in genomic DNA from BALB/c and C57BL/6 mice and recombinant inbred and congenic strains, two of which were used in the present study, derived from these two strains. The segregation of one *Eco*RI and three *Hin*dIII fragments indicated linkage of these fragments to the minor histocompatibility locus *H-15*, near the brown coat color locus (4). We have recently determined the gene order, which is *Mup-1*, *b*, IFN-α (unpublished results). Like IFN-α genes in humans, the MuIFN-α genes are clustered; this is evident from the presence of two complete and part of a third MuIFN-α gene in one phage and two MuIFN-α genes in another phage belonging to a BALB/c genomic library (35); furthermore, a 28-kilobase region of BALB/c mouse genomic DNA was shown to contain four different IFN-α genes (17). The congenic HW13 strain has a BALB/c fragment of chromosome 4 extending beyond *Mup-1* on one side and well beyond *H-15* on the other, which corresponds to a distance greater than 35 cM (12). There is therefore little doubt that these mice carry the complete IFN-α BALB/c gene cluster, although we could only follow the segregation

TABLE 4. HSV-1-induced IFN levels in parental and congenic strains[a]

Time after inoculation (h)	Major antigenic component (%)	Sex	HSV-1-induced IFN level (IFN units/0.2 ml) in strain (range)[b]:			
			BALB/c	C57BL/6	HW13	HW13J
3	IFN-α (≥75)	F	96 (60–120)	480	960	960
3	IFN-α (≥75)	M	50 (50–60)	570 (480–960)	360 (120–480)	430 (240–960)
6	IFN-α/IFN-β (50/50)	F	96 (60–120)	430 (240–480)	960 (480–1,920)	720 (480–960)
6	IFN-α/IFN-β (50/50)	M	75 (30–120)	575 (480–960)	480	530 (240–960)

[a] Mice 2 to 3 months old each received an intravenous injection of 0.2 ml of HSV-1 (strain WAL), corresponding to 2×10^7 PFU.
[b] Each value is the mean of five mice.

of the four fragments for which there is RFLP between BALB/c and C57BL/6. We do not have the same certainty regarding the IFN-β gene since it has not been possible to follow its segregation in the congenic lines, owing to a lack of RFLP between BALB/c and C57BL/6 DNA restricted with seven different enzymes. The chromosomal fragment of BALB/c origin in HW13J mice is shorter than that of HW13 mice, since as a result of further backcrossing the BALB/c *b*, *H-16*, *H-20*, and *H-21* loci were lost; its length can be estimated to be about 15 cM. The IFN-β structural gene is, like the IFN-α genes, on chromosome 4 (4, 16, 20, 31), and based on segregation of RFLP in an interspecies cross of DBA/2 and Spretus mice, we have shown that the IFN-α and IFN-β genes are closely linked (3), as they are in humans (23, 28, 30). It is therefore a likely assumption that the congenic HW13 and HW13J strains also carry the BALB/c IFN-β structural gene. However, the conclusion of the present work does not depend on whether the BALB/c IFN-β structural gene is present in these animals, since at peak levels (7 h), NDV- and Sendai virus-induced IFN is over 95% IFN-α, and HSV-1-induced IFN at 3 h is 75% IFN-α. From the results in Tables 2 to 5 we can therefore conclude that in spite of the presence of the BALB/c structural IFN-α genes, the congenic HW13 and HW13J strains have a C57BL/6-type IFN production since they are high producers.

With NDV induction, the high IFN production by the HW13 and HW13J strains confirms by a different approach the previous observation that high and low IFN production is determined by the presence of the *h* and *l* alleles at *If-1*, on the distal part of chromosome 3. This explains why mice of the HW81 strain (B6.C*H-28*^{c}*If-1*^{l}) congenic with BALB/c at *If-1* but having the C57BL/6 structural loci on chromosome 4 are low producers (Table 2). Lines congenic at other *If* loci are not available. The results obtained in HW13 and HW13J mice, however, show that also for Sendai virus, HSV-1, and poly(rI-rC), low IFN production by BALB/c mice and high IFN production by C57BL/6 mice is not directly attributable to some feature of the IFN structural genes. We can therefore conclude that the primary cause of different IFN levels is the presence of high- and low-producer alleles at *If* loci, which are unlinked to the structural loci. Furthermore, the *If* loci are not closely linked to one another, as shown for example by independent segregation of NDV-, Sendai virus-, mouse mammary tumor virus-, and HSV-1-induced high and low IFN production in recombinant inbred strains derived from BALB/c and C57BL/6 parental strains (6). For some reason, the BALB/c strain acquired the low-producer alleles at these different loci when it was developed; furthermore, BALB/c mice are also low producers when infected with Friend leukemia virus, lymphocytic choriomeningitis virus, and cytomegalovirus (6), but genetic analysis has not yet been performed.

Obviously, our results do not rule out that different levels of IFN production can be caused by features of the regulatory regions of the structural genes, such as different transcription rates owing to the promoter regions or to the presence of enhancer regions or different efficacies of induction as a result of structural differences in the regions responsible for virus induction, upstream of the gene (10, 11, 18, 26). What we have shown in the present study is that such differences are not responsible for the quantitative differences in IFN production between BALB/c and C57BL/6 mice with a variety of viral inducers and with poly(rI-rC), since the introduction of the BALB/c structural IFN genes into a C57BL/6 background does not result in a lowered IFN production. Rather, different alleles at *If* loci are responsible for different levels of IFN production. We do not know by what mechanisms *If* loci influence IFN production. They do not do so by an effect on virus replication, which could result in different levels of IFN-inducing viral RNA, since IFN induction with UV-inactivated NDV and Sendai virus is also under the influence of these loci, as is induction by poly(rI-rC) (6). Understanding the mode of action of *If* loci poses an interesting challenge, since, through their effect on IFN production, they influence the pathogenesis of viral infection. The *Ir* loci of the mouse provide another example of loci with a quantitative effect on the expression of structural genes on a different chromosome, since they are on chromosome 17 and influence the synthesis of immunoglobulins whose structural genes are on chromosomes 6, 12, and 16 (24).

TABLE 5. Poly(rI-rC)-induced IFN levels in parental and congenic strains[a]

Sex	IFN (IFN units/0.2 ml) induced by poly(rI-rC) in the following strain at 3 h after inoculation (range)[b]:			
	BALB/c	C57BL/6	HW13	HW13J
F	1,920 (960–3,840)	9,210 (7,680–15,360)	4,800 (3,840–7,680)	4,600 (3,840–7,680)
M	1,920 (960–3,840)	3,450 (1,920–3,840)	2,690 (1,920–3,840)	3,840

[a] Mice 2 to 3 months old each received an intravenous injection of 0.2 ml of phosphate-buffered saline containing 25 μg of poly(rI-rC).
[b] Each value is the mean of five mice. The major antigenic component was 60% IFN-β and 40% IFN-α.

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