BALB/c Myeloma Retroviruses Have Mink Cell Focus-Inducing Activity

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We have determined the *in vitro* host range of the cloned MO-21 and FL-1 murine myeloma retroviruses grown in SC-1 cells that were originally isolated from cloned MOPC-21 and FLOPC-1 BALB/c plasmacytoma cell lines. These viruses are able to replicate in murine (BALB/3T3, NIH/3T3) as well as numerous heterologous cell lines. These myeloma retroviruses also exhibit mink cell focus-inducing activity. MO-21 and FL-1 shared interference patterns with each other, but their replication was not interfered with by ecotropic, xenotropic, or amphotropic viruses. The lack of cross-interference with ecotropic or xenotropic viruses distinguishes these isolates from other mink cell focus-inducing viruses.

Murine retroviruses have been grouped into four major classes based on their *in vitro* host range. Viruses which replicate exclusively in murine cells are termed ecotropic (20) and are designated as N-tropic, B-tropic, or NB-tropic according to their ability to preferentially replicate in NIH Swiss, BALB/c, or both types of cells (12). The second class is termed xenotropic because these viruses can replicate in many heterologous cells but not in murine cells (19). The next class is the amphotropic viruses which have been isolated from feral mouse populations; these viruses replicate in murine (NIH Swiss mouse) as well as heterologous cells (11, 24, 25). The final class of viruses is termed polytropic (14) because of their ability to replicate in murine (NB-tropic) and heterologous cells. However, these viruses differ from the amphotropic viruses in neutralization and interference patterns, and subsequent work has demonstrated that these retroviruses arise by recombination between the envelope (*env*) genes of ecotropic and xenotropic viruses (7-9). Another difference between amphotropic and polytropic viruses is that the latter may induce cytopathic changes in mink lung fibroblasts, and they are therefore referred to as mink cell focus-inducing (MCF) viruses (13).

In this report, we describe our findings that the cloned BALB/c myeloma-associated retroviruses, MO-21 and FL-1, have an NB-polytropic host range and that they exhibit MCF activity. However, unlike other MCF isolates (15, 28), the myeloma viruses do not share interference patterns with ecotropic or xenotropic viruses. The possible significance of these findings is discussed.

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MATERIALS AND METHODS

Cell cultures and viruses. BALB/3T3 and NIH/3T3 cell lines were obtained from George Todaro. Rabbit corneal (SIRC, CCL60), mink lung (Mv1, CCL64), Chinese hamster peritoneal (B14FAF, CCL14), Pekin duck embryo (PDE, CCL141), and human embryonal rhabdomyosarcoma cells (RD, CCL136) were obtained from the American Type Culture Collection, Rockville, Md. Dually permissive 3T3 FL cells were obtained from Robert Bassin, and dually restrictive BALB × NIH F₁ cells were provided by John Stephenson. Guinea pig kidney (GPK) cells and Syrian hamster kidney (HAK) cells were obtained from Flow Laboratories. Janet Hartley provided the NRK and wild mouse embryo SC-1 cells. Edward Scolnick provided another strain of Mv1 cells. The K-NRK rat cell line nonproductively infected with Kirsten murine sarcoma virus was provided by John Stephenson, and the K-BALB cell line was obtained from George Todaro. Alex Papageorge provided the mink lung S⁺L⁻ cells.

MCF 247 and 1504A viruses were obtained from Janet Hartley and were passaged in SC-1 or Mv1 (1504A) cells. B-CI-11 virus (B-tropic) and N-CI-35 virus (N-tropic) were provided by Naomi Rosenberg. BALB-virus 2 (BV-2) was given to us by Stuart Aaronson, and it was grown in human A673 cells. FL-1 and MO-21 BALB/c myeloma viruses were isolated and cloned as reported previously (15, 26). These viruses were passaged in SC-1 cells, and all cells were grown as described previously (26).

Host range analysis. The *in vitro* host range of the viruses was determined by assaying infected cultures for extracellular reverse transcriptase as described previously (17).

Interference assays. Pseudotypes of all the retroviruses were generated by cocultivating virus-infected cells with the K-NRK line of nonproducer normal rat kidney cells (1) or K-BALB nonproductively transformed BALB/c cells. The murine sarcoma virus pseudotypes were collected at cell pass five after infection and were titrated on either NRK or SC-1 cells; subconfluent monolayers were infected in 10% heated

fetal calf serum in Dulbecco-modified Eagle medium containing polybrene and were changed to medium containing 1%, fetal calf serum 5 to 7 days postinfection. All monolayers were stained with Gurr Giemsa stain 10 to 12 days postinfection, and the number of foci was counted using a Nikon dissecting microscope.

Interference assays were performed with SC-1 or NRK cells. Cultures were infected with the appropriate retrovirus and were serially transferred for 1 to 2 weeks. These cells were used for titration of the murine sarcoma virus pseudotypes.

Mink S⁺L⁻ assay. The mink lung S⁺L⁻ assay for xenotropic viruses was performed as described by Peebles (22).

RESULTS

Host range. Previous publications from our laboratory have shown that the BALB/c murine myeloma-associated viruses are able to replicate in NIH/3T3 and BALB/3T3 cells and therefore were termed NB-ecotropic (16, 17, 26). We extended our analysis of the in vitro host range of two of these cloned viruses (MO-21, FL-1) to determine whether they also possess xenotropic properties (Table 1). These data demonstrated that both MO-21 and FL-1 have the ability to replicate in cells from heterologous species including mink, hamster, guinea pig, rabbit, duck, and human, although to different levels. There was no substantial difference between the biological activity of these two viruses. These isolates also have the same host range characteristics as the S/A-1 virus, which was isolated in our laboratory after cocultivation of SIPC-2 myeloma cells with A₃₁ BALB/3T3 cells (15). The prototype amphotropic virus, 1504A, differs from MO-21 and FL-1 since it is N-amphotropic (15, 25). Furthermore, the two myeloma viruses and 1504A have different envelope properties since they do not interfere with each other's replication (see below).

Even though our virus preparations were cloned by limiting dilution and single cell isolation, we wanted to further confirm their purity, since interpretation of the host range data depends upon the assumption that the virus populations are homogeneous. Our previous studies showed that two subclones of MO-21 exhibited NB ecotropism even after extensive cloning procedures were performed to eliminate any possibility that the viruses were mixtures (26). We passed one of these isolates (A2) through SC-1, F₁, ML, and PDE cells and determined the limited host range of the progeny virus that was produced (Table 2). This treatment did not alter the overall polytropic activity of the virus, although there were some variations in the level of replication in various cell lines. The differences between the relative reverse transcriptase

TABLE 1. *Host range of MO-21 and FL-1 BALB/c myeloma retroviruses^a*

Cell line	cpm incorporated by virus:		
	FL-1	MO-21	1504A
BALB/3T3	23,700	44,080	310
NIH/3T3	13,110	15,260	324,100
SC-1	119,520	231,480	196,000
3T3-FL	30,490	37,540	NT ^b
F ₁	30,410	46,760	14,310
NRK	16,420	34,790	67,360
Mv1	28,850	26,640	86,500
HAK	10,940	15,160	7,350
B14FAF	20,940	9,540	76,115
GPk	9,130	11,825	14,970
SIRC	26,040	29,150	18,900
RD	8,960	15,600	25,110
PDE	13,240	18,100	25,200

^a These data are the counts per minute of [³H]TMP incorporated per 15 ml of culture medium in a reverse transcriptase reaction using poly(rA)·oligo(dT)₁₂₋₁₈ as the template, incubated at 37°C for 30 min. Medium was removed from the cultures 2 weeks postinfection, and viral pellets were obtained by centrifugation through a 30% sucrose cushion at 320,000 × g for 1.5 h.

^b NT, Not tested.

TABLE 2. *Host range of MO-21 clone A2 progeny virus produced in various cell lines^a*

Cell line	cpm incorporated by virus produced by ^a :			
	SC-1	F ₁	Mv1	PDE
F ₁	402,533	192,135	185,507	4,404
Mv1	411,979	81,017	266,531	14,052
B14FAF	2,091	26,823	91,585	1,892
SIRC	931	2,658	1,170	60,550
RD	ND ^c	ND	ND	2,354
PDE	50,566	2,124	2,394	12,354

^a MO₂₁ murine myeloma-associated virus clone A2 is a subclone of MO₂₁ murine myeloma-associated virus isolated from a single infected cell (26). Data are from reverse transcriptase reactions as outlined in Table 1.

^b A2-MO₂₁ murine myeloma-associated virus was used to infect the indicated cells. Three weeks later, the medium from these cells was used to infect the indicator cell lines. These cultures were tested for virus production 2 weeks postinfection.

^c ND, Not detectable

levels in this table and those shown in Table 1 are probably due to differences in cell culture conditions as well as the age of the synthetic template used in the reverse transcriptase assay (15). Adaptation or selection of virus appeared to occur when the MO-21 clone A2 virus was passaged through a given cell line, since the corresponding activity with that indicator cell was generally higher than the activity for the other cells (e.g., A2-Mv1 in Mv1 cells). It also

appeared as though virus passaged through PDE cells had an expanded host range since the progeny replicated more efficiently in SIRC and RD cells than did MO-21 (see Discussion). Our preliminary studies with FL-1 virus have shown the same host range patterns even after limiting dilution passage through the various cell lines described above (data not shown).

MCF assays. A recent report listed a retro-

virus isolated from a pristane-induced BALB/c plasmacytoma (CB 208) under the category of MCF viruses (5). We therefore tested our myeloma viruses for this activity by infecting a strain of mink lung cells obtained from E. Scolnick. The monolayer of Mink lung fibroblasts infected with MO-21 and FL-1 showed definite focal areas where cell morphology was altered (Fig 1). This type of cytopathology resembled that ob-

FIG. 1. Phase-contrast photomicrograph showing that MO-21 and FL-1 have MCF activity. *Mv1* cells were infected with clarified supernatants from cultures replicating MCF 247 (B), MO-21 (C), and FL-1 (D) virus. (A) is a picture of normal *Mv1* cells. Foci appeared after the cultures reached confluence. Approximately $\times 375$ magnification.

served by another investigator (28). Also shown in Fig. 1 is a characteristic focus induced by MCF 247, which is the prototype AKR-MCF virus originally described by Hartley et al. (13). Xenotropic viruses did not exhibit any MCF activity in these assays (data not shown). The focus-inducing activity of MO-21 and FL-1 was proportional to the dilution of the virus used to infect the monolayers (Table 3), suggesting a one-hit type of phenomenon. In our studies, the myeloma retroviruses had approximately the same titer of MCF activity as the prototype MCF viruses (data not shown). The data in Table 3 also show that the MCF activity was directly related to the input level of viral reverse transcriptase activity. Taken together, these data suggested that the MCF activity was due to the replication of the nondefective myeloma virus and not to the presence of a replication

defective component in the virus population (13, 32).

Mink S^+L^- assay. Hartley et al. (13) reported that the MCF viruses they isolated were inefficient in the mink S^+L^- assay. This assay is very sensitive for the detection of xenotropic murine leukemia virus (22). Table 4 shows that the myeloma MCF viruses were also 10- to 100-fold less efficient than the xenotropic BV-2 virus in inducing S^+L^- foci.

Interference assays. We next wished to determine if MO-21 and FL-1 shared viral envelope properties with any of the prototype retroviruses used in this study. The results of interference assays are shown in Table 5. It can be seen that the myeloma viruses were not interfered with by the ecotropic, xenotropic, or amphotropic viruses used in these assays. These data suggest that MO-21 and FL-1 cross-interfere with each other but that they have unique envelope properties which distinguish them from the tested prototype viruses. It was also clear that the myeloma MCF viruses are different from the prototype MCF 247 virus, since this latter virus shared interference properties with ecotropic and xenotropic viruses but not with the two myeloma viruses (Table 5). This interference pattern has been observed previously (13, 28).

TABLE 3. Titration of MCF viruses^a

Virus	Dilution	No. of foci	Reverse transcriptase ^b (cpm)
MO-21	10 ⁻²	196	27,500
	10 ⁻³	25	2,530
	10 ⁻⁴	3	320
	10 ⁻⁵	0	ND
FL-1	10 ⁻²	207	22,200
	10 ⁻³	20	2,100
	10 ⁻⁴	2	290
	10 ⁻⁵	0	ND

^a Culture medium from productively infected SC-1 cultures was clarified of cells by centrifugation and filtered (0.45 μ m), and then 10-fold dilutions were used to infect duplicate cultures of mink lung fibroblasts. Culture medium was removed for reverse transcriptase activity at 5 days postinfection, at which time the cultures were stained to allow enumeration of foci.

^b The reverse transcriptase assays were performed as described in Table 1. For these experiments, counts of >200 cpm were considered positive because infectious virus could be isolated from these cultures after additional cell passage. ND, Not detectable.

TABLE 4. S^+L^- focus-inducing activity of MCF viruses^a

Virus	Avg no. of foci per ml of dilution			
	10 ⁻¹	10 ⁻²	10 ⁻³	10 ⁻⁴
BV-2	>250	110	12	2
N-CL-35	ND ^b	ND	ND	ND
MCF 247	27	3	ND	ND
MO-21	22	2	ND	ND
FL-1	36	2	ND	ND

^a Culture medium was filtered (0.45 μ m), and 1-ml samples were used to infect duplicate subconfluent monolayers of S^+L^- cells. All cultures were infected with virus preparations containing approximately the same level of reverse transcriptase activity.

^b ND, Not detectable.

TABLE 5. Interference properties of MO-21 and FL-1 viruses

Group	Strain	% of MSV focus induction in cells preinfected with ^a :					
		B-CL-11	BV-2	1504A	MCF 247	FL-1	MO-21
Ecotropic	B-CL-11	14	91	123	90	88	83
Xenotropic	BV-2	98	9	93	93	112	104
Amphotropic	1504A	102	83	14	120	130	80
Polytropic	MCF 247	20	28	77	5	73	84
	MO-21	115	60	75	>200	33	8
	FL-1	82	74	60	>200	13	40

^a Relative to uninfected cells. Interference assays using SC-1 and NRK cells were done as described in the text. The data represent the average percentage from duplicate monolayers infected with three different concentrations of murine sarcoma virus (MSV) pseudotypes.

However, the interference pattern observed with MCF 247 virus was unusual. For example, preinfection of SC-1 or NRK cells with ecotropic or xenotropic murine leukemia virus inhibited focus induction by a MCF 247 pseudotype, whereas SC-1 cells preinfected with MCF 247 did not inhibit focus induction by pseudotypes of either ecotropic or xenotropic murine leukemia virus. This nonreciprocal, one-way type of interference has been observed previously with other MCF isolates (9, 13). Our previous work has already demonstrated that the envelope glycoproteins of the myeloma virus (gp75, gp90) are somewhat larger than the gp69/71 of the murine leukemia viruses (26).

DISCUSSION

The data presented in this paper have demonstrated that the MO-21 and FL-1 BALB/c myeloma viruses have an NB-polytropic host range. Furthermore, these viruses exhibited (MCF) activity. Unlike other MCF viruses, however, MO-21 and FL-1 do not share interference patterns with ecotropic or xenotropic viruses. Each of these findings is discussed below.

We previously demonstrated that the MO-21 and FL-1 virus had an NB-ecotropic host range, but we had not tested for any possible xenotropic characteristics (16, 17, 26). The data in Table 1 clearly show that the cloned viruses can infect a wide variety of cells and they therefore have been classified in the NB-polytropic host range class. It should be mentioned that the host range characteristics of the 1504A amphotropic virus presented in Table 1 are somewhat different from those described by Hartley and Rowe (11). These authors showed that 1504A did not replicate in hamster cells or duck cells, whereas it clearly does in our assays. Although we do not know the reasons for these discrepancies, we suspect that the continual passage of this virus in Mv1 cells in our laboratory may have slightly altered its host range. This type of phenomenon has been described recently for the recombinant HIX virus (9). In this case, HIX virus grown in human RD (HIX-RD) cells shifted its host range pattern to become more xenotropic in character. It was also shown by peptide mapping studies that the envelope gp70 proteins of HIX and HIX-RD viruses were different. The authors speculated that these differences may have resulted from either mutation or recombination within the host cell. Murray and Kabat (21) have also demonstrated an alteration in the gp70 of Friend virus which appears to be the result of adaptation of the virus to a given cell line. Host range analysis of the Friend virus variants, how-

ever, was not done. We are presently investigating the possibility that the envelope proteins of the MO-21 and FL-1 viruses may be altered by passage through heterologous cell lines. Another possibility is that a cell line merely selects out a variant which replicates more efficiently than the parental virus. Either explanation would be consistent with the host range data presented in Table 2.

The demonstration that MO-21 and FL-1 possess MCF activity is very interesting in light of the recent studies of Cloyd et al. (5). These authors reported that they had isolated an MCF virus with a B-polytropic host range from a BALB/c plasmacytoma, designated as CB 208. Since MCF viruses have been implicated in certain neoplastic diseases (10, 13, 32), these authors tested CB 208 for potential lymphomagenicity (6). CB 208 was not lymphomagenic in these assays, but the data showed that only MCF viruses originally isolated from thymic lymphomas were able to induce this type of tumor. Studies are under way to determine whether CB 208 as well as MO-21 and FL-1 have any role in tumor induction in BALB/c mice. We are particularly interested in determining whether these agents accelerate the induction of plasmacytomas in this mouse strain (2, 23). We have also begun studies to determine whether these agents can transform hematopoietic cells in vitro (3, 4).

We have recently shown that CB 208, MO-21, and FL-1 have the same interference patterns, and peptide mapping studies indicated that they appear to have identical gp70 envelope proteins (D. R. Spriggs and R. G. Krueger, *Virology*, in press). The CB 208 plasmacytoma was never adapted to growth in tissue culture, so we feel confident that the MO-21 and FL-1 viruses are not just aberrant viruses generated while the plasmacytoma cell lines were grown in vitro. The finding that these three myeloma MCF viruses have indistinguishable gp70's is unusual since all the MCF viruses described to date have unique gp70's which are presumed to have been generated by recombination (7, 8). Another unique property of the myeloma MCF viruses is evident in the interference studies (Table 3). These data show that, unlike the prototype MCF 247 virus, the replication of the myeloma MCF isolates is not interfered with by ecotropic or xenotropic viruses. Furthermore, the MO-21 and FL-1 viruses are XC positive (17), whereas all previously described MCF isolates have been shown to lack this activity. These studies suggest that the MCF viruses isolated from BALB/c plasmacytomas may have been generated differently from other MCF viruses (7, 8, 27).

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