Amphotropic Host Range of Naturally Occurring Wild Mouse Leukemia Viruses[1]

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Seven murine leukemia virus field isolates (uncloned) from wild mice *(Mus musculus)* of four widely separated areas in southern California show an unusually wide in vitro host range. They replicate well in human, feline, canine, guinea pig, rabbit, rat, and mouse cells, whereas bovine, hamster, and avian cells are resistant. Since this host range includes that of both mouse tropic (ecotropic) and xenotropic murine leukemia viruses, they are designated as "amphotropic." No purely xenotropic virus component is detectable in these field isolates. They may represent the "wild" or ancestral viruses from which the ecotropic and xenotropic murine leukemia virus strains of laboratory mice have been derived.

Murine type C oncornaviruses have been grouped in two major classes according to their in vitro host range. Those viruses that grow in mouse cells (mouse tropic or ecotropic) (18) are characterized as N-tropic, B-tropic, or NB-tropic, according to their ability to preferentially replicate in National Institutes of Health (NIH) Swiss, BALB/c, or in both types of cells (24). The susceptibility of these mouse cells is governed by the alleles Fv-1^n and Fv-1^b, which are dominant for relative resistance to B- and N-tropic viruses, respectively (24). Most of the ecotropic strains of murine type C virus show a low efficiency of infection in heterologous host cells. The second major class is the xenotropic virus which productively infects only heterologous cells and not cells of their species of origin (19). We have found that type C viruses isolated from wild mice *(Mus musculus)* often show the combined in vitro host range of both eco- and xenotropic viruses. They thus constitute a third major class of naturally occurring type C viruses designated as amphotropic (ampho, Greek = both), a term suggested to us by J. A. Levy. The identification of these field isolates and their in vitro host range is described.

MATERIALS AND METHODS

Viruses. Viruses were isolated from wild mice of four trapping areas in southern California (Table 1). Four virus isolates (292, 4070, 11235, and 7926) were from Lake Casitas (LC) mice and one each from La Puente (LP) (1504), Munneke (Mu) (672), and Bou-

quet Canyon (BC) (2221) mice. Six isolates (1504, 4070, 11235, 7926, 672, and 2221) were released spontaneously from wild mouse embryo or tumor cultures and were maintained in their natural cells of origin. A seventh isolate (292) was grown in NIH Swiss embryo cells after recovery from an NIH Swiss mouse initially inoculated with pooled spinal cord extracts from three naturally paralyzed LC wild mice (5). Strain 1504 (7) was also grown in NIH Swiss cells after harvest from the brain of an experimentally paralyzed NIH Swiss mouse.

For virus stocks, tissue culture fluids were harvested from virus-producing cells 48 h after media change, clarified by centrifugation, filtered through 0.45-μm membrane filters (Millipore Corp.), and frozen at −96 C in 1-ml aliquots. All viruses were tested without cloning or end-point dilution purification and are thus referred to as "field isolates." Only one pool for each virus was used throughout the present studies except for 292 virus, from which two different pools were tested.

Cell cultures. A total of 23 different human and animal cell lines or strains were tested for their susceptibility to infection with the seven different field isolates from wild mice (Table 2). The cells included human rhabdomyosarcoma RD (20), fibrosarcoma (25), and embryo and placenta fibroblasts (S.R.), monkey DBS-FRhL-1 (28), two cat embryo cultures from the Naval Biomedical Laboratory, dog sarcoma D17 from R. M. McAllister, rabbit cornea SIRC (American Type Culture Collection), guinea pig embryo kidney (Flow Laboratories, Rockville, Md.), rat kidney NRK-9 (16), Fischer rat embryo (S.R.), NIH Swiss mouse 3T3 (14), BALB/c embryo clone CL-1 (9), BC wild mouse embryo clone SC-1 (10), hamster NIL-2 from R. Weiss, bovine skin and muscle (Microbiological Associates, Inc., Bethesda, Md.), bovine kidney (American Type Culture Collection), and chicken, duck, and squab embryo fibroblasts (S.R.). All the cultures except SC-1 were

TABLE 1. *Type C virus field isolates from wild house mice*

Virus identification no.	Trapping area	Incidence of spontaneous lymphoma in mouse colonies	Tissue of origin	Virus grown in:	Morphology of virus-producing cells
1504	La Puente	High	Whole embryo culture	Tissue of origin	Fibroblastic
292	Lake Casitas	High	Spontaneous paralysis-CNS[a] pooled	NIH Swiss cells	Fibroblastic
4070	Lake Casitas	High	Whole embryo culture	Tissue of origin	Fibroblastic
11235	Lake Casitas	High	Spontaneous lymphoma (lymph node) culture	Tissue of origin	Lymphoid
7926	Lake Casitas	High	Normal kidney culture from 1-day-old-mouse	Tissue of origin	Fibroepithelioid
672	Munneke	Low	3-Methylcholanthrene-induced fibrosarcoma culture	Tissue of origin	Fibroblastic
2221	Bouquet Canyon	Low	Spontaneous liposarcoma culture	Tissue of origin	Fibroblastic

[a] CNS, Central nervous system.

TABLE 2. *Host range of wild mouse field isolates[a]*

Species	Designation of cell line	RDP[b] (cpm/ml)		CF[c]	
		Control uninfected	Infected with virus no. 292	Control uninfected	Infected with virus no. 292
Susceptible cells					
Human	RD	90	291,840	<1	≥8
	1080	19	500,900	<1	≥8
	776 (embryo)	0	49,100	<1	4
	598 (placenta)	0	162,200	<1	4
Monkey	DBS-FRhL-1	0	217,040	<1	≥8
Cat	H927 (embryo)	0	403,720	<1	≥8
	OSU (embryo)	6	171,320	<1	≥8
Dog	D17	15	39,610	<1	≥4
Rabbit	SIRC (cornea)	13	13,840	<1	4
	VX-2	0	17,630	<1	4
Guinea pig	GP-K (kidney)	16	99,570	<1	4
Rat	F-1 (embryo)	63	46,430	<1	4
	NRK-9	220	180,110	<1	4
Mouse	NIH Swiss 3T3	60	412,200	<1	≥8
	BALB/c (CL-1)	0	12,000	<1	4
	SC-1	2	75,270	<1	≥8
Resistant cells					
Hamster	NIL-2	0	10	<1	<1
Bovine	BE-S/M	0	0	<1	<1
	CCL-22	0	20	<1	<1
Avian	Chicken (embryo)	0	0	<1	<1
	Duck	0	14	<1	<1
	Squab	10	0	<1	<1

[a] Each of the seven isolates was separately tested on every cell listed in this table. All the virus-exposed and unexposed cultures were tested for RDP and CF p30 activity at 21 to 28 days (see Materials and Methods). Results similar to the one presented here for strain 292 were also obtained from strains 1504, 4070, 11235, 7926, 672, and 2221.

[b] RNA-directed DNA-polymerase activity. Incorporation of [H³]TMP oligo(dT)-poly(rA) counts per minute per milliliter of culture medium; background counts (without template) subtracted from each. 1,000 or more RDP counts were considered positive and correlated well with CF.

[c] Reciprocal of highest titers giving 3 to 4+ complement fixation with MuLV p30 antiserum (see Materials and Methods).

maintained in Eagle minimal essential medium with Earle salts (MEM) supplemented with 10% heat-inactivated fetal bovine serum, 2 mM glutamine, and 50 μg of gentamicin. The SC-1 cells were maintained in MEM with 5% heat-inactivated fetal bovine serum plus glutamine and gentamicin. Subcultures were made once a week using 0.1% trypsin containing 0.2 mg of EDTA per ml.

Virus assays. Exponentially growing cultures (3 × 10⁵ cells/60-mm dish), pretreated with polybrene (2 μg/ml) for 24 h, were exposed separately to 0.4 ml of different undiluted viruses. These inocula contained approximately 10^3 to 10^7 mean tissue culture infective doses per ml as determined by COMUL (complement fixation for murine leukemia) test (11) on SC-1 cells (Table 3) and 10^7 to $10^{9.5}$ particles/ml by negative-stain electron microscopy (EM). After 1 h of adsorption at 37 C in a humidified atmosphere containing 5% CO_2, the cultures were fed with maintenance medium. The cells were subcultured weekly and the culture fluids were tested approximately 21 days after infection for RNA-directed DNA-polymerase (RDP) activity (15), and the sonicated cell packs (20% wt/vol) were tested for murine leukemia virus (MuLV) gs p30 antigen (1, 22) by the complement fixation (CF) test (11). The antiserum used (Moloney sarcoma virus MSV-30) was prepared in Fischer rats bearing transplanted Moloney sarcoma virus-induced tumor transplants. This antiserum was shown to be specific and highly sensitive to the gs antigen based upon a comparison with guinea pig antisera prepared against the purified isoelectric-focused murine p30 antigen (8). By EM each isolate was examined using thin sections of cultured cells and negative staining of culture fluids. In addition, 10 randomly selected virus-infected cultures from different field isolates were examined by EM to confirm the positive RDP and CF results. Labeling of the virus with [³H]uridine and determination of

density in sucrose gradients, RDP assay, and the procedures for thin-section and negative-stain EM were previously described (2, 15, 26). For UV-XC plaque assay (27) NIH Swiss embryo cells infected separately with wild mouse viruses were used. Syncytium formation (17) was also scored by adding XC cells to virus-producing stock cultures. Furthermore, the undiluted virus stocks of field isolates were directly assayed on XC cells for cell fusion or plaque formation.

The seven field isolates were titrated on SC-1 cells and on a human fibrosarcoma cell line, HT-1080 (25). Two plates of exponentially growing cells per each $\log_{10}$ dilution, pretreated with 2 μg of polybrene per ml, were exposed to limiting dilutions of the virus and were cultured, harvested, and tested separately. The titration end points were determined by the detection of RDP activity in the culture fluids and by induction of murine CF p30 antigen in the cell packs 21 days after virus infection (Table 3).

The helper activity of these isolates was tested by cocultivating in 1:1 ratio the virus-producing cells with hamster HT-1 cells (13) or Kirsten MSV-transformed NRK-1255 B-7 cells (16) bearing nonproductive MSV genomes. Culture fluids were harvested at 7 to 10 days after cocultivation and assayed for focus formation in NRK and NIH Swiss embryo cells pretreated with 2 μg of polybrene medium per ml. The maintenance medium contained 5% calf serum and 1% Me_2SO in MEM. The foci were scored 7 to 10 days after infection with the MSV pseudotypes (Table 4).

RESULTS

Origin of the field isolates. We isolated four virus strains (292, 4070, 11235, 7926) from mice trapped at a squab farm near Lake Casitas and one isolate (strain 1504) from a mouse trapped at a duck farm near La Puente. Wild mice from these two sites, located 40 miles apart, show a high level of indigenous type C virus activity throughout life and a high incidence of spontaneous lymphoma and a hind-leg paralysis upon aging in the laboratory (4, 5). Two other isolates (strains 672 and 2221) were recovered, respectively, from mice trapped at an egg ranch in Mu in south-central Los Angeles, and a squab farm in BC in northern Los Angeles County. Mice from these two sites, located

TABLE 3. *Titers of wild mouse viruses in human and wild mouse SC-1 cells*[a]

Virus stock	Human sarcoma cell line (1080)	Wild mouse (SC-1)
1504	5.9	7.4
292	5.9	5.9
11235	4.9	5.4
4070	5.4	6.4
7926	· 2.9	4.9
672	2.9	2.9
2221	4.9	NT[b]

[a] By COMUL assay (11). Titers expressed in $\log_{10}$ $TCID_{50}$/ml. The virus stocks used for infectivity assays contained by negative-stain electron microscopy $10^{7.0}$ to $10^{9.5}$ particles/ml.

[b] Not tested. The virus stock of 2221 contained low amounts of lymphocytic choriomeningitis virus which interfered with infectivity assay on SC-1 and NRK cells. The presence of lymphocytic choriomeningitis was confirmed by J. Parker at Microbiological Associates, Inc., Bethesda, Md. However, this did not interfere with the host range infectivity assay.

TABLE 4. *Determination of the optimum system for focus assay of wild mouse MSV-(MuLV)*[a]

Pseudotype virus	FFU[b]/ml in:	
	NRK cells	NIH Swiss cells
KiMSV (1504)	$10^{3.8}$	$<10^{0.9}$
KiMSV (292)	$10^{4.5}$	$10^{0.9}$
KiMSV (4070)	$10^{4.5}$	$10^{1.9}$

[a] See Materials and Methods for details.
[b] FFU, Focus-forming unit.

about 20 miles from the LC and LP trapping areas, showed a low level of indigenous type C virus activity throughout life and a low incidence of spontaneous lymphoma with aging in the laboratory (6). They were totally resistant to the spontaneous paralytic disease.

General characteristics of viruses. Each of the seven isolates showed typical type C particle morphology by thin-section and negative-stain EM, a density of 1.14 to 1.16 g/cm^3 in sucrose gradients, RDP activity, MuLV-specific p30 antigen, and the ability to rescue the defective MSV genome. Six major protein peaks separated by gel filtration in guanidine-hydrochloride were detected in five viruses examined (strains 1504, 292, 4070, 11235, and 672) and the virion 70S RNA could be dissociated into heterogeneous lower-molecular-weight RNA species (23; B. K. Pal, unpublished observations) in the two viruses studied in this way (strains 1504 and 292). Strain 1504 virus showed no difference in RNA or polypeptide profile after passage through an NIH Swiss mouse and propagation in NIH Swiss embryo cells. Thus, these type C viruses were identified as genotypes of the MuLV family.

Host range and specific properties of wild mouse MuLV. The seven uncloned field isolates showed a wide in vitro host range. Each virus isolate was tested in every cell line/strain listed in Table 2 for its ability to induce CF p30 antigen in cells and RDP activity in the culture fluids. The viruses replicated well in a wide variety of mammalian cells; human, monkey, cat, dog, guinea pig, rabbit, and mouse cells were susceptible (Table 2), as depicted by positive CF p30 and RDP activity. Ten randomly selected cultures also showed typical budding and free type C particles. The limiting dilution titrations of each of the seven viruses on wild mouse (SC-1), and human sarcoma (1080) cell lines is shown in Table 3. Two of the isolates titrated equally well on both cell lines and the others showed 1 to 2 log_{10} higher titers on the SC-1 cell line than on human 1080 cells. Based on several other tests (data not shown) the SC-1 cells were the most sensitive indicator cultures for detecting infectious ecotropic or amphotropic virus of wild mouse origin. Among the mammalian cells tested, only hamster and bovine cells were resistant. Chicken, duck, and squab (pigeon) embryo cells were also totally resistant. Strain 1504 virus showed no difference in in vitro host range after passage through NIH Swiss mice and re-isolation in NIH Swiss embryo cells. Viruses of purely xenotropic host range were not isolated after terminal dilution purification of the seven isolates in

human HT-1080 cells, as judged by their subsequent growth in SC-1 cells.

No morphological alteration was observed in any of the mammalian cells infected with these different isolates over a period of 5 to 6 weeks.

The MSV pseudotypes of these wild mouse viruses transformed both rat and mouse cells in vitro (Table 4). However, strains 1504, 292, and 4070 produced more distinct foci with higher titers on NRK cells than on NIH Swiss cells.

The seven uncloned wild mouse MuLV's did not produce XC syncytia formation typical of laboratory MuLV strains. Only a very small number (12 to 13) of XC syncytial plaques were detectable when 0.4 ml of undiluted 1504 and 292 viruses (showing a titer of $10^{5.9}$ mean tissue culture infective dose per ml on 1080 cells) were directly inoculated on XC cells.

In vivo pathogenicity. Virus harvested from supernatant fluids of cultures from mice of each of the four trapping areas (LC, LP, Mu, and BC) induced lymphomas in newborn NIH Swiss mice. Virus strains 1504, 292, and 4070 caused both lymphoma and the paralytic disease, whereas strains 11235 and 672 caused only lymphoma. Strain 1504 virus re-isolated after passage through NIH Swiss mice and growth in NIH cells induced both lymphoma and paralysis.

DISCUSSION

Our findings show that each of the seven viruses isolated from wild mice shows typical morphological, physical, and biochemical properties of prototype MuLV strains from laboratory mice. However, their biological activity is somewhat different because they replicate both in mouse cells and in cells of many heterologous mammalian species. Their host range includes that of both mouse tropic (ecotropic) and xenotropic MuLV's. They thus represent a third class of MuLV designated as "amphotropic." As shown by Hartley and Rowe (10a), they are also distinct by interference and virus neutralization tests from the prototype mouse-tropic and xenotropic MuLV classes. However, in contrast to the xenotropic MuLV's none of the field isolates described here have given productive infection in avian cells. The amphotropic host range property suggests that these field isolates may consist of a mixture of mouse-tropic (ecotropic) and xenotropic viruses or, alternatively, of virions carrying a genetic combination of eco- and xenotropic genes and envelope antigens. Our results and those of M. Bryant and V. Klement (Virology, in press) and Hartley and Rowe (10a) indicate that no purely xenotropic virus is detectable in these field iso-

lates after in vitro cloning through human and other mammalian cells. However, several of the field isolates apparently do contain a mixed population of mouse-tropic and amphotropic virus strains (10a; Bryant and Klement, Virology, in press). The amphotropic virus strains of wild mouse origin might be either a genetic recombinant of ecotropic and xenotropic viruses or, more likely, the "wild" or ancestral viruses from which the ecotropic and xenotropic MuLV strains of laboratory mice have been derived. The recent identification of a novel MuLV with dual eco- and xenotropic properties as a minor component of a clonal isolate of Moloney MuLV grown in Swiss 3T3 FL cells (3) suggests that amphotropic MuLV may not be unique to wild mice.

Amphotropism appears to be a general characteristic of wild mouse MuLV since such virus has been isolated from wild mice in four widely separated trapping areas in southern California. There is no evidence that these amphotropic viruses arose by recombination of MuLV and type C virus exogenously acquired from another animal species indigenous to the trapping areas. Squabs, ducks, peromyscus species, and wild rats from the LC, LP, and BC trapping areas have been negative for MuLV p30 antigen by CF, for evidence of type C virus production in cultured cells, or for 1504 viral sequences in cellular DNA. Nor is there any sero-epidemiological evidence for infectivity of the amphotropic MuLV for squabs, ducks, and humans in close contact, including our laboratory personnel.

Experimental virus transmission (5, 21) and in vivo neutralization studies (12) have established these field isolates as the essential determinants of both lymphoma and the paralytic disease. Lymphoma has been transmitted to susceptible laboratory mice with field isolates from wild mice from each of the four trapping areas. However, to date, the paralytic disease, with or without concomitant lymphoma, has been experimentally transmitted only with field isolates from the LC and LP wild mice, which are susceptible to these diseases under natural conditions. Preliminary findings indicate that lymphoma is experimentally induced by both amphotropic and ecotropic clones, whereas paralysis is transmissible only with the ecotropic clones from LC and LP mice. This difference in pathogenicity suggests that strain differences, possibly related to different envelope properties, exist among the field isolates of wild mice. Efforts are in progress to characterize in vitro cloned mouse-tropic and amphotropic viruses from these and additional wild mouse field MuLV isolates to explore the genetic and biochemical basis for the apparently unique neurotropic property of certain MuLV strains of wild mouse origin.

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