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Reticuloendotheliosis Type C and Primate Type D Oncoretroviruses Are Members of the Same Receptor Interference Group

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The reticuloendotheliosis viruses (REVs), originally isolated from avian species, constitute a group of retroviruses which are more closely related to mammalian retroviruses than to other avian retroviruses. The envelope glycoproteins of members of the REV group display a striking amino acid sequence identity with a group of primate oncoretroviruses which belong to a single receptor interference group and include all of the type D and some type C primate oncoretroviruses. Members of the REV group also have a broad host range which covers most avian cells and some mammalian cells, including those of simian and human origin. In view of this broad host range and the envelope sequence similarities, we investigated the cross-interference pattern between REV and primate virus groups to determine whether they utilized the same receptor. Superinfection experiments using a vector virus containing an *Escherichia coli lacZ* gene showed that reticuloendotheliosis and simian oncoretroviruses constitute a single receptor interference group on both human and canine cells and indicate that the viruses bind to the same receptor to initiate infection. These results suggest that this receptor binding specificity has been maintained over a wide range of retroviruses and may be responsible for the broad spread of these retroviruses between different orders of vertebrates.

The first step in retroviral infection is the specific interaction of viral envelope glycoproteins with a cell surface receptor. The phenomenon of superinfection interference reflects the specificity of this interaction. When cells are infected with a particular retrovirus, they become resistant to superinfection by the same virus or to infection by a different virus possessing envelope glycoproteins that bind the same receptor (51, 52). This is thought to occur because viral envelope glycoproteins occupy receptors and competitively block binding by exogenous virus with the same envelope specificity (51, 52).

Retroviruses have been classified into different receptor interference groups on the basis of their pattern of superinfection interference. Avian leukosis viruses, for which retroviral receptor interference was first demonstrated (40), feline leukemia viruses, and murine leukemia viruses have all been classified into distinct receptor interference subgroups, according to their interference patterns on appropriate target cells (36, 37, 53, 60). Recently, 20 mammalian type C and type D retroviruses have been categorized into seven receptor interference groups on the basis of their patterns of interference on human cells (47). One of these groups includes all of the known type D simian retroviruses, such as simian retrovirus (SRV) serotypes 1 to 5 (SRV-3 is also named Mason-Pfizer monkey virus [MPMV]), squirrel monkey retrovirus (SMRV), and langur endogenous retrovirus (PO-1-Lu), as well as endogenous type C viruses of feline (strain RD114) and simian (baboon endogenous virus [BaEV]) origins (47). For simplicity, in this report we will refer to this interference group as the SRV group.

The reticuloendotheliosis viruses (REVs) are a group of closely related oncoretroviruses that includes REV strain A (REV-A), spleen necrosis virus (SNV), chicken syncytial virus, duck infectious anemia virus, and the acutely transforming virus REV strain T (7, 17, 24, 33, 34). Although these viruses were all isolated from avian species (7, 34), they are more closely related to mammalian oncoretroviruses than to other avian retroviruses, as demonstrated by serological cross-reactivity (2, 3, 55, 56) and sequence similarities (17, 19, 23, 38, 49, 54–56, 61). For example, comparison of the sequences of REV-A and MPMV envelope glycoproteins shows an overall 42% amino acid sequence identity, with 33% sequence identity between the surface (SU) glycoproteins and 61% sequence identity between the transmembrane (TM) glycoproteins (SU and TM are the two glycoproteins encoded by the retroviral *env* gene) (16, 49). There is also a striking conservation of cysteine residues (49).

It has been shown that REV-A and SNV have a broad host range which includes avian, rat, canine, simian, and human cells (21, 34, 59). Given the *env* sequence similarity between members of the REV and SRV groups (14, 19, 49, 54), and given that the host range of at least some members of the REV group extends to primate cells (21), it is possible that these two virus groups comprise a single interference group and thus utilize a common receptor. To assess this possibility, we used an SNV-based vector virus containing an *Escherichia coli lacZ* gene and investigated the patterns of interference conferred by viruses of the two groups. We found that canine and human cells chronically infected with replication-competent viruses from the SRV group displayed significant interference when challenged with vector virus produced by using the viral proteins of either SNV or REV-A. Moreover, canine cells chronically infected with replication-competent SNV or REV-A also resisted superinfection when challenged with vector virus pseudotyped by using the viral proteins of BaEV. These results indicate that

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TABLE 1. Oncoretroviruses used in interference studies

Virus[a]	Morphology	Form
Mammalian retroviruses		
I		
SRV-1	Type D	Exogenous
SRV-2	Type D	Exogenous
MPMV (SRV-3)	Type D	Exogenous
RD114	Type C	Endogenous
BaEV	Type C	Endogenous
II, AmMLV	Type C	Exogenous
III, NZB	Type C	Exogenous
IV, GaLV	Type C	Exogenous
REVs		
V		
REV-A	Type C	Exogenous
SNV	Type C	Exogenous

[a] Roman numerals denote retroviruses grouped according to their previously described receptor interference patterns (11, 47).

members of the REV and SRV groups belong to a single receptor interference group and utilize the same receptor for initiating infection.

MATERIALS AND METHODS

Cells and viruses. D17 is a canine cell line derived from an osteosarcoma (39). HOS is a human cell line also derived from an osteosarcoma (25). D17.2G is an REV-A-based packaging cell line derived from D17 cells (13). Replication-competent oncoretroviruses used for superinfection interference experiments are listed in Table 1. REV-A and SNV were both isolated from birds and are closely related to each other (17, 18). The mammalian type C retroviruses used in this study are BaEV strain M7 (BaEV), feline endogenous retrovirus strain RD114 (RD114), amphotropic murine leukemia virus strain 4070A (AmMLV), xenotropic murine leukemia virus strain NZB (NZB), and gibbon ape leukemia virus strain SF (GaLV). Type D SRV-1 to -3 (SRV-3 as MPMV) were kindly provided by Preston A. Marx.

Establishment of cells chronically infected with replication-competent retroviruses. D17 cells were infected with REV-A, SNV, RD114, BaEV, AmMLV, NZB, or GaLV. HOS cells were infected with SRV-1, SRV-2, SRV-3, or GaLV. The cell lines were maintained in culture for at least 2 months to establish chronic productive infections, and retroviral replication was periodically monitored by assaying for reverse transcriptase (RT) activity.

Vector virus production and infections. The SNV-derived vector plasmid pCXL contains an *E. coli lacZ* gene expressed from the long terminal repeat (LTR) promoter (26). CXL vector virus was propagated by using either helper virus or helper cells. Vector virus using helper virus was produced by cotransfecting 5.0 μg of pCXL and 0.2 μg of pSV2Neo (50) into chronically infected D17 cells and selecting with 300 μg of G418 per ml. Vector virus was then harvested from the supernatant of G418-resistant cells. Production of vector virus stocks from REV-A-based helper cells and infection of target cells was carried out as previously described (21, 26). Briefly, target cells were seeded at a density of 5×10^4 cells per 60-mm tissue culture dish. Approximately 4 days later, the target cells were infected with 10-fold serial dilutions of the viral stocks in 0.4 ml of medium containing 50 μg of Polybrene per ml. Viral titers are expressed as focus-forming units (FFU) per milliliter of virus stock; FFU represent the number of blue-staining foci obtained after infection, fixation, and 5-bromo-4-chloro-3-indolyl-β-D-galactopyranoside (X-Gal) staining, multiplied by the dilution factor.

X-Gal staining. Twenty-four hours postinfection, cells were fixed with 2% paraformaldehyde and then stained with X-Gal as previously described (10).

RT assay. RT activity was measured from the supernatants of retrovirus-infected cells as previously described (15). Mn^{2+}-dependent RT activity was assayed in 50 mM Tris-HCl (pH 8.3)–20 mM dithiothreitol–0.6 mM $MnCl_2$–60 mM NaCl–0.05% Nonidet P-40–5 μg of oligo$(dT)_{12-18}$ per ml–10 μg of poly(A) per ml–10 μM dTTP–3.3 nM [α-^{32}P]dTTP. Mg^{2+}-dependent RT activity was assayed in 50 mM Tris-HCl (pH 8.0)–5 mM dithiothreitol–20 mM $MgCl_2$–150 mM KCl–0.05% Nonidet P-40–5 μg of oligo$(dT)_{12-18}$ per ml–10 μg of poly(A) per ml–33 nM [α-^{32}P]dTTP.

Sequence analysis. The *env* gene sequences for MPMV, SRV-1, SRV-2, BaEV, and SMRV were obtained from GenBank and EMBL data bases. The SNV proviral sequence was kindly provided by Vineet N. KewalRamani, Antonito T. Panganiban, and Michael Emerman. The REV-A *env* gene was sequenced by our laboratory when discrepancies between the published sequence (61) and its restriction map were noted. The sequencing involved subcloning the *Hin*dIII fragment (sequence coordinates 1054 to 2630 of reference 61) and the *Hin*dIII-*Sac*I fragment (sequence coordinates 2631 to 3146 of reference 61) of pSW253 (59) into M13mp18 (27) and M13mp19 (27). The two fragments together contain the entire coding sequence of the REV-A *env* gene. Cloning techniques, bacterial transformation and screening, phage growth, single-stranded DNA isolation, and gel electrophoresis were performed according to standard procedures (42). The DNA sequencing was done by the dideoxy-chain termination method (43), using Sequenase version 2.0 (United States Biochemical Corp.). The sequence was confirmed by sequencing both strands.

Sequence analysis was performed with the aid of the Genetics Computer Group software package (12). The amino acid sequence alignment was done with the program PILEUP, using a gap penalty of 2.5 and a length weight of 0.5. The search through sequence data bases to find similarity to the proteins of SNV was done with the TFASTA program, using a word size of 2. Sequences with best scores were then individually aligned to the corresponding sequences of SNV with the program BESTFIT, using a gap weight of 3.0 and a gap length weight of 0.1.

RESULTS

Amino acid sequence alignment of the envelope glycoproteins of members of the REV and SRV groups. The *env* gene of retroviruses encodes a polyprotein which is proteolytically processed into an SU glycoprotein and a TM protein (16). The deduced amino acid sequences of *env* genes from members of the REV and SRV groups for which the sequences are known were aligned, and a consensus sequence was derived (Fig. 1). Positions in which the amino acids matched for six of seven viruses are indicated by an uppercase letter on lines labeled consensus (Fig. 1).

The envelope glycoproteins of REV-A and SNV showed 92.7% amino acid sequence identity (Fig. 1), as previously indicated by nucleic acid hybridization (17, 18). Striking amino acid sequence similarities throughout the envelope proteins of members of the REV and SRV groups were also evident (Fig. 1). For example, of 23 cysteine residues in REV-A, 19 fell into the consensus when compared with the

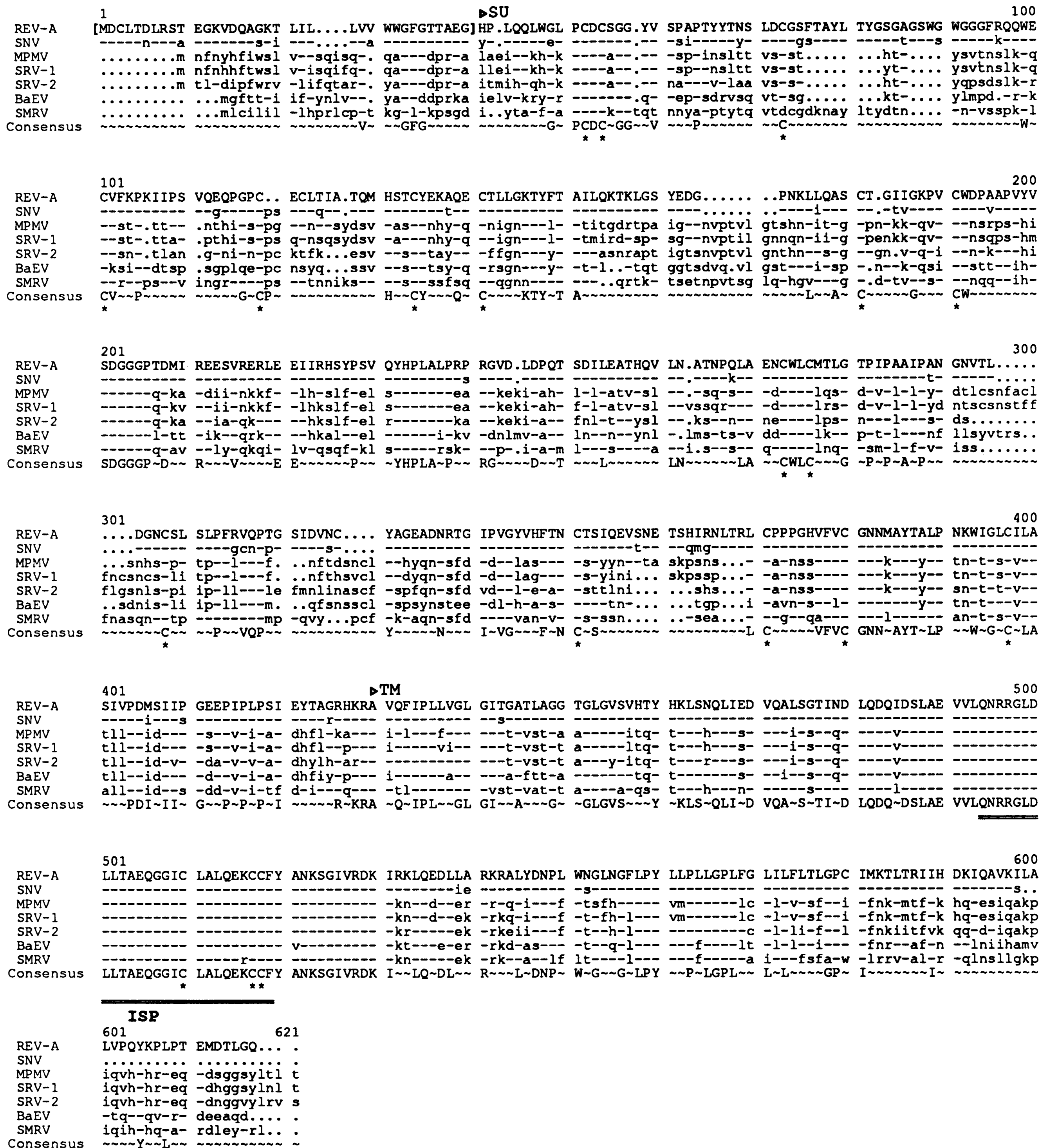

FIG. 1. Alignment of amino acid sequences of envelope glycoproteins from viruses of the REV and SRV groups. The deduced amino acid sequence of REV-A *env* gene, shown in uppercase letters, was compared to the analogous sequences of SNV, MPMV (49; SRV-3), SRV-1 (32), SRV-2 (54), BaEV (19), and SMRV (28). In the alignment, the sequence identity to the REV-A sequence is illustrated by a dash, whereas a mismatch is indicated by a lowercase letter. A dot indicates a gap introduced for optimal alignment. Below the alignment, a consensus sequence is shown. An uppercase letter on the consensus line indicates sequence identity among at least six of seven viruses at that position; otherwise it is marked ~. The conserved cysteine residues in the consensus are marked *. The bracketed sequence is the signal peptide for the *env* gene of REV-A. The amino terminals of fully processed gp90 (SU glycoprotein) and gp20 (TM glycoprotein) of REV-A are marked ▷SU and ▷TM, respectively (56). The sequence underlined with a double line represents the immunosuppressive peptide core (ISP) (9).

TABLE 2. Titers of CXL vector virus packaged with SNV or REV-A proteins on D17 cells chronically infected with different replication-competent retroviruses[a]

Virus	Titer (FFU/ml of virus stock)[b]	
	CXL [SNV]	CXL [REV-A]
None	5.3×10^3	5.5×10^4
REV-A	5	0
SNV	0	0
RD114	0	0
BaEV	0	0
AmMLV	7.8×10^3	8.6×10^4
NZB	5.0×10^3	4.4×10^4
GaLV	5.3×10^3	6.5×10^4

[a] Vector virus was produced by transfecting the vector plasmid pCXL into D17 cells chronically infected with SNV (CXL [SNV]) or REV-A (CXL[REV-A]). Supernatant was harvested from the vector virus-producing cells and used to inoculate D17 cells chronically infected with the indicated replication-competent retroviruses. Approximately 24 h postinfection, cells were fixed and then stained with X-Gal overnight.

[b] The experiment was done twice, and the results obtained were very similar. Data are representative of one of the experiments.

other envelope glycoproteins (Fig. 1). In addition, 31.4% of the amino acid residues of REV-A SU, the glycoprotein which binds directly to a cellular receptor (16), yielded a consensus sequence match (Fig. 1). This similarity among the SU proteins of the REV and SRV groups prompted us to test whether these viruses were members of the same receptor interference group.

Receptor interference on canine cells. For initial studies, we used canine D17 cells because these cells can be productively infected by REV-A, SNV, AmMLV, and RD114 (35, 39, 59). We first determined whether retroviruses of the SRV group and members of other mammalian receptor interference groups (47) could productively infect D17 cells. D17 cells were inoculated with a variety of replication-competent retroviruses, and RT activity in the culture supernatants was assayed 7 days postinfection. RD114 and BaEV, both of which are members of the SRV group, as well as NZB and GaLV, which are members of other receptor interference groups, were found to productively infect D17 cells (data not shown; 39).

For receptor interference experiments, we used the SNV-based vector CXL, which contains an *E. coli lacZ* gene expressed from the SNV LTR promoter (26). Infection by CXL was detected by fixing and staining cells with X-Gal 24 h postinoculation. Titers were then obtained by counting the number of blue-staining foci, which were typically a single cell or two adjacent cells. CXL vector virus using either SNV or REV-A as helper virus was used to inoculate uninfected D17 cells or cells chronically infected with RD114 or BaEV, and titers were determined (Table 2). The CXL viral titer on cells chronically infected with RD114 or BaEV was at least 1,000-fold lower than that obtained on uninfected cells (Table 2). As a positive control for interference, D17 cells chronically infected with REV-A or SNV were also challenged with the CXL virus yielding, as expected (11), a profound interference quantitatively similar to that observed in RD114- or BaEV-infected cells (Table 2). D17 cells chronically infected with retroviruses from other receptor interference groups, such as AmMLV, NZB, and GaLV, showed no evidence of interference as reflected by CXL viral titers similar to those obtained with uninfected cells (Table 2).

TABLE 3. Titers of CXL vector virus pseudotyped with BaEV or AmMLV proteins on D17 cells chronically infected with different replication-competent retroviruses[a]

Virus	Titers (FFU/ml of virus stock)[b]	
	CXL [BaEV]	CXL [AmMLV]
None	1.8×10^2	1.0×10^3
REV-A	3	0.8×10^3
SNV	8	1.2×10^3
RD114	0	0.9×10^3
BaEV	0	0.5×10^3
AmMLV	1.8×10^2	0
NZB	ND[c]	0.8×10^3

[a] Vector virus was produced by transfecting the vector plasmid pCXL into D17 cells chronically infected with BaEV (CXL [BaEV]) or AmMLV (CXL [AmMLV]). Infection and staining were performed as described in footnote *a* of Table 2.

[b] The experiment was reproduced three times, and the data are representative one of the experiments.

[c] ND, not determined.

Interference patterns of CXL virus pseudotyped with BaEV or AmMLV proteins. We next tested whether CXL virus pseudotyped with the proteins of BaEV displayed the same interference pattern on D17 cells as CXL virus, using SNV or REV-A proteins. Although the CXL vector virus titer on uninfected cells was relatively low, probably because of inefficient pseudotyping, the titer was significantly lower on D17 cells chronically infected with REV-A, SNV, RD114, or BaEV (Table 3). In contrast, the titer obtained on AmMLV-infected cells was similar to that found on uninfected cells (Table 3).

We also tested whether CXL virus pseudotyped with AmMLV proteins exhibited an interference pattern different from that seen in the previous experiments. Viral titers obtained on uninfected D17 cells or D17 cells infected with REV-A, SNV, RD114, BaEV, or NZB were very similar, whereas cells infected with AmMLV yielded a greatly reduced titer (Table 3). This demonstrated that interference assay worked properly when a challenge virus of a different receptor interference group was used.

Receptor interference on human cells. Interference to REV-A superinfection was also examined on HOS cells, a human osteosarcoma cell line (25). HOS cells were found to support productive infection by SRV-1, -2, and -3 (47), although the level of virus production fluctuated considerably over time, as indicated by RT activity (data not shown). The HOS cells could also be productively infected by GaLV, a member of a different interference group (data not shown; 47). It was not possible to obtain a chronic, productive infection of HOS cells with SNV or REV-A (data not shown). Infection of HOS cells or any other human cells tested to date by SNV or REV-A results in a semipermissive infection and not a productive infection (21, 22).

To challenge chronically infected human cells, CXL virus stocks were obtained from REV-A-based helper cells (26). As target cells, uninfected HOS cells or HOS cells chronically infected with SRV-1, SRV-2, SRV-3, or GaLV were used. As shown in Table 4, CXL viral titer was at least 100-fold lower on cells infected with SRVs than on uninfected cells, whereas the CXL viral titer on GaLV-infected cells was similar to that on uninfected cells. In agreement with the previous results, interference to REV-A superinfection was observed on cells chronically infected with members of the SRV group but not on cells infected with GaLV, a virus from a different receptor interference group.

TABLE 4. Titers of CXL vector virus packaged with REV-A proteins on HOS cells chronically infected with various replication-competent retroviruses[a]

Virus	Titer (FFU/ml of virus stock)[b]
None	0.9×10^4
SRV-1	6.5×10^1
SRV-2	5.8×10^1
MPMV (SRV-3)	4.8×10^1
GaLV	1.3×10^4

[a] Supernatant was harvested from REV-A-based helper cells stably transfected with pCXL vector plasmid and used to inoculate HOS cells chronically infected with the retroviruses indicated. Approximately 24 h postinfection, cells were fixed and then stained with X-Gal overnight.

[b] Data are representative of one of five experiments.

DISCUSSION

The superinfection interference experiments revealed that titers obtained with vector virus containing the envelope glycoproteins from members of either the REV or SRV group were significantly reduced on canine and human cells chronically infected with replication-competent viruses from either group (Tables 2 to 4). These results demonstrate that members of the REV and SRV groups exhibit the same pattern of interference, thus indicating that they use a common cellular receptor. Despite the fact that these viruses were isolated from widely different species, horizontal transmission has apparently occurred via the same receptor.

The results described in this report and the close relationship of REVs to mammalian oncoretroviruses raise a question about the origin of the REV group. So far, probing avian cellular DNA isolated from uninfected cells with the REV sequence has not yielded significant hybridization signals (18, 45). This suggests that there is no endogenous sequence in the avian genome related to the REV group and that transmission has occurred by horizontal spread. As described above, the envelope glycoproteins of members of the REV group are closely related to those of oncoretroviruses represented by both endogenous and exogenous primate type C and type D retroviruses (14, 19, 49, 54) (Fig. 1). Moreover, when the amino acid sequences of the SNV *gag* and *pol* genes were optimally aligned to the corresponding sequences of other oncoretroviruses, the most similarity was obtained with GaLV, a primate type C retrovirus, which utilizes a different receptor (data not shown). This finding is in agreement with previous results in which nucleic acid hybridization, terminal amino acid sequence analysis, and serological studies showed that the *gag* and *pol* regions of REV were closely related to the corresponding regions of GaLV/simian sarcoma-associated virus as well as primate endogenous type C retroviruses (2, 38, 55). Thus, the entire coding region of viruses of the REV group bears a striking resemblance to that of primate retroviruses. This similarity suggests that members of the REV group are descendants of primate type C oncoretroviruses and have subsequently diverged to give rise to the present REV isolates.

In addition to being related by *env* sequence similarity and receptor usage, members of the REV and SRV groups are linked by their ability to induce immunosuppression in natural hosts (4, 6, 41). A small portion of the TM protein, the immunosuppressive peptide, has been implicated in this immunosuppression (8, 46). This region in the TM protein is highly conserved not only within the REV and SRV groups (19, 28, 49, 54) (Fig. 1) but also within mammalian oncoretroviruses that use different cellular receptors, such as human T-lymphotropic virus types I and II, feline leukemia virus, murine leukemia virus, and GaLV (9, 31). It should be noted that although the effects of the immunosuppressive peptide and the TM protein on immune system are well documented (4, 29, 46), cellular factors involved in this phenomenon have so far not been identified. It is conceivable, however, that interaction between a portion of TM and the different receptors are directly immunosuppressive, since binding of SU to receptor brings the immunosuppressive peptide into close proximity to the receptor. More information about the REV/SRV receptor may help to shed light on this phenomenon.

Two oncoretrovirus receptor genes, those for ecotropic murine leukemia virus and GaLV, have been cloned and sequenced (1, 30). Both receptors appear to be permeases (20, 57, 58), suggesting that these type C oncoretroviruses subverted the function of ubiquitous permease proteins to gain entry into cells. Whether the REV/SRV group has subverted a similarly conserved protein as its receptor remains to be seen. Chromosomal assignment experiments indicate that the receptor gene resides on the human chromosome 19 (5, 44), in the q13.1-13.2 region (48), but the gene encoding the receptor for the REV/SRV group remains to be identified. Given the broad species and tissue distribution of the REV/SRV receptor, the large number of different retroviral isolates that utilize it, and its possible role in pathogenesis, identification of the gene and its cellular function should prove interesting.

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