Cell Surface Receptors for Gammaretroviruses

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1 Introduction . . . 31

2 Historical Perspectives Concerning Interference. . . . 33

3 The γ-Retrovirus Receptors Are Few in Number, and They All Contain Multiple Transmembrane Sequences. . . . 37

4 Despite the Rarity of Receptor Repertoire Expansions Throughout Millions of Years of Retrovirus Evolution, Limited Switches Can Occur Within Single Infected Animals . . . 45
4.1 Evolution of Coreceptor Usage in HIV-1/AIDS . . . 45
4.2 In Vivo Adaptations of Ecotropic MuLVs and Formation of Polytropic MuLVs . . . 46
4.3 Evolution of Altered Receptor Usages in Domestic Cats Infected with FeLV-A. . . . 48

5 Threshold Effects of Receptor Concentrations on γ-Retroviral Infections . 50

6 Receptor Transport Activities Are Not Required for γ-Retrovirus Infections . . . 52

7 Host Range Control of γ-Retrovirus Entry into Cells . . . 56
7.1 Previous Hypotheses and Recent Alternative Interpretations. . . . 56
7.2 Mouse CAT1, the Receptor for Ecotropic MuLVs . . . 59
7.3 Pit 1 and Pit 2 Receptors. . . . 63
7.4 Xenotropic and Polytropic MuLVs . . . 66
7.5 The RD114 Superfamily of Retroviruses . . . 69
7.6 The FeLV-C Receptor. . . . 73
7.7 A Pair of PERV-A Receptors. . . . 74

8 The Role(s) of Receptors in γ-Retrovirus Infections. . . . 75
8.1 General Issues . . . 75
8.2 Adsorption onto Cell Surfaces. . . . 75
8.3 Binding to Receptors Initiates a Pathway of Cooperative Interactions Between Env Glycoproteins . . . 77

9 Summary . . . 81

References. . . . 83

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Abstract Evidence obtained during the last few years has greatly extended our understanding of the cell surface receptors that mediate infections of retroviruses and has provided many surprising insights. In contrast to other cell surface components such as lectins or proteoglycans that influence infections indirectly by enhancing virus adsorption onto specific cells, the true receptors induce conformational changes in the viral envelope glycoproteins that are essential for infection. One surprise is that all of the cell surface receptors for γ-retroviruses are proteins that have multiple transmembrane (TM) sequences, compatible with their identification in known instances as transporters for important solutes. In striking contrast, almost all other animal viruses use receptors that exclusively have single TM sequences, with the sole proven exception we know of being the coreceptors used by lentiviruses. This evidence strongly suggests that virus genera have been prevented because of their previous evolutionary adaptations from switching their specificities between single-TM and multi-TM receptors. This evidence also implies that γ-retroviruses formed by divergent evolution from a common origin millions of years ago and that individual viruses have occasionally jumped between species (zoonoses) while retaining their commitment to using the orthologous receptor of the new host. Another surprise is that many γ-retroviruses use not just one receptor but pairs of closely related receptors as alternatives. This appears to have enhanced viral survival by severely limiting the likelihood of host escape mutations. All of the receptors used by γ-retroviruses contain hypervariable regions that are often heavily glycosylated and that control the viral host range properties, consistent with the idea that these sequences are battlegrounds of virus-host coevolution. However, in contrast to previous assumptions, we propose that γ-retroviruses have become adapted to recognize conserved sites that are important for the receptor's natural function and that the hypervariable sequences have been elaborated by the hosts as defense bulwarks that surround the conserved viral attachment sites. Previously, it was believed that binding to receptors directly triggers a series of conformational changes in the viral envelope glycoproteins that culminate in fusion of the viral and cellular membranes. However, new evidence suggests that γ-retroviral association with receptors triggers an obligatory interaction or cross-talk between envelope glycoproteins on the viral surface. If this intermediate step is prevented, infection fails. Conversely, in several circumstances this cross-talk can be induced in the absence of a cell surface receptor for the virus, in which case infec-

tion can proceed efficiently. This new evidence strongly implies that the role of cell surface receptors in infections of γ-retroviruses (and perhaps of other enveloped animal viruses) is more complex and interesting than was previously imagined.

Recently, another gammaretroviral receptor with multiple transmembrane sequences was cloned. See Prassolov, Y., Zhang, D., Ivanov, D., Lohler, J., Ross, S.R., and Stocking, C. Sodium-dependent myo-inositol transporter 1 is a receptor for Mus cervicolor M813 murine leukemia virus.

1 Introduction

Research during the last few years has greatly advanced our understanding of the cell surface receptors for retroviruses and their roles in controlling viral host ranges and in mediating interference, a process whereby infection of a cell with a retrovirus that encodes an envelope glycoprotein (Env) usually prevents superinfection by viruses that use the same receptor as the primary virus. These advances were achieved largely by identification and molecular cloning of the cell surface proteins that have been subverted for use as retroviral receptors and by parallel advances in studies of the viral Env glycoproteins that bind to the receptors. Another key area of new insights concerns the physical chemical process of viral adsorption and of pulling the virus closely onto the cellular membrane. Indeed, adsorption is a severely limiting step in retroviral infections of cultured cells, and the initial attachment often does not involve the receptors that ultimately mediate infections (Andreadis et al. 2000; Guibinga et al. 2002; Pizzato et al. 1999, 2001; Sharma et al. 2000; Ugolini et al. 1999). Thus we need to distinguish between cell surface molecules such as heparan sulfate proteoglycans, DC-SIGN, or integrins that can enhance infections by concentrating retroviruses onto cells (Bounou et al. 2002; Geijtenbeek et al. 2000; Jinno-Oue et al. 2001; Lee et al. 2001; Mondor et al. 1998; Pöhlmann et al. 2001a; Saphire et al. 2001) from authentic receptors that induce conformational changes in Env glycoproteins that are prerequisite for fusion of the viral and cellular membranes.

Retroviral membranes are studded with trimeric Env glycoprotein “knobs” that have monomers consisting of two subunits, a surface (SU) glycoprotein that binds to receptors and a transmembrane subunit that

participates in the membrane fusion reaction (Hunter 1997; Hunter and Swanstrom 1990; Wilk et al. 2000). In contrast to previous assumptions, recent evidence suggests that γ-retrovirus binding to receptors probably does not directly trigger the membrane fusion process. Rather, it induces a conformational change in SU that enables neighboring SU molecules in the virus to interact in a manner that appears to be necessary and in some instances even sufficient for the membrane fusion step of infection (Anderson et al. 2000; Barnett and Cunningham 2001; Barnett et al. 2001; Lavillette et al. 2000, 2001, 2002b). In specific cases, γ-retrovirus binding to receptors can be bypassed by *trans*-acting SU-related factors (Barnett and Cunningham 2001; Barnett et al. 2001; Lavillette et al. 2002b). We will discuss this evidence because it helps to define the role(s) that receptors perform in the infection pathway. Moreover, it supports other evidence that multiple receptors and SU glycoproteins may be required for membrane fusion (Bachrach et al. 2000; Battini et al. 1995; Blumenthal et al. 1996; Boulay et al. 1988; Chung et al. 1999; Damico and Bates 2000; Danieli et al. 1996; Ellens et al. 1990; Frey et al. 1995; Gunther-Ausborn et al. 2000; Kuhmann et al. 2000; Layne et al. 1990; Platt et al. 1998; Salaün et al. 2002; Siess et al. 1996; Valsesia-Wittmann et al. 1997) and suggests that "cross-talk" and collaboration occurs between Env molecules on retroviral surfaces (Anderson et al. 2000; Lavillette et al. 2000; Rein et al. 1998; Salzwedel and Berger 2000; Zhao et al. 1997).

An important feature of our review derives from our belief that the γ-retrovirus interference groups each formed by divergent evolution from a common origin and that the members of each group have remained faithful to their receptor for millions of years. Consistent with this hypothesis, γ-retroviruses use a surprisingly small number of receptors, which all have the common feature of being proteins with multiple transmembrane (TM) sequences. In contrast, nearly all other groups of animal viruses including the α- and β-retroviruses (Adkins et al. 1997; Ban et al. 1993; Bates et al. 1993; Brojatsch et al. 1996; Golovkina et al. 1998; Rai et al. 2001; Young et al. 1993) exclusively use receptors that have single TM sequences, with the sole proven exception we know of being the coreceptors used by lentiviruses. On the basis of this and other evidence, we propose that a commitment to using receptors with common structural features has been a previously unrecognized general aspect of animal virus evolution. Despite this commitment of viruses to using specific types of cell surface receptors, it is notable that limited

switches in receptor specificities are very common in nature and underlie many important aspects of viral diseases, including AIDS, feline leukemia, and the use of animal reservoirs by influenza A viruses. We attempt to explain this apparent paradox between the long-term evolutionary commitment of viruses to their receptors and their often facile ability to shift to somewhat different receptors very quickly.

It has been generally accepted that many membrane enveloped viruses such as influenza A, Semliki Forest virus, and mouse mammary tumor viruses enter cells by receptor-mediated endocytosis and that membrane fusion is triggered by a decrease in pH that occurs within the endosomes (Flint et al. 2000; Kielian and Helenius 1986; Mothes et al. 2000; Redmond et al. 1984; Ross et al. 2002; Skehel et al. 1995; White et al. 1980; White 1995). In contrast, other viruses such as HIV-1 and most γ-retroviruses are believed to fuse at cell surfaces because of receptor-triggered changes in conformations of Env glycoproteins (Damico and Bates 2000; Damico et al. 1998; Flint et al. 2000; Gilbert et al. 1990, 1995; Katen et al. 2001; Kizhatil and Albritton 1997; McClure et al. 1990; Portis et al. 1985; Ragheb and Anderson 1994; Sommerfelt 1999), and these viruses often cause considerable fusion of uninfected with infected cells at neutral pH (Lavillette et al. 2002a; Ragheb and Anderson 1994; Rein et al. 1998; Siess et al. 1996; Zhao et al. 1997). Although there is no clear evidence for acid-induced fusogenic changes in γ-retroviral Env glycoproteins, some evidence concerning these issues has been ambiguous or dependent on the cells used for the assays (Katen et al. 2001; Kizhatil and Albritton 1997; McClure et al. 1990; Mothes et al. 2000; Portis et al. 1985; Sommerfelt 1999).

For different perspectives concerning γ-retrovirus entry pathways and for more details regarding particular topics, we refer the reader to other recent reviews (Boeke and Stoye 1997; Flint et al. 2000a,b; Hernandez et al. 1996; Hunter 1997; Hunter and Swanstrom 1990; Hunter et al. 2000; Overbaugh et al. 2001; Rosenberg and Jolicoeur 1997; Sommerfelt 1999; Weiss 1992) and to the original articles that are cited here and in those other sources.

2
Historical Perspectives Concerning Interference

Retroviruses were historically classified on the basis of multiple criteria including their core morphologies, their species of origin and interfer-

ence properties, the diseases they induce, the complexities of their genomes, and the evolutionary lineages of their sequences (Coffin 1992; Hunter et al. 2000; Vogt 1997). It should be understood that all of these criteria are ambiguous and that extensive genetic recombination has occurred throughout retroviral evolution (Benit et al. 2001; Jin et al. 1994; Martin et al. 1999; Ott et al. 1990). Indeed, although HIV-1 is a relatively new virus, recombination between evolutionarily distinct HIV-1 lineages (termed clades) has already occurred and recombination also occurs frequently within infected individuals (Jung et al. 2002; Robertson et al. 1995). As a consequence, evolutionary distances and trees can depend dramatically on whether they are based on comparisons of reverse transcriptase or of other sequences (Benit et al. 2001; Martin et al. 1999). For example, the type D primate retroviruses were recently classified as β-retroviruses (Hunter et al. 2000; Overbaugh et al. 2001). However, they are recombinants that have Env glycoproteins closely related to the γ-retroviruses RD114, BaEV, and HERV-W (Boeke and Stoye 1997; Hunter et al. 2000; Kekuda et al. 1997), and these viruses also use a common cell surface receptor (Blond et al. 2000; Lavillette et al. 2002a; Rasko et al. 1999; Tailor et al. 1999). Moreover, the evolutionary lineages of retroviruses do not always correspond to the lineages of their host species because interspecies jumps (termed zoonoses) have occurred (Benit et al. 2001; Martin et al. 1999). Although retroviral zoonoses appear to be most frequent between closely related species, larger jumps have also occurred. For example, the gibbon ape leukemia virus (GALV) occurs in Asia, but its closest known relatives occur in mice and also in marsupial koalas in Australia (Martin et al. 1999). Presumably, there must have been an intermediate host in the transfer involving Australia, but it is unclear how this could have occurred. Thus retroviral lineages cannot be unambiguously rooted by knowledge of host species evolution.

Until recently, the γ-retroviruses were described as the mammalian type C oncoretroviruses. Evidence concerning their cell surface receptors was derived indirectly by determining their host ranges and cross-interference properties (Hunter 1997; Hunter and Swanstrom 1990; Rein and Schultz 1984). For example, murine γ-retroviruses were classified into four principal host range/interference groups termed ecotropic, amphotropic, polytropic (sometimes called dualtropic), and xenotropic (Hunter 1997; Levy 1978; Rein and Schultz 1984), and these groupings were later expanded to include the 10A1 and the *Mus dunni* endogenous viruses (Bonham et al. 1997; Miller and Wolgamot 1997; Miller et al.

1996; Prassolov et al. 2001). Although it was initially believed that each interference group would use a distinct cell surface receptor, it was subsequently found that the interference groupings depended unexpectedly on the cells used for the assays (Chesebro and Wehrly 1985) and were often nonreciprocal (Chesebro and Wehrly 1985; Miller and Wolgamot 1997). Thus, for example, xenotropic MuLVs are endogenously inherited in mice and are naturally produced in some inbred strains such as NZB, but they cannot infect cells of these inbred mice and were therefore termed xenotropic (Lee et al. 1984; Levy 1973, 1978; O'Neill et al. 1986; Tomonaga and Coffin 1998). Similarly, some other endogenous γ-retroviruses such as the baboon endogenous virus and the feline endogenous virus RD114 cannot infect the species in which they are inherited (Boeke and Stoye 1997; Levy 1978). It is likely that mutations in the cell surface receptors accumulated after these viruses had become endogenous, thus protecting the species from additional infections. Because xenotropic MuLVs cannot infect or bind to receptors on NZB cells, it is perhaps not surprising in hindsight that expression of the NZB viral Env glycoprotein in NZB fibroblasts did not cause any interference to infections by polytropic MuLVs (Chesebro and Wehrly 1985; Levy 1978; Rein and Schultz 1984). However, it was later observed that xenotropic MuLVs strongly interfere with polytropic MuLV infections in human or mink cells and even in fibroblasts from Asian wild mice such as *Mus dunni* that are susceptible to both groups of virus, implying that these viruses might use a common receptor in these cells (Bassin et al. 1982; Kozak 1985; Miller and Wolgamot 1997; Ruscetti et al. 1981). However, interference in these cells is nonreciprocal, with polytropic MuLVs causing only weak or negligible interference to superinfections by xenotropic MuLVs (Chesebro and Wehrly 1985; Miller and Wolgamot 1997). Indeed, polytropic MuLVs generally only interfere weakly with superinfections by other polytropic MuLVs, and this results in massive pathogenic superinfections by these viruses in cell cultures and in vivo (Chesebro and Wehrly 1985; Herr and Gilbert 1984; Kozak 1985; Marin et al. 1999; Yoshimura et al. 2001). Similarly, several other highly pathogenic retroviruses such as FeLV-T and SNVs also bind to their receptors only weakly and therefore cause only weak interference to superinfection (Anderson et al. 2000; Delwart and Panganiban 1989; Donahue et al. 1991; Keshet and Temin 1979; Kristal et al. 1993; Moser et al. 1998; Overbaugh et al. 2001; Reinhart et al. 1993; Rohn et al. 1998; Temin 1988; Weller et al. 1980). Such results were very difficult to understand before receptor

cDNAs were cloned and analyzed. The basic outcome of the recent cloning studies is that polytropic and xenotropic MuLVs are closely related viruses that use a common receptor termed the X-receptor that is highly polymorphic in different mouse strains (Battini et al. 1999; Marin et al. 1999; Tailor et al. 1999a; Yang et al. 1999). The complexities in the interference results derive from the fact that retroviruses that use a common receptor need not have the same host ranges or binding affinities for the receptor ortholog that occurs in a particular animal. In addition, in some cases retroviruses can use several related cell surface proteins as receptors (see below). Similar complexities occur in other groups of retroviruses including the avian leukosis virus groups B, D, and E, which do not always cross-interfere despite the fact that they use a common polymorphic receptor (Adkins et al. 1997, 2001).

Interference appears to operate by multiple synergistic mechanisms that have different efficiencies. Coexpression of an Env glycoprotein with its receptor generally results in association of the newly synthesized proteins within the rough endoplasmic reticulum, which inhibits processing of both components to the cell surfaces (Chen and Townes 2000; Heard and Danos 1991; Hunter 1997; Jobbagy et al. 2000; Kim and Cunningham 1993; Murakami and Freed 2000). In addition, Env glycoprotein or SU that is shed from cells or added exogenously can bind to the cell surface receptor and in some cases stimulate partial receptor endocytosis (Hunter 1997; Overbaugh et al. 2001). If these processes that remove receptors from cell surfaces were efficient, the normal function of the receptor would be eliminated with attendant pathological consequences. Although such severe downmodulation of receptors may occur in some instances, chronic infections by γ-retroviruses generally do not cause complete removal of receptors from cell surfaces and it appears that the residual receptor is active in performing its normal cellular function, despite the fact that it becomes saturated with SU and therefore unavailable to serve as a receptor for superinfecting viruses (Wang et al. 1992).

Coexpression of Env with its receptor in infected cells can inhibit processing of the Env glycoprotein to cell surfaces. If this is severe, infectious virus production is reduced, especially in cells that synthesize less Env than receptor. In this context, it should be understood that the extent of viral protein expression depends substantially on the site of proviral DNA integration in the host cell chromosomes and can therefore differ by at least 100-fold in different infected cells (see, e.g., Kabat et al. 1994; Kuhmann et al. 2000)). Consequently, the degree of interfer-

ence and of infectious virus production varies within a chronically infected population of cells. In the case of HIV-1, the virus overcomes this problem by using two viral-encoded accessory proteins, Nef and Vpu, to eliminate the CD4 receptor from infected cells (Chen et al. 1996; Piguet et al. 1998, 1999; Schubert et al. 1998). Because CD4 is not essential for viability of T cells or macrophages, its elimination enhances virus production and release (Bour et al. 1999; Cortex et al. 2002; Lama et al. 1999; Ross et al. 1999).

Despite the enormous number of target cells available to a retrovirus in vivo, it is clear that interference has a major influence on the infection process within animals (Corbin et al. 1994; Gardner et al. 1986; Ikeda and Sugimura 1989). In diseased tissues, large proportions of cells often become infected. Accordingly, replication-defective retroviruses such as the Friend spleen focus-forming virus or the Moloney sarcoma virus are efficiently produced in mice in concert with a replication-competent helper virus (Kabat 1989; Rosenberg and Jolicoeur 1997). In this situation, the defective pseudotyped virus often enters the cell first and it is later rescued into virions after the same cell becomes infected by the helper virus. Similarly, retroviruses that do not cause significant interference such as FeLV-T or polytropic MuLVs have a replicative advantage in chronically infected animals and they often accumulate at high proviral copy numbers per cell late in the process of infection (Herr and Gilbert 1984; Keshet and Temin 1979; Reinhart et al. 1993; Weller et al. 1980; Yoshimura et al. 2001).

3 The γ-Retrovirus Receptors Are Few in Number, and They All Contain Multiple Transmembrane Sequences

Figure 1A summarizes current evidence concerning the cell surface receptors used by γ-retroviruses, including depictions of their presumptive topologies and with their abbreviated names listed below and the virus groups that use them listed above. They are also shown from left to right in the order in which they were molecularly cloned and identified, with the PERV-A receptors being the most recent additions.

It should be understood that all retroviruses likely bind at least weakly to multiple cell surface components not shown in Fig. 1, such as heparan sulfate proteoglycans, DC-SIGN, integrins, or glycolipids (Bounou et al. 2002; Cantin et al. 1997; Fortin et al. 1997; Jinno-Que et al. 2001; Lee

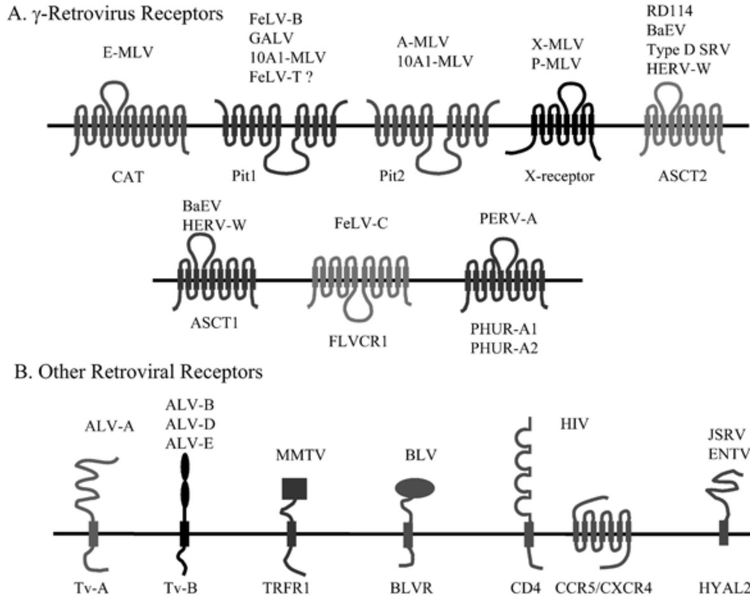

Fig. 1A, B Schematic representation of the cell surface receptors of γ-retroviruses and their comparison to other retroviral receptors. **A** γ-Retrovirus Receptors. All of the known receptors used by γ-retroviruses contain multiple transmembrane (*TM*) segments with short extracellular loops, compatible with their identifications as solute transporters. E-MLV uses a cationic amino acid transporter of mice (*mCAT-1*) as a receptor, whereas FeLV-B, GALV, A-MLV and 10A1-MLV use the sodium-dependent phosphate symporters Pit1 and/or Pit2. The large group of retroviruses that include RD114, BaEV, HERV-W and type D simian retroviruses (*SRVs*) use the neutral amino acid transporter, ASCT2. Recent studies showed that BaEV and HERV-W can also use the related neutral amino acid transporter ASCT1 as a receptor. The normal cellular functions of the receptors for X-MLV/P-MLV (*X-receptor*) and for FeLV-C (*FLVCR1*) are unknown. However, FLVCR1 is a member of the major facilitator superfamily of transporters, suggesting that it is likely to be a transporter of organic anions. The PERV-A receptors have not been functionally characterized, but they occur in many tissues and may also be transporters. **B** Receptors for other retroviruses. This shows the receptors for the avian leukosis virus (*ALV*) subgroups A, B, D, and E, mouse mammary tumor virus (*MMTV*), the complex bovine leukemia virus (*BLV*), the Jagsiekte sheep lung carcinoma virus, and the two different receptors used by human immunodeficiency virus (*HIV*). Interestingly, the receptors for these other retroviruses, are type 1 membrane proteins with only one hydrophobic TM segment, with the exception of the lentiviruses such as HIV-1, which use chemokine receptors with seven TM domains. The Jagsiekte receptor is attached to the cells by a single phosphatidylinositol-linked lipid anchor rather than by a TM peptide (Overbaugh et al. 2001; Rai et al. 2001). The MMTV receptor is transferrin receptor 1 (*TRFR1*) (Ross et al. 2002)

et al. 2001; Mondor et al. 1998; Saphire et al. 1999, 2001). Although such binding substances probably do not induce conformational changes in SU glycoproteins that are necessary for membrane fusion, they can enhance viral adsorption and substantially increase efficiencies of infections, thus contributing to pathogenesis (Alvarez et al. 2002; Bounou et al. 2002; Geijtenbeek et al. 2000; Jinno-Que et al. 2001; Lee et al. 2001; Saphire et al. 2001). Because such binding proteins contribute to infections, it can be difficult to unambiguously distinguish them from receptors that directly mediate the membrane fusion process, especially for retroviruses that bind to their authentic receptors only weakly (e.g., in the cases of FeLV-T or polytropic MuLVs; Anderson et al. 2000; Donahue et al. 1991; Herr and Gilbert 1984; Kristal et al. 1993; Lauring et al. 2001; Marin et al. 1999; Reinhart et al. 1993; Temin 1988; Yoshimura et al. 2001). We emphasize this because pathogenic variants of different animal viruses have often been associated with abilities to bind to apparently novel cell surface components and it has sometimes been inferred that the viruses have switched their receptor specificities. In these instances it has generally not been established that the cell surface binding components are receptors that directly mediate infections.

Because many details concerning the γ-retrovirus receptors are described in following sections, we make only several general conclusions here. First, the receptors all contain multiple TM sequences, consistent with their identification in known instances as transporters of small solutes. Thus CAT1 is a facilitative transporter for cationic amino acids (Kavanaugh et al. 1994b; Kim et al. 1991; Wang et al. 1991); Pit1 and Pit2 are Na^+-dependent phosphate symporters (Kavanaugh et al. 1994a; Olah et al. 1994; Wilson et al. 1995); and ASCT1 and ASCT2 are Na^+-dependent exchangers of neutral amino acids (Marin et al. 1999; Rasko et al. 1999; Tailor et al. 1999b; Torres-Zamorano et al. 1998; Utsunomiya-Tate et al. 1996). In addition, the receptor for FeLV-C (FLVCR1) is a member of the major facilitator superfamily of transporters (Pao et al. 1998; Quigley et al. 2000; Tailor et al. 1999c) although its solute specificity is unknown. Second, the viruses listed in Fig. 1 are broad groupings with numerous members. For example, hundreds of ecotropic MuLVs have been isolated and/or cloned. The GALV group has subgroups including viruses that infect woolly monkeys (Delassus et al. 1989; Martin et al. 1999). Other close relatives occur in mice (MuRRS) and in koalas (Martin et al. 1999), and it is likely that they also use Pit1 as a receptor. The HERV-W family of human endogenous retroviruses contains

approximately 646 representative sequences in the human genome (Pavlicek et al. 2002), and it is also closely related to other viruses including the HERV-H and MuERV-U1 families (Benit et al. 2001). Considered from this perspective, the total number of viruses represented by the summary in Fig. 1A is very large and likely includes the majority of γ-retroviruses. Indeed, only a small number of γ-retroviruses that have been analyzed for their infectivities do not use the receptors shown in Fig. 1A. These include the *Mus dunni* endogenous virus (MDEV) and FeLV-A groups, which use unknown receptors. Third, it should also be understood that each member of a virus group differs from other isolates and that they also differ to a degree in their interactions with receptors. Thus, for example, some FeLV-B isolates use human Pit2 in addition to human Pit1, whereas others use only human Pit1 (Sugai et al. 2001). In domestic cats, FeLV-Bs frequently can use both of the feline Pit proteins as receptors (Anderson et al. 2001). Similarly, GALV uses hamster Pit2 (Wilson et al. 1995). Thus the receptor specificities listed in Fig. 1 pertain to particular members of the virus group as assayed with receptors derived from one or a small number of species. Fourth, many γ-retroviruses use receptors that have close relatives (e.g., Pit1 or Pit2, ASCT1 or ASCT2, FLVCR1 or FLVCR2, and PHuR-A1 or PHuR-A2) and these viruses generally have an inherent ability to use both receptors, at least in certain species as illustrated by the above examples of GALV and FeLV-B. Frequently, the inability of a virus to use one member of a related pair of receptors can be changed by a single amino acid substitution in that receptor (see below). Furthermore, it is likely that additional examples of closely related receptor pairs will be identified in the future for reasons discussed below. For example, we have proposed that the FeLV-A receptor is likely to be closely related to FLVCR1 (Tailor and Kabat 1997). In addition, there is evidence that ecotropic MuLVs can weakly use mouse CAT3, a transporter that is related to mouse CAT1 (mCAT1) (Masuda et al. 1999). FeLV-C isolates can use FLVCR1 and, to a lesser extent, FLVCR2 (C. Tailor, unpublished results). Use of closely related pairs of receptors has been advantageous for γ-retroviruses, presumably in part because it makes host escape mutations much less likely (see below).

A corollary of the above conclusions is that the receptors shown in Fig. 1A probably include a substantial proportion of the receptors that have been successfully exploited by γ-retroviruses and that they are certainly at least representative of all the receptors that have been used.

Thus the total number of receptors used by γ-retroviruses is quite small. Furthermore, several of these receptors are closely related pairs (~60% identity), which implies an additional limitation in their overall diversity. This idea is also strongly supported by the fact that γ-retroviral interference groups initially identified within different species were later shown to use a common receptor (e.g., the FeLV-B and GALV groups). Such overlaps would be unexpected if the total number of receptors was very large. Considered together with the fact that these receptors are all structurally similar in having multiple TM sequences, these results strongly imply that expansions in the repertoire of receptors have been severely limited and constrained throughout millions of years of γ-retrovirus evolution.

It was recently suggested that unrelated γ-retroviruses may have independently chosen to use a common receptor by a process of convergent evolution (Overbaugh et al. 2001), presumably because of some advantageous but unknown aspect of the receptor's structure or function. However, we believe that an hypothesis of convergent evolution would be very difficult to reconcile with the fact that more distantly related families of retroviruses use receptors that exclusively have single TM domains (see Fig. 1B; Adkins et al. 1997, 2001; Ban et al. 1993; Bates et al. 1993; Brojatsch et al. 1996; Golovkina et al. 1998; Rai et al. 2001; Ross et al. 2002; Young et al. 1993). These retroviruses include the avian leukosis viruses, MMTV, bovine leukemia virus, and Jaagsiekte sheep lung carcinoma virus groups, which have lifestyles similar to those of the γ-retroviruses. Furthermore, there is very solid evidence for divergent evolution of γ-retroviruses within their specific interference groups. Most strikingly, the only avian retroviruses known to use a receptor with multiple TM domains is the SNV/REV-A group that is closely related to the baboon endogenous virus (BaEV) and probably originated by a rare zoonosis from a primate into a bird followed by adaptive infectious radiation into gallinaceous and anseriform birds (Barbacid et al. 1979; Boeke and Stoye 1997; Hunter 1997; Kewalramani et al. 1992; Koo et al. 1992, 1991; Martin et al. 1999). Similarly, the RD114 feline endogeneous retrovirus and BaEVs appear to have derived from a common ancestor (Mang et al. 1999; van der Kkuyl et al. 1999), as did the xenotropic and polytropic MuLVs (Khan 1984). The Env sequences that can be used to trace evolutionary lineages are also compatible with the hypothesis that the interference groups of γ-retroviruses each derived by divergent evolution from a common ancestor, although it is also clear that genetic recombi-

nations have shuffled these sequences and made it difficult to trace the lineages of the receptor-recognition domains of the SU glycoproteins (Benit et al. 2001). However, the immunosuppressive domain of the transmembrane Env subunit has provided useful lineage information (Benit et al. 2001). Similarly, the amino-terminal PHQ motif in SU that is involved in *trans*-stimulation (Lavillette et al. 2000) is conserved in several γ-retrovirus interference groups but is absent or modified in other interference groups, implying distinct evolutionary lineages (D. Lavillette, unpublished results). Divergent evolution also occurs during retroviral replication *i*n vivo, which can involve minor shifts in usage between closely related receptors (e.g., shifts of CCR5 to CXCR4 coreceptor usage for HIV-1) as discussed below and during in vitro selection in cultured cells that express different orthologs of a common receptor for avian leukosis virus subgroups B, D, and E (Holmen et al. 2001; Taplitz and Coffin 1997).

Despite this strong evidence for divergent evolution of the γ-retrovirus interference groups, we emphasize that a limited degree of convergent evolution in receptor choice cannot be fully excluded. This has been proposed mainly with respect to the γ-retroviruses that use Pit1 and Pit2 receptors, in part because it has been difficult to identify close lineage relationships among some of these viruses and because several studies implied that GALV, FeLV-B, and A-MuLV viruses may interact rather differently with distinct regions of the Pit receptors (Overbaugh et al. 2001; Pedersen et al. 1995). In contrast, other evidence suggests that these viruses interact with the same regions of these receptors (Dreyer et al. 2000; Eiden et al. 1996; Johann et al. 1993; Lundoft et al. 1998; Tailor and Kabat 1997; Tailor et al. 1993, 2000b). Indeed, corresponding sites in the FeLV-B and A-MuLV SU glycoproteins interact with homologous sites in Pit1 and Pit2 in a common orientation (Tailor and Kabat 1997; Tailor et al. 2000b). We believe that the simplest interpretation of the available evidence is that these viruses all interact with Pit1 and Pit2 in a common orientation that involves several contact sites in both the receptors and the SU glycoproteins. However, the affinities of interactions at specific contact sites can differ for particular virus isolates. Similarly, R5 and X4 strains of HIV-1 interact somewhat differently with different regions of their coreceptors, as do distinct isolates of SIV (Brelot et al. 1997; Chabot and Broder 2000; Edinger et al. 1997; Lu et al. 1997; Picard et al. 1997; Pontow and Ratner 2001). Nevertheless, all of these immunodefi-

ciency viruses diverged from a common ancestor, and the structures of the SU-coreceptor complexes must also be very similar.

On the basis of the above considerations, we propose that throughout a period of evolution that may have exceeded 100 million years the γ-retroviruses have been only rarely able to expand their repertoire of cell surface receptors. Presumably, an early γ-retrovirus progenitor became adapted to use a receptor with multiple TMs, and its descendants thereby were committed to the constraints imposed by this adaptation. Consequently, the few successful receptor switches that subsequently occurred had this same structural constraint. Thus, as is typical in evolution, an initial accident that is followed by adaptation imposes severe limits on subsequent evolutionary options.

Our conclusion that γ-retroviruses have had difficulty in expanding their repertoire of receptors also may apply to other virus groups. Thus avian leukosis viruses use a small number of receptors that have the common feature of being single-TM proteins (see Fig. 1B). Intriguingly, this is also true of other animal viruses. For example, all proven receptors for coronaviruses, herpesviruses, adenoviruses, and picornaviruses have only single TM domains (Flint et al. 2000a). Indeed, there are only a few receptors for animal viruses other than γ-retroviruses that have been reported to have multiple TM sequences, with CD81, a tetraspanin binding factor for hepatitis C virus (Baranowski et al. 2001; Higginbottom et al. 2000; Pileri et al. 1998), and the lentivirus coreceptors being the most convincing examples. However, a single -TM protein, the low-density lipoprotein receptor, was recently shown to be a specific entry receptor for hepatitis C virus (Agnello et al. 1999; Baranowski et al. 2001), and CD81 is evidently only a binding factor (Meola et al. 2000; Petracca et al. 2000; Pileri et al. 1998). In addition, it was reported that rabies virus may use an acetylcholine receptor with multiple TM sequences (Burrage et al. 1985; Flint et al. 2000a; Thoulouze et al. 1998), but this is not essential for infection and is also believed to be a binding protein rather than a true receptor.

Our proposal that all virus groups have been severely limited throughout evolution in the types of receptors they can employ may initially appear inconsistent with evidence that some viruses can switch their receptor specificities with apparent ease. This has been most dramatically suggested by shifts of influenza A viruses between animal reservoirs, which involve single amino acid changes in the viral hemagglutinin that enable recognition of different sialic acid structures (e.g., *N*-acetyl or

N-glycolyl neuraminic acids in α2,6 or α2,3 linkages to galactose) that predominate in the different host species (Baranowski et al. 2001; Rogers et al. 1985; Skehel and Wiley 2000; Suzuki et al. 1989, 2000). Similarly, slight changes in specificity for receptors accompanied emergence in 1978 of the canine parvovirus (Domingo et al. 1999; Parker et al. 2001). However, these are small shifts in receptor specificities rather than global jumps to dissimilar receptors. Similar slight shifts are involved in the change from CCR5 to CXCR4 coreceptor usage during AIDS progression (Scarlatti et al. 1997). Small shifts in usages of closely similar receptors also have been reported to occur during cell culture selections of subgroup B, D, and E avian leukosis viruses that all use polymorphic variants of the same TVB receptor (Holmen et al. 2001; Taplitz and Coffin 1997) and during cell culture selections of HIV-1 variants (Platt et al. 2001). These issues are discussed further below (see Sect. 4).

Several viruses have been reported to use multiple alternative receptors or even alternative pathways for infection of cells. For example, measles virus isolates appear to be capable of using CD46 or SLAM, which both contain single TM domains (Baranowski et al. 2001; Oldstone et al. 1999; Tatsuo et al. 2000). Complex viruses such as herpesviruses that contain several distinct envelope glycoproteins are also typically able to bind to several cell surface components (Baranowski et al. 2001; Borza and Hutt-Fletcher 2002; Flint et al. 2000a). The foot-and-mouth disease picornavirus (FMDV) may also use multiple receptors including heparan sulfates and integrins and may in addition be able to invade cells via immunoglobulin F_c receptors when the virus is coated with antibodies (Baranowski et al. 2001; Mason et al. 1994). This alternative entry route is also used by the dengue flavivirus, which may explain the extremely strong pathogenesis that occurs when it reinfects previously exposed individuals (Baranowski et al. 2001). In the case of FMDV, it has not been established whether heparan sulfate is a true receptor that directly mediates infection or merely a binding factor that influences infection indirectly by enhancing virus adsorption. HIV-1 infections are also strongly stimulated by accessory cell surface binding components including heparan sulfates, glycolipids, and DC-SIGN (Bounou et al. 2002; Geijtenbeek et al. 2000; Lee et al. 2001; Pöhlmann et al. 2001a,b; Zhang et al. 2002). Similarly, a paralysis-inducing neurotropic variant of Friend MuLV binds more strongly than the parental virus to heparan sulfate, and it thereby becomes more infectious for brain capillary endothelial cells while still remaining dependent on the CAT1 recep-

tor (Jinno-Oue et al. 2001). These examples illustrate how changes in affinities for accessory binding substances can dramatically alter cellular tropisms and pathogenesis of viruses, and why it has often been difficult to distinguish such accessory binding factors from true receptors or coreceptors that are essential for infections. On the basis of these considerations, we believe that the available evidence strongly supports our proposal that all virus groups have been severely constrained in the types of receptors they can employ for infection of cells. However, some viruses have evolved several pathways for infection, and viruses such as HIV-1 have evolved distinct sites in a single SU glycoprotein for recognition of dissimilar receptors and coreceptors. In addition, viruses including γ-retroviruses have become adapted to interact with accessory binding factors on cell surfaces, and these accessory associations often have major effects on viral transmission and pathogenesis.

4 Despite the Rarity of Receptor Repertoire Expansions Throughout Millions of Years of Retrovirus Evolution, Limited Switches Can Occur Within Single Infected Animals

4.1 Evolution of Coreceptor Usage in HIV-1/AIDS

It is well-known that HIV-1 invades cells via a sequential interaction of its gp120 SU glycoprotein with at least two cell surface proteins, the CD4 receptor and a coreceptor (Choe et al. 1996; Deng et al. 1996; Doranz et al. 1996; Dragic et al. 1996; Feng et al. 1996; Flint et al. 2000a,b; Moore et al. 1997; Weiss 1992). CD4 is normally involved in T cell activation, whereas coreceptors are closely related members of a group of heterotrimeric G protein-coupled receptors that are activated by small chemoattractant cytokines termed chemokines (Littman 1998). Like other retroviruses HIV-1 mutates rapidly in vivo, and one consequence is often an expansion in its coreceptor specificity. HIV-1 involved in initial transmission exclusively uses CCR5 as a coreceptor (Liu et al. 1996). However, during viral evolution within approximately 50% of infected individuals, mutations of gp120 in one disulfide-bonded loop called variable loop 3 (V3) expand the coreceptor repertoire to allow additional or eventually even exclusive use of CXCR4 (Connor et al. 1997; Pollakis et al. 2001; Polzer et al. 2001; Scarlatti et al. 1997; Speck et al. 1997). Uti-

lization of CXCR4 enables HIV-1 to more readily infect the immunologically naive, unactivated $CD26^{low}$ $CD45RA^{+}$ $CD45R0^{-}$ subset of T lymphocytes, and this expansion in cell tropism coincides with and is likely to be the proximal cause of an accelerated destruction of the host immune system (Blaak et al. 2000; Bleul et al. 1997; Camerini et al. 2000; Kreisberg et al. 2001; Kwa et al. 2001; Lee et al. 1999; Schramm et al. 2000; Unutmaz and Littman 1997).

This cycle of viral variation within infected individuals is poorly understood. However, it recapitulates itself in each infected individual. Thus, even when transmission occurs by a blood transfusion or needle stick that contains X4 strains of HIV-1, the virus reverts to R5 specificity early in the new infection (Beaumont et al. 2001; Cornelissen et al. 1995), suggesting that entry via the mucosal endothelium is not required for selection of the CCR5 specificity. Rather, it is likely that R5 strains of HIV-1 have a selective advantage in the milieu of the newly infected individual, in part because CCR5 is a substantially stronger coreceptor than CXCR4 (Doranz et al. 1996, 1999; Hoffman et al. 2000; Mondor et al. 1998) and in part because at the early phase of infection there are abundant memory T cells that express adequate concentrations of CD4 and CCR5 (Blaak et al. 2000; Bleul et al. 1997; Lee et al. 1999; Unutmaz and Littman 1997). CXCR4 contains an N-linked oligosaccharide in its amino-terminal region that inhibits its utilization by R5 strains of HIV-1 (Chabot et al. 2000). Viral transmission to these memory T cells is also facilitated by antigen-presenting follicular dendritic cells that contain DC-SIGN (Geijtenbeek et al. 2000; Lin et al. 2000). After substantial disruption of the lymph node follicles and depletion of the follicular dendritic cells and memory T cells, the immune system becomes weaker and viral variants that can more efficiently use CXCR4 begin to have improved opportunities.

4.2 In Vivo Adaptations of Ecotropic MuLVs and Formation of Polytropic MuLVs

Infections with ecotropic MuLVs (E-MuLVs) have also resulted in selection of adapted viral variants. Normally, E-MuLVs can infect cells of mice or rats but cannot infect Chinese hamster ovary cells (CHO-K1 cells) unless the cells are pretreated with tunicamycin, which inhibits N-linked glycosylation of proteins (Masuda et al. 1996; Miller and Miller

1992; Wilson and Eiden 1991). However, passage of the Friend strain of E-MuLV in rats reproducibly causes paralysis with degeneration of the central nervous system, and the virus recovered from these passages also causes the same disease when injected into newborn mice (Masuda et al. 1992, 1996a,b; Park et al. 1994; Takase-Yoden and Watanabe 1999). Compared with the original molecular clone of Friend E-MuLV, the Env SU glycoprotein of the passaged virus PVC-211 is altered in a variable region that contains disulfide-bonded loops and is known to be involved in receptor binding (Battini et al. 1998; Fass et al. 1997; Masuda et al. 1996a,b). In addition, this variant Friend virus is able to efficiently infect CHO-K1 cells in the absence of tunicamycin, and it binds relatively strongly to heparan sulfates (Jinno-Oue et al. 2001; Masuda et al. 1996b). These novel properties of the PVC-211 virus are all caused by mutations in the SU glycoprotein (Masuda et al. 1996b). An implication of these results is that growth of the Friend E-MuLV in rats, which contain a CAT1 protein distinct from the mouse ortholog, selected for SU changes that coincidentally enabled efficient infection of CHO-K1 cells and invasions of brain capillary endothelial cells. Indeed, as described below, the CAT1 orthologs in rats and hamsters have common sequences that distinguish them from mouse CAT1.

When E-MuLVs are injected into mice or when they are expressed endogenously as in newborn AKR strain mice, they often recombine with endogenously inherited polytropic *env* sequences to produce recombinant viruses that encode chimeric Env glycoproteins, with the amino-terminal receptor-binding domains of SU deriving from polytropic endogenous sequences and the remainder corresponding to the E-MuLV parental virus (Fischinger et al. 1975; Kabat 1989; Rosenberg and Jolicoeur 1997; Stoye et al. 1991). In addition, recombinations also often occur in the viral LTRs (Kabat 1989; O’Neill et al. 1986; Stoye et al. 1991). These recombinant viruses have a polytropic host range and use the X-receptor for infection (Battini et al. 1999; Tailor et al. 1999a; Yang et al. 1999). Because they form as recombinants when E-MuLVs replicate in mice, polytropic MuLVs were first discovered as “contaminants” in preparations of E-MuLVs (Fischinger et al. 1975; Hartley et al. 1977; Kabat 1989; Rosenberg and Jolicoeur 1997). In such preparations, the polytropic MuLVs generally are pseudotyped with the E-MuLV envelope, a phenomenon called “genomic masking” (Fischinger et al. 1978). Accordingly, isolation of polytropic MuLVs generally has required infection of mouse cells at low multiplicities by the contaminated E-MuLVs, fol-

lowed by harvest of the released virions before the E-MuLV can spread into all cells and subsequent infection of cells that are resistant to E-MuLVs such as CCL64 mink cells (Fischinger et al. 1975, 1978; Hartley et al. 1977). Because polytropic MuLVs cause foci in mink cells they have been termed mink cell focus-inducing viruses (MCFs). MCFs cause only weak interference, and they massively superinfect susceptible cells *i*n vitro and in vivo (Hartley et al. 1977; Herr and Gilbert 1984; Marin et al. 1999; Yoshimura et al. 2001).

Interestingly, many diseases of mice initially believed to be caused by E-MuLVs were later shown to be substantially accelerated by the MCF contaminants (Chesebro et al. 1984; Cloyd et al. 1980; Hartley et al. 1977; Kabat 1989; Rosenberg and Jolicoeur 1997; Stoye et al. 1991), and they were in several cases inhibited by the R_{mcf} gene that blocks the X-receptor and interferes with MCF infections (Bassin et al. 1982; Jung et al. 2002; Kabat 1989; Kozak 1985; Ruscetti et al. 1981, 1985). These results implied that polytropic MuLVs may be causal agents for many diseases including T cell leukemias, lymphomas, and erythroleukemias (Hartley et al. 1977; Kabat 1989; Ruscetti et al. 1981). This hypothesis has been difficult to test with pure MCFs because there are inhibitory lipoprotein factors in sera of many mice that specifically inactivate polytropic and xenotropic MuLVs by an unknown mechanism (Levy 1978; Wu et al. 2002). In contrast, when MCFs are partially or fully genomically masked by replication in the presence of E-MuLVs, the MCFs resist this inactivation system and contribute to pathogenesis. Consequently, the mixture of an E-MuLV plus an MCF is often much more pathogenic than either virus alone.

4.3 Evolution of Altered Receptor Usages in Domestic Cats Infected with FeLV-A

Although domestic cats initially become infected via saliva only with the FeLV-A subgroup of feline leukemia viruses, which use an unknown cell surface receptor, chronically infected animals often also contain FeLV-B, FeLV-C, and/or FeLV-T viruses (Linenberger and Abkowitz 1995; Moser et al. 1998; Overbaugh et al. 1988, 2001). The FeLV-B viruses form by recombination of the replicating FeLV-A with endogenously inherited FeLV-B *env* gene sequences that occur in high copy numbers in the genome of these animals (Boomer et al. 1994; Overbaugh et al. 1988; Roy-

Burman 1995; Sheets et al. 1993; Stewart et al. 1986). This recombination closely resembles the formation of MCFs in mice initially infected with E-MuLVs (see above). Accordingly, the FeLV-B recombinants encode chimeric SU glycoproteins that have amino-terminal receptor-binding domains corresponding to the endogenous FeLV-B-specific portion (Roy-Burman 1995; Sheets et al. 1992; Stewart et al. 1986). Interestingly, the endogenous FeLV-B envelope sequences are more homologous to the amino termini of the amphotropic and 10A1 MuLV SU sequences than to the corresponding regions of other FeLV Env glycoproteins. This similarity to murine retroviruses suggests that FeLV-B may have formed as a zoonosis of cats by a virus of rodent origin. Accordingly, FeLV-B and 10A1 MuLV both use human Pit proteins as receptors (see Fig. 1A; Miller and Miller 1994; Takeuchi et al. 1992; Wilson et al. 1994). Although it is believed that endogenously inherited FeLV-B SU glycoproteins preferentially employ feline Pit1 as a receptor, many FeLV-B isolates from infected cats also employ feline Pit2, and these probably are adapted variants with a broadened cellular tropism that evolved *i*n vivo (Anderson et al. 2001; Boomer et al. 1997). The contributions of FeLV-B to pathogenesis have been difficult to determine unambiguously (Bechtel et al. 1999; Neil et al. 1991). However, FeLV-B Env glycoproteins can in some cases facilitate infections by other viral subgroups (Anderson et al. 2000; Lauring et al. 2001, 2002).

In contrast, formation of FeLV-C viruses occurs sporadically in FeLV-A-infected cats because of accumulation of a small number of mutations in one disulfide-bonded loop of the SU glycoprotein (Brojatsch et al. 1992; Neil et al. 1991; Rigby et al. 1992). These mutations shift the receptor specificity from that of FeLV-A toward use of the FLVCR1 receptor. Interestingly, formation of FeLV-C *i*n vivo coincides with onset of aplastic anemia also called fatal red cell aplasia (Abkowitz et al. 1987; Linenberger and Abkowitz 1992, 1995; Onions et al. 1982; Rojko et al. 1996). Accordingly, infections of cats with FeLV-C induce this disease, which can also be mimicked in bone marrow cultures (Abkowitz et al. 1987; Linenberger and Abkowitz 1992, 1995; Onions et al. 1982; Rojko et al. 1986; Testa et al. 1983). FLVCR1 expression occurs in multiple hematopoietic lineages, which also become infected by FeLV-C *i*n vivo and *i*n vitro, suggesting that erythroblasts or their supporting bone marrow microenvironment may be especially sensitive to the virus rather than uniquely susceptible to infection (Abkowitz et al. 1987; Dean et al. 1992; Linenberger and Abkowitz 1992, 1995). Because SU glycoproteins of

FeLV-C and FeLV-A differ specifically only at a few positions in one disulfide-bonded loop region, and because analogous changes in disulfide-bonded loops cause small shifts in receptor or coreceptor specificities for HIV-1 (Connor et al. 1997; Pollakis et al. 2001; Polzer et al. 2001; Scarlatti et al. 1997; Speck et al. 1997), E-MuLVs (Masuda et al. 1992, 1996a,b; Park et al. 1994), and avian leukosis viruses (Holmen et al. 2001; Taplitz and Coffin 1997), we have proposed that FeLV-A probably uses a receptor that is very similar in structure to FLVCR1 (Tailor et al. 1999c). Thus we anticipate that the FeLV-A receptor may also be a member of the major facilitator superfamily of transporters (Pao et al. 1998).

In addition to FeLV subgroups A, B, and C, several virus isolates from domestic cats have been termed FeLV-T because they selectively destroy T cell cultures and cause a severe feline acquired immunodeficiency syndrome (FAIDS) (Donahue et al. 1991; Overbaugh et al. 1988; Rohn et al. 1998). FeLV-T SU glycoproteins appear to have only minute binding affinities for susceptible cells, and they accordingly cause negligible interferences to superinfections (Donahue et al. 1991; Kristal et al. 1993; Overbaugh et al. 1988, 2001; Reinhart et al. 1993). Consequently, T cells become massively superinfected with FeLV-T, which may explain the immunosuppressive effects of this virus (Donahue et al. 1991; Reinhart et al. 1993). Furthermore, FeLV-T is not interfered with by FeLV subgroup A, B, or C viruses, which has led to the proposal that FeLV-T may use a unique receptor (Kristal et al. 1993; Moser et al. 1998; Reinhart et al. 1993). However, an effort to clone an FeLV-T receptor yielded only an FeLV-B-related SU glycoprotein fragment termed FELIX (Anderson et al. 2000) that binds to Pit1 and facilitates FeLV-T infection by a *trans*-complementation mechanism that is discussed below (see Sect. 8.3).

5
Threshold Effects of Receptor Concentrations on γ-Retroviral Infections

The γ-retrovirus receptors were all cloned based on transfection or transduction of receptor-encoding nucleic acid sequences from susceptible species into cells that are resistant to the corresponding viruses. An expectation of this strategy is that the resistant cells used for the cloning must lack functional receptors for the virus. Although this has generally been true, several important and informative exceptions have been reported. One exception concerns the resistance of CHO cells to amphotropic MuLVs (A-MuLV), which was initially interpreted to suggest

that the CHO Pit2 protein was inactive in mediating infection by this virus (Chaudry et al. 1999; Miller and Miller 1992; Wilson et al. 1994). In contrast, E36 cells, which also were derived from a Chinese hamster, are susceptible to A-MuLVs. Furthermore, the E36 Pit 2 protein differs from that of CHO cells and was found to confer susceptibility to A-MuLVs when it was expressed in CHO cells (Wilson et al. 1994). Subsequently, it was unexpectedly found that the CHO Pit 2 protein is also an active receptor for A-MuLVs when its cDNA is transfected into CHO cells (Tailor et al. 2000a). Another example occurs with FeLV-C, which naturally infects human cells but not NIH/3T3 or *Mus dunni* mouse fibroblasts (Tailor et al. 1999c, 2000a). Indeed, human FLVCR1 was cloned on the basis of its ability to confer susceptibility of NIH/3T3 cells to FeLV-C (Tailor et al. 2000a). Consequently, it was surprising to find that the FLVCR1 ortholog cloned from *Mus dunni* fibroblasts also efficiently facilitated FeLV-C infections when it was overexpressed in *Mus dunni* fibroblasts (Tailor et al. 2000a). These and an additional example (Chung et al. 1999) strongly suggest that potentially active receptors may completely fail to mediate γ-retrovirus infections when they are expressed at low subthreshold levels and that they can mediate infections efficiently when they are overexpressed in the same cells from which they were originally derived.

Two general models have been invoked to explain such threshold requirements of receptor concentrations for infections. According to one model, there may be interfering retroviral-related SU glycoproteins or other receptor-masking substances that are endogenously expressed in the cells that are resistant to infection. Such interfering substances would block infections if they were present in excess of the receptor, but the receptor would become active if it was expressed in excess of the mask (Tailor et al. 2000a). Consistent with this idea, inhibitory substances have been identified in conditioned media from some cell cultures (Miller and Miller 1992, 1993). Furthermore, endogenously inherited Env glycoproteins are often synthesized in small amounts and they can interfere with infections of some γ-retroviruses (Bassin et al. 1982; Ikeda and Sugimura 1989; Kozak 1985; Lyu and Kozak 1996; Lyu et al. 1999; Ruscetti et al. 1981, 1985).

According to a second model, a receptor may be inherently weak in its ability to associate with a virus, so that it would mediate infection efficiently only when it is expressed at high concentrations. Furthermore, if infection requires a complex containing multiple receptors, as is be-

lieved to be the case for several enveloped viruses (Battini eta l. 1995; Blumenthal et al. 1996; Damico and Bates 2000; Danieli et al. 1996; Ellens et al. 1990; Kuhlmann et al. 2000; Salaün et al. 2002), a plot of virus titer versus receptor concentration would have a sigmoidal or stepwise shape, with negligible infectivity at low receptor concentrations and efficient infectivity above the transitional concentration (Damico and Bates 2000; Kuhmann et al. 2000; Platt et al. 2001). Precedent for this model is provided by studies of HIV-1 (Kuhmann et al. 2000; Platt et al. 2001). For example, the G163R substitution in human CCR5 causes a large reduction in its affinity for HIV-1 (Kuhmann et al. 2000; Siciliano et al. 1999). This mutant coreceptor is therefore inactive at low concentrations, but it is almost as active as wild-type CCR5 at high concentrations (Kuhmann et al. 2000). Furthermore, the G163R substitution is not anomalous because it naturally occurs in African green monkey CCR5 and it does not interfere with chemokine signaling or with infections by the simian immunodeficiency viruses that are endemic in those monkeys (Siciliano et al. 1999). Mathematical analyses of these sigmoidal shaped curves support the conclusion that a minimal complex of four to six CCR5s is necessary for HIV-1 infections (Kuhmann et al. 2000; Platt et al. 2001). Other studies also suggested that multiple Env glycoproteins function cooperatively in retroviral infections (Bachrach et al. 2000; Rein et al. 1998; Salzwedel and Berger 2000; Zhao et al. 1997).

6 Receptor Transport Activities Are Not Required for γ-Retrovirus Infections

Despite the fact that γ-retrovirus infections often inhibit superinfection efficiencies by 3–4 orders of magnitude, cell surface receptor concentrations usually appear to be downmodulated only partially (by ~60%–90%) (Wang et al. 1992). This downmodulation is partly caused by association of newly synthesized receptors and Env glycoproteins in the rough endoplasmic reticulum, which blocks their processing to cell surfaces, and partly by enhancement of receptor endocytosis (Heard and Danos 1991; Jobbagy et al. 2000; Kim and Cunningham 1993). In addition, production and shedding of SU glycoproteins by the infected cells causes saturation of the residual cell surface receptors and this evidently contributes to the interference. Because this saturation does not completely block transport activity of the receptor, residual transport occurs,

and it is likely that this ameliorates pathogenic effects and enhances survival and replication of the infected cells. Thus it appears that a limitation in loss of the normal transport function of the receptor has probably been advantageous for γ-retrovirus replication. However, there are alternative compensatory mechanisms to protect infected cells from loss of the transporter/receptor. For example, downmodulation of Pit1 transport activity causes upregulation of Pit2 expression and vice versa (Chien et al. 1997; Kavanaugh et al. 1994a). Similarly, in other cases there are redundant mechanisms for transport of key solutes. It should be noted in this context that ASCT1 and ASCT2 transport an overlapping but nonidentical set of neutral amino acids, with the major difference being the exclusive transport of glutamine by ASCT2 (Kekuda et al. 1996, 1997). Thus downmodulation of ASCT2 cannot be fully compensated by upregulation of ASCT1.

Several studies have suggested that γ-retroviral receptor function does not require transporter activity. In the case of mouse CAT1, mutation of a conserved glutamic acid at position 107 in a hydrophobic transmembrane region to an aspartic acid (i.e., E107D) completely eliminated transport activity without significantly inhibiting infections by E-MuLVs (Wang et al. 1994). In the case of human Pit2, recent mutagenesis studies demonstrated the same conclusion (Bottger and Pedersen 2002). Moreover, we recently found that the ASCT2 protein consists of multiple isoforms that have diverse truncations at their amino-terminal ends (Tailor et al. 2001). The ASCT2 isoforms are translationally initiated by a leaky scanning process (Kozak 1999) at a series of CUG and GUG codons that occur in optimal Kozak consensus sequence contexts and that are situated downstream of the normal AUG initiation codon that occurs in a suboptimal and inefficient sequence context. Thus leaky scanning results in the synthesis of multiple ASCT2 isoforms that have substantial truncations at their amino termini. Interestingly, truncated human ASCT2 isoforms lacking at least 23 amino acids from their amino termini were active both in transport and in retroviral reception, whereas an isoform with a 79-amino acid truncation that eliminated the first TM sequence was active in viral reception but not in amino acid transport (Tailor et al. 2001).

A related question concerns the effects of SU glycoprotein binding on the transporter functions of the receptor. This has been most extensively studied in the case of E-MuLV interactions with the mouse facilitative transporter of cationic amino acids (mCAT1) (Wang et al. 1992). Extra-

cellular addition of a saturating concentration of the SU glycoprotein gp70 derived from the Friend strain of E-MuLV had no effect on K_m values but caused a substantial (~25%) inhibition in the V_{max} for mCAT1-mediated uptake of Arg without any effect on mCAT-1 mediated Arg export from the cells. As expected, the gp70 did not bind to control nonrodent cells (mink CCL64 cells) and it had no effect on Arg uptake or export from cells that lacked mCAT1. A four-state alternating gate model for Arg transport by mCAT1 that can explain these results is diagrammed in Fig. 2A. The basic concept is that extracellular Arg binds to mCAT1 (A-B transition) to induce a conformational change (B-C transition) that enables release of Arg into the cytosol (C-D transition) and that the empty transporter then undergoes an additional conformational change (D-A transition) that restores mCAT1 to its original state A. Net import of Arg requires clockwise cycling between these states, whereas efflux of Arg requires counterclockwise cycling. In either cycling direction, the rate-limiting step for almost all transporters is the conformational reorientation of the empty transporter (i.e., A←→D transition), whereas the solute binding and release steps occur at least 100 times more rapidly. Strong evidence supporting this idea in the case of CAT1 derives from the occurrence of *trans*-stimulation (Christensen 1989; White 1985; White et al. 1982). Specifically, the presence of extracellular unlabeled Arg greatly stimulates CAT1-mediated efflux of intracellular l-[^{3}H]Arg, implying that the reversible exchanger partial cycle (D←→C←→B←→A) is much faster than the full efflux cycle that includes the A→D conformational change. Similarly, influx of l-[^{3}H]Arg into cells is greatly *trans*-stimulated by preloading of the cells with unlabeled Arg (Christensen 1989; White 1985; White et al. 1982), implying that the D→A conformational change is rate-limiting for the full import cycle. Because E-MuLV gp70 slows net uptake of Arg but has no affect on K_m, it was inferred from transition-state rate theory (Tinoco et al. 1978) that its binding onto mCAT1 stabilizes structure D more than it stabilizes the D←→A transition state. Conversely, because gp70 had no effect on Arg export, it was inferred that its binding equally stabilizes structure A and the A←→D transition state. Thus, as diagrammed in Fig. 2B, gp70 binding increases the energy barrier for the D→A conformational change but has no effect on the energy barrier for the A→D conformational change. The basic conclusion of this study was that E-MuLV gp70 binds more strongly to the mCAT1 conformations that have the Arg binding site exposed to the cytosol than to the A-D transition

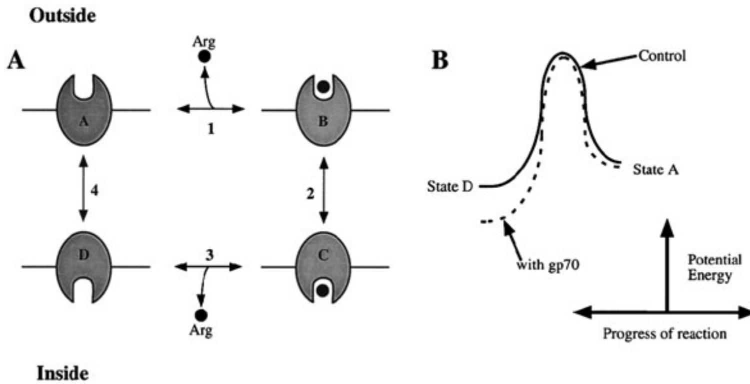

Fig. 2A, B Four-state model of the arginine transporter function of CAT-1 and interpretation of the gp70 inhibitory effects. **A** The four-state model is shown. In the import cycle (*clockwise*), state A binds extracellular Arg to form the Arg-B complex. The transporter then changes conformation to form Arg-C from which the amino acid can dissociate into the cytoplasm to form the empty D state. The final step in the import cycle occurs by conformational change of D to regenerate A. The Arg export cycle operates in the *counterclockwise* direction. Substantial evidence (Christensen 1989; White 1985) suggests that the D to A transition is the rate-limiting step of the amino acid import cycle and that the opposite A to D transition rate-limits the export cycle. This evidence derives in part from the existence of *trans*-stimulation. **B** Effects of gp70 binding are interpreted in terms of the energetics of the D to A transition, because these are believed to be the rate-limiting steps of the import and export cycles. The basic interpretation is that gp70 binding to CAT-1 stabilizes state D and has relatively little effect on state A or on the A-D transition state. In the *curve*, the *ordinate scale* represents the potential energy, and the *abscissa* represents the progress of the reaction. Because by transition state theory the rate of any reaction is proportional to the probability of reaching the transition state and because this probability is related by the Boltzmann distribution to the energy required (Tinoco et al. 1978), this model predicts that gp70 would inhibit the Arg import cycle (i.e., D to A transition) but have no effect on the Arg export cycle (i.e., limited by the A to D transition) (see also Wang et al. 1991). These results suggest that gp70 binds with higher affinity to the mCAT1 conformations that have the amino acid binding site exposed to the cytosol and with lower affinity to the conformations that allow Arg binding from the extracellular medium

state or to the mCAT1 conformations that have the Arg binding site accessible to the extracellular medium. Importantly, this apparent difference in gp70 affinities for the distinct mCAT1 conformations is clearly insufficient to freeze the transporter so that it cannot transport essential amino acids. Conversely, the changes in the free energy of gp70 binding

that accompany the transport cycle are also clearly insufficient to induce release of the bound gp70. These results suggest that the interaction of gp70 with mCAT1 is dynamic and that it perturbs but does not block the amino acid transport cycle.

7 Host Range Control of γ-Retrovirus Entry into Cells

7.1 Previous Hypotheses and Recent Alternative Interpretations

The sections below review evidence concerning the interactions of γ-retroviruses with their cell surface receptors and the coevolutionary changes in the viral SU glycoproteins and receptors that have influenced viral host ranges. Although this evidence previously seemed fragmentary and confusing, we believe that recent investigations have substantially clarified this subject. In this section we describe our overall perspective concerning these issues.

We believe that host range control of γ-retrovirus infections can best be understood from a coevolutionary perspective. Clearly, it is disadvantageous for a species to harbor a horizontally transmitted and/or endogenously inherited infectious retrovirus. Indeed, it is well known that host proteins necessary for infections of parasites, bacteria, and viruses or for immunity become highly polymorphic at functionally important sites (Hill 1998; Murphy 1993; Penn et al. 2002). Accordingly, the critical sites in cell surface receptors for viruses have become highly polymorphic, with high ratios of nonsynonymous to synonymous nucleotide substitutions suggestive of strong selection for changes in the amino acid sequence and with extensive and variable glycosylation in these regions (Feigelstock et al. 1998; Hill 1998). An example occurs in the CCR5 sequences of African green monkeys, which are believed to have been chronically infected at high frequencies (~60% of adults) with immunodeficiency viruses (SIVagm) since ancient times before dispersal of these monkeys throughout Africa (Kuhlmann et al. 2001). Similarly, viruses also often become polymorphic because of the selection of mutants able to overcome these host barriers (Taplitz and Coffin 1997; Wilson et al. 2000). An example of such γ-retrovirus diversity occurs in the xenotropic-polytropic family of MuLVs. The X-receptors of mice are highly polymorphic, with many European mice being resistant to X-MuLVs but sus-

ceptible to P-MuLVs and with most wild mice being susceptible to both X-MuLVs and P-MuLVs or sometimes resistant to both (Kozak 1983; Kozak and O'Neill 1987; Lyu and Kozak 1996; Lyu et al. 1999; Marin et al. 1999). Presumably, the diversity of these viruses has coevolved to contend with this host diversity.

The receptors that have been successfully exploited by γ-retroviruses and the characteristics of the viral-receptor interactions appear to reflect this coevolutionary "arms race." From the perspective of the virus, survival seems to have depended on several factors. First, it has been advantageous for the virus to make functionally redundant interactions with several sites in the receptor, so that single-receptor mutations cannot generally cause host escape (Platt et al. 2001). As a consequence, in comparisons of receptor orthologs from susceptible and resistant species, it has usually been found that multiple-amino acid substitutions are required to inactivate the susceptible ortholog, whereas single changes at different positions often suffice to convert the resistant ortholog into a functional receptor (Dreyer et al. 2000; Eiden et al. 1993, 1994, 1996; Lundorf et al. 1998, 1999; Marin et al. 1999, 2000). Presumably for the same reason, it has been useful for the viruses to recognize two closely related receptors such as Pit1 and Pit2, ASCT1 and ASCT2, or PHuR-A1 and PHuR-A2 (see Fig. 1A) in a redundant or partially redundant manner. In this circumstance, mutations in a single receptor confer only a small survival advantage to the host and this reduces penetrance of the mutation into the species and provides a better opportunity for compensatory viral adaptations. Finally, it appears to have been advantageous for the viruses to interact with sites in the receptors that are important for the protein's normal function, presumably because these sites are relatively conserved and their mutation would cause a substantial loss of fitness to the host species. As a result, we believe that it has been difficult for the hosts to mutate the primary viral attachment site(s) in the receptors. Consequently, we believe that the resistance mutations in the receptors have largely been restricted to the nearby regions that control viral access to the primary viral attachment sites. Thus we hypothesize that these hypervariable sites in the receptors are negative control regions rather than primary viral interaction sites. These negative control regions often contain bulky residues, including sites for N-linked glycosylation, that may interfere with viral access to the receptors (Chabot et al. 2000; Eiden et al. 1994; Lavillette et al. 2002a; Marin et al. 2000; Wentworth and Holmes 2001). A model for the γ-retroviral receptors is

shown in Fig. 3, with a conserved viral attachment site within a hypervariable negative-control access channel that may be heavily glycosylated. We emphasize that this basic model does not require that the viral attachment site be situated within a channel, because the negative control region could presumably function by other mechanisms.

It is helpful to compare this model with assumptions that have previously dominated this field. Specifically, the most common strategy for analyzing host range control of γ-retroviral receptors has been to compare the sequences of receptor orthologs from a susceptible and a resistant species and to then generate chimeras and/or substitution mutations between these orthologs to identify the active site(s) necessary for infection. Moreover, it has generally been assumed that the sequence differences between the orthologous proteins occur at the active sites for virus attachment. On the contrary, we are proposing that the divergent areas are generally negative control sequences that occur adjacent to the primary virus interaction site(s). According to our interpretation, the primary attachment sites are generally conserved in the receptor orthologs from susceptible and resistant species and they would therefore have been overlooked in the previous investigations. Consistent with our model, the hypervariable sequences in the receptor orthologs uniformly occur adjacent to sequences that are very highly conserved. Furthermore, the degree of diversity within the hypervariable sequences is often so great that common features cannot be discerned in these regions of receptors from distinct susceptible species.

The common occurrence of variably situated N-linked oligosaccharides within the hypervariable sequences of γ-retrovirus receptors from different species is also compatible with our interpretation that these are negative control regions rather than primary virus binding sites. Indeed, there is evidence in several cases that these N-linked oligosaccharides negatively influence viral receptor function (Chabot et al. 2000; Eiden et al. 1994; Kuhmann et al. 2001; Lavillette et al. 2002a; Marin et al. 2000; Wentworth and Holmes 2001). These N-linked oligosaccharides often inhibit but do not completely block receptor function, and in some cases full blockade requires cooperative inhibition by more than one N-linked oligosaccharide (Marin et al. 2000).

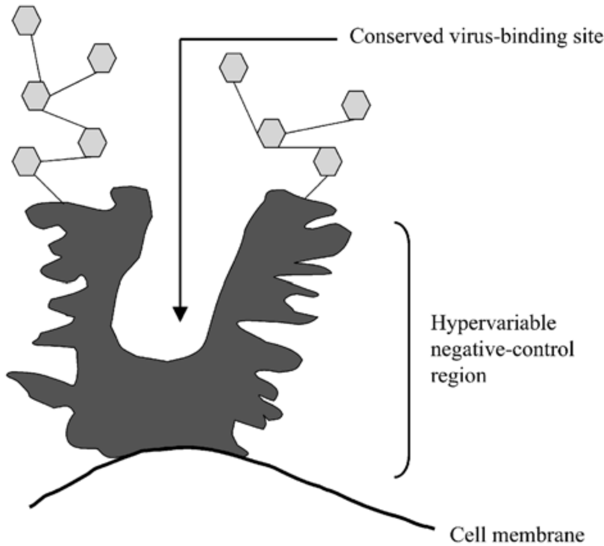

Fig. 3 A model of the γ-retroviral binding sites in the cell surface receptors. The model proposes that the viral binding site(s) occur in conserved sequences that are surrounded by hypervariable negative control regions that inhibit access of virus to the receptor. These negative control regions often contain N-linked oligosaccharides, which are depicted in *open stick* forms

7.2
Mouse CAT1, the Receptor for Ecotropic MuLVs

The mouse receptor for E-MuLVs was the first retroviral receptor that was molecularly cloned in a seminal investigation by Albritton and Cunningham (Albritton et al. 1989). It was later shown to be a broadly expressed transporter for the cationic amino acids Lys, Arg, and ornithine (Kim et al. 1991; Wang et al. 1991) that closely corresponds to the y^+ transport system previously characterized by extensive physiological studies (Christensen 1989; White 1985; White et al. 1982). These correspondent features include its Na^+ independence, amino acid specificity, *trans*-stimulation properties (see Sect. 6), and surprising ability to transport homoserine only in the presence of Na^+ (Christensen 1989; Wang et al. 1991; White 1985; White et al. 1982). This latter feature suggests that a Na^+-homoserine complex can mimic a cationic amino acid in the CAT1 active site. CAT1 is a glycoprotein that has both amino and car-

boxyl termini in the cytosol and is believed to contain 12 or 14 TM sequences and 6–7 extracellular (ECL) loops (Albritton et al. 1989, 1993; Kavanaugh et al. 1994b). CAT1 may have evolved by duplication of a smaller half-protein (Kavanaugh et al. 1994b).

After the molecular cloning and functional identification of mouse CAT1, other CAT family members were identified. These include CAT2α (in lymphocytes) and CAT2β (in liver), which are identical except for a divergent region of 43 amino acids that is encoded by alternatively spliced exons (Closs et al. 1993a–c; Kavanaugh et al. 1994c). Consistent with the fact that liver lacks a high-affinity uptake system for Arg, these CAT2 isoforms differ greatly in their K_m values for Arg, with CAT2α having a K_m of 38 μM and CAT2β having a K_m of 2.7 mM (Closs et al. 1993a,b; Kavanaugh et al. 1994c). Because liver contains urea cycle enzymes for conversion of Arg to urea, its lack of a high-affinity uptake system prevents Arg depletion from blood and preserves its supply to other tissues. Neither mouse CAT2 isoform is active as a receptor for E-MuLVs, but mouse CAT1/CAT2 chimeras are active receptors if they contain mouse CAT1 ECL3 (Closs et al. 1993b; Kavanaugh et al. 1994c). Conversely, in these same chimeras, the K_m for Arg is determined exclusively by the alternatively spliced exon of the CAT2 mRNAs (Closs et al. 1993b; Kavanaugh et al. 1994c). Furthermore, an additional transporter termed CAT3 has been identified (Hosokawa et al. 1997; Ito and Groudine 1997). Although CAT3 is normally synthesized exclusively in the brain, CAT1 knockout mice appear to express CAT3 in other tissues (Nicholson et al. 1998). Mouse CAT3 has been reported to have weak activity as a receptor for E-MuLVs (Masuda et al. 1999).

Consistent with the fact that E-MuLVs can only infect mice and rats, it is not surprising that human CAT1, which is 87% identical to mCAT1, is inactive as a viral receptor when it is expressed in naturally resistant cells. This enabled two groups to construct human-mouse CAT1 chimeras and to establish that the ECL3 region of mCAT1 is necessary for E-MuLV infections (Albritton et al. 1993; Yoshimoto et al. 1993). Consistent with the hypothesis that it is a battlefield in host-virus coevolution, the ECL3 sequences of CAT1 proteins are hypervariable in comparison to other regions; they contain proven sites for N-linked glycosylation (Albritton et al. 1993; Kim and Cunningham 1993; Yoshimoto et al. 1993); and they contain portions with a relatively high ratio of nonsynonymous to synonymous nucleotide sequence changes, implying that they have been under strong negative selection pressure in rodents. Fig-

```
          210 214      222 223          229    235 237   242
           |   |         |  |            |        |  |      |
                            *               *
mCAT1      VKGSIKNWQLTEK---NFS---CNNNDTNVKYG-EGGFMP
MDTF       ....V........---...---...........G......
CHO-K1     ............EDFL.R.SPL.G.......H.-......
BHK 21     ............EDFL.SPSAPLG.........-......
Rat        .....E......----.K.SPL.G.........-......
Mink       ............EDFQ.T.SHR.LS...KQGTLGA.....
Human      ....V.......EDFG.T.GPL.L....KEGKPGV.....
```

Fig. 4 Comparison of hypervariable ECL3 sequences of the mouse CAT1 receptor with corresponding orthologous sequences of other species. The region shown has a major effect on binding and infectivity of ecotropic host-range MuLVs. Sites for N-linked glycosylation are shown with *asterisks*. Consistent with Fig. 3, the variable sequences are surrounded by highly conserved regions

ure 4 compares the ECL3 sequences of CAT1 proteins from NIH Swiss mice with the corresponding sequences of Asian wild mice (*Mus dunni*), Chinese (CHO) and Syrian (BHK-21) hamsters, rats, mink, and humans, with the underlined regions denoting the Asn-X-Ser/Thr consensus sites for N-linked glycosylation. The hypervariable sequences are bordered on both sides by highly conserved ECL3 sequences that are presumably important for normal transporter function.

Although previous comparative studies of mCAT1 with the CAT1 orthologs shown in Fig. 4 were interpreted based on the assumption that the functionally important sequence differences occur at sites for direct binding of E-MuLVs, we believe that the evidence is more consistent with the model described above in Sect. 7.1 and in Fig. 3, which proposes that the divergent sequences are principally negative control regions that restrict viral access to relatively conserved viral attachment site(s). For example, initial comparisons of mCAT1 with human CAT1 by chimera constructions and site-directed mutagenesis implied that the YGE sequence (positions 235–237) in mCAT1 might be most important. Thus substitution of YGE for PGV in the human sequence resulted in a partially active receptor when it was expressed at high levels in the cells (Albritton et al. 1993; Yoshimoto et al. 1993). However, in the same studies the mCAT1 residues N232, V233, and E237 and the deletion shown in that region also made important contributions compared with the human counterpart sequences (Yoshimoto et al. 1993). Although the *Mus dunni* CAT1 protein has two differences in this ECL3 region (I214V and G inserted within YGE to make a YGGE), it is an excellent receptor for

the Rauscher strain of E-MuLV but is inactive as a receptor for Moloney E-MuLV (Eiden et al. 1993). Reversal of the change at position 214 converted the *Mus dunni* CAT1 into an active receptor for Moloney MuLV (Eiden et al. 1993). Subsequently, the same group found that treatment of *Mus dunni* fibroblasts with tunicamycin, an inhibitor of N-linked glycosylation, also made the cells susceptible to Moloney MuLV and that elimination of the N-linked oligosaccharide at the NDT site by mutagenesis had the same effect (Eiden et al. 1994). Thus *Mus dunni* CAT1 can be converted into an active receptor for Moloney MuLV either by reversing the I214V substitution or by eliminating the distal N-linked oligosaccharide at position 229. The results further suggest that the N-linked oligosaccharide at position 229 is inhibitory for viral reception but its influence depends on the remainder of the ECL3 sequence and on the particular virus strain that is analyzed. Although CHO-K1 and BHK-21 hamster cells are resistant to E-MuLVs, they become highly susceptible when treated with tunicamycin (Masuda et al. 1996; Miller and Miller 1992; Wilson and Eiden 1991), strongly suggesting that N-linked glycosylation at position 229 also inhibits receptor function of these hamster CAT1 proteins. Moreover the CHO-K1 CAT1 contains HGE rather than YGE, suggesting that Y235 is not essential for E-MuLV infections. Interestingly, when the Friend strain of E-MuLV replicates in rats, neurotropic variants form that can bind more strongly to rat CAT1 than to mouse CAT1 (Masuda et al. 1996a,b; Park et al. 1994). Studies of the adapted neurotropic virus PVC-211 also showed that it efficiently infects CHO-K1 and BHK-21 cells in the absence of tunicamycin (Masuda et al. 1996b). Thus the inhibitory effect of glycosylation at position 229 in the CHO-K1 and BHK-21 receptors can also be overcome by viral mutations in SU (Masuda et al. 1996b). Other interesting neurotropic variants of E-MuLVs have been identified and analyzed in other laboratories (see, e.g., Chung et al. 1999; Lynch et al. 1994; Park et al. 1994; Saha and Wong 1992; Shikova et al. 1993; Takase-Yoden and Watanabe 1999). Considered together, these results suggest that sequence differences throughout ECL3 (at least between the positions numbered 214–237 in Fig. 4) influence viral receptor function. It is very difficult to ascertain from current data whether any mCAT1 amino acids in divergent regions of ECL3 play a direct role in viral binding or whether they are merely less inhibitory than alternative sequences in CAT1 orthologs from resistant species. However, it is clear that some sequences in this region (e.g., the sites of glycosylation) have negative modulatory effects on infectivity. Moreover,

it seems very likely that the divergent sequences have been selected during evolution of mice and other species for their inhibitory effects on viral replication and pathogenesis.

Infectivities of E-MuLVs can also be restricted by endogenously inherited Env glycoproteins. For example, the Fv-4 resistance allele of mice encodes a secreted E-MuLV-related SU glycoprotein that binds to mCAT1 and interferes with viruses that use that receptor (Gardner et al. 1986; Ikeda and Sugimura 1989; Taylor et al. 2001).

7.3
Pit 1 and Pit 2 Receptors

Pit1 and Pit2 are closely related ($\sim$60% identity) type III Na^+-dependent phosphate transporters that are widely expressed in somatic cells (Johann et al. 1993; Kavanaugh et al. 1994a; Miller et al. 1994; Miller and Miller 1994; Overbaugh et al. 2001; Werner et al. 1998). They differ almost completely in sequence from type I and II Na^+-phosphate symporters that function in the apical membranes of epithelial cells to control phosphate reuptake from bile, urine, and intestines (Werner et al. 1998). Indeed, Pit1 and Pit2 are the major transporters that mediate phosphate flux between blood and tissues. A notable exception is erythrocytes that transport phosphate via the Cl^-/HCO_3^- exchanger (Wehrle and Pedersen 1989; Werner et al. 1998). This exception may be important because retrovirus entry into enucleated erythrocytes would be wasteful. Depletion of extracellular phosphate causes enhanced expression of Pit1 and Pit2, and inhibition of either transporter also causes upregulation of the other (Chien et al. 1997; Kavanaugh et al. 1994a). The Pit proteins may have originated by duplication of a smaller half-protein progenitor (Salaun et al. 2001).

Initially, human Pit1 was cloned as the receptor for the GALV group of γ-retroviruses, which includes woolly monkey viruses (O'Hara et al. 1990), and it was later also identified as the receptor for the B-subgroup of feline leukemia viruses (Takeuchi et al. 1992) and for the 10A1 MuLV (Miller and Miller 1994; Wilson et al. 1994). On the basis of chimera and mutagenesis comparisons of human Pit1 with Pit1 orthologs from *Neurospora crassa* and European mice, which cannot function as receptors for GALV, it was inferred that an important region for GALV interaction with human Pit1 occurs in a hydrophilic sequence of nine amino acids at positions 550–558 called region A that is hypervariable in different

species (see Fig. 5). An extended region A of 13 amino acids between positions 546 and 558 was later found to be critical for infections by FeLV-B (see Fig. 5) (Dreyer et al. 2000). In addition, other regions of the human Pit1 receptor have also been shown to be very important for both GALV and FeLV-B, although relative contributions of these different regions can depend on the virus isolate and on the overall receptor chimera that is analyzed (Chaudry and Eiden 1997; Leverett et al. 1998; Lundorf et al. 1999; Tailor and Kabat 1997; Tailor et al. 2000b). Subsequently, human Pit2 was identified as a receptor for A-MuLVs and it was also found that the 10A1 recombinant isolate of MuLV can utilize both human Pit1 and Pit2 (Miller and Miller 1994; Wilson et al. 1994, 1995). Chimera and mutagenesis studies also indicated that the regions of human Pit2 that contribute to A-MuLV infections generally correspond to the sites in Pit1 that are used by FeLV-B, including the extended region A (Dreyer et al. 2000; Lundorf et al. 1999; Pedersen et al. 1995; Tailor and Kabat 1997).

One approach that has been used to address the above issues was based on the observation that chimeric FeLV-B/A-MuLV Env glycoproteins that were spliced between the VRA-VRB variable loops of SU (these loops contribute to receptor recognition properties of γ-retroviruses; Battini et al. 1992, 1995)) were unable to use either human Pit1 or Pit2 but were able to efficiently use certain Pit1/Pit2 chimeras (Tailor and Kabat 1997, 2000b). By analyzing various combinations of Env chimeras and site-directed mutants for abilities to use distinct Pit1/Pit2 chimeric receptors, evidence was obtained concerning the regions in the Env glycoproteins that functionally interact with specific sites of human Pit1 and Pit2. Interestingly, these results suggested that FeLV-B and A-MuLV SU glycoproteins interact with their receptors at precisely correspondent contact sites in the same overall orientations (Tailor and Kabat 1997, 2000b). However, differences between viral strains can affect the absolute and relative energetic contributions of specific contact sites. We believe that, considered together, the evidence in this field supports the conclusion that the viruses that use Pit1 and Pit2 interact with them in the same orientation at a correspondent contact surface, consistent with the idea that these viruses formed by divergent evolution from a common origin.

In accordance with this idea and with the model described in Fig. 3, recent evidence strongly suggests that the viruses originally identified as being specific for Pit1 or Pit2 actually are generally rather promiscuous

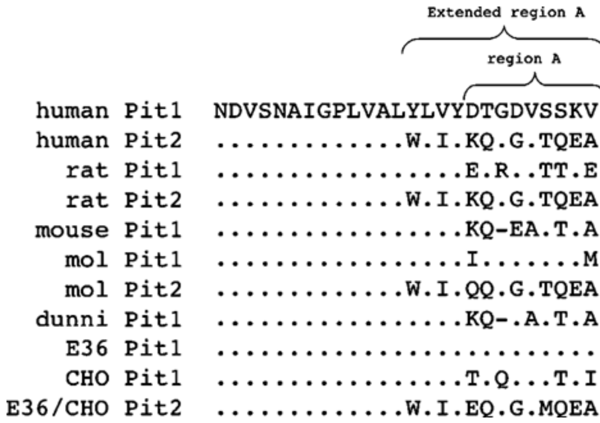

Fig. 5 Comparison of an important hypervariable region in the Pit1 and Pit2 proteins of different mammalian species. The sequences indicated as *region A* and *extended region A* have been shown to have a major influence on ability of the corresponding proteins to function as γ-retroviral receptors. It is generally believed that Pit1 and Pit2 have identical topologies, consistent with their common function as highly homologous Na^{+}-phosphate symporters, and that the sequences indicated comprise an extracellular loop (ECL4) that interacts with the viruses. However, this hypothesis has not been proven unambiguously. Moreover, other regions (e.g., ECL2) of the Pit proteins also contribute to the interactions with viruses. The variable sequences occur amid highly conserved regions

in their abilities to use both receptors. Thus, for example, FeLV-B uses both Pit1 and Pit2 in domestic cats, with distinct FeLV-B isolates differing somewhat in their abilities to use feline Pit2 (Boomer et al. 1997; Sugai et al. 2001). Furthermore, the abilities of FeLV-B viruses to use feline Pit2 seem to be acquired by selection during their replication in vivo (Anderson et al. 2001). In addition, some FeLV-B isolates can even use hamster Pit2 (Boomer et al. 1997). Similarly, GALV can use hamster Pit1 and Pit2 (Wilson et al. 1994) and Japanese feral mouse Pit1 and Pit2 (Schneiderman et al. 1996; Wilson et al. 1994). A single amino acid change in human Pit2 enables it to function as a receptor for GALV (Eiden et al. 1996), and a single amino acid insertion in region A of murine Pit1 makes it a functional receptor for A-MuLVs (Lundorf et al. 1998). Interestingly, a Pit ortholog in the fungus *Neurospora crassa* was recently shown to function as a receptor for the 10A1 MuLV (L. Pedersen, personal communication). This evidence strongly supports the hypothesis (see Sect. 7.1 and Fig. 3) that the viruses that use Pit1 and/or

Pit2 recognize common features in these proteins but inhibitory sequence changes during evolution have partially or fully restricted infections by particular viruses. This interpretation is also supported by evidence that the divergent extended A regions of Pit1 and Pit2 are bordered by highly conserved areas (see Fig. 5) and by mutagenesis studies that imply that individual amino acids in the divergent region are unnecessary for infections (Chaudry and Eiden 1997).

7.4 Xenotropic and Polytropic MuLVs

The interactions of these closely related viruses with X-receptors of mice provides an excellent illustration of host-virus coevolution and of host range control. As mentioned above, X-MuLVs were initially termed xenotropic because they cannot infect inbred strains of mice derived from European origins (Levy 1978). However, X-MuLVs are frequently endogenously inherited in these inbred mice and they are sometimes expressed during their lifetimes (Kozak and O'Neill 1987; Levy 1978). In addition, X-MuLVs can infect many wild strains of mice such as *Mus spretus* and *Mus dunni* (Kozak 1985). In contrast, polytropic MuLVs (MCFs) efficiently infect almost all mice and they are often highly pathogenic (Cloyd et al. 1980; Hartley et al. 1977; Kabat 1989; Kozak 1985; Rosenberg and Jolicoeur 1997; Ruscetti et al. 1981; Stoye et al. 1991). Certain mice are, nevertheless, resistant to MCFs and/or to X-MuLVs because of endogenous interfering Env glycoproteins (Bassin et al. 1982; Jung et al. 2002; Kozak 1985; Lyu and Kozak 1996; Lyu et al. 1999; Ruscetti et al. 1981, 1985), transcriptional repression (Aaronson and Stephenson 1973; Levy 1978), and/or production of a serum lipoprotein factor that specifically inactivates these viruses (Levy 1978; Wu et al. 2002). Although it is unknown how this lipoprotein factor specifically inactivates X-MuLVs and P-MuLVs, it is interesting that a lipoprotein can also inactivate hepatitis C virus (Enjoji et al. 2000). In addition, *Mus castaneus* mice are completely resistant to X-MuLVs and P-MuLVs primarily because of a small deletion mutation in their X-receptor gene (Marin et al. 1999). However, *Mus castaneus* mice also inherit an X-MuLV-related Env glycoprotein (Lyu and Kozak 1996; Lyu et al. 1999). As determined by genetic crosses, this Env glycoprotein interferes with infections mediated by X-receptors from wild mice that interact with the X-MuLV Env but not with infections mediated by X-receptors from Eu-

ropean mice that cannot interact with X-MuLVs. Thus this Env glycoprotein blocks MCF and X-MuLV infections in *Mus castaneus* x *Mus spretus* F1 hybrids, but does not block MCF infections of *Mus castaneus* x *Mus musculus* F1 hybrids (Lyu and Kozak 1996; Lyu et al. 1999). This supports the idea that interference requires strong binding of an interfering Env glycoprotein to the receptor that occurs in the specific animal. Furthermore, hamster cells are resistant to infections by both X-MuLVs and MCFs (Marin et al. 1999; Miller and Miller 1992).

Interestingly, when expressed in CHO cells the X-receptors from these European and Asian strains of mice and from hamster, mink, and humans conferred viral susceptibilities that were identical to the susceptibilities of the cells used for the X-receptor cDNA isolations (Marin et al. 1999). Thus xenotropism in this system is caused by inherent properties of the X-receptor orthologs. Figure 6 compares the sequences of these X-receptors in their critical presumptive ECL3 and ECL4 regions. These regions of the X-receptors contain consensus sites for N-linked glycosylation and are much more polymorphic than other regions of the proteins (see Marin et al. 1999).

X-receptors were recently cloned independently by three groups (Battini et al. 1999; Tailor et al. 1999a; Yang et al. 1999). Subsequently, a mutagenesis study was done to identify sequences responsible for the ability of X-MuLVs to use the *Mus dunni* X-receptor but not the NIH Swiss mouse ortholog (Marin et al. 1999). Interestingly, it was found that the NIH Swiss X-receptor contains two key differences (identified in Fig. 6 as K500E in ECL3 and T582Δ in ECL4) that are both necessary to prevent its utilization by X-MuLVs. Thus reversal of either of these mutations is sufficient to enable use of the NIH Swiss X-receptor by X-MuLVs. Conversely, both K500E and T582Δ must be substituted into the *Mus dunni* protein to prevent its use by X-MuLVs. These results suggest that X-MuLVs interact with different sites in the X-receptor, so that elimination of both sites in the *Mus dunni* protein is needed for resistance to infection. Furthermore, neither the K500E nor the T582Δ mutation had any effect on MCF infections, implying that MCFs rely on sites in the X-receptors that are unimportant for X-MuLVs and vice versa. It is noteworthy, however, that residues corresponding K500 and T582 both occur in the hamster X-receptor and that K500 occurs in the *Mus castaneus* X-receptor, despite the fact that they cannot mediate X-MuLV infections. Consequently, the latter X-receptors must contain other in-

```
                                                   ECL 3
Human X-MLV    LKWDESKGLLPNNSEESGICHKYTYGVRAIVQCIPAWLRFIQCCLRRYRDTKRAFPHLVNAGKYSTTFFM
NIH Swiss      ............DPQ.PEF....S.........................N.R.................T
M. dunni       ............DPQ.PEF....S...........................R.................T
SC-1           ............DPQ.PEF....S...........................R.................T
M.spretus      ............DPQ.PEF....S...........................R.................T
M.castanteus   ............DPQ.PEF....S...........................R.................T
Hamster        .....N.S....DLQ.PEF....R..............................................T
Mink           ......G.........PE.....S.........V....................................T

                          500
Human X-MLV    VTFAALYSTHKERGHSDTMVFFYLWIVFYIISSCYTLIWDLKMDWGLFDKNAGENTFLREEIVYPQKAYY
NIH Swiss      ..........E.QN....V......VF.C.........................................
M. dunni       ............QN....V......VF.C.........................................
SC-1           ......................................................................
M.spretus      ............QN....V......VF.C.........................................
M.castanteus   ............QN....V......VF.C.........................................
Hamster        ............Q.....V..L...V..CA........................................
Mink           ............................C.............................P.......R...

                                   ECL 4
                                    582
Human X-MLV    YCAIIEDVILRFAWTIQISITSTTLLPHSGDIIATVFAPLEVFRRFVWNFF
NIH Swiss      .....................A-.FK..V.N....................
M. dunni       .....................A..FK..V......................
SC-1           .....................A..FK..V..................L...
M.spretus      .....................A..FK..V......................
M.castanteus   ..............I......A-----.V......................
Hamster        .....................A.AFQ..V......................
Mink           ..T............V......M............................
```

hibitory mutation(s) that override the permissive effects of K500 and/or T582.

A striking aspect of this system is that MCFs cause only weak interference to superinfections, whereas X-MuLVs cause strong interference that seems to depend on the presence of K500 and to a lesser extent on T582 (Marin et al. 1999). Accordingly, MCFs, which seem to ignore K500 and T582, have only weak interference and massively superinfect cells in culture and in vivo, which likely contributes to their pathogenic effects (Chesebro and Wehrly 1985; Herr and Gilbert 1984; Kozak 1985; Marin et al. 1999; Temin 1988; Yoshimura et al. 2001). An hypothesis that could explain these results is that mutations in the X-receptors of European mice corresponding to K500E and T582Δ (perhaps in cooperation with other changes) enabled the mice to escape from X-MuLVs and that P-MuLVs then evolved to overcome these host barriers by changing their *env* genes. However, because the K500E and T582Δ receptor mutations are probably inhibitory barriers that reduce accessibility of the viruses, the MCFs bind weakly and cause negligible interference. These data appear to support a ratchet model of coevolution in which polymorphisms in receptors lead to compensatory adaptations in the viruses in an endless progression that results in increasing diversity of the host receptors and of the viruses.

7.5 The RD114 Superfamily of Retroviruses

The RD114 superfamily, which generally use human ASCT2 as a common receptor (Blond et al. 2000; Lavillette et al. 2002a; Marin et al. 2000; Rasko et al. 1999; Tailor et al. 1999b), is the most widely dispersed interference group of retroviruses. This group includes not only the RD114 feline endogenous virus but also BaEV, HERV-W, type D primate retro-

Fig. 6 Comparison of an important region in the X-receptors that mediates infections by X-MuLVs and P-MuLVs (*MCFs*). Hypervariable regions identified as *ECL3* and *ECL4* are believed to control infections by these viruses, with the sequences indicated by *diamonds* (identified at positions 500 and 582) being especially important. Identical residues are indicated by *dots* and deletions by *dashes*. The TM regions in the human sequence are *underlined*. Sites for N-linked glycosylation are indicated with *asterisks*

viruses, and avian REVs and SNVs (Gautier et al. 2000; Kewalramani et al. 1992; Koo et al. 1991, 1992; Lavillette et al. 2002a; Marin et al. 2000; Sommerfelt and Weiss 1990). Strong evidence suggests that the *env* genes of these viruses evolved by divergent evolution from a common origin (Benit et al. 2001; Boeke and Stoye 1997). In particular, it is believed that the avian group formed by a rare zoonosis from a primate progenitor into a bird (Barbacid et al. 1979; Kewalramani et al. 1992; Koo et al. 1991, 1992) and that RD114 may also have arisen by infection of a cat by a primate γ-retrovirus related to BaEV (Barbacid et al. 1979; van der Kuyl et al. 1999). Consistent with the hypothesis that they had a common origin, these viruses all contain an immunosuppressive domain in TM (Benit et al. 2001; van der Kuyl et al. 1997); they all lack the PHQ motif for transactivation that occurs near the amino terminus of SU in other γ-retroviruses; and they all interact with the same region of the receptors (see below). This viral superfamily probably also includes many additional members that have not yet been analyzed for their receptor usages, including, for example, the HERV-F family that is very similar to HERV-W (Benit et al. 2001). This system has provided particularly strong evidence that the viruses have evolved to recognize conserved amino acids in the receptor that are difficult for the host to mutate without loss of fitness, and that the host response has been to drastically alter nearby regions that can interfere with access of virus to the recognition site, as proposed in Fig. 3. These host changes include insertions and deletions and additions of bulky N-linked oligosaccharides. Because the viruses recognize highly conserved sequences, they are generally capable of using both ASCT2 and the related transporter ASCT1 (Lavillette et al. 2002a; Marin et al. 2000). The ASCT transporters are members of the glutamate transporter superfamily, which have been extensively investigated for their topology and structure (Brocke et al. 2002; Kanai 1997; Seal et al. 2000; Slotboom et al. 1999; Utsunomiya-Tate et al. 1996; Zerangue and Kavanaugh 1996). These transporters all contain an associated Cl^- anion channel that is gated open in the presence of a transported amino acid. However, the Cl^- flux is uncoupled from the amino acid flux (Broer et al. 2000; Slotboom et al. 1999; Zerangue and Kavanaugh 1996).

The human ASCT2 receptor was originally cloned from cDNA libraries based on the natural resistance of NIH Swiss mouse fibroblasts to RD114 (Rasko et al. 1999; Tailor et al. 1999b). Consistent with this strategy, the mouse ASCT2 ortholog was found to be inactive as a recep-

tor for RD114 (Marin et al. 2000, 2003). By using human/mouse ASCT2 chimeras it was then found that the critical sequence difference occurred in ECL2, which is shown in Fig. 7. Specifically, it was found that region C in the carboxyl-terminal portion of ECL2 in human ASCT2 was necessary for infections by RD114, BaEV, and type D primate retroviruses and that substitution of this region into mouse ASCT2 generated an active receptor for all of these viruses (Marin et al. 2003). Interestingly, this ECL2 region is hypervariable compared with other regions of the human and mouse ASCT2 proteins (see Fig. 7).

Despite the general use of human ASCT2 as a common receptor, the viruses of this interference group have distinct host ranges. For example, BaEV and HERV-W efficiently infect mouse cells. Furthermore, RD114 and type D primate retroviruses can also infect mouse cells that have been pretreated with tunicamycin to eliminate N-linked oligosaccharides (Marin et al. 2000). Interestingly, hamster cells are resistant to all viruses of this superfamily including BaEV and HERV-W, but the hamster cells also become susceptible after treatment with tunicamycin (Marin et al. 2003). Further studies showed that mouse ASCT2 is not a receptor for BaEV and that N-deglycosylated mutants of mouse ASCT2 also are nonfunctional as receptors for BaEV, RD114, or type D primate retroviruses. These viral host range properties were explained by the finding that human and mouse ASCT1, which are approximately 58% identical to human ASCT2, are strong receptors for BaEV and HERV-W but not for RD114 or type D viruses. Furthermore, N-deglycosylation of the mouse ASCT1 C-region by mutagenesis converted it into a strong receptor for all of the viruses including RD114 and type D primate viruses (Lavillette et al. 2002a; Marin et al. 2000, 2003).

Figure 7 compares the ECL2 sequences of human and mouse ASCT2 and ASCT1 and of the hamster ASCT1 protein. Significantly, the only two N-linked glycosylation sites in mouse and human ASCT1 occur within ECL2 region C, and elimination of either of these sites by mutagenesis is sufficient to activate mouse ASCT1 as a receptor for RD114 and the type D viruses (Marin et al. 2000). Thus the two N-linked oligosaccharides in mouse ASCT1 collaborate to block interaction with RD114 and type D viruses, and neither one alone is sufficient. However, these two oligosaccharides are unable to block interactions with BaEV and HERV-W. Interestingly, hamster ASCT1 contains a third N-linked oligosaccharide in ECL2 region C (see Fig. 7) and this oligosaccharide by itself is sufficient to prevent infection of all the viruses in this super-

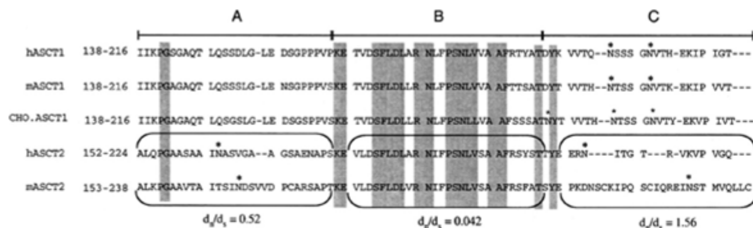

Fig. 7 Comparison of the critical ECL3 regions of ASCT1 and ASCT2 proteins from different species. Chimera and site-directed mutagenesis studies indicated that region C within ECL3 is critical for control of the viral receptor functions of these proteins. Amino acids that are identical in all of the proteins are shown by *shading*. Sites for N-linked glycosylation have been proven to occur and are indicated by *asterisks*. The ratios of nonsynonymous to synonymous nucleotide sequence substitutions in the cDNAs (i.e., the dn/ds ratios) of the human and mouse ASCT2 sequences are indicated below the protein sequences. These ratios confirm that region *C* has been under strong evolutionary pressure to diverge and that the adjacent region *B* has been under strong positive selection pressure to be retained. This supports other evidence that region *C* has been a battlefield in host-virus coevolution and that the N-linked glycosylations in this region negatively influence viral utilization. Despite the enormous diversity in region *C* of these ASCT1 and ASCT2 proteins, many γ-retroviruses efficiently and promiscuously use them as receptors (see text). These results strongly support the model in Fig. 3, implying that the viruses recognize conserved sequences that are situated amid hypervariable negative control regions

family (Marin et al. 2003). This additional N-linked oligosaccharide occurs in CHO ASCT1 between two highly conserved amino acids that are not only common to ASCT1 and ASCT2 proteins of both humans and mice but are also conserved in all other members of the glutamate transporter superfamily. Thus the hypervariable region C occurs adjacent to a highly conserved region that is likely to be important for normal transporter function. Although all of the viruses in this interference group have a substantial ability to use both ASCT2 and ASCT1 when the latter is N-deglycosylated, the HERV-W Env is especially promiscuous because it alone can also use N-deglycosylated mouse ASCT2 as a receptor (Lavillette et al. 2002a). Such broad abilities of viruses to use ASCT1 and ASCT2 proteins as receptors is surprising, particularly because common features cannot be discerned within the critical control region C (see Fig. 7). The only reasonable interpretation in our opinion is that the viruses recognize invariant features in ECL2 that are highly conserved and that the variable region C is a negative control area that modulates

viral reception by steric hindrance and other inhibitory mechanisms, as proposed by the model in Fig. 3.

A corollary of this interpretation is that it has been advantageous for mammals to change region C of ECL2 and to conserve the adjacent region B. In agreement with this hypothesis, the ratios of nonsynonymous to synonymous nucleotide substitutions determined by a comparison of the human and mouse ASCT2 cDNAs is 0.125 for the complete coding sequences and 0.52, 0.042, and 1.56 for the A, B, and C regions of ECL2, respectively, as shown in Fig. 7. This analysis supports the conclusions that ASCT2 is an important protein that has been conserved throughout evolution, that region B in ECL2 has been under especially strong selection pressure to remain conserved, and, conversely, that region C has been under extremely strong pressure to diverge in its amino acid sequence, presumably because of viral attack. These results strongly support the general interpretations outlined above in Sect. 7.1 and in Fig. 3.

7.6 The FeLV-C Receptor

The receptor for FeLV-C, FLVCR1, was recently cloned from human and domestic cat cDNA libraries (Quigley et al. 2000; Tailor et al. 1999c). It is a member of the major facilitator superfamily (MFS) of transporters that contains 12 TM domains and is weakly homologous to MFS transporters for small organic anions such as glycerol-3-phosphate and glucarate. MFS transporters contain common features including 12–14 TM domains, a large hydrophilic loop between TM6 and TM7, and a conserved sequence between TM2 and TM3 (Pao et al. 1998). FLVCR1 has been classified as MFS subfamily member 28 of unknown function. Other MFS subfamilies include the widely studied 12-TM glucose transporters.

Because the SU envelopes of FeLV-C evolve in vivo from FeLV-A by accumulation of a few mutations in one disulfide-bonded loop that has been implicated in receptor interactions (Brojatsch et al. 1992; Rigby et al. 1992), it was proposed that the receptor for FeLV-A might be an MFS transporter that is closely related to FLVCR1 (Tailor et al. 1999c). Consistent with this hypothesis, a 70-kDa protein of unknown function has been implicated as a FeLV-A receptor (Ghosh et al. 1992). Similarly, small adaptive changes in disulfide-bonded loop regions of SU cause slight shifts of coreceptor specificities of HIV-1 (Chabot and Broder 2000; Connor et al. 1997; Glushakova et al. 1998; Littman 1998; Platt et

al. 2001) and of other retroviruses (Masuka et al. 1996a,b; Taplitz and Coffin 1997). On the basis of these considerations, a human protein termed FLVCR2 that is closely related to FLVCR1 (52% amino acid identity) was recently cloned (C. Tailor, manuscript in preparation). Human FLVCR2 is a weak receptor for FeLV-C but does not mediate infections by FeLV-A, which was expected because human cells are resistant to FeLV-A. Because FeLV-A is principally infectious for feline cells, it will be important to clone the feline ortholog of FLVCR2 to determine whether it is a receptor for FeLV-A. Based on their similarities, chimeras of the human FLVCR1 and FLVCR2 proteins were generated. Their analysis identified ECL6 of FLVCR1 as a critical region for FeLV-C receptor function (C. Tailor, manuscript in preparation). This region is highly diverse compared with other regions of FLVCR1 and FLVCR2 and differs at 7 of 10 amino acids.

7.7
A Pair of PERV-A Receptors

Recently, Ericsson et al. (C. Patience, personal communication) molecularly cloned two closely related human proteins, PHuR-A1 and PHuR-A2, that function as receptors for PERV-A and are widely expressed in human tissues, consistent with previous viral susceptibility studies (Takeuchi et al. 1998; Wilson et al. 2000). These novel receptors have unknown functions and have hydrophobicity profiles suggesting that they contain 10–11 TM domains, consistent with the other receptors for γ-retroviruses, which also contain multiple TM sequences. The widespread expression of these receptors in human tissues is of special concern because of the use of pig organs for xenotransplantation. The use by PERV-A of the closely related receptor pairs PHuR-A1 and PHuR-A2 is intriguing in view of the other examples of receptor pairs (e.g., Pit1 and Pit2, ASCT1 and ASCT2, FLVCR1 and FLVCR2) discussed above.

8
The Role(s) of Receptors in γ-Retrovirus Infections

8.1
General Issues

As discussed in the sections below, the interactions of retroviruses with cell surfaces involve multiple steps, including adsorption from the extracellular medium, binding of Env glycoproteins to receptors, cooperative interactions between Env glycoproteins within the trimeric SU-TM complexes and between trimers (i.e., cross-talk), and irreversible conformational changes of the Env glycoproteins that lead to the formation of a membrane fusion pore. Although receptors appear to be essential for the overall process, they seem to be expendable for many of the individual steps. For example, in some situations γ-retroviruses can infect cells that lack the cognate receptor (Barnett and Cunningham 2001; Barnett et al. 2001; Innes et al. 1990; Lavillette et al. 2002b; Sharma et al. 1997, 2000). Furthermore, the viral adsorption process seems to occur independently of the receptors (Andreadis et al. 2000; Pizzato et al. 1999, 2001; Sharma et al. 2000), and it is also unclear whether the receptors perform a hit-and-run function or whether they participate in the final membrane fusion steps. Because these issues are critical for understanding the roles of receptors, we will discuss them briefly.

8.2
Adsorption onto Cell Surfaces

Adsorption of viruses onto cultured cells from the medium is usually a very slow and inefficient process, principally because of the slow rates of their diffusion into contact with the cell surfaces (Allison and Valentine 1960; Andreadis et al. 2000; Valentine and Allison 1959). In general, the rate of contact cannot be significantly enhanced by mixing or stirring because the boundary layer of relatively stationary fluid that surrounds walls or other large objects (e.g., cells) in flowing liquids is substantial compared with the rate of virus diffusion, so that the stirring does not increase the concentration of virus that surrounds this boundary zone (Allison and Valentine 1960; Palsson and Andreadis 1997; Valentine and Allison 1959).

In the case of retroviruses, it has become especially clear that adsorption is a severely limiting step in infection of cultured cells. In classic studies in which virus samples were incubated with cells for several hours before washing with fresh medium and subsequently detecting the foci of infection, it was estimated that only 1/1,000 or fewer of the virions in the medium were infectious. In contrast to previous interpretations, recent studies suggested that this low infectivity-to-virion ratio is principally caused by the inefficiency of adsorption (Andreadis et al. 2000). Accordingly, serial incubation of a virus-containing medium for 2-h periods with sequential cell cultures results in the same titers in each of the cultures after correction for spontaneous viral decay (Kabat et al. 1994). Furthermore, centrifuging the virus down onto the cultured cells (i.e., spinoculation) often increases retroviral titers by 1–2 orders of magnitude (Bahnson et al. 1995; Damico and Bates 2000; Forestell et al. 1996; O'Doherty et al. 2000).

Recently, it has become possible to count retrovirions adsorbed onto cell surfaces by confocal immunofluoresence microscopy or by quantitative PCR methods (Marechal et al. 2001; O'Doherty et al. 2000; Pizzato et al. 1999). Such studies have demonstrated that receptors for viral entry are irrelevant for initial adsorption of retrovirions onto surfaces of most cells (Pizzato et al. 1999, 2001). On the contrary, the initial steps of virus attachment seem to more critically depend on accessory cellular binding substances such as heparan sulfates, integrins, or lectins including DC-SIGN (Bounou et al. 2002; Guibinga et al. 2002; Jinno-Oue et al. 2001; Lee et al. 2001; Mondor et al. 1998; Saphire et al. 2001; Zhang et al. 2002). By forming multivalent weak reversible bonds with such abundant cell surface components, a virus would become efficiently bound in a manner that would allow it to graze until it makes appropriate contact with a true receptor (Haywood 1994; Park et al. 2000). A similar grazing or rolling process occurs when lymphocyte selectins contact their carbohydrate ligands in the capillary endothelium (Li et al. 1996a,b; McEver et al. 1995). In essence, the accessory binding factors would be expected to more efficiently attach the virus onto the cell surface in a manner that allows it to move, thus enabling it to make improved and repetitive contacts with a small number of receptors. Formation of such "capture complexes" (Park et al. 2000), may be especially important for viruses such as FeLV-T, MCFs, SNVs, and primary patient isolates of HIV-1 that bind to their receptors with very low affinities. By a similar mechanism, heparan sulfates enhance chemokine and growth factor signaling processes

(Aviezer et al. 1994; Bounou et al. 2002; Jinno-Oue et al. 2001; Lee et al. 2001; Park et al. 2000; Schlessinger et al. 1995). Binding of the PVC-211 neurotropic variant of Friend E-MuLV onto heparan sulfates is also believed to increase its infection of brain capillary endothelial cells (Jinno-Oue et al. 2001). In this context it should be recognized that a small number of cell surface receptors (e.g., 10^3 per cell) is theoretically capable of efficiently capturing any tight-binding ligand that diffuses onto the cell surface, so that accessory binding substances would not necessarily enhance attachment of a high-affinity virus or hormonal ligand to its receptor (Berg and Purcell 1977). Bacteriophage lambda is an example of a virus that binds efficiently onto its receptor even when the receptor concentration is low (Schwartz 1975, 1976). However, such accessory associations can be critically important for viruses or other ligands that bind only weakly and reversibly onto their receptors. Such ligands would be more likely to dissociate from the cells if they were not anchored to the binding substances.

8.3 Binding to Receptors Initiates a Pathway of Cooperative Interactions Between Env Glycoproteins

Recent evidence has suggested that assembly of a complex containing several receptors may be a prerequisite for the membrane fusion step of retrovirus infections and that multiple Env molecules cooperatively participate in this process. For example, several Env glycoprotein trimers appear to be necessary for retroviral infectivity (Bachrach et al. 2000; Frey et al. 1995; Layne et al. 1990). In the case of HIV-1, the presence of more than one CD4 in contact with the virus enhances the infectivity dramatically and reduces the concentration of coreceptor needed for infection (Platt et al. 1998). Further investigation of this system has implied that a critical complex containing approximately four to six coreceptors is a requirement for infection, although it is not known whether this complex performs a transient role and then disperses or is maintained throughout the membrane fusion process (Kuhmann et al. 2000; Platt et al. 2001). Despite some uncertainties, several lines of evidence have suggested that three to six hemagglutin trimers may cooperatively participate in the influenza A virus-mediated membrane fusion reaction (Blumenthal et al. 1996; Boulay et al. 1988; Danieli et al. 1996; Ellens et al. 1990; Gunther-Ausborn et al. 2000) and that multiple envelope glyco-

protein trimers are required for rabies virus-mediated membrane fusion (Roche and Gaudin 2002). Receptor clusters also appear to enhance infectivities of MuLVs (Battini et al. 1995; Davey et al. 1999; Salaün et al. 2002; Valsesia-Wittmann et al. 1997). In the case of ALV-A, titration studies by Damico and Bates also strongly support the idea that a multivalent Env-receptor complex is essential for infection (Damico and Bates 2000).

Cooperative interactions have also been reported between the monomeric units of the SU-TM trimeric complexes. Infectious γ-retrovirions can be produced by cells that coexpress two mutant Env glycoproteins that are individually incapable of forming infectious virus pseudotypes (Zhao et al. 1997). For example, a MuLV mutant with a defect in SU that prevents receptor attachment was complemented by a fusion-defective TM mutant (Rein et al. 1998; Zhao et al. 1997). Similar studies with HIV-1 implied that binding to CD4 and to coreceptors can involve different monomers within the Env trimeric complexes (Salzwedel and Berger 2000). However, the latter investigation was based on syncytia assays and was done with cells that expressed very high concentrations of the Env glycoproteins. The basic conclusion of these investigations was that two Env monomers that are defective at different stages of the fusion pathway can form heterotrimers that work in concert to mediate fusion. In agreement with these ideas, Env glycoprotein trimers function as concerted units in inserting the amino termini of their TM subunits into target cell membranes (Carr et al. 1997; Carr and Kim 1993; Chan et al. 1997; Li et al. 1996; Salzwedel and Berger 2000; Wahlberg et al. 1992; Zhao et al. 1997, 1998). This conformational change initially produces a trimeric coil that undergoes a further conformational change to form a six-stranded coiled coil (Carr and Kim 1993; Chan et al. 1997).

Recent investigations have also strongly suggested that intertrimer cooperative interactions may also be prerequisite for membrane fusion mediated by γ-retroviruses (Barnett and Cunningham 2001; Barnett et al. 2001, 2002; Lavillette et al. 2000, 2001, 2002b). This line of inquiry was initiated by studies of Bae et al. (1997) of a conserved PHQ motif that occurs near the amino-terminal ends of SU glycoproteins in all γ-retroviruses with the exception of those that use ASCT1 or ASCT2 as receptors. In addition, the motif is modified in the PERV viruses, being SHK and PHR for PERV-A and PERV-B, respectively (Patience et al. 2001; Takeuchi et al. 1998). Mutation of this PHQ motif blocked membrane fusion but had no effect on receptor attachment (Bae et al. 1997;

Lavillette et al. 2002b; Zavorotinskaya and Albritton 1999). Subsequently, Lavillette and coworkers (2000) discovered that noninfectious γ-retrovirions lacking this histidine could be transactivated by addition to the cultured cells of a soluble SU or of an amino-terminal fragment of SU called the receptor-binding domain (RBD) (Battini et al. 1992, 1995, 1998). Initially, it was found that transactivation requires the use of cells that contain receptors for both the ΔHis virus and for the RBD but that the receptor specificity of the RBD need not match that of the ΔHis virus (Barnett and Cunningham 2001; Barnett et al. 2001, 2002; Lavillette et al. 2000, 2001). Thus, for example, a Friend E-MuLV RBD can trans-complement ΔHis viruses derived from A-MuLV, MCF, X-MuLV, FeLV-B, or FeLV-T (Barnett and Cunningham 2001; Barnett et al. 2001, 2002; Lavillette et al. 2000). Similarly, an A-MuLV RBD can at least weakly transactivate ΔHis E-MuLV (Lavillette et al. 2000, 2001) and ΔHis FeLV-B (D. Lavillette, unpublished observation). FeLV-T can be transactivated by FELIX, FeLV-B, or MuLV-E (Anderson et al. 2000; Barnett et al. 2002; Lauring et al. 2001, 2002). Despite such examples of cross-reactivity, transcomplementation reactions are often nonreciprocal or even specific (Barnett and Cunningham 2001; Farrell et al. 2002). For example, complementation of fusion-defective PHQ motif mutants of GALV requires a GALV RBD (Farrell et al. 2002). Further investigations of transcomplementation have suggested the hypothesis that receptor engagement of a retroviral SU glycoprotein may induce exposure of the amino terminal PHQ motif (or a site that is controlled by this motif) and a region termed C2 in the carboxyl-terminal portion of the SU and that these exposed sites in nearby trimers may then associate in a manner that is essential for the membrane fusion reaction (Barnett and Cunningham 2001; Barnett et al. 2002; Lavillette et al. 2001, 2002b). Because transcomplementation can be achieved by a soluble RBD, it is clear that the activation can occur from outside of the virus-associated ΔHis Env trimer. This implies that the natural process of γ-retroviral infection may involve corresponding intertrimer interactions on the viral surface.

Although initial studies indicated that transcomplementation required association of both the RBD and the ΔHis virus with their cognate receptors, as mentioned above, recent investigations demonstrated that several γ-retroviruses with mutant or recombinant Env glycoproteins can be transactivated in the absence of their receptors, as long as the receptor for the RBD is present (Barnett and Cunningham 2001; Barnett et al. 2001, 2002; Lavillette et al. 2002b). For example, Cunningham and

coworkers reported that γ-retroviruses with a deletion of sequences needed for receptor binding can be transactivated by RBDs bound to their cognate receptor (Barnett and Cunningham 2001; Barnett et al. 2001, 2002). A likely interpretation is that the C2 Env regions in those mutant and recombinant viruses may be exposed in the absence of a receptor. In this circumstance, binding of an RBD to its receptor can enable it to transactivate a virus that is not attached to a receptor.

Recent studies by Overbaugh and coworkers have demonstrated that similar transactivation processes can occur in natural infections by γ-retroviruses. Specifically, they found that infections by the immunosuppressive FeLV-T virus, which has a Pro in place of His in its PHQ motif (Donahue et al. 1991; Overbaugh et al. 1988), require transactivation either by a soluble FeLV-B-related SU glycoprotein termed FELIX that is endogenously expressed in cat T cells or by an FeLV-B SU glycoprotein (Anderson et al. 2000; Lauring et al. 2001, 2002). These transactivations require the natural FeLV-B receptor Pit1 (Anderson et al. 2000; Lauring et al. 2001). The FeLV-T SU glycoprotein binds with negligible affinity to susceptible cells (Donahue et al. 1991; Kristal et al. 1993; Lauring et al. 2001; Moser et al. 1998; Reinhard et al. 1993; Rohn et al. 1998), and it is consequently unclear whether FeLV-T can be transactivated in the absence of a primary receptor or might also interact with Pit1. The former possibility is supported by recent evidence that FeLV-T can be transactivated by a MuLV-E RBD in cells that contain mouse CAT1 but lack functional Pit1 receptors (Barnett et al. 2002). Similarly, it was recently found that MCFs can infect cells that lack functional X-receptors if they are transactivated by the Friend E-MuLV RBD (J. Cunningham, personal communication). As described above in Sect. 4.2, MCFs naturally occur only in mice that also contain replicating E-MuLVs (Fischinger et al. 1978; Kabat 1989; Rosenberg and Jolicoeur 1997; Stoye et al. 1991). Presumably, MCFs may have the C2 region of their SU glycoproteins in an exposed conformation in the absence of X-receptors. Interestingly, both FeLV-T and MCFs are examples of γ-retroviruses that emerge late in natural infections initiated by other viruses (FeLV-A and E-MuLV, respectively), that bind to receptors weakly or negligibly, and that cause massive superinfections with cytopathic consequences (Donahue et al. 1991; Hartley et al. 1977; Herr and Gilbert 1984; Marin et al. 1999; Moser et al. 1998; Rohn et al. 1998; Yoshimura et al. 2001). Transactivation is clearly a powerful means for such retroviruses to overcome interference barriers in chronically infected animals.

Although it seems likely that such a fundamental mechanism of viral activation by receptors must have been highly selected during evolution, we emphasize that transcomplementation has not yet been reported for other genera of retroviruses or even for all γ-retroviruses. For example, the PHQ motif is absent in the RD-114 and BaEV family of γ-retroviruses that use ASCT1 and ASCT2 as their receptors and it is substantially altered in the PERV viruses.

The evidence reviewed in this section provides very strong support for the hypothesis that attachment of γ-retroviruses to their receptors initiates a pathway that obligatorily contains intermediate steps. These intermediate steps very likely include viral association with multiple receptors, cooperative conformational changes within Env glycoprotein trimers, and cross-talk between Env trimers on the viral surfaces. A hallmark of an obligatory pathway is that blockage of intermediate steps causes a failure in the process. The transcomplementation evidence supports this idea because it suggests that a failure in Env-Env cross-talk prevents membrane fusion. Indeed, this evidence suggests that virus binding to receptors does not directly induce irreversible structural changes in SU-TM complexes as was previously believed. Rather, it implies that the binding to receptors induces SU-SU interactions that are prerequisites for later steps in a highly coordinated membrane fusion pathway. We anticipate that similar intermediate steps are likely to be involved in infections by other groups of retroviruses and perhaps in infections by other membrane-enveloped viruses.

9 Summary

Evidence obtained during the last few years has greatly extended our understanding of the cell surface receptors that mediate infections of retroviruses and has provided many surprising insights. In contrast to other cell surface components such as lectins or proteoglycans that influence infections indirectly by enhancing virus adsorption onto specific cells, the true receptors induce conformational changes in the viral envelope glycoproteins that are essential for infection. One surprise is that all of the cell surface receptors for γ-retroviruses are proteins that have multiple TM sequences, compatible with their identification in known instances as transporters of important solutes. In striking contrast, almost all other animal viruses use receptors that exclusively have single TM se-

quences, with the sole proven exception we know of being the coreceptors used by lentiviruses. This dichotomy strongly suggests that virus genera have been prevented because of their previous evolutionary adaptations from switching their specificities between single-TM and multi-TM receptors. This evidence also implies that γ-retroviruses formed by divergent evolution from a common origin millions of years ago and that individual viruses have occasionally jumped between species (zoonoses) while retaining their commitment to use the orthologous receptor of the new host. Another surprise is that many γ-retroviruses use not just one receptor but pairs of closely related receptors as alternatives. This appears to have enhanced viral survival by severely limiting the likelihood of host escape mutations. All of the receptors used by γ-retroviruses contain hypervariable regions that are often heavily glycosylated and that control the viral host range properties, consistent with the idea that these sequences are battlegrounds of viral host coevolution. However, in contrast to previous assumptions, we propose that γ-retroviruses have become adapted to recognize conserved sites that are important for the receptor's natural function and that the hypervariable sequences have been elaborated by the hosts as defense bulwarks that surround the conserved viral attachment sites. Previously, it was believed that binding to receptors directly triggers a series of conformational changes in the viral envelope glycoproteins that culminate in fusion of the viral and cellular membranes. However, new evidence suggests that γ-retroviral association with receptors triggers an obligatory interaction or cross-talk between envelope glycoproteins on the viral surface. If this intermediate step is prevented, infection fails. Conversely, in several circumstances this cross-talk can be induced in the absence of a cell surface receptor for the virus, in which case infection can proceed efficiently. This new evidence strongly implies that the role of cell surface receptors in infections of γ-retroviruses (and perhaps of other enveloped viruses) is more complex and interesting than was previously imagined.

Recently, another gammaretroviral receptor with multiple transmembrane sequences was cloned. See Prassolov, Y., Zhang, D., Ivanov, D., Lohler, J., Ross, S.R., and Stocking, C. Sodium-dependent myo-inositol transporter 1 is a receptor for Mus cervicolor M813 murine leukemia virus.

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