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REVIEW ARTICLE

ANTIVIRAL DRUG SUSCEPTIBILITY PATTERNS IN GAMMARETROVIRIDAE: LESSONS FROM XMRV AND RELATED RETROVIRUSES

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SUMMARY

Gammaretroviruses include several well-characterized, exogenous mammalian retroviruses that cause cancer and other diseases following infection of susceptible hosts. Recent reports of a newly discovered gammaretrovirus, xenotropic murine leukemia virus-related virus (XMRV), in patients with prostate cancer and chronic fatigue syndrome (CFS) have fueled a renewed interest in the susceptibility of gammaretroviruses to antiretroviral inhibitors. Although evidence linking XMRV infection to human disease is currently insufficient to support the use of antiretrovirals in prostate cancer or CFS patients, studies of XMRV have complemented a large body of historical literature describing the antiviral drug sensitivities of gammaretroviruses from diverse mammalian hosts. This review summarizes the available drug susceptibility data for gammaretroviruses, including XMRV, murine leukemia virus (MLV), murine sarcoma virus (MSV), feline leukemia virus (FeLV) and porcine endogenous retrovirus (PERV). Collectively, these findings reveal patterns of drug sensitivity that are shared by members of the genus gammaretroviridae and suggest strategies for preventing or treating gammaretroviral infections in humans should the need arise.

INTRODUCTION

Gammaretroviruses have been identified in a variety of vertebrate species and are causative agents of leukemia, lymphoma, sarcoma and other diseases. The most thoroughly studied gammaretroviruses, the murine leukemia viruses (MLVs), exist in both endogenous (germ line transmitted) and exogenous (horizontally or vertically transmitted) forms, and are further classified according to the host ranges conferred by their envelope genes (1). Gammaretroviral sequences have also been identified in the human genome (i.e., class I human endogenous retroviruses, or HERVs) (2), indicating infection by actively replicating members of this genus at multiple points in our ancestry. At present, all endogenous human gammaretroviruses contain one or more inactivating mutations (3) and thus require complementation or restorative mutations to produce infectious particles. Additional examples of well-characterized mammalian gammaretroviruses include feline leukemia virus (FeLV), gibbon ape leukemia virus (GALV) and porcine endogenous retrovirus (PERV).

From a historical perspective, studies of gammaretroviruses have provided crucial insight into the underlying mechanisms of retroviral entry, replication, variation and pathogenesis (4). In addition, several important advances in the development of modern antiretroviral therapy for HIV can be traced to earlier work with gammaretroviral models. As discussed below, initial experiments with replication-competent murine and feline gammaretroviruses provided the first examples of the ability of small-molecule inhibitors to interrupt retroviral disease. Although infection of rhesus macaques with simian immunodeficiency virus (SIV) or SIV/HIV recombinant viruses (SHIVs) has largely supplanted the murine and feline models, studies with MLV continue to play a role in investigating new strategies for treating or preventing retroviral infection and retrovirus-induced diseases (5-9), and provide a tractable, cost-effective alternative to SIV-based approaches.

Recent reports of a novel gammaretrovirus, xenotropic murine leukemia virus-related virus (XMRV), in human prostate tumor tissues (10-12) and in individuals with chronic fatigue syndrome (CFS) (13) have rekindled interest in gammaretroviral biology among the broader scientific community. Studies of XMRV have made significant contributions to our understanding of gammaretroviral replication, enzymology and virus–host interactions (10, 11, 14-19), but have also challenged the initial classification of XMRV as an authentic human retrovirus (see 20, 21 for review). With regard to drug susceptibility, the in vitro activities of 32 different antiretroviral compounds, including all of the drugs currently used to treat HIV-1 infection, have

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now been tested against XMRV (22-25), making this newcomer the most extensively characterized example of the genus gammaretroviridae.

Taken together, studies of murine viruses, feline viruses, XMRV and PERV have identified agents from multiple antiretroviral classes that may prove useful for treating novel or emerging gammaretroviral infections. This review summarizes the available information regarding the antiviral drug sensitivities of mammalian gammaretroviruses, with emphasis on the similarities and differences between these viruses and the lentivirus HIV-1. I begin with an overview of early studies showing that treatment of experimentally infected animals with AZT inhibits gammaretroviral infection and arrests pathogenesis. Next, studies assessing the in vitro and in vivo activity of other chain-terminating nucleoside analogues are discussed. Lastly, the activities of inhibitors that target the viral reverse transcriptase (RT), protease and integrase enzymes are summarized for two gammaretroviruses of potential medical importance: XMRV and PERV. These findings reveal an overall pattern of antiviral drug susceptibility that is shared among members of the genus gammaretroviridae.

INITIAL STUDIES OF ZIDOVUDINE SUSCEPTIBILITY

The nucleoside analogue 3′-azido-3′-deoxythymidine (zidovudine, AZT) was the first antiretroviral drug approved by the U.S. Food and Drug Administration for treating HIV infection. As with other inhibitors in the nucleoside class, AZT is phosphorylated to its corresponding 5′-triphosphate form by cellular kinases and serves as a pseudosubstrate for RT-catalyzed DNA synthesis. Incorporation of AZT 5′-monophosphate into newly synthesized viral DNA results in chain termination and subsequent arrest of viral replication.

Eleven years before the first reports of AZT sensitivity in HIV-1 (26), Ostertag et al. examined the effect of AZT treatment on the production of Friend virus (FV) complex (a mixture of replication-competent and -defective murine leukemia viruses [MLVs]) in immortalized murine cells (27). This study represents the earliest demonstration that AZT can inhibit retroviral replication, although it should be noted that exceptionally high concentrations of drug (250 µM) were used in these experiments.

More convincing data were obtained in studies involving Rauscher MLV (R-MLV). Using plaque reduction assays, Ruprecht et al. showed that low nanomolar concentrations of AZT block the replication of R-MLV, as well as the T-cell-tropic SL3-3 MLV, in cultured murine cell lines (28). Furthermore, the addition of AZT (1 mg/mL) to the drinking water of R-MLV-infected BALB/c mice reduced plasma-associated titers of the virus and prevented splenocyte infection and splenomegaly. These protective effects coincided with an increase in mean survival time from 26 days to > 55 days; all AZT-treated animals were sacrificed at day 55 due to drug-associated toxicity. Lower doses of AZT (0.1 mg/mL) also led to significant prolongation of survival time, although splenomegaly was not prevented. Collectively, these findings showed that AZT treatment protects BALB/c mice from R-MLV-induced disease, but is also associated with substantial host toxicity. These data were published as the first clinical studies of AZT monotherapy were under way (29).

The utility of AZT treatment was further demonstrated in other gammaretroviral model systems. Tavares et al. showed that AZT inhibited FeLV replication in cell culture and that administration of AZT to kittens immediately following FeLV infection provided substantial reductions in viremia, frequently leading to viral clearance (30). Furthermore, Sharpe et al. showed that AZT inhibits the replication of Cas-Br-E (a neurotropic murine gammaretrovirus) in culture and delays the onset of Cas-Br-E-induced neurological disease in mice infected with the virus in utero, with corresponding increases in median survival (31). These experiments provided the first evidence that AZT crosses the placenta and is active during embryonic development. Additional demonstrations of AZT efficacy during gestation and in the perinatal period were obtained in studies of Moloney MLV (MoMLV) (32, 33). Taken together, these findings provided important experimental support for the use of AZT in preventing mother-to-child transmission of HIV-1.

Further studies in inbred mouse strains experimentally infected with LP-BM5 MLV (34-36) and FV complex (37, 38) showed that AZT treatment delays the onset of virus-induced immunological abnormalities and prolongs survival. These results were accompanied by data showing that AZT inhibits FV replication in culture-based assays (39). Finally, Huang et al. demonstrated that AZT 5′-triphosphate inhibits DNA synthesis by purified MoMLV RT in cell-free reactions, and confirmed that chain termination is the principal mechanism responsible for this effect (40). These reports collectively solidified the role of AZT as a potent inhibitor of gammaretroviral replication in culture, in infected animals and at the biochemical level.

STUDIES OF DIDEOXYNUCLEOSIDE ANALOGUES

In addition to AZT, other nucleoside reverse transcriptase inhibitors (NRTIs) have been shown to inhibit the replication of FeLV in vitro and in vivo, albeit with varying efficacy (41-43). 2′,3′-Dideoxycytidine (ddC, zalcitabine) blocked FeLV infection of feline lymphoid cells and fibroblasts in culture at low micromolar concentrations, but substantially higher doses of the drug were required to inhibit FeLV replication in primary bone marrow cells (42). Accordingly, nontoxic doses of ddC protected lymphoid and epithelial tissues in FeLV-infected cats, but merely delayed bone marrow infection in drug-treated animals. Higher doses of ddC resulted in severe thrombocytopenia and death. These results foreshadowed the drug-associated toxicities observed in ddC-treated HIV-1 patients, which eventually led to the discontinuation of ddC for antiretroviral therapy of HIV-1.

2′,3′-Didehydro-3′-deoxythymidine (d4T, stavudine) and 2′,3′-dideoxyinosine (ddI, didanosine) were also evaluated for antiviral activity against FV and FeLV, respectively (39, 41, 43). Although d4T administration resulted in lower splenic and plasma titers in FV-infected mice, the EC_{50} for d4T in culture was 10-fold higher than that of AZT (39). Similarly, EC_{50} values for inhibition of FeLV by ddI in various human cell lines ranged from 5- to 200-fold higher than the corresponding values for AZT (43). These results indicate that, relative to AZT, d4T and ddI are less effective inhibitors of FV and FeLV replication.

The relative superiority of AZT against gammaretroviruses was further demonstrated in two independent studies of MLV vector viruses (replication-competent retrovirus [RCR] and LGPS; 44, 45) and in a comparison of the activities of various NRTIs against amphotropic MLV-A, HIV-1 and other retroviruses. Although different host cell

lines were used for each of the viruses tested, AZT was the most potent inhibitor of MLV-A replication and was equally active against MLV-A and HIV-1 (46). In contrast, EC_{50} values for ddC, ddI, d4T and the carbocyclic dideoxynucleoside abacavir were 10- to 100-fold higher for MLV-A relative to HIV-1. MLV-A, RCR and LGPS were also highly resistant to (–)-β-L-2′,3′-dideoxy-3′-thiacytidine (3TC, lamivudine) (44-46), a potent inhibitor of HIV-1 that contains an oxathiolane pseudosugar in the unnatural L-conformation. The insensitivity of MLV to 3TC was subsequently confirmed in experiments showing that purified MoMLV RT exhibits high-level resistance to 3TC 5′-triphosphate (relative to HIV-1 RT) in cell-free polymerase assays (47).

DEVELOPMENT AND TESTING OF ACYCLIC NUCLEOSIDE PHOSPHONATES

An important limitation to the antiviral activity of NRTIs is the requirement of cellular enzymes for the initial phosphorylation step. Most NRTIs are relatively poor substrates for the kinases that catalyze 5′-monophosphorylation, and thus only a fraction of the intracellular drug pool is converted to its active 5′-triphosphate form. To circumvent this barrier, DeClerq et al. at the Rega Institute (Belgium) synthesized a series of acyclic nucleoside analogues containing a metabolically stable phosphonate group. Following intracellular uptake, these compounds are converted to their corresponding diphosphates and are incorporated by RT, resulting in chain termination.

Animal model studies involving murine and feline gammaretroviruses played a crucial role in the development of acyclic nucleosides for HIV treatment. Initially, De Clercq et al. showed that 9-(2-phosphonomethoxyethyl)adenine (PMEA, adefovir) and related compounds inhibit the transformation of murine fibroblast cells by Moloney murine sarcoma virus (MoMSV) in culture (48, 49). Subsequent demonstrations of the activity of PMEA against HIV-1 in vitro were strengthened by data showing that PMEA treatment results in dose-dependent suppression of tumorigenesis and associated mortality in MoMSV-infected mice (50). Further experiments with MoMSV showed that prodrug modifications to PMEA and to the related compound *R*-9-(2-phosphonomethoxypropyl)adenine (PMPA, tenofovir), conferred improvements in oral bioavailability and in vivo activity (51, 52). Together with assessments of the activity of PMEA and PMPA against LP-BM5 MLV (53), FeLV (54), SIV (55-59), FIV (60-62) and HIV-1 (49, 63, 64; see also 65 for review), these findings led to the eventual licensing of tenofovir disoproxil fumarate (TDF) for the treatment of HIV-1 infection.

Collectively, the results discussed above demonstrate that murine and feline gammaretroviruses are sensitive to AZT and to acyclic nucleoside phosphonates such as PMEA and PMPA, but are relatively resistant to dideoxynucleoside analogues, and are highly resistant to the L-form nucleoside 3TC. Data regarding the susceptibility of MLV to other RT inhibitors, as well as other drugs targeting the protease and integrase enzymes, are discussed in the following section.

ANTIRETROVIRAL DRUG SUSCEPTIBILITY OF XMRV

Investigations of the relationship between retroviral infection and cancer date back to the earliest studies of avian sarcoma/leukosis viruses (66, 67), and have yielded fundamental discoveries regarding the genetic and molecular basis of tumorigenesis. Studies of animal retroviruses, including the gammaretroviruses MLV and FeLV, have revealed key insights, such as the importance of cellular proto-oncogenes in tumor formation and the potential for certain retroviral genes and regulatory sequences to initiate oncogenic transformation (4). The discovery and isolation of HTLV-1 in 1980 (68) provided the first example of a transmissible, cancer-causing retrovirus in humans. Although other retroviruses have been proposed as mediators of human cancer, causal relationships between infection and oncogenesis have not been established, and thus, the role of these viruses in human disease remains uncertain (69).

In 2006, Urisman et al. reported the discovery of XMRV in prostate tumor tissues from patients with a specific defect in *RNASE L* (12). Subsequent descriptions of XMRV in samples from a second cohort of prostate cancer patients (11) and in an immortalized prostate cell line (22Rv1) (70) were followed by a remarkable report by Lombardi et al. of XMRV RNA, protein and infectious particles in patients suffering from CFS (13). In the months following the publication of the Lombardi study, widespread excitement changed to skepticism, as numerous surveys of prostate cancer and CFS patients worldwide failed to uncover evidence of XMRV infection (71-87), although some groups reported a low prevalence of the virus in prostate cancer patients (88-91). Adding to the complexity of the picture, a polymerase chain reaction (PCR)-based study by Lo et al. identified several polytropic and modified polytropic MLV sequences in blood samples from CFS patients, but no evidence of XMRV was found (92). Although it remains possible that XMRV and/or other MLV-related gammaretroviruses are circulating at some frequency in the human population, recent studies suggest that much of the evidence for XMRV/MLV infection in humans can be attributed to laboratory contamination (93-99). These findings have led to significant doubts regarding the provenance of XMRV and the potential connection between gammaretroviral infection, prostate cancer and CFS.

While the relationship between XMRV and human disease is tenuous at best, studies of XMRV have brought new information to light regarding the susceptibility of gammaretroviruses to antiviral inhibitors. Initial cell culture experiments with XMRV demonstrated that a single dose of AZT (10 μM) added 1 day postinfection inhibited the production of viral RNA in human prostate carcinoma DU 145 cells (100). Subsequently, Sakuma et al. showed that treatment of prostate carcinoma LNCaP cells with 30 nM AZT conferred a 25-fold reduction in the number of XMRV-infected cells, as assessed by flow cytometry. Additional experiments involving spreading infections of LNCaP cells and PCR-based quantification of XMRV cDNA synthesis during single-round infections provided further evidence that AZT is a potent inhibitor of XMRV replication. In contrast, 30-nM concentrations of the NRTIs 3TC, tenofovir and d4T, the non-nucleoside RT inhibitors (NNRTIs) efavirenz and nevirapine, and the integrase inhibitor 118-D-24 individually had no effect on XMRV infection. The protease inhibitors ritonavir, saquinavir and indinavir also showed no substantial effect on XMRV infection or Gag protein maturation at nontoxic doses (25). These preliminary findings suggested that, among the inhibitors tested, only AZT protected LNCaP target cells from XMRV infection.

Following these initial studies, Singh et al. tested 45 individual compounds for anti-XMRV activity in the breast cancer MCF7 cell line (24). The most potent inhibitors of XMRV were AZT, TDF and the integrase inhibitors raltegravir and L-870812. These compounds also blocked XMRV replication at noncytotoxic concentrations in LNCaP cells, and varying combinations of the drugs displayed synergistic effects against the virus. In contrast, nine protease inhibitors that are currently used for HIV-1 treatment, as well as other antiviral inhibitors of hepatitis B virus (HBV), herpesvirus or RNA virus infections, had no effect on XMRV replication. Two NNRTIs (nevirapine and a TIBO derivative) were also shown to be ineffective against the virus.

To further examine the intrinsic susceptibility of XMRV to antiretroviral agents, Paprotka et al. (23) and Smith et al. (22) directly compared the sensitivities of XMRV and HIV-1 to several RT and integrase inhibitors. Both groups used culture-based methods that limit viral replication to a single cycle, thereby ensuring that the dose–response results were not influenced by differences in the relative replication rates of the viruses. In addition, both groups of investigators used a single target cell type (LNCaP cells in the Paprotka et al. and MAGIC-5A cells in the Smith et al. studies) to quantify HIV-1 and XMRV infection in the presence of drug. The use of the same cell type is particularly important for comparisons of NRTI susceptibility, since the antiviral activity of these drugs can vary dramatically in different host cell environments (101, 102).

In concordance with earlier studies, XMRV and HIV-1 exhibited comparable susceptibilities to the NRTIs AZT, PMPA and TDF (22, 23). Smith et al. further showed that the two viruses are also equally sensitive to PMEA, as well as two NRTIs that are structurally related to AZT: 3′-azido-2′,3′-dideoxyadenosine (AZddA) and 3′-azido-2′,3′-dideoxyguanosine (AZddG) (22). In contrast, XMRV was approximately 10- to 30-fold resistant to ddI, d4T and abacavir, and ≥ 10-fold resistant to the L-nucleosides 3TC and FTC, relative to HIV-1 (22, 23). Collectively, these findings are in agreement with previous studies of MLV and other gammaretroviruses (see above) and reveal a pattern of NRTI susceptibility in XMRV that correlates with the structure of the pseudosugar group. In addition, the results obtained with AZT, AZddA, AZddG, PMEA and PMPA suggest that other 3′-azido or acyclic NRTIs might be active against the virus (22).

With regard to integrase inhibitors, the studies by Paprotka et al. and Smith et al. showed that raltegravir is comparably activity against XMRV and HIV-1 (22, 23), but Smith et al. reported that XMRV is moderately resistant to elvitegravir (EC_{50} 40-fold greater than that seen in HIV-1) (22). These findings for raltegravir and elvitegravir were later confirmed in an analysis of the integrase inhibitor susceptibility of retroviruses from diverse mammalian hosts (103), and are concordant with a recent report showing that FeLV is susceptible to raltegravir (104). The differential sensitivity of XMRV to raltegravir and elvitegravir is somewhat surprising, since these two drugs are structurally related and are believed to bind to the same location in the HIV-1 integrase active site (105, 106). However, in agreement with the XMRV data, previous analyses showed that MoMLV is sensitive to raltegravir but moderately resistant to elvitegravir in culture (sevenfold increase in EC_{50} relative to HIV-1; 107, 108). The similarity between MoMLV and XMRV with regard to integrase inhibitor sensitivity is consistent with the high degree of amino acid identity (90%) shared by these viruses in the integrase catalytic core domain.

In contrast to NRTIs and integrase inhibitors, XMRV is intrinsically resistant to all NNRTIs tested to date (22, 24, 25) and is also resistant to each of the nine protease inhibitors approved for HIV-1 treatment (22, 24). The latter phenotype is consistent with the marked differences in the substrate specificities of MLV and HIV-1 protease (109-113) and the higher concentrations of saquinavir, indinavir, ritonavir, nelfinavir and amprenavir needed to block MLV protease activity relative to the HIV-1 enzyme (113). Although an earlier study identified three peptidomimetic compounds that show comparable activity against R-MLV, HIV-1 and SIV (114), it appears that XMRV and other gammaretroviruses are broadly resistant to all of the protease inhibitors currently used for antiretroviral therapy of HIV-1 (see also the following section).

AGENTS FOR PROPHYLAXIS AND TREATMENT OF PERV INFECTION

Prior to the discovery of XMRV, studies of endogenous gammaretroviruses in pigs raised concerns that replication-competent PERV could be transmitted to human recipients of porcine organs and tissues (115-117). Accordingly, inhibitors of HIV-1 RT and protease have been evaluated for anti-PERV activity in a variety of culture-based and biochemical assays (118-122).

PERV was initially identified by electron microscopy in 1971 (123) and was later shown to replicate in immortalized pig cells in culture (124). Early studies of the host range of the virus suggested that PERV replication is restricted to cells of porcine origin (124, 125). However, in 1997, Weiss et al. demonstrated that PERV isolates obtained from PK-15 pig cells can infect immortalized human cells in culture (115). Further analyses showed that mitogenic activation stimulates the release of PERV from pig-derived peripheral blood mononuclear cells (PBMCs) and that the resulting particles can productively infect human 293 cells (116). Presently, two distinct classes of human-tropic PERV (-A and -B) have been identified (126, 127), and expression of the human PERV-A receptor (HuPAR) has been demonstrated in a broad range of human tissues, including PBMCs (128). These findings raise the possibility that PERVs might be transmitted to human recipients following xenotransplantation of pig cells, tissues or organs (117), and potentially lead to hematopoietic malignancies, given the close genetic relationship of PERVs to other oncogenic gammaretroviruses.

In order to identify antiretroviral drugs that could be used for the treatment or prophylaxis of PERV infection, Powell et al. (118) tested the relative efficacies of AZT, ddI, d4T, 3TC and the protease inhibitor indinavir against PK-15-derived PERV in 293 cells. AZT was the most potent inhibitor of PERV infection, with an EC_{50} of approximately 250 nM. ddI also showed considerable activity against PERV (EC_{50} = 1 μM), but the remaining drugs had no effect on PERV replication at concentrations as high as 20-50 μM. The sensitivity of PERV to AZT was subsequently confirmed using an immunoperoxidase cell-staining assay (120).

To further characterize the drug sensitivity profile of PERV, Qari et al. evaluated the anti-PERV activities of 11 different RT and protease inhibitors in culture and in cell-free polymerase assays. Virion-derived PERV and HIV-1 RTs were similarly sensitive to the 5′-triphosphates of AZT, ddC and ddA (the active form of ddI), although the IC_{50} values for these drugs were 3- to 5-fold higher for PERV RT

relative to the HIV-1 enzyme. In culture-based assays, PERV exhibited slight resistance to AZT (4-fold) and high-level resistance to ddC, ddI, d4T, 3TC and nevirapine (≥ 20-fold relative to HIV-1) (119). PERV was also highly resistant to the protease inhibitors saquinavir, ritonavir, indinavir, nelfinavir and amprenavir; doses that were > 200-fold higher than the corresponding IC_{50} values for HIV-1 had no effect on PERV protease activity in infected cell lysates.

The sensitivity of purified recombinant PERV RT to NNRTIs was also evaluated using analogues of 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT) (121). HEPT compounds bind to the same hydrophobic pocket in HIV-1 RT that is targeted by TIBO, nevirapine and other NNRTIs (129-133). Several HEPT derivatives exhibit excellent activity against HIV-1 RT, but are ineffective against the PERV polymerase (IC_{50} = 0.3-5 μM vs. > 50 μM, respectively) (121). These findings are consistent with the narrow antiretroviral specificities of other NNRTIs, which generally show potent activity against HIV-1 RT only.

Lastly, Shi et al. examined the susceptibility of PERV to several acyclic nucleoside phosphonate analogues (122). As described for FeLV, MoMSV and MLV (see above), PMEA and PMPA were both active against PERV in culture; EC_{50} values for these inhibitors were comparable to that of d4T (~3 μM vs. 8 μM, respectively), but were substantially higher than the value observed for AZT (0.02 μM). Surprisingly, two other acyclic nucleosides, (*R*)-9-(2-phosphonylmethoxypropyl)-2,6-diaminopurine ([*R*]-PMPDAP) and [6-(2-phosphonylmethoxy)ethoxy]-2,4-diaminopyrimidine (PMEO-DAPy), were approximately 10-fold more active against PERV than PMPA, with EC_{50} values of 0.28 and 0.18 μM, respectively. These data are consistent with earlier reports of the superior activity of (*R*)-PMPDAP relative to PMPA, as shown for HIV-1, HIV-2 and MoMSV, and are also consistent with the potent antiviral activity of (*R*)-PMPDAP in MoMSV-infected mice (134). These and other findings indicate that (*R*)-PMPDAP and PMEO-DAPy are highly active inhibitors of gammaretrovirus replication and are attractive candidates for further development as anti-HIV therapeutics (65).

CONCLUSIONS

The aforementioned studies of MLV, MSV, FeLV, XMRV and PERV suggest a general pattern of drug susceptibility that is shared among gammaretroviruses from diverse mammalian hosts. Relative to HIV-1 and other lentiviruses, gammaretroviruses are sensitive to AZT, PMEA and PMPA, but exhibit moderate- to high-level resistance to the dideoxynucleosides ddC, ddI, d4T and abacavir. Gammaretroviruses are also highly resistant to the L-nucleoside analogues 3TC and FTC (and their corresponding 5′-triphosphates) in vitro and in cell-free polymerase assays. These phenotypes are likely attributable to specific amino acid residues in the polymerase core of RT, as discussed elsewhere (22, 45, 47, 118). Furthermore, NNRTIs and protease inhibitors that are highly active against HIV-1 show little or no efficacy against gammaretroviruses in culture or at the biochemical level, a result congruent with structural information from crystallographic studies of HIV-1, MLV and XMRV proteins (16, 132, 135, 136). Finally, emerging data suggest that gammaretroviruses vary in their susceptibilities to different integrase strand transfer inhibitors, as shown in comparisons of the in vitro activities of raltegravir and elvitegravir (22, 103). The amino acid residues responsible for intrinsic elvitegravir resistance in MLV and XMRV are presently unknown.

In conclusion, gammaretroviruses have played pivotal roles in the development of modern antiretroviral therapy and will likely continue to serve as useful models for testing novel treatment strategies. Although the findings discussed above indicate that certain inhibitors can block gammaretroviral replication at pharmacologically achievable doses, it is important to note that the involvement of gammaretroviruses in human disease remains unclear (and, in the case of XMRV, is the subject of ongoing debate), and thus, the present information does not support the off-label use of antiretroviral drugs for treating suspected cases of XMRV infection. However, studies of XMRV have yielded valuable insights regarding the patterns of intrinsic antiviral drug resistance that distinguish gammaretroviruses from HIV and other lentiviruses, and may eventually provide useful information for preventing or treating gammaretroviral infections in humans should the need arise.

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DISCLOSURES

The author states no conflicts of interest.

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