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Short Communication

Hyperediting of human T-cell leukemia virus type 2 and simian T-cell leukemia virus type 3 by the dsRNA adenosine deaminase ADAR-1

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RNA editing mediated by adenosine deaminases acting on RNA (ADARs) converts adenosine (A) to inosine (I) residues in dsRNA templates. While ADAR-1-mediated editing was essentially described for RNA viruses, the present work addresses the issue for two δ-retroviruses, human T-cell leukemia virus type 2 and simian T-cell leukemia virus type 3 (HTLV-2 and STLV-3). We examined whether ADAR-1 could edit HTLV-2 and STLV-3 virus genomes in cell culture and *in vivo*. Using a highly sensitive PCR-based method, referred to as 3DI-PCR, we showed that ADAR-1 could hypermutate adenosine residues in HTLV-2. STLV-3 hypermutation was obtained without using 3DI-PCR, suggesting a higher mutation frequency for this virus. Detailed analysis of the dinucleotide editing context showed preferences for 5′ ArA and 5′ UrA. In conclusion, the present observations demonstrate that ADAR-1 massively edits HTLV-2 and STLV-3 retroviruses *in vitro*, but probably remains a rare phenomenon *in vivo*.

RNA editing mediated by adenosine deaminases acting on RNA (ADARs) has been shown to be one of the most prevalent post-transcriptional RNA modification mechanisms in higher eukaryotes (Bass, 2002; Samuel, 2001). These enzymes convert adenosine (A) to inosine (I) residues in dsRNA templates. Inosine is essentially recognized by the translational machinery as guanine (G), leading to proteins that are frequently non-functional (Li *et al.*, 1991). Three ADAR genes are known. They are specific for dsRNA. While ADAR-1 and ADAR-2 are expressed in many tissues, ADAR-3 is only expressed in the nervous system (Bass, 1997, 2002; Chen *et al.*, 2000; Melcher *et al.*, 1996). ADAR-1 gene consists of 17 exons across a 30 kb sequence (George & Samuel, 1999; Wang *et al.*, 1995). ADAR-1 transcription is initiated from multiple promoters, one being inducible by type I and II interferons (IFNs), while the others are constitutively active (George & Samuel, 1999; Liu *et al.*, 1997). Interestingly, of the ADAR-1 gene transcripts i.e. ADAR-1L and -1S, only the former can be induced by IFN-α/β and γ, underlining its role in antiviral responses. ADAR-1 editing was initially described in the context of subacute sclerosing panencephalitis, a rare chronic degenerative disease that occurs several years after measles virus infection (Cattaneo *et al.*, 1987, 1988; Patterson *et al.*, 2001; Wong *et al.*, 1989, 1991). ADAR-1 editing was originally confined to negative-stranded viruses such as measles virus, vesicular stomatitis virus (O'Hara *et al.*, 1984), human parainfluenza virus (Murphy *et al.*, 1991), lymphocytic choriomeningitis virus (Grande-Pérez *et al.*, 2002), respiratory syncytial virus (Martínez *et al.*, 1997; Rueda *et al.*, 1994), influenza virus (Suspène *et al.*, 2011; Tenoever *et al.*, 2007) and Rift Valley fever virus (Suspène *et al.*, 2008). Recently, measles and influenza virus genomes derived from inactivated seasonal influenza and live-attenuated measles vaccines were also shown to be edited by ADAR-1 (Suspène *et al.*, 2011).

ADAR editing is not restricted to negative-stranded viruses since the hepatitis C virus (Taylor *et al.*, 2005) genome was also found to be edited. Among retroviruses, A→G editing was first described for Rous-associated virus RAV-1 (Hajjar & Linial, 1995), avian leukosis virus (Felder *et al.*, 1994) and more recently for human immunodeficiency virus-1 (HIV-1) (Doria *et al.*, 2009; Phuphuakrat *et al.*, 2008) although at a low frequency. The δ-retrovirus group includes four human T-cell leukemia viruses (HTLV-1−4), and their simian T-cell leukemia virus counterparts (STLV-1, -2 and -3) (Mahieux & Gessain, 2011; Slattery *et al.*, 1999). STLV-1 is widely distributed in Asian and African non-human primates with STLV-3 being only found in African non-human primates (Mahieux & Gessain, 2011).

HTLVs- or STLVs-edited genomes have not been described so far. Since, these viruses mostly replicate through clonal expansion of the infected cell, they may be less prone to genetic editing (Wattel *et al.*, 1995). We have recently developed a PCR-based method, referred to as 3DI-PCR, that allows selective amplification of ADAR-edited RNAs (Suspène *et al.*, 2008). Here, we show that HTLV-2 and STLV-3 RNAs can be efficiently and massively edited by ADAR-1.

In the first series of experiments, 293T cells were transfected (PolyFect; Qiagen) for 48 h with 2 μg plasmid encoding the full-length HTLV-2 genome (pH 6neo) (Chen *et al.*, 1983), in the presence or absence of 0.5 μg ADAR-1 expression plasmid. Total RNA was recovered using Trizol and cDNA was synthesized by using random primers. A fragment of the HTLV-2 *pX* gene (nt 6660–6937) was amplified by using the previously described 3DI-PCR technique (Suspène *et al.*, 2008). pH 2Sout 5′-CATAACCAGTAT-

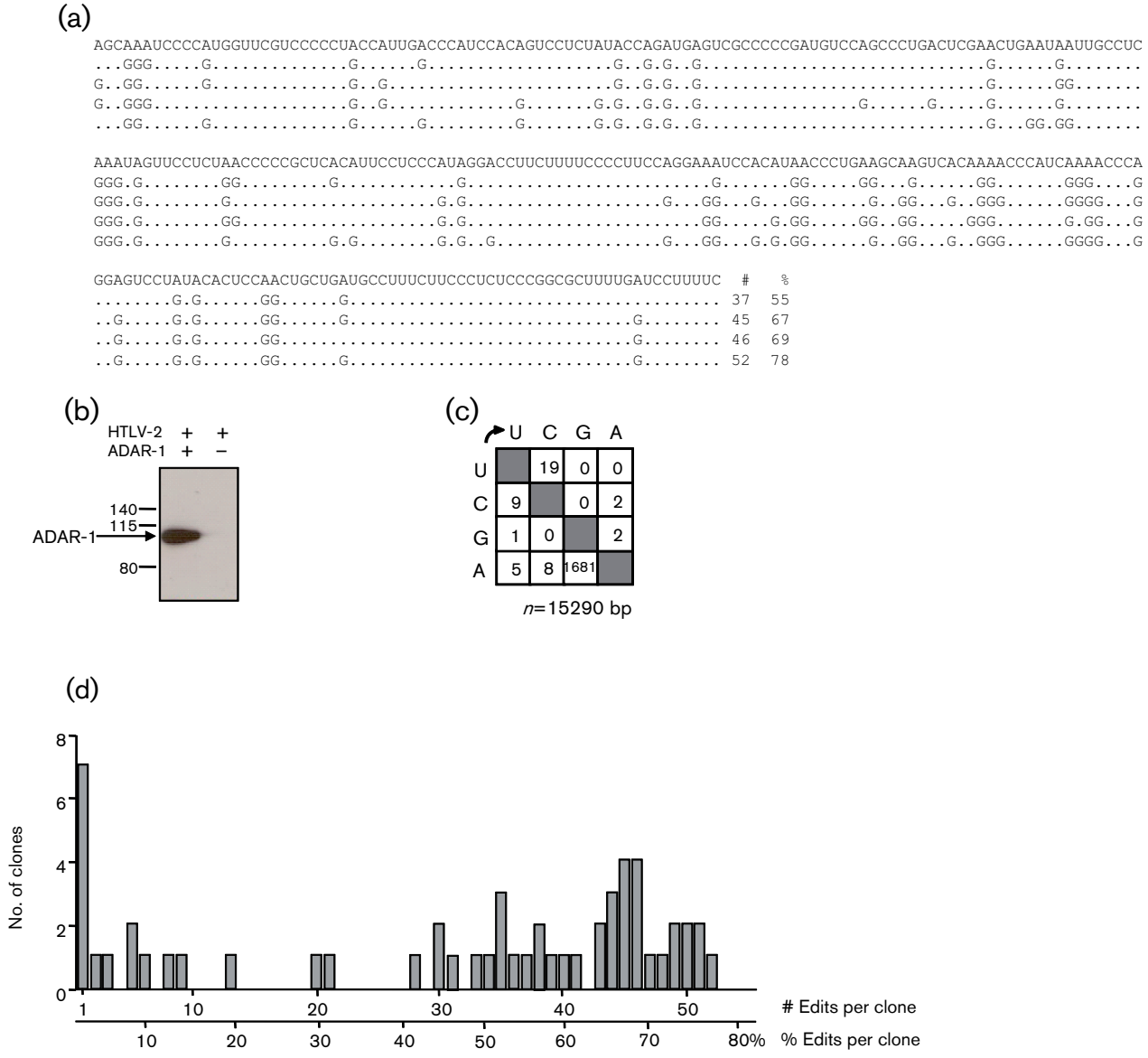

Fig. 1. HTLV-2 genome is susceptible to ADAR-1 editing. (a) Selection of ADAR-1 hypermutated HTLV-2 sequences. The HTLV-2 sequence is given with respect to the retroviral plus strand. Only differences among hypermutated sequences are shown. The number of substitutions per sequence is indicated to the right. # and % indicates the number of A→G transitions and the percentage of A targets edited to G, respectively. (b) 293T cells were transfected or not with an ADAR-1 expression plasmid. Twenty-four hours after transfection, cell extracts were processed for Western blot analysis using an anti-ADAR-1 (ab88574; Abcam) antibody. (c) Mutation matrices of HTLV-2 hyperedited sequences. The 19 U→C transitions are distributed among several sequences. No U→C hyperedited sequence was found. (d) Frequency distribution of A→G editing per clone [# and % as in (a)].

TCCCTTATCAACCC-3′ and pH 2Rout 5′-TTCTGCAG-GAGCGTGAGGAGCGGGAGC-3′ primers were used for the first PCR round, while pH 2Rin 5′-GCTATAATA-GACCTGCTAGCTTCTGC-3′ and pH 2Sin 5′-CGGC-GCAGAAAGGAGCGCCTGCGG-3′ primers were used for the second PCR round. 3DI-PCR products corresponding to extracts obtained only from cells that have been transfected with both HTLV-2 and the ADAR-1 plasmid were recovered at a PCR denaturation temperature as low as 64.8 °C. They were then cloned and sequenced.

In the first series of analyses, 55 extensive and monotonously A⟶G-edited HTLV-2 *pX* sequences were recovered (Fig. 1a). As a control, a Western blot analysis was performed in cells transfected or not with the ADAR-1 expression plasmid (Liu *et al.*, 1997) (Fig. 1b). ADAR-1 enzyme was able to extensively deaminate HTLV-2 RNA (Fig. 1a, c). Of note, hyperedited sequences could not be recovered in the absence of exogenously expressed ADAR-1 (data not shown). The A⟶G editing frequency distribution per clone shows some lightly edited genome with 1–5 mutations (~20 %) and a majority of highly mutated genomes (i.e. >20 mutations ~73 % of all A nucleotides, Fig. 1d). The mean editing frequency was ~46 % (range 1.5–78 %) (Fig. 1d). The dinucleotide context associated with adenosine editing showed a clear preference for 5′ArA and 5′ UrA and an aversion for 5′ GrA and 5′ CrA (Fig. 2a, left panel), which is in agreement with the literature (Lehmann & Bass, 2000; Suspène *et al.*, 2008, 2011). In contrast, we could not detect any obvious 3′ context (Fig. 2a, right panel).

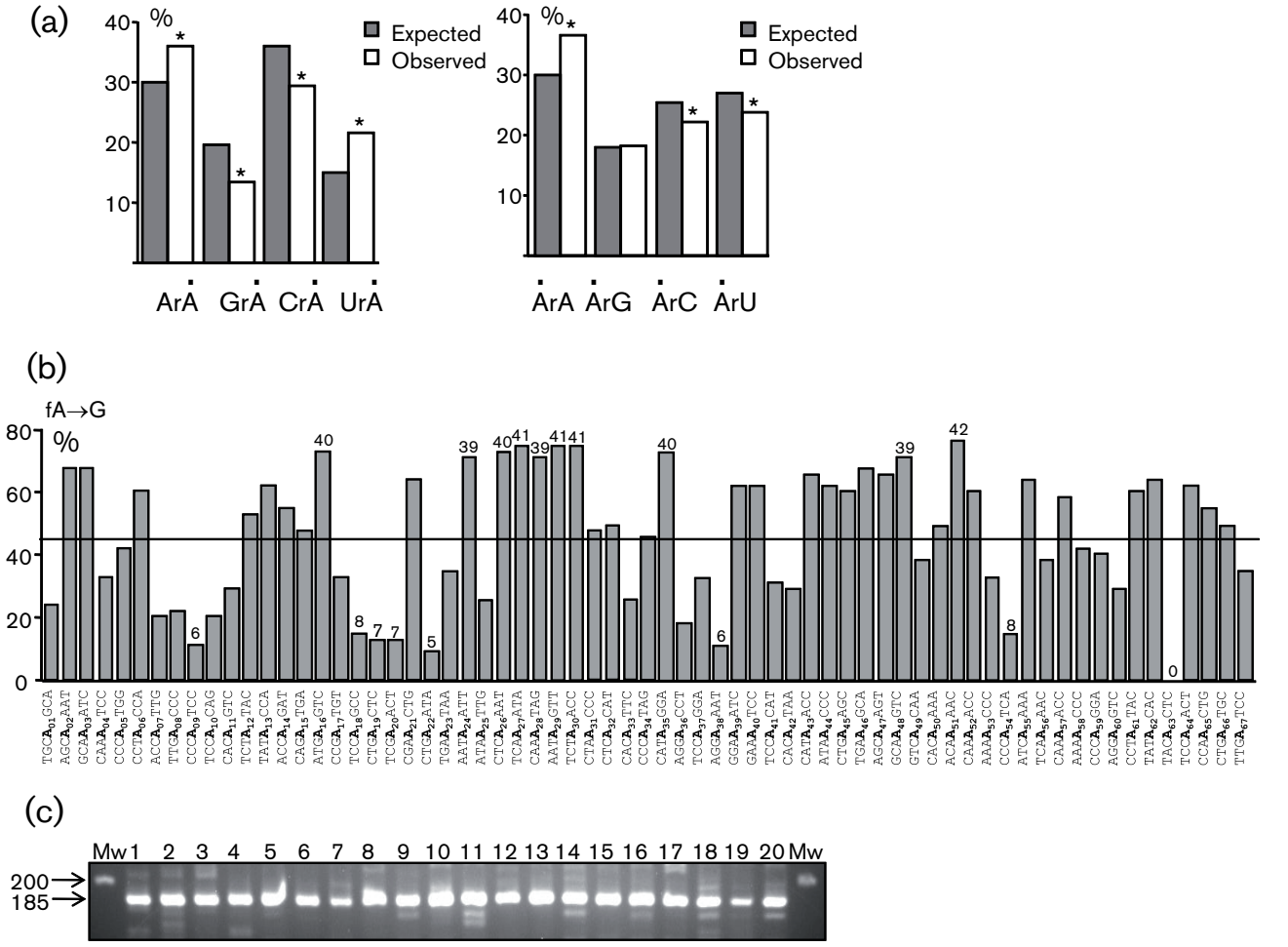

Fig. 2. HTLV-2 sequence context among sites of ADAR-1 deamination. (a) Dinucleotide analysis in 5′ (left) and 3′ (right) of HTLV-2-edited genomes. Dots indicate the edited base. χ^2 analysis indicates dinucleotide frequencies that significantly deviate from the expected values ($P<0.05$, *). (b) Deamination frequencies across the HTLV-2 target sequence. Base-specific deamination frequencies were calculated among a collection of 55 sequences from all the reactions and are given as a function of local sequence context. The horizontal bar indicates the mean site deamination frequency, assuming no effect of the sequence context. Values on the top of each histogram represent the number of deaminated A among the 55 ADAR-1 HTLV-2-edited sequences. (c) Amplification of ADAR-1 cDNA obtained from 20 HTLV-2-infected individuals. The expected size of the amplified product is 185 bp. Mw, Molecular mass marker.

(a)

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UAGGUGGAAGCCAUCUCUGGAUCCCGUGGCGCCUCCUAAAAAGGGGUAUAUGCCCAAGACCCGAAAGCAGCGCAGCCGCCGACCCAAAAAUCAGAGACCA
.G......G.............................G........G........G.G.....GG...................GGG...G.......
........G.............................GGG.........................G..................GG...........
............................................................................................................

UCAACUCCAUGGCAGGGAGCCAUAGUUCUCGCCUUCACUAGACACCCAGAUACAGCAUAAUCCUGAGGAAUCCCCUUCGACGUCAACACCCUGGCCCCAA
...G.........G.........G..............G..............G........G...G...............G...........G
.......................G..............G................G......G...G.............GG............G
............---......G.G..............G...........G......GG.....G...G..............G..............

CAGUCCAUAUACCAGAAGUAUUCCUCUAAGGAUUCUUCGCAGCCUGCGCGUAGCUGCUGGUUCUCCUGCUCCAAAAAAUCUAUGUAGCCCCCUAGCAAGU
..........G.....................................................................................G..
................G..G........G...........G.........G.....................G.......................
.G......G.G....GG..G.......GG...........G.........G.....................GGGG.........G.......G..GG..

CACAAAACCCCUCGAACCCCAGCGCGUCUAUACAAUCCAACUGUUGUCGC  #   %
....G.......................................... 24  25
.......................................... 21  22
.G..GGG.....................G.G..G...GG.......... 36  38
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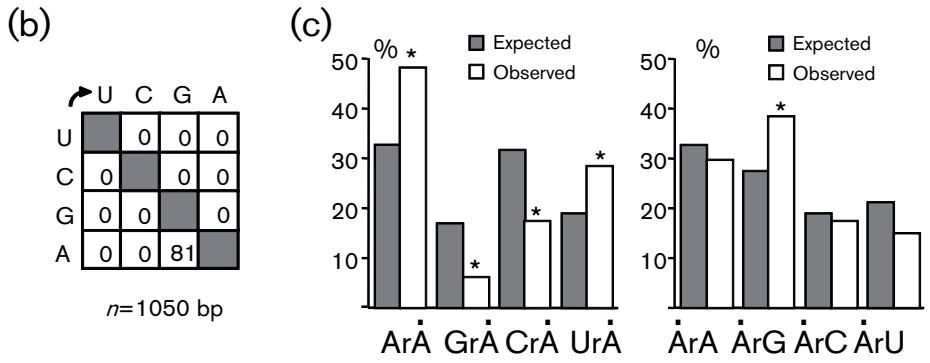

Fig. 3. STLV-3 genome is susceptible to ADAR-1 editing. (a) The sequence is given with respect to the retroviral plus strand. Only differences among hypermutated sequences are shown. The number of substitutions per sequence is indicated to the right. # and % indicate the number of A→G transitions and the percentage of A→G edited, respectively. (b) Mutation matrices of STLV-3 hyperedited sequences. (c) Dinucleotide analysis in 5′ (left) and 3′ (right) of STLV-3-edited genomes. Dots indicate the edited base. χ^2 analysis indicates dinucleotide frequencies that significantly deviate from the expected values ($P<0.05$, *).

With a large number of clones sequenced, we defined site-specific editing frequency (Fig. 2b). Among the sixty-seven potential adenosine targets that are present in the HTLV-2 *pX* RNA template, we observed that some positions were highly refractory to mutations (see for example A_{09}, A_{22} and A_{38}). On the other hand, others were strongly deaminated. As an example, A_{51} was edited in 42 out of 55 clones sequenced (i.e. ~76 %). One residue (A_{63}) was totally refractory to ADAR-1 editing.

In order to demonstrate a possible effect of ADAR-1 editing *in vivo*, peripheral blood mononuclear cells were obtained from 20 HTLV-2-infected individuals and immediately frozen (Douceron *et al.*, 2012). Total RNA was extracted and cDNA was subsequently obtained using random primers. Given the fact that *tax* is usually expressed in less than 50 % of all HTLV-infected individuals, we amplified an *env* region by PCR and 3DI-PCR. However, hyperedited sequences could not be recovered upon cloning and sequencing of the 20 different 3DI-PCR products, suggesting that ADAR-1 editing is a rare event *in vivo* in HTLV-2-infected individuals (data not shown). As a control, ADAR-1 expression was detected by RT-PCR among the 20 HTLV-2-infected individuals, demonstrating that all *ex vivo* samples contained detectable levels of the ADAR-1 transcript (Fig. 2c).

To determine whether ADAR-1 editing could occur for another δ-retrovirus, 293T cells were transfected (Polyfect; Qiagen) with an STLV-3 (PPAF-3) infectious molecular clone (Calattini *et al.*, 2006; Chevalier *et al.*, 2007) without overexpressing ADAR-1. Forty-eight hours post-transfection, total cellular RNA was recovered and cDNA was synthesized with random primers as described above. A fragment of the PPAF-3 *pX* mRNA was amplified by a nested PCR procedure. PCR products obtained at a 95 °C denaturation temperature were cloned and sequenced. Surprisingly, out of five clones sequenced, we recovered three ADAR-edited sequences (Fig. 3a). These sequences uniquely displayed A→G transitions (Fig. 3b), with a ~29 % mean adenosine

substitution frequency per clone (range ~22–38 %). Once again and similar to the HTLV-2 results (Fig. 2), a significant preference for 5′ ArA and 5′ UrA contexts was observed (Fig. 3c). As ADAR-1 is constitutively expressed in 293T (Wang & Samuel, 2009), the majority of STLV-3-edited sequences can probably be ascribed to the ADAR-1 deaminase.

The present study shows that HTLV-2 and STLV-3, two primate retroviruses, can be massively edited by ADAR-1 in cell culture. For HTLV-2, the selective and sensitive 3DI-PCR method was necessary to recover ADAR-1-edited sequences. By contrast ADAR-1-edited STLV-3 sequences were recovered after conventional nested-PCR. Since 293T cells were used for both experiments and since HTLV-2 and STLV-3 sequences were cloned in the same backbone SV2neo vector, this differential sensitivity to ADAR-1 is likely to be related to the viral genome. HTLV-2 and STLV-3 have different genetic structure at the 3′ end of their genome, although none of their gene products are known to be IFN antagonists. Another variable could be the degree of secondary structure in the target sequence. Indeed, ADAR-1 editing occurs by flipping out the adenosine in a dsRNA structure. Local structural differences might therefore explain the differences between HTLV-2 and STLV-3 results. If ADAR-1 was packaged more efficiently into STLV-3 capsids, the viral genome would probably be more efficiently edited. In any case, the susceptibility of STLV-3 to restriction by ADAR-1 is striking. The present data do not exclude editing of viral mRNAs in the cytoplasm as opposed to editing of genomic RNA within the virion.

The contrasts between the ADAR-1 and APOBEC3G editing enzymes are remarkable. Indeed, both are induced by IFN-α and target HTLV-1 or HIV-1 retroviruses. While these two retroviruses infect the same $CD4^+$ T-lymphocytes, ADAR-1 massively edits HTLV-2 sequences *in vitro*, albeit at low frequency. While recent work has shown that HIV-1 can be edited by ADAR-1, very few A⟶G mutations could be detected (Doria *et al.*, 2009; Phuphuakrat *et al.*, 2008). Of note, we also failed to detect massive editing of HIV-1 *TAR* or *env* RNA with our 3DI-PCR approach (data not shown). In contrast, in the absence of Vif, HIV-1 cDNA is massively edited by APOBEC3G and 3DPCR(Suspène *et al.*, 2005) is not needed to recover these sequences. By contrast, HTLV-1 cDNA is susceptible to APOBEC3G editing, but sensitive 3DPCR is necessary to recover edited sequences.

In conclusion, the present observation demonstrates that ADAR-1 massively edits HTLV-2 and STLV-3 retroviruses *in vitro*, but probably remains a rare phenomenon *in vivo*.

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References

Bass, B. L. (1997). RNA editing and hypermutation by adenosine deamination. *Trends Biochem Sci* **22**, 157–162.

Bass, B. L. (2002). RNA editing by adenosine deaminases that act on RNA. *Annu Rev Biochem* **71**, 817–846.

Calattini, S., Chevalier, S. A., Duprez, R., Afonso, P., Froment, A., Gessain, A. & Mahieux, R. (2006). Human T-cell lymphotropic virus type 3: complete nucleotide sequence and characterization of the human tax3 protein. *J Virol* **80**, 9876–9888.

Cattaneo, R., Rebmann, G., Schmid, A., Baczko, K., ter Meulen, V. & Billeter, M. A. (1987). Altered transcription of a defective measles virus genome derived from a diseased human brain. *EMBO J* **6**, 681–688.

Cattaneo, R., Schmid, A., Eschle, D., Baczko, K., ter Meulen, V. & Billeter, M. A. (1988). Biased hypermutation and other genetic changes in defective measles viruses in human brain infections. *Cell* **55**, 255–265.

Chen, I. S., Quan, S. G. & Golde, D. W. (1983). Human T-cell leukemia virus type II transforms normal human lymphocytes. *Proc Natl Acad Sci U S A* **80**, 7006–7009.

Chen, C. X., Cho, D. S., Wang, Q., Lai, F., Carter, K. C. & Nishikura, K. (2000). A third member of the RNA-specific adenosine deaminase gene family, ADAR3, contains both single- and double-stranded RNA binding domains. *RNA* **6**, 755–767.

Chevalier, S. A., Walic, M., Calattini, S., Mallet, A., Prévost, M. C., Gessain, A. & Mahieux, R. (2007). Construction and characterization of a full-length infectious simian T-cell lymphotropic virus type 3 molecular clone. *J Virol* **81**, 6276–6285.

Doria, M., Neri, F., Gallo, A., Farace, M. G. & Michienzi, A. (2009). Editing of HIV-1 RNA by the double-stranded RNA deaminase ADAR1 stimulates viral infection. *Nucleic Acids Res* **37**, 5848–5858.

Douceron, E., Kaidarova, Z., Miyazato, P., Matsuoka, M., Murphy, E. L. & Mahieux, R. (2012). HTLV-2 APH-2 expression is correlated with proviral load but APH-2 does not promote lymphocytosis. *J Infect Dis* **205**, 82–86.

Felder, M. P., Laugier, D., Yatsula, B., Dezélée, P., Calothy, G. & Marx, M. (1994). Functional and biological properties of an avian variant long terminal repeat containing multiple A to G conversions in the U3 sequence. *J Virol* **68**, 4759–4767.

George, C. X. & Samuel, C. E. (1999). Human RNA-specific adenosine deaminase ADAR1 transcripts possess alternative exon 1 structures that initiate from different promoters, one constitutively active and the other interferon inducible. *Proc Natl Acad Sci U S A* **96**, 4621–4626.

Grande-Pérez, A., Sierra, S., Castro, M. G., Domingo, E. & Lowenstein, P. R. (2002). Molecular indetermination in the transition to error catastrophe: systematic elimination of lymphocytic choriomeningitis virus through mutagenesis does not correlate linearly with large increases in mutant spectrum complexity. *Proc Natl Acad Sci U S A* **99**, 12938–12943.

Hajjar, A. M. & Linial, M. L. (1995). Modification of retroviral RNA by double-stranded RNA adenosine deaminase. *J Virol* **69**, 5878–5882.

Lehmann, K. A. & Bass, B. L. (2000). Double-stranded RNA adenosine deaminases ADAR1 and ADAR2 have overlapping specificities. *Biochemistry* **39**, 12875–12884.

Li, Y., Kappes, J. C., Conway, J. A., Price, R. W., Shaw, G. M. & Hahn, B. H. (1991). Molecular characterization of human immunodeficiency virus type 1 cloned directly from uncultured human brain tissue: identification of replication-competent and -defective viral genomes. *J Virol* **65**, 3973–3985.

Liu, Y., George, C. X., Patterson, J. B. & Samuel, C. E. (1997). Functionally distinct double-stranded RNA-binding domains associated with alternative splice site variants of the interferon-inducible double-stranded RNA-specific adenosine deaminase. *J Biol Chem* **272**, 4419–4428.

Mahieux, R. & Gessain, A. (2011). HTLV-3/STLV-3 and HTLV-4 viruses: discovery, epidemiology, serology and molecular aspects. *Viruses* **3**, 1074–1090.

Martínez, I., Dopazo, J. & Melero, J. A. (1997). Antigenic structure of the human respiratory syncytial virus G glycoprotein and relevance of hypermutation events for the generation of antigenic variants. *J Gen Virol* **78**, 2419–2429.

Melcher, T., Maas, S., Herb, A., Sprengel, R., Higuchi, M. & Seeburg, P. H. (1996). RED2, a brain-specific member of the RNA-specific adenosine deaminase family. *J Biol Chem* **271**, 31795–31798.

Murphy, D. G., Dimock, K. & Kang, C. Y. (1991). Numerous transitions in human parainfluenza virus 3 RNA recovered from persistently infected cells. *Virology* **181**, 760–763.

O'Hara, P. J., Nichol, S. T., Horodyski, F. M. & Holland, J. J. (1984). Vesicular stomatitis virus defective interfering particles can contain extensive genomic sequence rearrangements and base substitutions. *Cell* **36**, 915–924.

Patterson, J. B., Cornu, T. I., Redwine, J., Dales, S., Lewicki, H., Holz, A., Thomas, D., Billeter, M. A. & Oldstone, M. B. (2001). Evidence that the hypermutated M protein of a subacute sclerosing panencephalitis measles virus actively contributes to the chronic progressive CNS disease. *Virology* **291**, 215–225.

Phuphuakrat, A., Kraiwong, R., Boonarkart, C., Lauhakirti, D., Lee, T. H. & Auewarakul, P. (2008). Double-stranded RNA adenosine deaminases enhance expression of human immunodeficiency virus type 1 proteins. *J Virol* **82**, 10864–10872.

Rueda, P., García-Barreno, B. & Melero, J. A. (1994). Loss of conserved cysteine residues in the attachment (G) glycoprotein of two human respiratory syncytial virus escape mutants that contain multiple A-G substitutions (hypermutations). *Virology* **198**, 653–662.

Samuel, C. E. (2001). Antiviral actions of interferons. *Clin Microbiol Rev* **14**, 778–809.

Slattery, J. P., Franchini, G. & Gessain, A. (1999). Genomic evolution, patterns of global dissemination, and interspecies transmission of human and simian T-cell leukemia/lymphotropic viruses. *Genome Res* **9**, 525–540.

Suspène, R., Henry, M., Guillot, S., Wain-Hobson, S. & Vartanian, J. P. (2005). Recovery of APOBEC3-edited human immunodeficiency virus G→A hypermutants by differential DNA denaturation PCR. *J Gen Virol* **86**, 125–129.

Suspène, R., Renard, M., Henry, M., Guétard, D., Puyraimond-Zemmour, D., Billecocq, A., Bouloy, M., Tangy, F., Vartanian, J. P. & Wain-Hobson, S. (2008). Inversing the natural hydrogen bonding rule to selectively amplify GC-rich ADAR-edited RNAs. *Nucleic Acids Res* **36**, e72.

Suspène, R., Petit, V., Puyraimond-Zemmour, D., Aynaud, M. M., Henry, M., Guétard, D., Rusniok, C., Wain-Hobson, S. & Vartanian, J. P. (2011). Double-stranded RNA adenosine deaminase ADAR-1-induced hypermutated genomes among inactivated seasonal influenza and live attenuated measles virus vaccines. *J Virol* **85**, 2458–2462.

Taylor, D. R., Puig, M., Darnell, M. E., Mihalik, K. & Feinstone, S. M. (2005). New antiviral pathway that mediates hepatitis C virus replicon interferon sensitivity through ADAR1. *J Virol* **79**, 6291–6298.

Tenoever, B. R., Ng, S. L., Chua, M. A., McWhirter, S. M., García-Sastre, A. & Maniatis, T. (2007). Multiple functions of the IKK-related kinase IKKε in interferon-mediated antiviral immunity. *Science* **315**, 1274–1278.

Wang, Y. & Samuel, C. E. (2009). Adenosine deaminase ADAR1 increases gene expression at the translational level by decreasing protein kinase PKR-dependent eIF-2α phosphorylation. *J Mol Biol* **393**, 777–787.

Wang, Y., Zeng, Y., Murray, J. M. & Nishikura, K. (1995). Genomic organization and chromosomal location of the human dsRNA adenosine deaminase gene: the enzyme for glutamate-activated ion channel RNA editing. *J Mol Biol* **254**, 184–195.

Wattel, E., Vartanian, J. P., Pannetier, C. & Wain-Hobson, S. (1995). Clonal expansion of human T-cell leukemia virus type I-infected cells in asymptomatic and symptomatic carriers without malignancy. *J Virol* **69**, 2863–2868.

Wong, T. C., Ayata, M., Hirano, A., Yoshikawa, Y., Tsuruoka, H. & Yamanouchi, K. (1989). Generalized and localized biased hypermutation affecting the matrix gene of a measles virus strain that causes subacute sclerosing panencephalitis. *J Virol* **63**, 5464–5468.

Wong, T. C., Ayata, M., Ueda, S. & Hirano, A. (1991). Role of biased hypermutation in evolution of subacute sclerosing panencephalitis virus from progenitor acute measles virus. *J Virol* **65**, 2191–2199.