Biochemical and Biophysical Research Communications 377 (2008) 170–175

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Characterization of ADAR1-mediated modulation of gene expression

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ARTICLE INFO

Article history:
Received 10 September 2008
Available online 7 October 2008

Keywords:
RNA editing
dsRNA-specific adenosine deaminase
Reporter gene expression
Inosine
ADAR
Adenosine deamination

ABSTRACT

Conversion of adenosine into inosine in RNA molecules constitutes an important post-transcriptional mechanism for generating transcript diversity and is catalyzed by adenosine deaminases acting on RNA (ADARs). Intriguingly, we observed that the editing enzyme ADAR1 enhances reporter gene expression in a cellular, plasmid-based system. The induction of gene expression is independent of the used reporter transgene or the promoter type, but relies on the RNA editing activity and specificity of ADAR1. More detailed analysis indicates that the effect is due to enhanced reporter gene transcription. Induction of gene expression by ADAR1 is lost when the reporter expression cassette is placed in a chromosomal environment. Our results suggest that a cellular, ADAR1-specific RNA editing substrate causes upregulation of plasmid-based gene expression.

A-to-I RNA editing is an important process for generating transcript and protein diversity in mammals. Adenosines (A) in partially double-stranded RNA molecules can be converted into inosine (I), which is consequently interpreted as guanosine by the translation machinery. Editing events can therefore result in codon changes if the targeted adenosine is located within the translated region of an mRNA molecule. These codon changes have pronounced effects on protein product function [1,2]. Thirteen mammalian genes have been discovered so far where editing results in a codon alteration [2,3]. The regulation of protein function through single A-to-I substitutions in mRNA constitutes an important cellular role of RNA editing [2].

A-to-I editing also occurs in non-coding RNA molecules. Recently, editing has been detected in miRNA transcripts with diverse effects, such as inhibition in miRNA processing or altered substrate recognition [4]. A-to-I editing can also have an impact on the processing of RNA molecules, including alterations of splice sites [5] or nuclear retention of edited transcripts [6]. Interestingly, we and others have shown that in human the majority of editing events occur in Alu repeats present in untranslated regions of pre-mRNA molecules [7–9], with yet unknown functional consequences.

The editing reaction is catalyzed by the family of adenosine deaminases acting on RNA (ADARs). ADAR1 and ADAR2 recognize distinct substrates with an overlapping specificity, while no editing activity for ADAR3 has been observed to date [1,10,11]. The ADAR1 gene encodes for two major protein variants, a large 150 kDa protein (ADAR1-p150) and a smaller 110 kDa protein (ADAR1-p110). Both variants contain three double-stranded (ds)RNA-binding domains and the deaminase domain, yet ADAR1-p110 lacks the Z-DNA binding domains that are present in ADAR1-p150 [12]. Also, ADAR1-p150 is interferon inducible and shuttles between the nucleus and cytoplasm [12] .

Besides the presence of a dsRNA structure [13], there are several additional characteristics of editing substrates that can be used to computationally predict novel editing sites [3]. When a novel site is discovered, a common approach to subsequently evaluate the functional consequences of editing is by performing transient co-transfections into mammalian cells, using plasmids that encode an individual ADAR together with an expression vector that contains the editing substrate [14–17].

Interestingly, we demonstrate in this study that ADAR1-p150 as well as ADAR1-p110, but not ADAR2, can induce the expression of genes when assayed in a plasmid-based cellular transfection system. This induction of gene expression was observed using different reporter genes and different promoter types and was dependent on the editing activity of ADAR1. In addition, we show that the increased gene expression is due to direct alterations in transcriptional activity. Most importantly, in the context of promoters embedded within chromatin, this effect was not observed, indicating that ADAR1 is not likely to influence endogenous gene transcription under physiological conditions. We therefore propose that transient overexpression of ADAR1 may result in the editing of an as yet unknown ADAR1-specific substrate, which subsequently upregulates plasmid-based gene expression.

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doi:10.1016/j.bbrc.2008.09.109

Methods

Cell culture. The human cervical cancer cell line HeLa (ATCC CCL-2) and the human embryonic kidney cell line 293 (ATCC CRL-1573) were cultured under standard conditions. The generated stable cell lines were cultured similarly, but with the addition of 200 μg/ml geneticin G-418 sulfate (Teknova, Hollister, CA) to the culture medium.

Constructs. The construction of the ADAR1-p150 and ADAR2-encoding plasmids are described in detail elsewhere [18]. To obtain ADAR1-p110, the ADAR1-p150 construct was restricted with BglII to remove the Z-DNA binding domains. Subsequently, site-directed mutagenesis with the primers 5′-CGATGACGATAAGAGATCTCTT GAGCCTTTTATTGC-3′ and 5′-GCAATAAAAGGCTCAAGAGATCTCTTA TCGTCATCG-3′ was performed to remove a thymidine, restoring the correct ADAR1-p110 open reading frame.

To generate a catalytically inactive ADAR1 protein, the amino acid sequence CHAE in the catalytic domain of ADAR1-p150 was replaced with the sequence SQAD. This alteration has been shown previously to abolish the editing activity of ADARs [19]. Altering this amino acid sequence was accomplished by site-directed mutagenesis with the primers 5′-GGAGAAACTGTCAATGACTCCCA AGCAGATATAATCTCCCGGAGAGG-3′ and 5′- CCTCTCCGGGAGATTA TATCTGCTTGGGAGTCATTGACAGTTTCTCC-3′.

The luciferase-expressing reporter constructs used in this study are all commercially available. The effect of the ADAR proteins on the SV40, HSV-TK or CMV promoter was tested using the vectors pRL-CMV, psiCHECK-2, or pGL3-control (Promega, Madison, WI). The effect of the ADAR proteins on GFP was examined using pEGFP-C2 (Clontech, Mountain view, CA), the effect on firefly luciferase was tested using respectively psiCheck-2 or pGL3-control (Promega), and the effect of the different ADAR proteins on *Renilla* luciferase was tested using either psiCheck-2 or pRL-CMV (Promega).

Generation of stable cell lines. To examine the effect of the different ADAR proteins on transcription in the context of chromosomal DNA, stably transfected HeLa and 293 cell lines were generated. The cell lines were transfected with a plasmid containing the HSV-TK firefly luciferase expression cassette from siCHECK-2 (Promega) which was incorporated into the pCI-neo plasmid (Promega). Stable transfections were performed using Superfect Transfection Reagent (Qiagen) according to the manufacturer's instructions. After 48 h, the transfected cells were plated at a low density to allow for the selection of single clones.

Transient transfections. To determine the effect of different ADAR proteins on transgene expression, transient transfections were performed in native Hela or 293 cell lines, or in (HeLa or 293) cells stably expressing a reporter construct. All transfections were performed using Superfect Transfection Reagent (Qiagen, Valencia, CA) according to the manufacturer's instructions.

For the co-transfections, a GFP or luciferase-expressing reporter plasmid and a plasmid containing one of the ADAR variants were combined prior to transfection. For each experiment, the total amount of DNA consisted of 40% reporter plasmid and 60% ADAR plasmid. When the amount of ADAR plasmid was altered, the difference was adjusted with the empty vector pCI-neo (Promega), such that the amount of transfected DNA was constant. For the stable cell lines, cells were transiently transfected with either pCI-neo or with an ADAR plasmid. Again, when the amount of ADAR-expressing plasmid was altered, the difference was adjusted with the empty vector pCI-neo

After 24–48 h, the cells were either monitored for GFP expression or lysed with cell culture lysis buffer (Promega) and the lysates were analyzed for luciferase activity on a luminometer (Thermo Fisher Scientific, Waltham, MA). All values are depicted as percentage luciferase activity compared to the same transfection with the empty vector pCI-neo (Promega) instead of the ADAR-expressing plasmid.

Expression of the proteins was confirmed using immuno-fluorescence microscopy. For the detection of recombinant ADAR proteins, cells were transfected with ADAR1-p150-, ADAR1-p110-, ADAR2, or the ADAR1-p150 mutant SQAD-encoding plasmid using Superfect Transfection Reagent (Qiagen). After 48 h, the cells were fixated with 3.2% formaldehyde. Expression of all proteins was confirmed by immuno-staining against the FLAG epitope-tag using the anti-FLAG M2 monoclonal antibody (Sigma-Aldrich, St Louis, MO) and an anti-mouse secondary antibody conjugated to Cy3 (Jackson Immunoresearch, PA).

Quantitative analysis of reporter RNA levels. The RNA levels of *Renilla* luciferase and firefly luciferase were analyzed to determine if the observed enhancement in gene expression was due to an increase in transcriptional activity. To this end, HeLa cells were transfected with the reporter vector siCheck-2 (Promega) in combination with either the empty vector pCI-neo (Promega) or with a plasmid expressing ADAR1-p150. The total DNA amount consisted of 40% reporter plasmid and either 60% pCI-neo, or 45% pCI-neo and 15% ADAR1-p150 expressing plasmid. All transfections were performed using Superfect Transfection Reagent (Qiagen) according to the manufacturer's instructions.

After 48 h, the isolated RNA was treated several times with DNAse (Promega). The RNA was reverse transcribed and subsequent real-time PCRs were performed using the Power SYBR Green PCR master mix (Applied Biosystems, Foster city, CA) and the 7300 real-time PCR system (Applied Biosystems) according to the manufacturer's protocol. The primers for *Renilla* luciferase were 5′-GGC AGGTGTCCACTCCCAGTTCAATT-3′ and 5′-CAG TGATCATGCGTTTGC GTTGCT-3′ and for firefly luciferase 5′-GTCT ACCGGCCTGCCTAAG-3′ and 5′-ATGGCACCACGCTCAGAATA-3′. All samples were analyzed in triplicate and normalized against 18S rRNA (Ambion, Austin, TX). Values are expressed as fold increase in comparison to cells transfected with the reporter vector together with the empty plasmid pCI-neo according to the $\Delta\Delta C_t$ method.

Results and discussion

Enhancement of reporter gene expression by ADAR1 is independent of promoter type or reporter gene

Initially, we observed the effect of ADAR1-p150 on gene expression when using a plasmid expressing the green fluorescent protein (GFP) under the control of the CMV promoter. Co-transfection in HeLa cells with an ADAR1-p150 expressing plasmid resulted in a clear increase in GFP expression in comparison to co-transfection of the same GFP-expressing plasmid with an empty vector (Fig. 1A). To investigate whether this effect was restricted to this single reporter construct and to quantify the effect of ADAR1-p150 on transgene expression we subsequently explored the effect of ADAR1-p150 on several luciferase-based reporters. In each experiment, we co-transfected the reporter expression cassette with either an ADAR-expressing plasmid or, as a control, with an empty pCI-neo vector.

First, plasmids containing the SV40 promoter controlling either the firefly luciferase gene (derived from *Photinus pyralis*) or the *Renilla* luciferase gene (derived from *Renilla reniformis*) were co-transfected with the ADAR1-p150 encoding plasmid. Firefly and *Renilla* luciferase are only weakly related in sequence sharing 35.5% nucleotide identity and only 11.9% identity on the amino acid level. ADAR1-p150 caused a two to fourfold increase in both firefly and *Renilla* luciferase activity (Fig. 1B). Thus, the fact that we observe induction of gene expression by ADAR1-p150 with

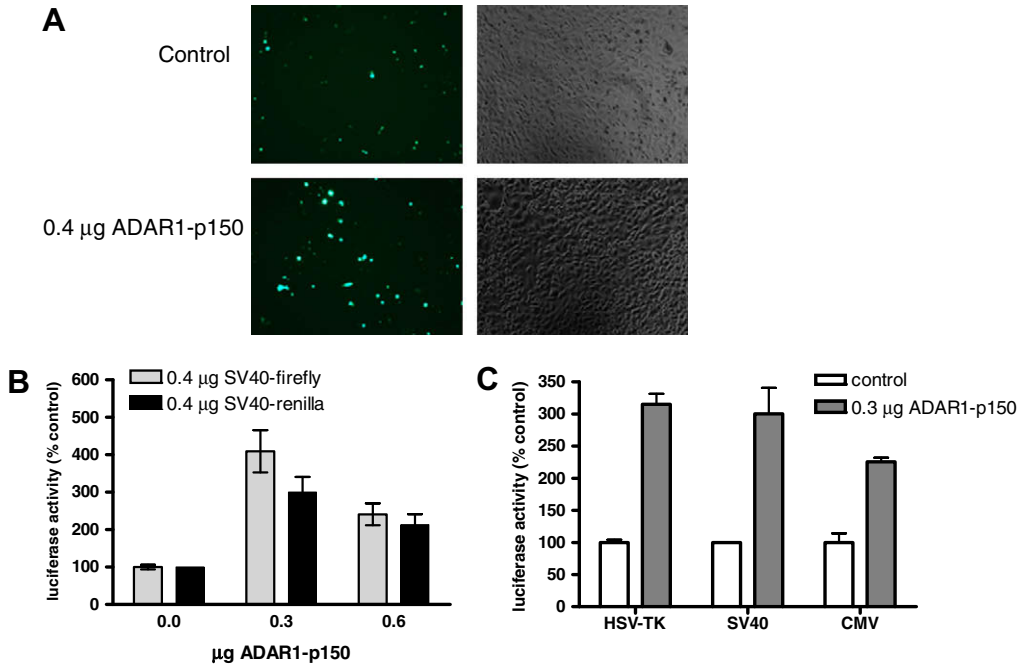

Fig. 1. ADAR1-p150 induces transgene expression independent of promoter or transgene type. (A) A GFP-encoding plasmid was co-transfected with either an empty vector or with an ADAR1-p150 expressing plasmid. After 48 h, GFP expression was monitored microscopically and representative pictures were taken. The experiment was performed in duplicate and repeated three times. (B) The ADAR1-p150 encoding plasmid was co-transfected with a plasmid containing the SV40 promoter controlling the expression of either firefly or *Renilla* luciferase. After 48 h, the transfected HeLa cells were lysed and luciferase expression was analyzed. Transfections were performed in duplicate and the experiments were repeated at least three times. A representative experiment is shown. (C) HeLa cells were co-transfected with an ADAR1-p150 expressing plasmid and a plasmid containing a luciferase gene under the control of respectively the SV40, HSV-TK, or CMV promoter. The cells were lysed 48 h after transfection and luciferase expression was analyzed at a later time point. All transfections were performed in duplicate. The experiments were repeated at least three times and a representative experiment is shown. The data are depicted as percentage luciferase expression, in comparison to transfection with an empty vector together with the same reporter plasmid.

three independent reporter genes suggests that this effect is not RNA-transcript specific.

Next, we evaluated if ADAR1-induced gene expression was limited to specific promoter types. To this end, we co-transfected an ADAR1-p150 expressing plasmid together with a luciferase reporter gene under the control of either a SV40, CMV, or HSV-TK promoter into human HeLa cells. We observed, a more than threefold (SV40 and HSV-TK) or more than twofold (CMV) increase in luciferase expression after co-transfection with ADAR1-p150 in comparison to the empty control vector (Fig. 1C).

The enhancement in luciferase expression was not limited to a single cell type, but also occurred when performing the same experiment using human embryonic kidney (HEK 293) cells (data not shown).

Interestingly, a promoter-specific upregulation of gene expression by ADAR1 has been reported previously [20]. Nie et al. concluded that the enhanced gene expression was due to the interaction between ADAR1 and the transcription factor nuclear factor 90 (NF90). In contrast, we observed an induction in reporter gene expression with every promoter tested, and our data does therefore not support the mechanism suggested by Nie et al. [20]. Rather, the promoter type independent upregulation of reporter gene expression by ADAR1 described in this study suggests a molecular mechanism that is not restricted to a transcription factor specific interaction.

Induced transgene expression is specific for ADAR1

There are two mammalian pre-mRNA editing enzymes known to convert adenosine into inosine in vivo, ADAR1 and ADAR2 [11,21]. To investigate whether ADAR2 could also enhance luciferase gene expression, cells were co-transfected with a luciferase reporter and an ADAR2-expression plasmid. Interestingly, at the same concentration where ADAR1 showed a substantial induction in luciferase activity, no such effect was seen with ADAR2 (Fig. 2A) for all promoters tested.

Subsequently, we investigated the two main ADAR1 protein variants in mammalian cells: the interferon-inducible ADAR1-p150 and the constitutively expressed ADAR1-p110 [12].

In comparison to the control, luciferase expression increased after ADAR1-p110 co-transfection in a similar fashion as with ADAR1-p150 (Fig. 2B). The increase was also not dependent on the type of promoter, but occurred with both the HSV-TK as well as the SV40 promoter. This suggests that the observed effect is not mediated by the Z-DNA binding domains that are unique to ADAR1-p150. Also, this is further supported by the notion that co-transfection of the reporter plasmid with a plasmid encoding solely the Z-DNA binding domains of ADAR1-p150 did not increase luciferase activity (data not shown).

Editing activity as well as dsRNA-binding contributes to the enhancement of transgene expression

To establish whether the observed induction in luciferase activity is dependent on ADAR1 editing activity, a catalytically inactive protein variant was generated. In ADAR1-SQAD the amino acid sequence CHAE is replaced by the sequence SQAD within the catalytic domain, which abolishes editing activity [19].

Interestingly, ADAR1-SQAD did not cause the profound induction of luciferase activity as seen with ADAR1-p150 wildtype in a co-transfection experiment with an SV40-luciferase encoding plasmid, which strongly indicates that RNA editing activity is required for this effect.

With increasing concentrations of ADAR1-SQAD plasmid, we did observe a small-scale, dose-dependent increase in luciferase expression, in comparison to the control (Fig. 3A). To a lesser ex-

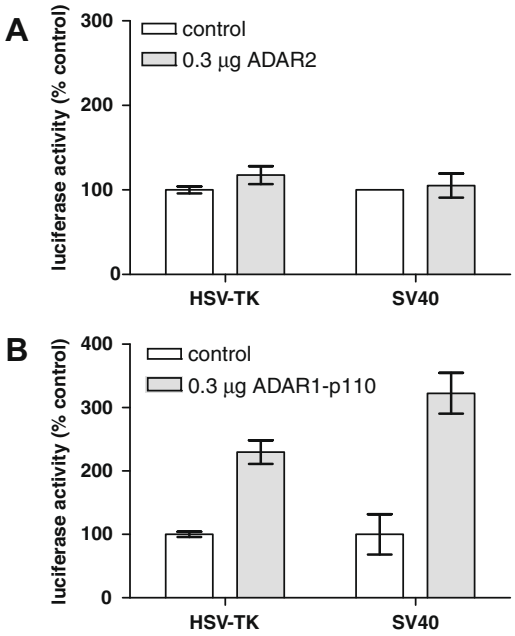

Fig. 2. ADAR1–p110 but not ADAR2 can induce transgene expression. Forty eight hours after co-transfection with a luciferase-expressing reporter plasmid and the ADAR2 (A) or ADAR1-p110 (B) encoding plasmid, cells were lysed and luciferase expression was analyzed. All transfections were performed in duplicate. The experiments were repeated at least two times and a representative experiment is shown. Data are shown as percentage luciferase expression, in comparison to co-transfection with the same reporter plasmid and an empty control vector.

tent, this dose-dependent induction in luciferase expression was also observed when analyzing the effect of ADAR1-SQAD on HSV-TK promoter-controlled luciferase expression (Fig. 3B). These data may indicate that sequestration of dsRNA by increasing amounts of ADAR1 could lead to a slight increase in luciferase expression also in the absence of RNA editing activity, potentially by reducing the availability of dsRNA for other proteins. For example, the double-stranded RNA-activated protein kinase PKR requires binding of dsRNA for activation, and in turn, represses protein expression [22]. This idea is further supported by the finding that ADAR2 slightly induced firefly expression as well when increasing ADAR2 concentrations are used (Fig. 3B).

In contrast, the pronounced effect exerted specifically by ADAR1-p150 and ADAR1-p110 occurs at low concentrations (Fig. 3) and was not seen with ADAR1-SQAD. Therefore, our data suggest that ADAR1 may edit a specific substrate that in turn, directly or indirectly, activates gene expression. At this time that substrate is unknown and it is therefore not possible to assess if it is targeted by endogenous levels of ADAR1.

ADAR1-induced gene expression is due to an enhancement in gene transcription and only affects exogenous transgene expression

To investigate the effect of ADAR1-p150 in more detail, we analyzed potential changes in the RNA levels of *Renilla* and firefly luciferase using quantitative PCR. As shown in Fig. 4A, co-transfection of ADAR1-p150 with a *Renilla* and firefly luciferase-expressing plasmid results in a two to threefold increase in luciferase RNA levels, compared to co-transfection with an empty vector. The changes in RNA levels therefore indicate that ADAR1-p150 either has a direct influence on transcriptional activity or might generally increase RNA stability.

To investigate the underlying mechanism for the ADAR1-induced expression, we established a stable HeLa cell line that expresses the firefly luciferase gene under the control of the HSV-

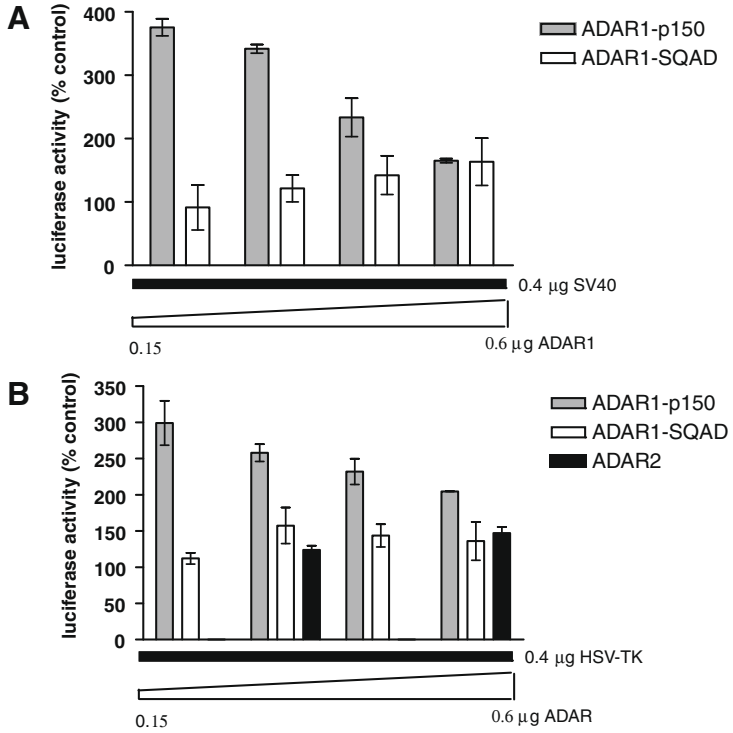

Fig. 3. Induction in luciferase expression is predominantly due to the editing activity of ADAR1. HeLa cells were transfected with different concentrations of a plasmid containing the editing-inactive ADAR1-SQAD, ADAR2, or ADAR1-p150 gene, together with a reporter plasmid. The reporter plasmid contained either the SV40 promoter (A) or the HSV-TK promoter (B) controlling the expression of luciferase. Cells were lysed 48 h after transfection and luciferase expression was quantified. All transfections were performed in duplicate. The experiments were repeated at least three times and one representative experiment is shown. The data are depicted as percentage luciferase expression, in comparison to the co-transfection of the same reporter plasmids with an empty control vector.

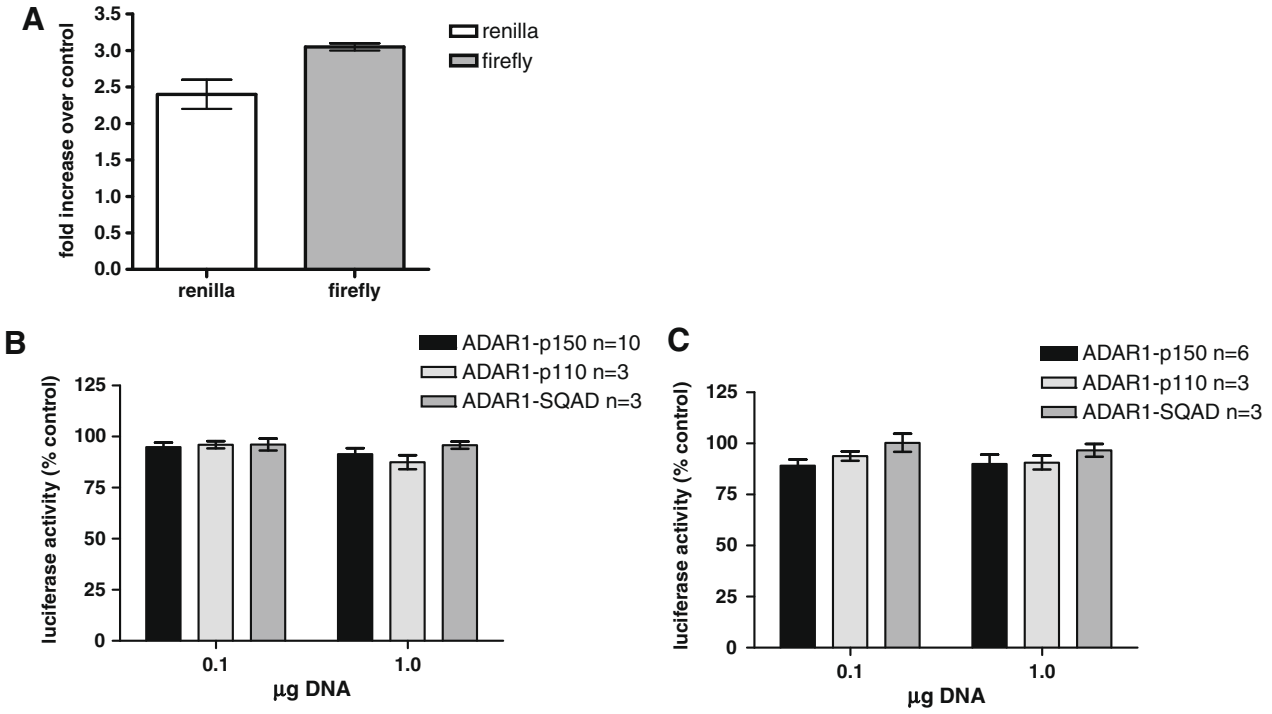

Fig. 4. ADAR1-p150 influences gene transcription in a plasmid-based system only. (A) RNA isolated from HeLa cells 48 h after co-transfection with a reporter plasmid expressing *Renilla* and firefly luciferase together with a plasmid expressing ADAR1-p150 or an empty vector. The RNA was reverse transcribed and the amount of *Renilla* and firefly cDNA was analyzed using real-time PCR. Values were normalized against 18 S rRNA and the data are depicted as fold increase over co-transfection with the empty vector. Stable HeLa (B) and 293 (C) cell lines were generated that expressed the luciferase gene under the control of the HSV-TK promoter in a chromosomal context. These cell lines were transfected with an empty vector, ADAR1-150, ADAR1-p110, or the editing-inactive variant ADAR1-SQAD. Cells were lysed 24 h after transfection and luciferase expression was measured at a later time point. Experiments are repeated as indicated in the graph and the mean of all experiments is shown. Data are expressed as percentage luciferase expression, in comparison to transfection with an empty control vector.

TK promoter. Intriguingly, using different plasmid concentrations, neither ADAR1-p150, ADAR1-p110, nor ADAR1-SQAD increased firefly luciferase expression in comparison to cells transfected with an empty control vector (Fig. 4B). To exclude that the absence of induction was due to the position of integration of the reporter or due to the cell type, we also generated stably transfected 293 cells, expressing the same reporter. In agreement with the results for the HeLa cell line, we observed no alteration in luciferase expression after transfection with ADAR1 (Fig. 4C). In addition, neither ADAR2, ADAR3, nor the Z-domains did influence luciferase expression (see Supplementary Figure 1).

Since the RNA transcripts derived from transiently transfected or chromosomally integrated reporter plasmids are the same, an alteration in the processing of the RNA molecules (such as RNA degradation) could not explain the effect exerted by ADAR1. Instead, our results indicate that reporter gene transcription is enhanced due to ADAR1-specific RNA editing activity.

Previously, it was suggested that ADAR1 can regulate transcription by interaction with NF90 [20]. However, regulation of gene expression by ADAR1-NF90 was not investigated under physiological conditions. We clearly show here that the increase in gene expression observed in transient co-transfections with ADAR1 is lost when the expression cassette is placed in a chromosomal context. This indicates that the suggested interaction between ADAR1 and NF90 by Nie et al. [20] may not reflect a physiological mechanism involving ADAR1 in vivo. Our finding that RNA editing activity is essential for ADAR1-induced gene expression further suggests a different molecular mechanism. Based on our data, we propose that overexpressed ADAR1 specifically edits a yet unknown cellular substrate, which in turn affects plasmid-based gene expression.

Acknowledgment

We are grateful to Dr. Jutta Marzillier for her help with the real-time PCR experiments.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bbrc.2008.09.109.

References

[1] B.L. Bass, RNA editing by adenosine deaminases that act on RNA, Annu. Rev. Biochem. 71 (2002) 817–846.
[2] W.M. Gommans, D.E. Dupuis, J.E. McCane, N.E. Tatalias, S. Maas, Diversifying exon code through A-to-I RNA editing, in: H.C. Smith (Ed.), RNA and DNA Editing, Wiley & Sons, Inc., New York, 2008. p. 27.
[3] W.M. Gommans, N.E. Tatalias, C. Sie, D. Dupuis, N. Vendetti, L. Smith, R. Kaushal, S. Maas, Screening of human SNP database identifies recoding sites of A-to-I RNA editing, RNA 14 (2008) 11.
[4] K. Nishikura, Editor meets silencer: crosstalk between RNA editing and RNA interference, Nat. Rev. Mol. Cell Biol. 7 (2006) 919–931.
[5] S.M. Rueter, T.R. Dawson, R.B. Emeson, Regulation of alternative splicing by RNA editing, Nature 399 (1999) 75–80.
[6] K.V. Prasanth, S.G. Prasanth, Z. Xuan, S. Hearn, S.M. Freier, C.F. Bennett, M.Q. Zhang, D.L. Spector, Regulating gene expression through RNA nuclear retention, Cell 123 (2005) 249–263.
[7] A. Athanasiadis, A. Rich, S. Maas, Widespread A-to-I RNA editing of Alu-containing mRNAs in the human transcriptome, PLoS Biol. 2 (2004) e391.
[8] D.D. Kim, T.T. Kim, T. Walsh, Y. Kobayashi, T.C. Matise, S. Buyske, A. Gabriel, Widespread RNA editing of embedded alu elements in the human transcriptome, Genome Res. 14 (2004) 1719–1725.
[9] E.Y. Levanon, E. Eisenberg, R. Yelin, S. Nemzer, M. Hallegger, R. Shemesh, Z.Y. Fligelman, A. Shoshan, S.R. Pollock, D. Sztybel, M. Olshansky, G. Rechavi, M.F. Jantsch, Systematic identification of abundant A-to-I editing sites in the human transcriptome, Nat. Biotechnol. 22 (2004) 1001–1005.

[10] T. Melcher, S. Maas, A. Herb, R. Sprengel, M. Higuchi, P.H. Seeburg, RED2 a brain-specific member of the RNA-specific adenosine deaminase family, J. Biol. Chem. 271 (1996) 31795–31798.
[11] T. Melcher, S. Maas, A. Herb, R. Sprengel, P.H. Seeburg, M. Higuchi, A mammalian RNA editing enzyme, Nature 379 (1996) 460–464.
[12] C.X. George, C.E. Samuel, 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. USA 96 (1999) 4621–4626.
[13] M. Higuchi, F.N. Single, M. Kohler, B. Sommer, R. Sprengel, P.H. Seeburg, RNA editing of AMPA receptor subunit GluR-B: a base-paired intron-exon structure determines position and efficiency, Cell 75 (1993) 1361–1370.
[14] T. Bhalla, J.J. Rosenthal, M. Holmgren, R. Reenan, Control of human potassium channel inactivation by editing of a small mRNA hairpin, Nat. Struct. Mol. Biol. 11 (2004) 950–956.
[15] C.M. Burns, H. Chu, S.M. Rueter, L.K. Hutchinson, H. Canton, E. Sanders-Bush, R.B. Emeson, Regulation of serotonin-2C receptor G-protein coupling by RNA editing, Nature 387 (1997) 303–308.
[16] P. Vitali, E. Basyuk, E. Le Meur, E. Bertrand, F. Muscatelli, J. Cavaille, A. Huttenhofer, ADAR2-mediated editing of RNA substrates in the nucleolus is inhibited by C/D small nucleolar RNAs, J. Cell Biol. 169 (2005) 745–753.
[17] W. Yang, T.P. Chendrimada, Q. Wang, M. Higuchi, P.H. Seeburg, R. Shiekhattar, K. Nishikura, Modulation of microRNA processing and expression through RNA editing by ADAR deaminases, Nat. Struct. Mol. Biol. 13 (2006) 13–21.
[18] S. Maas, S. Patt, M. Schrey, A. Rich, Underediting of glutamate receptor GluR-B mRNA in malignant gliomas, Proc. Natl. Acad. Sci. USA 98 (2001) 14687–14692.
[19] F. Lai, R. Drakas, K. Nishikura, Mutagenic analysis of double-stranded RNA adenosine deaminase, a candidate enzyme for RNA editing of glutamate-gated ion channel transcripts, J. Biol. Chem. 270 (1995) 17098–17105.
[20] Y. Nie, L. Ding, P.N. Kao, R. Braun, J.H. Yang, ADAR1 interacts with NF90 through double-stranded RNA and regulates NF90-mediated gene expression independently of RNA editing, Mol. Cell. Biol. 25 (2005) 6956–6963.
[21] M.A. O'Connell, S. Krause, M. Higuchi, J.J. Hsuan, N.F. Totty, A. Jenny, W. Keller, Cloning of cDNAs encoding mammalian double-stranded RNA-specific adenosine deaminase, Mol. Cell. Biol. 15 (1995) 1389–1397.
[22] C.E. Samuel, Antiviral actions of interferons, Clin. Microbiol. Rev. 14 (2001) 778–809. table of contents.