Apolipoprotein B mRNA-editing protein induces hepatocellular carcinoma and dysplasia in transgenic animals  
(cytidine deaminase/low density lipoprotein/oncogene/RNA processing)

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ABSTRACT Apolipoprotein (apo-) B mRNA editing is the deamination of cytidine that creates a new termination codon and produces a truncated version of apo-B (apo-B48). The cytidine deaminase catalytic subunit [apo-B mRNA-editing enzyme catalytic polypeptide 1 (APOBEC-1)] of the multi-protein editing complex has been identified. We generated transgenic rabbits and mice expressing rabbit APOBEC-1 in their livers to determine whether hepatic expression would lower low density lipoprotein cholesterol concentrations. The apo-B mRNA from the livers of the transgenic mice and rabbit was extensively edited, and the transgenic animals had reduced concentrations of apo-B100 and low density lipoproteins compared with control animals. Unexpectedly, all of the transgenic mice and a transgenic rabbit had liver dysplasia, and many transgenic mice developed hepatocellular carcinomas. Many of the mouse livers were hyperplastic and filled with lipid. Other hepatic mRNAs with sequence motifs similar to apo-B mRNA were examined for this type of editing (i.e., cytidine deamination). One of these, tyrosine kinase, was edited in livers of transgenic mice but not of controls. This result demonstrates that other mRNAs can be edited by the overexpressed editing enzyme and suggests that aberrant editing of hepatic mRNAs involved in cell growth and regulation is the cause of the tumorigenesis. Finally, these findings compromise the potential use of APOBEC-1 for gene therapy to lower plasma levels of low density lipoproteins.

Apolipoprotein (apo-) B mRNA editing is the deamination of a specific cytidine (nt 6666) to uridine in the apo-B transcript. This deamination changes a glutamine codon (CAA) to a termination codon (UAA) (1, 2) and results in the formation of an apo-B protein (apo-B48) about one-half the size of the full-length genomically encoded apo-B (apo-B100). In humans, the liver synthesizes apo-B100, the major protein component of plasma β-migrating low density lipoproteins (LDL). The small intestine produces apo-B48, a protein necessary for the secretion of chylomicrons (3–5). Lipoproteins containing apo-B48 are rapidly cleared from plasma and are not converted to LDL. In most mammals, apo-B mRNA editing occurs only in the small intestine, but in horses, rats, mice, and dogs, editing also occurs in the liver (6). Species with hepatic apo-B mRNA editing possess low plasma LDL concentrations (6), which suggests that expression of this activity in the livers of species lacking hepatic editing could lower LDL concentrations. Thus, induction of the expression of hepatic editing is a potential target for gene therapy to lower LDL and lipoprotein(a) concentrations (7, 8).

Whether apo-B mRNA editing physiologically modifies other mRNA substrates is unknown. However, if certain sequence motifs in the apo-B mRNA are inserted into a heterologous cDNA, the transcribed chimeric RNA can be edited in vitro (9, 10). Additionally, the occurrence of editing in cell lines and organs that do not synthesize significant amounts of apo-B suggests that editing may have other biological functions (11–13).

The apo-B mRNA editing enzyme is a multi-subunit complex (14–18). A single subunit that catalyzes the deamination was cloned recently (14) and designated apo-B mRNA-editing enzyme catalytic polypeptide 1 (APOBEC-1) (19). Besides APOBEC-1, one or more additional auxiliary protein components found in the liver and many other organs and cells are necessary for editing in vitro (16–18). Thus, in species devoid of hepatic editing activity, the hepatic expression of APOBEC-1 should be sufficient to generate edited apo-B mRNA.

To study the impact of hepatic apo-B mRNA editing on lipid metabolism and atherogenesis and to study other possible biological roles of apo-B mRNA editing, we developed transgenic mice and rabbits expressing editing activity in their livers.

MATERIALS AND METHODS

Generation of APOBEC-1 Transgenic Mice and Rabbits. A full-length cDNA fragment of rabbit APOBEC-1 was isolated from pREPR (18) by digestion with EcoRI and subcloned into pLlv11, which had been linearized with Mun I to produce the vector pLlvREPR. An Sal I–Spe I fragment of pLlvREPR was gel-purified by Qiagen (Qiagen, Chatsworth, CA) and micro-injected into fertilized oocytes of strain ICR mice (Charles River Breeding Laboratories) and New Zealand White rabbits (20). Founder pups were identified by Southern blot analysis of genomic DNA from mouse tails or rabbit ears with a 32P-labeled probe of rabbit APOBEC-1 cDNA. We estimated the transgene copy number by Southern blot analysis using the endogenous rabbit APOBEC-1 gene as a control.

Northern Blot Analysis. Total RNA (10 µg per lane) was isolated from tissues and analyzed by Northern blot as described (18).

Primer-Extension Analysis of Apo-B and Other mRNAs. Total RNA (5–10 µg) from liver was treated with RNase-free DNase I (1 unit) (Boehringer Mannheim) at 37°C for 15 min. After heat inactivation of DNase I (90°C for 10 min), the cDNA was prepared from this RNA using cDNA cycle kit (Invitrogen). Each mRNA sequence was amplified by PCR using primers described below, and the amplification product was purified by using MicroSpin S-300HR columns (Pharmacia). Two microliters of this product were analyzed by using a primer-extension assay to determine the relative proportions of edited and unedited mRNA (18). Primers used for PCR were M49mouse (CGATGCGATGACTGGGAGAGAACAGTCTG) and M50mouse (CGGATGATGACTGTTCATCAAGAA) for mouse

Abbreviations: apo-, apolipoprotein; LDL, low density lipoproteins; APOBEC-1, apo-B mRNA-editing enzyme catalytic polypeptide 1.

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apo-B, M49rabbit (CTGATGTCATTCCAATGGGAGAGAACTTCTCAAGAA) and M50rabbit (CGGATATGATAACGTGGGAGAGAACTTCTCAAGAA) for rabbit apo-B, FASU (TCCTGGGACCTTATCTCAAA) and FASL (CCATAGGTCGCCGCTTTT) for fatty acid synthase, P1U (CATTGCAAAAGGCTGGCATA) and P1L (TGAAGAGCAGTCAAATCTA) for P1 protein (P1), TECU (GGCATTTCTGAGACAGGAT) and TECL (GCACACAAACGCAAGACAG) for protein-tyrosine kinase (TEC), and TISU (TGTCAAAACCGTGGGGAATG) and TISL (AGTGTCAGAGTATGTC) for prostaglandin synthase. The locations of the primers for primer-extension analysis are indicated by underlining in Fig. 5A.

In Vitro Editing Assay. S100 extracts were prepared from five transgenic mice (I-20) and five age- and sex-matched control mice (21). A total of 5, 25, or 100 μg of S100 liver extract was incubated with substrate apo-B RNA for 2 hr at 30°C and analyzed by primer extension as described (18).

Histological Analysis. Livers were fixed with 4% formaldehyde, embedded in paraffin, and stained with either hematoxylin/eosin or trichrome stain for collagen. Histopathological diagnoses were based upon criteria described by Maronpot et al. (22).

Lipoprotein Analysis. For agarose gel analysis, 2 μl of plasma were separated by electrophoresis on a 1% agarose gel and stained with Fat Red 7B. For SDS/PAGE analysis, the d < 1.063 g/ml fraction was isolated from 1 ml of mouse plasma by ultracentrifugation. After dialysis against 5 mM ammonium bicarbonate, one-half of the sample was subjected to 5% SDS/PAGE and stained with Coomassie blue.

RESULTS AND DISCUSSION

To generate transgenic mice and rabbits expressing rabbit APOBEC-1, a full-length rabbit APOBEC-1 cDNA was subcloned into a vector (pLiv11) containing a promoter, an intron, and a hepatic control region, all from the human apoE gene. Other heterologous cDNAs previously cloned into this vector were expressed robustly and predominantly in the liver (20). A linearized fragment of this construct was used to generate three transgenic mouse founders and two transgenic rabbit founders. Additionally, transgenic mice were generated using a mutant form of APOBEC-1 that was enzymatically inactive. Four independent transgenic mouse lines (I-20, I-22, I-28L, and I-28H) were established from the three mouse founders expressing wild-type rabbit APOBEC-1, and their transgene copy numbers were estimated to be 7, 17, 3, and 10, respectively (Table 1). One transgenic rabbit founder had one copy of the transgene, and the other founder had 17 copies.

High levels of hepatic expression of the APOBEC-1 transgene mRNA were demonstrated by Northern blot analysis in all transgenic mouse lines. Trace amounts of transgenic APOBEC-1 mRNA also were found in the kidneys and heart (data not shown). Primer-extension analysis showed that hepatic apo-B mRNA from the transgenic mouse livers was edited extensively (Fig. 1). An average of 92% of apo-B mRNA was edited in the livers of all four transgenic mouse lines (n = 26). In the transgenic mouse line expressing the mutant transgene, no increase in the amount of edited apo-B mRNA (82%, n = 4) was observed over that of the nontransgenic mice (83%, n = 23).

Liver extracts from wild-type APOBEC-1 transgenic mice were 15-fold more active in editing a synthetic apo-B RNA substrate in vitro than liver extracts from age- and sex-matched control mice (Fig. 2). This finding demonstrated that APOBEC-1 was overexpressed, resulting in excess editing activity in the transgenic mouse livers. As expected, by agarose gel electrophoresis, β-migrating lipoproteins (LDL) were not detected in the plasma of the transgenic mice (Fig. 3A). The apparent lack of apo-B100 in the transgenic mouse lipoproteins was confirmed by SDS/PAGE (Fig. 3B).

The most striking phenotypic change in the transgenic mice was the finding of enlarged livers due to hepatic dysplasia and hepatocellular carcinoma (Table 1 and Fig. 4A). The livers of the transgenic mice were at least twice as large and, in some cases, 10 times larger than those of their nontransgenic littermates. One liver weighed 18 g, which was 40% of the weight of the entire mouse. Histological examination of the livers revealed that hepatocytes were dysplastic, exhibiting variations in nuclear and cellular morphology concomitant with changes in size and shape of both nucleus and cytoplasm, and clear cytoplasm filled with fat. Tumors with a trabecular pattern were diagnosed as hepatocellular carcinoma.

Table 1. Pathology of transgenic mouse livers

<table>
<thead>
<tr>
<th>Mouse lines</th>
<th>Mice studied, no.</th>
<th>Gene copy no.</th>
<th>Age at analysis, days</th>
<th>Liver/body weight ratios, % (n)</th>
<th>Normal–minimal dysplasia</th>
<th>Dysplasia with fatty change</th>
<th>Hepatocellular carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transgenic (wild-type)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-20</td>
<td>21</td>
<td>7</td>
<td>76–274</td>
<td>12.0 (16)</td>
<td>0</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>I-22</td>
<td>5</td>
<td>17</td>
<td>92–200</td>
<td>13.3 (1)</td>
<td>0</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>I-28H</td>
<td>5</td>
<td>10</td>
<td>29–121</td>
<td>23.2 (3)</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>I-28L</td>
<td>4</td>
<td>3</td>
<td>66–209</td>
<td>21.4 (1)</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Transgenic (mutant)</td>
<td>8</td>
<td>257–401</td>
<td>4.8 (4)</td>
<td></td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Control</td>
<td>20</td>
<td>66–140</td>
<td>5.5 (19)</td>
<td></td>
<td>20</td>
<td>0</td>
<td>0</td>
</tr>
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Pathological changes in livers were categorized as follows: normal–minimal dysplasia means normal liver architecture with occasional variation in nuclear size; dysplasia with fatty change involves disruption of normal architecture, variation in shape and size of both nucleus and cytoplasm, and clear cytoplasm filled with fat. Tumors with a trabecular pattern were diagnosed as hepatocellular carcinoma.
in the cytoplasm-to-nucleus ratio. Hepatocytes often exhibited a 3-fold nuclear enlargement. There was compression of sinusoidal cells by the thickened plates of hepatocytes that often contained variable amounts of clear, round vacuoles (Fig. 4B). Oil Red O staining revealed these cytoplasmic vacuoles to be filled with lipid droplets (data not shown). In all of the mouse lines, large multinodular tumors, having the typical morphological appearance of hepatocellular carcinomas, were observed (Fig. 4C). Evidence of mitosis was seen in poorly differentiated hepatocytes (data not shown). One transgenic mouse (I-28H) had severe hepatic hyperplasia, with nodules of trabecular carcinoma but only minimal lipid deposits at 24 days. The plasma glutamic-oxaloacetic transaminase and glutamic-pyruvic transaminase levels were elevated in transgenic mice (data not shown).

The transgenic rabbit with 17 copies of the transgene appeared normal at birth but grew more slowly than its nontransgenic littermate. After 8 weeks, it became weak and immobile and, therefore, was euthanized. The transgenic rabbit's weight was \( \approx 50\% \) of that of its littermate (1160 g vs. 2250 g). Necropsy revealed an enlarged liver, weighing \( \approx 1.5 \) times more than that of its nontransgenic littermate (112 g vs. 72 g). The transgenic rabbit's liver had visible scarring, fibrosis, and abnormal nodules on the surface. Histologically, the liver was characterized by distorted architecture, fibrosis, and cytoplasmic lipid droplets (Fig. 4D).

In the transgenic rabbit founder, as in the mice, APOBEC-1 mRNA was expressed mainly in the liver (data not shown). Primer-extension analysis showed that 78% of the apo-B mRNA was edited in the transgenic rabbit liver, whereas no significant editing of apo-B mRNA occurred in the control mouse

**Fig. 2.** In vitro editing activity of liver S100 extract of five transgenic (I-20) and five age- and sex-matched control mice, as described.

**Fig. 3.** Analysis of apo-B-containing lipoproteins in transgenic mice expressing APOBEC-1. (A) Agarose gel electrophoresis of plasma lipoproteins from transgenic (I-20) and control mice. Plasma (2 \( \mu l \)) was separated by electrophoresis on a 1% agarose gel and stained by Fat Red 7B. Arrowhead, migration origin of gel; \( \alpha \) and \( \beta \), electrophoretic migration positions. (B) SDS/PAGE of the \( d < 1.063 \) g/ml fractions from transgenic (I-20) and control mice identified by Coomassie staining.

**Fig. 4.** Pathological changes in mouse and rabbit livers. (A) Hepatocellular carcinoma in an 8-month-old transgenic mouse (I-22). T, transgenic mouse; C, nontransgenic littermate control. (B) Hepatic dysplasia in transgenic mouse (I-28L, 6 months old). The hepatocytic nuclei vary considerably in size (arrow) (hematoxylin/eosin). (\( \times 235 \)). (C) Hepatocellular carcinoma in transgenic mouse (I-22, 7 months old) (hematoxylin/eosin). (\( \times 235 \)). (D) Hepatic dysplasia in transgenic rabbit (17 copies of transgene) (trichrome stain for collagen). (\( \times 25 \)).
rabbit liver (Fig. 1). Although fasted plasma from normal rabbits contains only apo-B100, the lipoproteins isolated from the high copy number transgene rabbit contained >50% apo-B48 (data not shown).

The introduction of APOBEC-1 into the liver by gene transfer has the potential to be a powerful technique in lowering plasma LDL and lipoprotein(a) concentrations. Recently, Teng et al. (7) demonstrated that adenovirus-mediated transfer of rat APOBEC-1 into the livers of mice increased hepatic apo-B mRNA editing activity and lowered the concentration of lipoproteins containing apo-B100. Because apo-B mRNA editing is endogenously present in the livers of several mammals, it has been assumed that APOBEC-1 activity is innocuous. Moreover, it has been suggested that the editing activity resulting from the genetic transfer of APOBEC-1 into the liver of an animal normally lacking editing activity also would be harmless (7). However, our study using transgenic animals clearly demonstrates that the overexpression of APOBEC-1 in the liver can be genotoxic.

The hepatic abnormality and transformation depended upon the overexpression of apo-B mRNA-editing activity and was not due to vector insertion, transforming elements in the vector, or the increased formation of apo-B48 in the transgenic animals. The occurrence of dysplasia in all four independent transgenic mouse lines and in a transgenic rabbit indicates that this change was not the result of insertion effects of the transgene. Transgenic mice with a mutant, enzymatically inactive form of APOBEC-1 ligated into the pLIV11 vector had normal livers (Table 1). The same vector has been used to generate transgenic mice and rabbits expressing either human hepatic lipase or human apo-E, with no evidence of liver abnormality (20). Furthermore, gene targeting in embryonic stem cells has been used to generate mice that synthesize only apo-B48 (23). These “apo-B48-only” mice develop normally and have livers that are normal in size and morphology (R. V. Farese, Jr. and S. G. Young, personal communication). Histological analysis of the livers of six apo-B48-only mice (aged 144–260 days) showed no abnormalities, in contrast to what we observed in the APOBEC-1 transgenic mice, and their plasma glutamic-oxaloacetic transaminase and glutamic-pyruvic transaminase levels were normal.

We postulated that the mechanism for the dysplasia in the APOBEC-1 transgenic animals is the aberrant editing of other mRNAs. A specific 11-nt mooring sequence in apo-B mRNA occurring 5 nt downstream from C6666 is critical for editing in vitro (24, 25). When the mooring sequence is inserted into another location on apo-B or non-apo-B CDNA, the resulting chimeric RNA is edited in vitro, raising the possibility that mRNA with the mooring sequence and a cytidine 3–6 nt upstream could be edited in vivo (9, 10, 24, 25).

To identify candidate mRNAs, we searched the GenBank for sequences similar to the mooring sequence using the FASTA program (26). Twenty-three rodent sequences were found to have the exact mooring sequence. Among these are the mouse fatty acid synthase (27) and mouse P1 protein (28), both of which contain a cytidine residue 4–6 nt upstream from the mooring sequence (Fig. 5A). Furthermore, >100 sequences were identified with sequence motifs just 1 nt different from the mooring sequence. These include mouse protein-tyrosine kinase TEC (29) and mouse prostaglandin synthase (30), which contain a cytidine residue 5 or 7 nt upstream from the mooring sequence, respectively (Fig. 5A).

To determine whether these mRNAs are edited in vivo, RNAs isolated from control and transgenic mouse livers were amplified by reverse transcription–PCR. The PCR products were analyzed for editing by primer-extension analysis (Fig. 5B). None of the four mRNAs was edited in the livers of control mice, suggesting that the mooring sequence normally is not sufficient to support editing. Even in transgenic mice with high hepatic editing levels, three of the transcripts were not edited. However, mouse protein-tyrosine kinase TEC was edited in transgenic mice (Fig. 5B), providing a second example of C → U editing of an mRNA. The editing of the tyrosine kinase changed codon 411 from CUG to UUG. However, this is a silent codon change (Leu → Leu) and, therefore, cannot be the cause of the observed pathological phenotype. Nevertheless, these results establish that other cytidines in mammalian mRNAs can be the targets of APOBEC-1-mediated deamination. Specific C → U changes can result in the formation of new termination codons, new initiation codons, and missense mutations, all of which can have potentially severe biological consequences.

Although apo-B mRNA editing normally does not modify DNA, it is possible that the overexpressed APOBEC-1 also can modify small amounts of DNA. However, C6666 in a 282-bp apo-B DNA fragment, 6504–6785, was not edited in vitro. Moreover, PCR and primer-extension analysis of genomic apo-B DNA from transgenic mouse livers overexpressing APOBEC-1 indicated that the genomic C6666 was not edited in vivo (data not shown). It is most likely that the predisposition to hepatocellular carcinoma is not due to DNA modification but to aberrant editing of other mRNAs involved in growth and differentiation.

We report here that an RNA-editing protein can act as an oncogene. That APOBEC-1 may be the harbinger of another class of protooncogenes is supported by the finding of another association between RNA editing and oncogenesis (31). The mRNA of the tumor suppressor WT1 has been shown to be edited. This U → C editing, which is developmentally regulated, altered the function of the WT1 protein in a transcription-repression assay. Whether the editing of the WT1 protein

![Fig. 5](image-url) Analysis for editing of mRNA with motifs similar to apo-B mRNA in transgenic mice. (A) Sequences of fatty acid synthase (FAS), P1 protein (P1), prostaglandin synthase homologue (TIS10), and protein-tyrosine kinase (TEC) are compared with that of apo-B100. Asterisks indicate the mooring sequence. The cytidine edited in apo-B mRNA is nt 6666, which is indicated by outline font, as are the potential editing sites in the candidate mRNAs. Primers used for primer-extension analysis are underlined. (B) Primer-extension analysis of C → U conversions. Results from two control mice and two transgenic mice are shown for protein-tyrosine kinase TEC. P, C, and U indicate electrophoretic migration positions of primers, unedited sequences, and edited sequences, respectively.
activity indicate APOBEC-1 factor is high by lipoproteins, lead such transaminase that activity and the from either the hT 0). The rabbits, k' (copy)


We thank S. Young and B. Farese for providing their apo-B48-only mice; D. Sanan, D. Newland, and R. Quan for help with histology; D. Haumant for manuscript preparation; and A. Corder and J. Carroll for graphics. This work was supported in part by National Institutes of Health Program Project Grant HL47660 and University of California Tobacco-Related Disease Research Program Grant 3RT-0404.


![Fig. 6](image-url) Analysis of plasma lipoproteins from transgenic rabbit with a single APOBEC-1 transgene. (A) Distribution of cholesterol among lipoproteins separated by fast protein liquid chromatography. Plasma (200 μl) from either the transgenic rabbit or the five age- and diet-matched control rabbits, which included a nontransgenic littermate, was resolved by fast protein liquid chromatography using a Superose 6 column (HR10/30), and the cholesterol in the fractions was measured. The rabbits, which were 2 months old, had been weaned the day before and fasted the night before blood was drawn. Plasma cholesterol levels of the transgenic rabbit, a nontransgenic littermate, and the average of four nonlittermate control rabbits were 127 mg/dl, 163 mg/dl, and 149 ± 10 mg/dl, respectively. HDL, high density lipoprotein; VLDL, very LDL; IDL, intermediate density lipoprotein. (B) Agarose gel electrophoresis of plasma lipoproteins. Plasma (2 μl) from either the transgenic rabbit or its nontransgenic littermate was separated by electrophoresis on a 1% agarose gel and stained by Fat Red 7B. Arrow, migration origin of gel; α and β, electrophoretic α and β migration positions, respectively.

reduces its ability to function as a tumor suppressor has not been determined.

Although the overexpression of hepatic apo-B mRNA editing activity is pathogenic, a lower expression level, such as that normally occurring in the livers of mice and rats, may be innocuous. Our initial observations in rabbits suggest that a single copy of the APOBEC-1 transgene is either innocuous or much less harmful than multiple copies. In contrast to the rabbit founder with a high transgene copy number, the founder with a single transgene copy appears healthy, with normal growth and normal plasma activity for glutamic-oxaloacetic transaminase and glutamic-pyruvic transaminase. The plasma lipoprotein profile on fast protein liquid chromatography was characterized by decreased concentrations of very low density lipoproteins, intermediate density lipoproteins, and LDL and by increased levels of high density lipoproteins (Fig. 6A). These results were confirmed by agarose gel electrophoresis, which showed a decrease in β-migrating LDL and an increase in α-migrating high density lipoproteins (Fig. 6B). These results indicate that a more physiological level of expression of hepatic editing activity can alter the ratio of LDL to high density lipoprotein cholesterol concentrations.

In conclusion, the therapeutic potential of lowering plasma LDL concentrations by introducing the apo-B mRNA editing factor into the liver has been compromised by the finding that this protein can be oncogenic. The observation that other mRNAs, such as protein-tyrosine kinase TEC, can be edited by APOBEC-1 suggests that the mechanism for oncogenesis is the editing of mRNAs that encode proteins having significant roles in cell function. Identification of these target mRNAs may lead to an understanding of other roles of this type of editing (i.e., cytidine deamination) in mammalian biology.