Hyperediting of Multiple Cytidines of Apolipoprotein B mRNA by APOBEC-1 Requires Auxiliary Protein(s) but Not a Mooring Sequence Motif*

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An RNA-binding cytidine deaminase (APOBEC-1) and unidentified auxiliary protein(s) are required for apolipoprotein (apo) B mRNA editing. A sequence motif on apoB mRNA ("mooring sequence," nucleotides 6671-6681) is obligatory for the editing of cytidine 6666 (C6666), the only cytidine on apoB mRNA converted to uridine in normal animals. Transgenic animals with hepatic overexpression of APOBEC-1 develop liver tumors, and other non-apoB mRNAs were edited, suggesting a loss of the normally precise specificity. In this study, we examined apoB mRNA from these transgenic animals to determine if cytidines aside from C6666 are edited. Multiple cytidines downstream from C6666 in apoB mRNA were edited extensively by the overexpressed APOBEC-1. This pathophysiological "hyperediting" could be mimicked in vitro by incubating a synthetic apoB RNA substrate with the transgenic mouse liver extracts. Multiple cytidines in the synthetic apoB RNA were edited by recombinant APOBEC-1 but only with supplementation of the auxiliary protein(s). Mutations in the mooring sequence markedly decreased the normal editing of C6666 but, surprisingly, increased the hyperediting of downstream cytidines. Furthermore, cytidines in an apoB RNA substrate lacking the mooring sequence were also edited in vitro. These results indicate that the hyperediting of apoB mRNA by overexpressed APOBEC-1 depends upon auxiliary protein(s) but is independent of the mooring sequence motif. These results suggest that hyperediting may represent the first step in a two-step recognition model for normal apoB mRNA editing.

Apolipoprotein (apo) B48, the amino-terminal 2152 amino acids of apoB100, is synthesized by a novel post-transcriptional modification of mRNA, designated "mRNA editing" (1–3). The editing process deamidates a specific cytidine, nucleotide (nt) 6666, to form uridine (4, 5). This deamination changes the codon at position 2153 from a genomically encoded glutamine (CAA) to an in-frame stop codon (UAA) (6). Apolipoprotein B mRNA editing occurs in the small intestine of all mammals and also in the liver of rats, mice, dogs, and horses (7).

A protein that catalyzes the editing reaction has been cloned (8). This protein, designated "APOBEC-1" (apoB mRNA-editing enzyme catalytic polypeptide 1) (9), is the catalytic subunit of the apoB mRNA-editing complex that deaminates nt 6666 in apoB mRNA (5). APOBEC-1 is capable of binding to RNA (10, 11) but requires unidentified complementary or auxiliary protein(s), which apparently are part of a multicomponent editing complex, in order to edit apoB RNA (8, 12). These auxiliary protein(s) have a widespread distribution (12, 13), have been shown to bind to APOBEC-1, and may bind to apoB mRNA (14).

Both in vitro and in vivo, cytidine 6666 (C6666) in apoB mRNA is deaminated with extraordinary precision. Moreover, apoB mRNA is the only known substrate for the apoB-editing enzyme in normal animals. The sequence elements in the apoB mRNA necessary for this high specificity have been identified by site-directed mutagenesis (15–19). Mutation of any of 10 of the 11 nucleotides in an 11-nt region (nt 6671–6681) of the apoB mRNA either abolished or greatly reduced in vitro apoB mRNA editing, indicating that mRNA editing is dependent upon this sequence element (15, 18, 19) (i.e. the "mooring sequence"). In addition, this mooring sequence (recognition sequence) is sufficient to promote editing of an immediately upstream cytidine at a reduced efficiency in vitro or in cultured cells when it is inserted into a heterologous gene (e.g. albumin or luciferase) or heterologous sites in apoB mRNA (17, 19).

Recently, we have demonstrated that APOBEC-1 overexpressed in the livers of transgenic mice leads to hepatocellular dysplasia and carcinoma (20). The C6666 in apoB mRNA was virtually completely edited in the livers of these transgenic animals. Other hepatic mRNAs with sequence motifs similar to that of the mooring sequence were examined in these animals for cytidine deamination editing. The mRNA of tyrosine kinase was found to be edited in the transgenic mouse livers but not in those of the control mice. This mRNA has a sequence motif that differs by 1 nucleotide from the mooring sequence. Surprisingly, two other mRNAs containing the exact mooring sequence were not edited at cytidines 4–6 nucleotides upstream from this sequence (20). These results demonstrated that the mooring sequence is not sufficient for the APOBEC-1-mediated editing and that other sequence and/or structure element(s) are also required, even in the transgenic animals overexpressing APOBEC-1.

In this study, we considered the possibility that other sites in apoB mRNA might be edited when APOBEC-1 is overexpressed in transgenic animal livers and that the analysis of the pattern of editing could give us additional insights into the sequence requirements for apoB mRNA editing. We found that apoB mRNA was edited at multiple sites downstream from C6666. Moreover, the auxiliary protein(s), but not the mooring se-
Hyperediting of apoB mRNA in apoB mRNA-editing enzyme catalytic polypeptide 1 (APOBEC-1) transgenic animal livers as detected by sequence analysis. An approximately 350-base pair fragment of apoB mRNA was amplified by RT-PCR, sub cloned into pCRII vectors, and sequenced. By comparing these cDNA sequences with the genomic sequence, edited cytidines were determined. A, edited cytidines detected in four random cDNA clones of apoB from transgenic mouse livers are indicated by solid circles (●). B, the percentage of edited clones for each cytidine from nucleotides (nt) 6543 to 6651 is shown by shaded bars. Mouse apoB represents the mouse sequence from an APOBEC-1 transgenic mouse (n = 25); rabbit apoB, the rabbit sequence from an APOBEC-1 transgenic rabbit (n = 18); human apoB, the human sequence from a double transgenic mouse expressing both human apoB and rabbit APOBEC-1 (n = 10). No editing was detected in the upstream region from nt 6504 to 6642. Cytidines whose editing in the nt 6643–6851 region was not detected by sequence analyses are indicated by asterisks.

**RESULTS AND DISCUSSION**

Rabbit APOBEC-1 was overexpressed in transgenic mice and rabbits, predominantly in the liver (20). The purpose of the present study was to determine the effects of APOBEC-1 overexpression on apoB mRNA isolated from the livers of transgenic mice or rabbits. RNA from the APOBEC-1 transgenic animal livers and nontransgenic normal mouse and rabbit livers was amplified using RT-PCR from apoB mRNA in the vicinity of the normal editing site (C6666). In addition, human apoB mRNA was amplified by RT-PCR from transgenic mouse livers expressing human apoB (21) and double transgenic mouse livers expressing both human apoB and rabbit APOBEC-1. Previously, it was shown that, in transgenic mice expressing human apoB in their liver, human apoB mRNA was edited at the correct site (C6666) and to the same extent as mouse apoB mRNA (25). The PCR products were subcloned into pCRII vectors, and multiple clones were sequenced from each PCR product to look for additional editing sites.

As expected, apoB mRNA from normal rabbit liver was not edited (data not shown). The mouse apoB transcript from the normal mice and the human apoB transcript from the transgenic mice expressing only human apoB mRNA, but not rabbit APOBEC-1, were edited at the canonical site (nt 6666). In addition, C6806 in the human transcript was slightly edited. No other cytidines were edited in control animals.

In the transgenic animals expressing rabbit APOBEC-1, the hepatic apoB mRNAs of all three species were extensively edited at multiple sites (Fig. 1). We have designated this type of RNA editing “apoB mRNA hyperediting” to differentiate it from normal apoB mRNA editing. As illustrated by four randomly chosen clones, the pattern of editing appears to be stochastic (Fig. 1A). There was no apparent 5' to 3' or 3' to 5' preference in the distribution of the edited sites. There were two major and one minor clusters of edited cytidines in the apoB mRNAs. One major region of edited cytidines was C6762. The other was C6802–C6816. The minor cluster of edited cytidines was in the region of C6773–C6783 (Fig. 1). The data are expressed as means ± S.D.

**MATERIALS AND METHODS**

Production of Transgenic Mice and Rabbits—Transgenic mice and rabbits expressing rabbit APOBEC-1 cDNA in their liver were developed as described previously (20). Transgenic mice expressing both rabbit APOBEC-1 and human apoB in their liver were established by crossing rabbit APOBEC-1 transgenic mice with human apoB transgenic mice (21).

Reverse Transcription-Polymerase Chain Reaction (RT-PCR) Amplification of apoB and Other mRNAs—Total RNA was isolated from control and transgenic animal livers, and mRNAs of apoB, fatty acid synthase (22), P1 protein (23), and tyrosine kinase (24) were amplified by RT-PCR as described previously (20). The primers used for PCR were MBU1 (5'-TAATTGCTATAGTGGCTGAAAAG-3') and MBL1 (5'-ATTTTGTACTTTAGATGCTGAAAAG-3').

Primer Extension Analysis—PCR products were analyzed by primer extension analysis to detect the C→U editing as described previously (20). Primers used to detect the editing of multiple cytidines downstream from C6666 of mouse apoB mRNA were: M52 (5'-TTTTTGAACCAAAACCGTCTT-3'), M53 (5'-ATGACCAAAACCGTTCTTT-3'), and M54 (5'-TTTTTGAACCAAAACCGTCTT-3').

In Vitro Editing Assay—Plasmids containing 280 base pairs of wild-type baboon apoB DNA, mutant 118, or mutant 124 (19) were linearized by HinDIII digestion and transcribed by using MEGAscript RNA transcription kits (Ambion, Austin, TX) according to the manufacturer's protocol. The template DNA was destroyed by DNase I treatment. One hundred picograms of these synthetic RNAs were incubated with tissue or cell extracts in buffer D (13) at 30 °C for 2-16 h. After the incubation, the RNAs were extracted once with phenol/chloroform and once with chloroform. The baboon apoB sequences were then amplified by RT-PCR using BB1 and BB2 primers as described previously (20). The template DNA was destroyed by DNase I treatment. The template DNA was destroyed by DNase I treatment. The template DNA was destroyed by DNase I treatment. The template DNA was destroyed by DNase I treatment.
and C\textsubscript{6738} were edited in APOBEC-1 transgenic mice (Fig. 2) and rabbit (data not shown) but not in control animals. The band corresponding to the editing of C\textsubscript{6738} is much stronger than that corresponding to the editing of C\textsubscript{6743}. This suggests that these two cytidines are edited simultaneously in most transcripts, which is consistent with the results of the sequence analyses. The second primer (M53) detected the editing of C\textsubscript{6738} and C\textsubscript{6743} in the transgenic mouse liver. The third one (M52) revealed the editing of C\textsubscript{6738} and C\textsubscript{6743}.

Three findings are noteworthy and differentiate apoB mRNA hyperediting from normal apoB mRNA editing. First, C\textsubscript{6675} which is in the center of the mooring sequence, was edited in transcripts from all three species in APOBEC-1 transgenic animals. Previously, Shah et al. (18) demonstrated that cytidine at this site was crucial for normal apoB mRNA editing in vitro since the mutation of this residue to guanidine abolished editing at C\textsubscript{6666}. However, our results suggest that this nucleotide is not critical for the hyperediting of apoB RNA. The second surprising finding was that most of the alternate editing sites were downstream from the mooring sequence. Only a few cytidines were found by sequence analyses to be edited at low frequency (less than 10%) in the upstream region we examined (nt 6504–6666). Based on numerous in vitro studies, the accepted working model for apoB mRNA editing predicts that a protein or proteins (auxiliary protein(s)) bind to the mooring sequence and direct editing immediately upstream from the mooring sequence element (26, 27). The third finding is that apoB RNA hyperediting does not deaminate random cytidines but prefers cytidines surrounded by thymidine or adenosine. In three apoB mRNAs examined, a total of 40 different cytidines were edited. The nucleotide immediately upstream from the editing site was either thymidine (70%) or adenosine (30%). The nucleotide immediately downstream usually was adenosine (58%) or thymidine (27%) and, less frequently, cytidine (10%) or guanosine (5%). This same pattern of base preference also was found in another mRNA that we found to be edited at multiple sites.\textsuperscript{2} Thus, when APOBEC-1 is over-expressed in vivo, there is a striking “nearest neighbor” A or T preference, at least for apoB mRNA hyperediting. In contrast, Chen et al. (16) concluded that the bases in the immediate vicinity of the editing site are unimportant for normal apoB mRNA editing. In their study, 22 different mutants were created in which the bases immediately flanking C\textsubscript{6666} in apoB mRNA were altered. Twenty of these mutants were edited at C\textsubscript{6666} in vitro. The conclusion from this study was that, in the immediate vicinity of the editing site at C\textsubscript{6666}, there is a relatively lax sequence specificity for apoB mRNA editing. One of the two mutants not edited had thymidine immediately before and after the edited cytidine (16). However, in apoB mRNA hyperediting, several cytidines that were highly edited in apoB mRNA were flanked by thymidines.

We previously have examined whether the apoB mRNA-editing enzyme can edit other mRNAs with the same mooring sequence (i.e. fatty acid synthase and P1 protein) and mRNAs with motifs that differ from the apoB mooring sequence by a single nucleotide (i.e. prostaglandin synthase homologous and tyrosine kinase) (20). These mRNAs have cytidines 4–6 nt upstream from the mooring-like sequence motifs, which were not edited in the normal mouse liver. Only the cytidine upstream from the mooring-like sequence of tyrosine kinase was slightly edited (∼1%) in transgenic mice overexpressing APOBEC-1 (20). However, the hyperediting of apoB mRNA by overexpressed APOBEC-1 raised the possibility that other cytidines in these mRNAs, such as those downstream from the mooring-like sequences, might be edited in APOBEC-1 transgenic animals. To examine this possibility, 250–300 base pair fragments around the mooring-like sequences of fatty acid synthase, P1 protein, and tyrosine kinase were amplified by RT-PCR from APOBEC-1 transgenic mouse livers. The PCR products were subcloned, and 10 subclones of each mRNA (cDNA) were sequenced. In contrast to apoB mRNA, no cytidine at any position was edited in these mRNAs (data not shown), suggesting that sequence and/or structure element(s) other than the mooring sequence are required for both normal and hyperediting.

Normal apoB mRNA editing requires APOBEC-1, auxiliary protein(s), and the mooring sequence (wild-type: TGATCATATA) of apoB. Previously, we demonstrated that an apoB RNA with a double mutation in the mooring sequence (mutant 118: TGgTACTTgA) was edited at only 11% of the level of that of the wild-type apoB RNA (19). The mutant 124 (gGATgGAgAATA), with a triple mutation in the mooring sequence, was not edited in vitro by a rat enterocyte extract (19). By adjusting the conditions described under “Materials and Methods,” we were able to achieve apoB RNA hyperediting in vitro and were therefore able to determine if hyperediting is dependent upon auxiliary protein(s) and the mooring sequence of apoB. As shown in Fig. 3A, liver extract from a normal mouse edited 26 ± 6% (n = 5) of the C\textsubscript{6666} of wild-type RNA substrate but failed to edit the C\textsubscript{6666} of apoB RNA with mutations in the mooring sequence (Fig. 3A, mutants 118 and 124). Liver extract from a transgenic mouse overexpressing rabbit APOBEC-1 edited 70 ± 18% (n = 5) of C\textsubscript{6666} from wild-type apoB RNA, which was reduced to 38 ± 18% (n = 5) and 22 ± 15% (n = 5) for RNA mutants 118 and 124, respectively. As expected, the maltose-binding protein (MBP)-APOBEC-1 fusion protein expressed in Escherichia coli was unable to edit any of the RNAs (Fig. 3A). With the addition of rabbit liver extract that contains auxiliary protein(s), the C\textsubscript{6666} on the wild-type apoB RNA was edited 71 ± 13% (n = 5), with reduced editing (33 ± 7% n = 5) for the

\textsuperscript{2} S. Yamanaka, unpublished data.
Hyperediting of ApoB mRNA in vitro. A and B, synthetic baboon apoB RNA (280 base pairs) of either a wild-type (wt), mutant 118, or mutant 124 was incubated with either 100 μg of normal mouse liver extract (control liver), 100 μg of APOBEC-1 transgenic mouse liver extract (AP0BEC-1 transgenic liver), 5 μg of a fusion protein consisting of maltose-binding protein and APOBEC-1 (AP0BEC-1), or 5 μg of MBP-APOBEC-1 + 100 μg of normal rabbit liver extract containing the auxiliary protein(s) (APOBEC-1 + auxiliary protein(s)) at 30 °C for 16 h. The editing of C6666 (A) or C6673 (B) was determined by primer extension analyses.

To further confirm that hyperediting is independent of the canonical mooring sequence.

To further confirm that hyperediting is independent of the mooring sequence, we synthesized a shorter apoB RNA substrate (nt 6687–6824 of rabbit apoB mRNA) lacking the mooring sequence. When incubated with the recombinant MBP-APOBEC-1 and the auxiliary protein(s) in vitro, the editing was determined by primer extension analysis. As reported previously (19), the introduction of the second mooring sequence led to the editing of C6597, which was immediately upstream from the second mooring sequence (data not shown). In contrast, C6604, C6626, and C6639, which were downstream from the second mooring sequence, were not edited in either wild-type or SR2 RNA, showing that the introduction of the second mooring sequence did not lead to the hyperediting. These results are consistent with the concept that hyperediting is independent of the mooring sequence.

Another finding from the in vitro study is that the editing of C6666 is much more efficient than the hyperediting of C6738/6743. We studied the time-course of the editing and hyperediting by performing in vitro assays for 2–16 h (Fig. 4). The hyperediting of C6738/6743 was detected after 2 h (4%) and gradually increased up to 16 h (23%). In contrast, C6666 was edited 65% at 2 h and 81% at 4 h. There was no further increase in the editing of C6666 after 4 h. Thus, the editing of C6666 is more efficient and rapid than the hyperediting.

A model for the mechanism of apoB RNA hyperediting can be derived based on our knowledge of normal apoB mRNA editing and the results of this study. The apoB mRNA-editing complex consists of the catalytic cytidine deaminase subunit (APOBEC-1) and auxiliary protein(s). The auxiliary protein(s) bind to APOBEC-1 and, most likely, bind to the apoB mRNA. In normal animal livers, apoB mRNA editing requires both the mooring sequence and other mooring-independent element(s). When APOBEC-1 is overexpressed in transgenic animal livers, the hyperediting does not require the canonical mooring sequence, and the editing occurs at multiple sites.

We have formulated a plausible two-step recognition model to explain normal editing and hyperediting of apoB mRNA. The first step is the relatively loose recognition of the apoB mRNA sequence by either the auxiliary protein(s), APOBEC-1, or a complex of APOBEC-1 and the auxiliary protein(s). This step does not require the specific mooring sequence and is probably dependent upon unidentified sequence and/or structure element(s). Our hypothesis is that this first recognition step permits the apoB mRNA-editing complex to recognize a relatively short segment of apoB mRNA from tens of thousands of different transcripts. Transcripts that lack the unidentified element, such as P1 protein and fatty acid synthase, are not edited at canonical or multiple sites even though these mRNAs contain the exact mooring sequence.

The second step of normal apoB mRNA editing requires the specific mooring sequence that "anchors" the editing complex at the correct site on apoB for the deamination of C6666. In normal animals, where APOBEC-1 exists at relatively low levels, the
first step alone is not sufficient to support editing; without the canonical mooring sequence, normally there is insufficient editing complex concentrated at any one site to support the deamination reaction. However, when APOBEC-1 is overexpressed, sufficient editing complex is concentrated by the first recognition step on a short fragment of apoB mRNA to permit the hyperediting of multiple cytidines. This hyperediting seems to be independent of the second step. At the least, it does not require the specific mooring sequence, which is essential for normal editing of C<sub>6666</sub>. That the mutants in the mooring sequence enhanced the hyperediting is consistent with our two-step model. When the mooring sequence is mutated, the binding equilibrium of the editing complex naturally favoring the C<sub>6666</sub> is disrupted, allowing the less favorable interaction with downstream sites to occur more often.

If both the first (mooring-independent) step and the second (mooring-dependent) step are required for normal editing, why was the mooring sequence sufficient to elicit editing when inserted into heterologous RNAs such as luciferase (19) and albumin (17)? These RNAs probably contain the sequence and/or structure element(s) necessary in the first step. When the mooring sequence was inserted into apoE RNA, it failed to support editing (28). Apparently, apoE RNA lacks the element(s) necessary in the first step.

What are the element(s) required for the first step? One may be an AU-rich sequence element, as suggested by Backus et al. (17), who showed that a 3′ AU-rich sequence flanking the mooring sequence was important for efficient editing. The fragment of mouse apoB mRNA we amplified by RT-PCR contains 69.7% AU. In contrast, the mRNAs of P1 protein and fatty acid synthase contain only 47.7 and 41.9% AU, respectively. Furthermore, APOBEC-1 has been shown to bind to AU-rich mRNA (10, 11). However, the first-step recognition sequence element is more complex than simply the AU content of the mRNA, since the 3′-untranslated region of N-myc RNA is not edited in the APOBEC-1 transgenic animal livers (data not shown) despite the fact that this region contains 68.5% AU and a sequence motif only two nucleotides different from that of the mooring sequence.

In conclusion, we have reported that overexpressed APOBEC-1 edits non-random multiple cytidines of apoB mRNA in transgenic animals. The hyperediting is dependent upon auxiliary protein(s) but independent of the specific mooring sequence. We also have proposed a two-step recognition model for normal apoB mRNA editing that consists of an initial mooring sequence-independent step and a second, mooring sequence-dependent step. When APOBEC-1 is overexpressed in the liver, the first step becomes sufficient to support the editing of multiple cytidines on certain RNA transcripts. This may play an important role in the development of hepatocellular carcinoma in these animals. If this hypothesis is correct, the elucidation of the sequence and/or structure element(s) that support hyperediting should provide insight into the first critical step in the mechanism of apoB mRNA editing.

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