RNA Editing of the Apolipoprotein B Gene

A Mechanism to Regulate the Atherogenic Potential of Intestinal Lipoproteins?

Nicholas O. Davidson

Apolipoprotein B (apo B) circulates in two distinct isomorphic forms, each the product of a single gene. The larger form, referred to as apo B-100, is the major protein of plasma low-density lipoproteins (LDLs) and is synthesized by the human liver. The smaller form, referred to as apo B-48. is produced in the small intestine as a result of a site-specific cytidine deamination, which alters a CAA codon, encoding glutamine in the unedited (apo B-100) mRNA to UAA, which specifies an in-frame stop codon. Apo B-48 lacks the domains involved in LDL receptor interaction and in complex formation with apolipoprotein(a). DNA sequence analysis of the gene that mediates this site-specific cytidine deamination suggests that apo B mRNA editing is an evolutionary adaptation to limit the atherogenic potential of intestinal lipoproteins.
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• Apolipoprotein B mRNA Editing: An Overview and Biologic Perspective

Among the major risk factors for atherosclerosis susceptibility is the ambient plasma concentration of low-density lipoprotein (LDL)* and its major protein constituent, apolipoprotein B (apo B) [for a review, see Young (1990)]. Apo B is a large hydrophobic protein that is synthesized in the liver and small intestine and functions as an obligate surface component of triglyceride-rich lipoproteins (Young 1990). Apo B circulates in two distinct forms, referred to on a centile scale as apo B-100 and apo B-48, each the product of a single gene (Breslow 1989). In humans, the liver synthesizes a form of apo B containing 4536 residues, which is referred to as apo B-100 (Powell et al. 1987, Chen et al. 1987). Apo B-100 is the product of an mRNA that contains a genomically templated CAA codon (glutamine) at position 2153 of apo B-100 mRNA, while apo B-48 is produced in the small intestine as a result of posttranscriptional editing, which changes cytidine to uridine and produces a UAA or in-frame stop codon (Powell et al. 1987, Chen et al. 1987). As a result, apo B-48 mRNA translation terminates at residue 2152, thereby making apo B-48 colinear with the amino terminal 48% of apo B-100. The molecular mechanisms underlying tissue-specific production of these distinct isomorphic variants is the subject of this review.

Apo B-100 is secreted as an essential component of very low density lipoproteins (VLDLs) following a well-established cascade of lipolytic events that eventually result in the genesis of LDL, the principal transport vehicle for cholesterol in humans [for a review, see Breslow 1989). The catabolic clearance of LDL is highly dependent upon a specific interaction with a ubiquitously expressed cell-surface receptor, the low-density lipoprotein receptor (LDL-R) (Breslow 1989). This interaction, in turn, depends upon the presence of a domain in the carboxyl terminus of apo B-100, which functions as the ligand-binding site (Young 1990). Accumulation of apo B-100 and LDL in the plasma may result from defects in the function or expression of LDL-Rs (Breslow 1989) or defective binding to the LDL-R as a result of a defective apo B-100 (Innerarity et al. 1990). Apo B-100 also participates in the formation of lipoprotein(a) [Lp(a)], a hybrid lipoprotein composed of apo B-100 covalently linked to apolipoprotein(a) [apo(a)] and which is a separate, heritable risk factor for atherosclerosis (Scanu and Fless 1990). The functional consequences of apo B mRNA editing thus include the elimination from apo B-48 of the domains present in apo B-100 that are responsible for binding to the LDL-R and for the interaction with apo(a). The recent description of transgenic mice expressing human apo B-100 and Lp(a) will enable further resolution of the structural domains of apo B-100 involved in both LDL-R interaction and Lp(a) formation (Linton et al. 1993). Apo B-48-containing lipoproteins are cleared from the circulation in a matter of minutes by a, principally hepatic, receptor referred to as the chylomicron remnant receptor (Kowal et al. 1989). This contrasts with the average residence time of over 2 days for an LDL particle (Young 1990). Taken together, therefore, apo B mRNA editing has a profound impact on the metabolism of apo B-containing lipoproteins and, by extension, their respective contributions to atherosclerosis susceptibility.

• Apolipoprotein B mRNA Editing: Tissue-Specific, Developmental, Hormonal, and Nutritional Regulation

As just described, the human liver synthesizes and secretes apo B-100, while the small intestine secretes apo B-48. By contrast, the rat liver contains both edited and unedited apo B mRNA species, in approximately equal propor-

Nicholas O. Davidson is at the Department of Medicine, University of Chicago, Chicago, IL 60637, USA.

*Abbreviations: apo(a), apolipoprotein(a); apo B, apolipoprotein B; HDL, high-density lipoprotein; HEPR, human apo-B RNA-editing protein; LDL, low-density lipoprotein; LDL-R, low-density lipoprotein receptor; Lp(a), lipoprotein(a); mRNA, messenger ribonucleic acid; REPR, rat apo B RNA editing protein; and VLDL, very low density lipoprotein.

tions, and secretes both apo B-100 and apo B-48 (Davidson et al. 1988) Recent work has demonstrated that the liver of other mammals, including mouse, dog, and horse, contains edited apo B mRNA and is capable of synthesizing apo B-48 (Greeve et al. 1993). The biologic advantage to the liver cell of elaborating both isoforms of apo B, however, remains obscure. Hepatic apo B mRNA editing in the rat and mouse is developmentally regulated (Wu et al. 1990, Higuchi et al. 1992) and occurs in close temporal association with induction of the enzymes associated with hepatic triglyceride synthesis (Jamdar et al. 1978). Other studies have demonstrated that hepatic apo B mRNA editing is regulated in adult rats following treatment with thyroid hormone (Davidson et al. 1988), and also following fasting and refeeding a high-carbohydrate diet (Baum et al. 1990). These observations, in conjunction with the developmental studies noted here, suggest that alterations in hepatic triglyceride metabolism may be an important regulator of apo B mRNA editing and perhaps, in turn, function as an important mechanism to regulate apo B gene expression. Although this hypothesis may be true, exceptions to the paradigm have recently emerged from studies of rats treated with dexamethasone, where massive hepatic triglyceride accumulation is found in the absence of alterations in hepatic apo B mRNA editing (Inui et al. 1992). Of interest is the observation that apo B mRNA editing occurs as an intranuclear event, coincident with splicing and polyadenylation (Lau et al. 1991b), and is thus topographically distinct from complex lipid synthesis, which occurs within the endoplasmic reticulum. Although no clear mechanism has yet been found to account for the changes in hepatic apo B mRNA editing following nutritional and hormonal manipulations (as described later here), a major objective of further research will be the elucidation of the importance of distinct elements of hepatic lipid flux on apo B mRNA editing.

Apo B mRNA editing is developmentally regulated in the small intestine of several mammals, including humans (Teng et al. 1990b). An extensive evaluation (Teng et al. 1990b) revealed that intestinal apo B mRNA editing begins at approximately 12–13 weeks of gestation (10%), and that by 19 weeks apo B mRNA is edited to the same extent as in the adult (80%–90%). Other important information to emerge from this study was that both edited and unedited apo B mRNA were detectable in the adult small intestine and, as evidenced by incorporation of radiolabeled amino acids into immunoprecipitable apo B-100 and apo B-48, that both proteins were actively synthesized and secreted from adult human small intestinal organ culture explants into the medium (Teng et al. 1990b). These findings demonstrate that both the fetal and adult human small intestine have the capacity to synthesize apo B-100 in addition to apo B-48, although the proportion of apo B-100 was <1% of total apo B in the adult small intestine (Teng et al. 1990b). In this same study, Teng et al. were able to demonstrate, with the use of reverse transcription coupled with polymerase chain reaction amplification, that apo B mRNA was present at low levels in a number of human fetal tissues and, more interestingly, that it was edited in every tissue except the liver. These findings have been confirmed by others, who used chimeric minigenes containing the apo-B RNA-editing sequence, and suggest that the requisite editing machinery is present in cells other than small intestinal enterocytes (Bostrom et al. 1990). This then raises the intriguing question of the possible function of apo B RNA-editing machinery in cells that contain trivial amounts of apo B mRNA. The most appealing possibility is that other RNA species may undergo posttranscriptional editing, as has been described for glutamate-gated ion channels in the mouse brain (Sommer et al. 1991).

In regard to the developmental regulation of apo B mRNA editing in the small intestine, several groups have attempted to use the Caco-2 cell line as a model of enterocytic differentiation in which to recapitulate elements of this process in vitro [for a review, see Giannoni et al. (1994b)]. Initial reports of a large increase in apo B mRNA editing following culture of Caco-2 cells on semipermeable filters (Jiao et al. 1990) could not be reproduced (Giannoni et al. 1994b). Furthermore, with regard to fully differentiated Caco-2 cells, there was no evidence of modulation of apo B mRNA editing in response to alterations in cellular cholesterol, fatty acid, triglyceride, or phospholipid flux, suggesting that, unlike the rat liver, Caco-2 cells are unable to modulate apo B mRNA editing in response to alterations in lipid flux (Giannoni et al. 1994b).

• Sequence Requirements for Site-Specific Cytidine Deamination

In parallel with the advances made through understanding of the metabolic regulation of apo B mRNA editing, a major technical breakthrough occurred with the description that cell extracts, prepared from tissues competent to edit endogenous apo B mRNA, were capable of performing the same reaction on a synthetic apo B RNA template in vitro (Driscoll et al. 1989). Several reports have now confirmed that the RNA sequence within ~15 nucleotides flanking either side of the edited cytidine at position 6666 contains the requisite information to direct apo B RNA editing. Initial studies concluded that the nine nucleotides immediately flanking the edited base were not a stringent component of the recognition sequence (Chen et al. 1990). Other work (Shah et al. 1991) demonstrated, however, that an 11-nucleotide motif, located five nucleotides downstream of the edited base (UGAUCAGUAUA), was essential to apo B RNA editing since almost all mutations in this motif greatly reduced or eliminated in vitro RNA editing. Further work has confirmed these findings (Backus and Smith 1992) and it was proposed that this region of apo B RNA be termed the *mooring sequence* (Backus and Smith 1992). The distance of five nucleotides between the edited base and the mooring sequence was found to be optimal, with reduced editing efficiency noted following either additions to or deletions from this region, which was termed the *spacer sequence* (Backus and Smith 1992). The model proposed by these workers was recently confirmed and extended by others who demonstrated the importance of regions of apo B RNA 3′ to the edited base (Driscoll et al. 1993). A 14-nucleotide motif located five nucleotides upstream of the edited base (CUGCAGACAUAUAU) was found in which mutations reduced editing efficiency (Driscoll et al. 1993). Although this region is not as critical as the 11-nucleotide mooring sequence, its composition is likely to be an important factor in the overall efficiency of in vitro apo B RNA editing with

different templates and, accordingly, was named the *efficiency sequence* (Driscoll et al. 1993).

The apo B mRNA-editing reaction itself is most probably a cytidine deamination. This has been established independently by two groups who demonstrated that the edited apo B RNA, following digestion to nucleoside monophosphates and two-dimensional thin-layer chromatography, contained the edited base as uridine (Bostrom et al. 1990, Hodges et al. 1991). Recent work from one of these groups has now extended these findings by demonstrating that a deamination and not a base-exchange reaction accounts for the alteration of cytidine to uridine, although it remains a possibility that transamination is involved (Johnson et al. 1993). As these authors argued, there are substantial objections to this possibility, however, including the absence of reversibility and the independence from cofactors (Johnson et al. 1993).

Previous work demonstrated that mammalian apo B cDNAs flanking the edited base were highly conserved, particularly within 29 nucleotides immediately surrounding nucleotide 6666 (Teng et al. 1990a). Extending this work, Teng and Davidson (1992) found that the chicken apo B cDNA sequence from the homologous region was <70% conserved. This was important since endogenous chicken intestinal apo B mRNA was unedited and a synthetic chicken apo B RNA template was not editable by mammalian intestinal cell extracts (Teng and Davidson 1992). With the use of in vitro apo B RNA transcribed from a mammalian apo B cDNA template, it was demonstrated that chicken intestinal extracts were not competent to edit alone, but, surprisingly, they were found to enhance the efficiency with which mammalian extracts performed in vitro apo B RNA editing on a synthetic template (Teng and Davidson 1992). Thus, the chicken apo B RNA template is not an editable sequence, but chicken intestinal extracts, while unable to perform in vitro editing of a mammalian apo B RNA template when added alone, enhance the activity of mammalian intestinal extracts (Teng and Davidson 1992). Further characterization of this enhancement demonstrated that it is mediated by a protein(s) and is not dependent upon cofactors or other nucleotides (Teng and Davidson 1992).

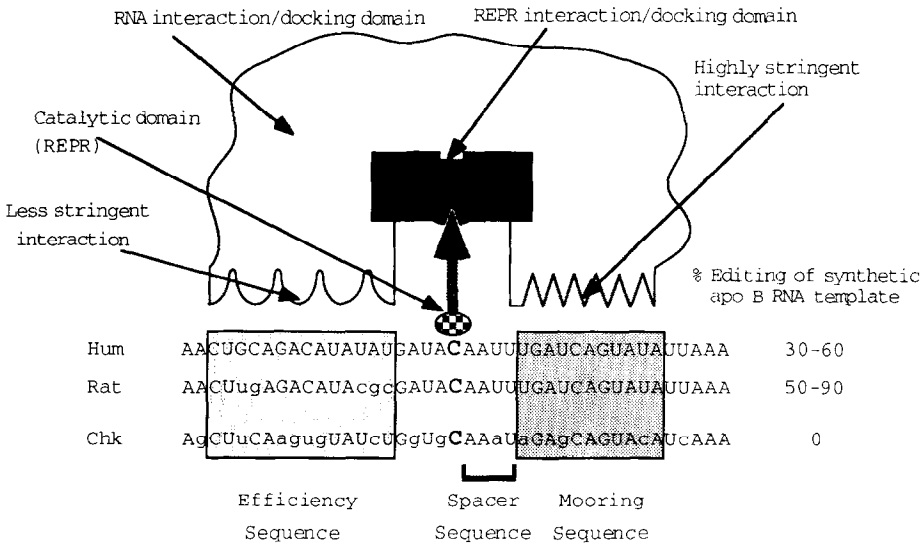

Figure 1. Working model of apolipoprotein B (apo B) mRNA editing enzyme. The model predicts that the editing enzyme is composed of multiple domains, including an RNA interaction–docking domain that recognizes the substrate apo B RNA and contains a separate domain into which the catalytic component of the editing enzyme (REPR or rat apo B RNA-editing protein) must fit. The RNA interaction domain has two separate levels of stringency in terms of apo B RNA sequence: a high-stringency domain that recognizes an 11-nucleotide mooring sequence downstream of the edited base and a less stringent interaction with a 14-nucleotide efficiency sequence located upstream of the edited base. Apo B RNA sequences from human (hum), rat, and chicken (chk) are included for comparison, along with the relative editing efficiency of the respective RNA templates in an in vitro assay.

The species-specific features of the apo B RNA sequence flanking the region homologous to nucleotide 6666 in human apo B cDNA, and the efficiency of in vitro apo B RNA editing, are shown in Figure 1 (lower portion).

• Defining the Machinery Involved in Site-Specific Cytidine Deamination

Since the initial demonstration of in vitro apo B RNA editing (Driscoll et al. 1989), the underlying molecular mechanisms regulating this process have been avidly pursued. Several reports have demonstrated the presence of proteins in cell extracts, which apparently bind with high specificity to the apo B RNA sequence flanking the edited base. One of the first reports was of a 40-kD protein from rat liver nuclei that was UV cross-linked to rat apo B RNA (Lau et al. 1991a). Other earlier reports suggested the size of the native editing complex to be 125 kD, as determined by gel filtration chromatography (Driscoll and Casanova 1990). These reports were later extended by the demonstration of proteins of 43 and 66 kD, which were UV cross-linked from rat liver and intestinal extracts to rat or human apo B RNA (Navaratnam et al. 1993b, Harris et al. 1993). These proteins were found to be associated with apo B RNA prior to detectable editing (Harris et al. 1993), findings in support of previous observations from this group that apo B RNA-editing involves the sequential assembly of a large complex, referred to as an *editosome* (Smith et al. 1991). There have been equally persuasive arguments against this model (Garcia et al. 1992). It has been demonstrated that these UV cross-linking proteins from cell extracts are unlikely to be related to apo B RNA editing since an indistinguishable pattern of cross-linking proteins was obtained with rat liver and baboon intestinal extracts when incubated with luciferase RNA (Driscoll et al. 1993). At present, there is no clear consensus as to the nature, significance, and identity of these various proteins detectable by UV cross-linking.

The findings just described here, with regard to the enhancement of apo B RNA editing by chicken intestinal extracts, suggested a different approach to the problem of identifying apo B RNA-editing proteins. Rat intestinal RNA was size fractionated and aliquots injected into *Xenopus* oocytes, which were then used as a source of in vitro editing

activity. Following supplementation with chicken intestinal extracts, a pool of size-fractionated intestinal RNA was identified with editing activity, which was progressively enriched until a single clone was identified (Teng et al. 1993). This clone was characterized and found to be a unique cDNA, referred to by the acronym REPR (*r*at apo B RNA-*e*diting *pr*otein). REPR encodes a 229-residue protein and, following expression in *Xenopus* oocytes, is able to edit a synthetic apo B RNA template, but only in the presence of a source of complementation activity, such as chicken intestinal extract (Teng at al. 1993). Several features of REPR are of interest. First, a region in the carboxyl terminus was identified with a striking leucine periodicity reminiscent of a leucine zipper motif. The possibility that this region was involved in the formation of a heterodimeric complex was tested by eliminating the carboxyl terminal region of the cDNA by linearization with a Sty I site located 5′ to the origin of the leucine zipper. RNA was then transcribed from the linearized template and injected into oocytes. Homogenates prepared from the truncated REPR failed to show editing activity (Teng et al. 1993). Other interpretations of this experiment should be considered, however, particularly since the region containing the leucine repeats has no obvious α helicity and additionally is rich in proline residues, which are known to break α helices. Our laboratory has recently cloned the human homologue of REPR and determined that this apparent leucine zipper is not present (Hadjiagapiou et al. 1994). Thus, a major question to emerge from these findings is the nature of the interaction between REPR and the complementation factor(s) that regulate apo B mRNA-editing. The human protein, referred to as HEPR (*h*uman apo B RNA- *e*diting *pr*otein), contains 236 residues and demonstrates 69% homology to REPR at both the amino acid and nucleotide level (Hadjiagapiou et al. 1994). Further analysis of the predicted amino acid sequence of REPR revealed a conserved histidine and paired cysteine residues in a homologous location to the zinc-binding region of other cytidine deaminases (Navaratnam et al. 1993a). Additionally, apo B RNA-editing activity of small intestinal extracts was abolished by incubation with the zinc chelator 1,10-*o*-phenanthroline but not the inactive analogue (Navaratnam et al. 1993a). It was also demonstrated that oocyte homogenates expressing REPR were found to have cytidine deaminase activity (Navaratnam et al. 1993a). Taken together, therefore, the data strongly suggest that REPR is a cytidine deaminase. The most plausible hypothesis to emerge from these studies would predict that REPR is the catalytic component of the apo B mRNA- editing complex (Figure 1). The obligate requirement of additional factor(s) for REPR to mediate in vitro apo B RNA editing suggests that the editing complex contains several distinct domains. These must include domains that recognize the apo B RNA template and position the catalytic component (REPR) over the cytidine to be edited. Studies described earlier here suggest that the interaction of the editing protein with the RNA motif downstream of the edited base is a highly stringent determinant, and that a less stringent interaction occurs with a region upstream of the edited base (Figure 1). Whether REPR or HEPR possesses intrinsic RNA-binding activity is currently under evaluation.

• Apolipoprotein B mRNA Editing as a Novel Form of Gene Therapy for Hypercholesterolemia

As described earlier here, the catabolic fate of apo B-100 and apo B-48 is divergent. It remains unknown why the human liver is unable to edit even a small portion of apo B mRNA, whereas the liver of many other mammals appears competent to do so. Recent studies have determined that human liver extracts will complement the activity of oocyte homogenates expressing REPR and will facilitate in vitro editing of a mammalian apo B RNA (Giannoni et al. 1994a). Thus, like chicken intestinal extracts, which themselves are not competent to edit apo B RNA, human liver extracts will complement the activity of REPR, suggesting that other components of the editing complex may be widely distributed. The nature and function of these factor(s), however, remain a subject of intense investigation. Transfection of REPR was undertaken into human HepG2 cells, a hepatoma cell line that contains only unedited apo B mRNA and that synthesizes and secretes only apo B-100 (Giannoni et al. 1994a). This experiment resulted in the acquisition of apo B RNA-editing activity by HepG2 cells and the synthesis and secretion of apo B-48 in addition to apo B-100 (Giannoni et al. 1994a). These findings emphasize the potential of introduction of REPR into liver cells as a means of truncating apo B-100 in human subjects who overproduce apo B or who have pathologically elevated levels of Lp(a), particularly in the latter instance, since there is no really effective pharmacotherapy. The underlying rationale for such an approach is strengthened by the demonstration that LDL levels are generally lower in animal species where hepatic apo B mRNA is edited (Greeve et al. 1993). Additionally, as recently reviewed, subjects with truncations of apo B, which arise from somatic mutations, are clinically associated with syndromes of hypobetalipoproteinemia, and heterozygotes will typically manifest total plasma cholesterol levels <140 mg/dL and LDL cholesterol levels <50 mg/dL [for a review, see Linton et al. (1993)]. Furthermore, these heterozygotes appear to be protected against coronary atherosclerosis (Linton et al. 1993). The implications of this association are that the targeted introduction of truncations in liver-derived apo B, by means of hepatic gene therapy, may be potentially beneficial in subjects who have elevated circulating levels of apo B-100.

Future developments in this area will undoubtedly focus on the nature of the complementation factor(s) and the mechanisms of apo B RNA recognition. It remains a major challenge to molecular biologists to clone proteins based only on a knowledge of their biologic activity. Thus, a substantial obstacle is the issue of whether the complementation factor(s) is single or multiple and whether its interaction with REPR is dependent upon the presence of apo B RNA. A larger question is the function of this complementation factor(s) in tissues where apo B RNA editing does not take place. Insight into the molecular mechanisms of this interesting process will be illuminating for many areas of biology.

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