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# APOBEC-1 MEDIATED RNA EDITING

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RNA editing defines a molecular process by which a nucleotide sequence is modified in the RNA transcript and results in an amino acid change in the recoded message from that specified in the gene. We will restrict our attention to the type of RNA editing peculiar to mammals, ie nuclear C to U RNA editing. This category of RNA editing contrasts with RNA modifications described in plants, ie organellar RNA editing (reviewed in [1]). Mammalian RNA editing is genetically and biochemically classified into two groups, namely insertion-deletional and substitutional [2]. Substitutional RNA editing is exclusive to mammals, again with two types reported, namely adenosine to inosine and cytosine to uracil (C to U) [3, 4]. This review will examine mammalian C to U RNA editing of apolipoproteinB (apoB) RNA and the role of the catalytic deaminase Apobec-1 [5, 6]. We will speculate on the functions of Apobec-1 beyond C to U RNA editing as implied from its ability to bind AU-rich RNAs and discuss evidence that dysregulation of Apobec-1 expression might be associated with carcinogenesis through aberrant RNA editing or altered RNA stability.

## Apobec-1 mediated C to U RNA editing: Overview, molecular mechanisms and functional contstraints

C to U apoB RNA deamination is exquisitely precise, targeting a single cytidine within a spliced ~14kb nuclear apoB mRNA, creating a **U**AA termination codon in the edited transcript from a genomically templated **C**AA (glutamine) codon [3, 7]. This site-specificity is regulated through stringent interactions of both *cis*-acting elements and stoichiometric regulation of *trans*-acting factors within the holo-enzyme complex. The *cis*-acting elements are well described [reviewed in [3]] and span ~50 nucleotides flanking the edited base with a 3′ 11-nt mooring sequence embedded in an AU-rich context which together with a 5′ efficiency sequence [8, 9] has been speculated to adopt a stable secondary structure that enhances specificity [10–12]. The minimal core of the C to U RNA editing holo-enzyme contains two proteins, namely Apobec-1, the RNA-specific cytidine deaminase [5] and a requisite cofactor, Apobec-1 complementation factor (ACF), which represents the RNA binding subunit [13, 14]. Recombinant Apobec-1 and ACF are together necessary and sufficient to mediate >90% C to U editing of a synthetic apoB RNA, supporting the concept that these two proteins represent a minimal functional enzyme complex [13, 14]. Apobec-1 is required for RNA editing in-vivo as evidenced by the complete loss-of-function in *Apobec1*$^{-/-}$ mice, indicating that there is no redundancy with other cytidine deaminases [15–17]. On the other hand, despite biochemical evidence for complementation of Apobec-1 mediated C to U deaminase activity in-vitro, there is as yet no definitive evidence that *Acf* is genetically required for apoB RNA editing in-vivo. From the perspective of mammalian physiology, apoB RNA editing in-vivo is not an all or nothing process but rather exhibits tissue and cell-specific regulation including developmental, hormonal and nutritional (reviewed in [18]). More specifically, C to U RNA editing of apoB RNA can vary from <1%

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U (as in human liver, [19]) to >90% U (as in human small intestine, [20, 21]). Furthermore, despite the 2-log range of C to U apoB RNA editing, site specificity is virtually always maintained (ie nucleotide 6666). How is apoB RNA editing constrained with such fidelity and how is enzymatic activity modulated? Answers to these questions, which in turn raise implications for alternative RNA targets, have emerged from studies of the subcellular itinerary of the core enzyme components and from studies examining the composition and role of other auxiliary factors.

## Cellular compartmentalization of Apobec-1 and ACF

Studies have demonstrated that both Apobec-1 and ACF undergo nuclear-cytoplasmic shuttling [22, 23] and since Apobec-1 and ACF interact physically, considerable effort has been directed to resolve whether this nuclear-cytoplasmic itinerary involves coordinated or independent transport processes. This is an important objective in view of the demonstration that C to U RNA editing is a nuclear event [24, 25]. Accordingly it is reasonable to speculate that increasing nuclear accumulation of the core enzyme components might in turn augment targeted RNA deamination. There is experimental support for this latter prediction, for example modulation of apoB RNA editing activity in conjunction with increased nuclear abundance of ACF [26–28]. Several functional motifs in Apobec-1 have been implicated in its subcellular distribution, including a bipartite nuclear localization sequence (NLS) at the amino-terminus and a nuclear export signal (NES) at the carboxy terminus [22, 23, 29, 30]. However none of these motifs were able to confer autonomous cytoplasmic export or nuclear import activity to a reporter protein [23] raising the question of whether Apobec-1 is the “driver” or the “passenger” in nuclear-cytoplasmic shuttling. On the other hand, ACF contains a nuclear localization signal (NLS) that efficiently redirects a cytoplasmic reporter protein to the nucleus [31]. These findings imply that ACF has the capacity to drive nuclear accumulation of heterologous proteins. Endogenous ACF, at least in human and murine tissues, reveals predominantly nuclear localization (Blanc, V and Davidson, NO unpublished data), even in cells that do not express Apobec-1, suggesting that ACF may drive nuclear transport of Apobec-1. Nuclear predominance of ACF was earlier confirmed in studies using epitope-tagged ACF expressed in rat hepatoma and monkey COS cells [31]. On the other hand studies in rat liver have demonstrated endogenous ACF in both nuclear and cytoplasmic compartments with comparable immunoreactivity in biochemical fractionation studies, yet after correcting for the total yields of cytoplasmic protein, the authors suggest that the dominant pool of ACF (96%) may be cytoplasmic [32]. Some of these apparent discrepancies may reflect species or methodologic issues. Resolution of the trafficking of endogenous ACF and Apobec-1 will require additional targeted mutant cell and animal lines, since to our knowledge there are no cells that express endogenous Apobec-1 yet lack ACF. In addition, limiting abundance of Apobec-1 in mammalian cells and the lack of efficient detection reagents currently preclude a definitive resolution of the relative role of these factors and their subcellular distribution under physiologic conditions.

Aside from Apobec-1 and ACF, the size and definitive protein composition of the apoB RNA editing holo-enzyme are incompletely resolved. However many candidate proteins have been proposed to function as components of a multimeric “editosome” based on their capacity to bind to apoB mRNA and/or interact with Apobec-1 [32, 33]. Most, including CUGBP-2, GRY-RBP, KSRP, hnRNPC1, ABBP1, ABBP2 [34–39], appear to inhibit C to U editing. The physiological relevance of these cofactors is implied from studies showing that the developmental regulation of apoB RNA editing is associated with decreased expression of CUGBP-2, followed by upregulation of Apobec-1 and ACF expression and concomitant down-regulation of GRY-RBP and hnRNPC1 [40]. These observations suggest that mammals have evolved adaptations to insure targeted and efficient C to U deamination of specific RNA targets and to limit potentially deleterious editing events. The emerging

consensus, based on the demonstration that these candidate cofactors interact physically with Apobec-1 and/or ACF, points to a model in which C to U RNA editing efficiency and fidelity depend on the stoichiometry of ACF and Apobec-1 and the accessibility of target RNAs.

Attempts to pursue the in-vivo stoichiometry of Apobec-1 and ACF have to date been limited by the surprising finding that germline deletion of *Acf* was early embryonic lethal [41]. Heterozygous $Acf^{+/-}$ mice, however, are viable and demonstrate the expected 50% reduction in ACF expression in liver, small intestine and kidney, with no change in Apobec-1 expression [41]. Despite a 50% reduction in ACF expression in $Acf^{+/-}$ mice, however, hepatic apoB RNA C to U editing at the canonical site was significantly *increased*, suggesting that decreasing ACF availability might paradoxically increase Apobec-1 mediated editing efficiency. Although the explanation for this observation is yet to be established biochemically, it is tempting to speculate that reducing ACF expression may attenuate inhibitory cofactor function, thereby increasing Apobec-1 mediated C to U RNA editing activity. It is tempting to speculate that the functional constraints on Apobec-1 mediated activity beyond apoB RNA may also reflect this chaperone role of ACF. Definitive resolution of these questions will require the establishment of conditional *Acf* deletor mice and ACF transgenic lines.

## Novel RNA targets for Apobec-1: Insights from animal models

In addition to its canonical target for C to U RNA editing (ie apoB), there is evidence that the neurofibromatosis type 1 RNA (NF1 RNA) undergoes C to U editing within an alternatively spliced exon in a subset of patients with peripheral nerve sheath tumors [42, 43]. This alternative target is to date the only known RNA editing substrate for Apobec-1 at physiological levels of expression (see discussion below for gain-of-function phenotypes with forced transgenic expression of Apobec-1).

Beyond its C to U deaminase activity on RNA substrates, Apobec-1 is an AU-rich RNA binding protein with a consensus binding site **UUUN[A/U]U** embedded in the 3′ untranslated region (3′UTR) of RNAs exhibiting rapid turnover, including c-myc, TNF-α and IL-2 [44]. Forced overexpression of wild-type, but not RNA binding defective Apobec-1, increased c-myc mRNA stability in F442 cells, suggesting that under defined conditions Apobec-1 has the capacity to interact with candidate AU-rich RNAs and modulate mRNA stability [44]. Since many of these candidate RNAs are involved in cytokine signaling, these findings imply that altered expression or subcellular localization of Apobec-1 may modulate a range of AU-rich, unstable RNAs. Other workers have demonstrated that Apobec-1 participates in nonsense mediated RNA decay, again suggesting a wider role in RNA metabolism beyond C to U RNA editing [22]. These possibilities have been pursued using mouse genetic models as summarized below.

## Loss-of-function phenotypes in *Apobec-1*$^{-/-}$ mice

*Apobec-1*$^{-/-}$ mice are healthy and viable yet demonstrate significantly reduced numbers of regenerating small intestinal crypts following radiation injury, which correlated with decreased cyclooxygenase 2 (COX-2) mediated stimulation of prostaglandin E2 (PGE2) synthesis, a known mediator of intestinal proliferation and the response to injury [45]. COX-2 gene expression is regulated at both transcriptional and post-transcriptional levels [46, 47]. In regard to post-transcriptional regulation, COX-2 mRNA contains multiple copies of AU-rich elements, among which a 116 nt AU-rich motif was demonstrated to mediate COX-2 mRNA decay in association with alterations in the expression of the RNA binding protein HuR [48], a protein with homology to ACF [14]. Apobec-1/COX-2 RNA complexes were immunoprecipitated from irradiated mouse intestinal epithelial cells and

that Apobec-1 confered stability to a luciferase reporter chimeric RNA containing COX-2 mRNA 3′UTR [45]. Taken together, these data suggest that Apobec-1 binds the AU-rich 3′UTR of COX-2 mRNA, stabilizing this mRNA and increasing PGE2 synthesis. Interestingly, *Apobec-1*$^{-/-}$ mice also showed reduced steady state levels of c-Myc mRNA [49], supporting previous observations (in F442) cells that Apobec-1 may modulate mRNA stability of this transcript [44].

A link was sought between Apobec-1 and COX-2 in the context of intestinal tumorigenesis, prompted by findings that prostaglandins regulate angiogenesis and cell proliferation and also that increased PGE2 production was associated with colon tumor development [50] and progression from adenoma to carcinoma [51]. Accordingly, it was predicted that attenuating COX-2 mRNA stabilization in *Apobec-1*$^{-/-}$ mice, would have a protective effect against intestinal adenoma formation in mice genetically predisposed to develop intestinal polyposis (*Apc*$^{min/+}$). Compound [*Apc*$^{min/+}$, *Apobec-1*$^{-/-}$] mice exhibited reduced tumor burden with increased intestinal apoptosis and reduced proliferation in the setting of attenuated COX-2 mRNA and reduced PGE2 production in the adenomatous tissues [49]. There was decreased abundance of other mRNAs including GM-CSF, EGFR and TNFα, all of which contain Apobec-1 consensus binding sites embedded in an AU-rich 3′UTR, in tumors from compound [*Apc*$^{min/+}$, *Apobec-1*$^{-/-}$] mice compared to the parental *Apc*$^{min/+}$ line. Since these putative RNA targets are expressed in distinct cell populations in the intestinal tract, key questions emerging from these findings are to understand the cell-specific factors involved in mediating Apobec-1:RNA interactions. In other words, is Apobec-1 expression within small intestinal enterocytes and colonocytes the major driver in regulating the stability of these candidate AU-rich mRNAs or is an adjacent cell compartment, such as stromal, mesenchymal, macrophage or vascular cell potentially implicated? Preliminary unpublished information (Blanc, V, Davidson, NO, unpublished observations) suggests that Apobec-1 is expressed in all these cellular compartments suggesting in principle that these target RNAs would be potential substrates. In addition, it is worth emphasizing that there is no detectable apoB mRNA in these non-epithelial cell types (Blanc, V, Davidson, NO, unpublished observations), raising the intriguing question of the range of physiologic RNA targets and the constraints for Apobec-1:RNA interactions in cells that do not express the canonical target RNA. Important lipid metabolism phenotypes have previously been elicited in *Apobec-1*$^{-/-}$ mice that reflect functional alterations in apoB RNA editing (ie apoB100-only), specifically spontaneous hypercholesterolemia when *Apobec-1*$^{-/-}$ mice are crossed into the *LDLR*$^{-/-}$ background [52] (a phenocopy of Familial Hypercholesterolemia) and also acquired lethal intestinal lipotoxicity when *Apobec-1*$^{-/-}$ mice are crossed into a conditional intestinal Mttp deletor background [53].

A new RNA target for Apobec-1 was identified through an unexpected loss-of-function phenotype in *Apobec-1*$^{-/-}$ mice. Quantitative trait locus mapping revealed a locus for gallstone susceptibility (*Lith6*) spanning the structural gene encoding APOBEC-1 and we demonstrated that *Apobec-1*$^{-/-}$ mice fed a lithogenic diet were dramatically more susceptible to form cholesterol gallstones [54]. The basis for this phenotype was reduced expression of the enzyme Cyp7a1, which catalyzes the initial and rate-limiting step in bile acid synthesis [55]. The 3′UTR of Cyp7a1 mRNA spans more than 2kb and contains several AUUUA motifs amidst consensus binding sites for Apobec-1. In-vitro binding assays, as well as in-vivo co-immunoprecipitation, revealed that Apobec-1 binds Cyp7a1 mRNA. Moreover, Cyp7a1 mRNA is known to be highly unstable in human and rodent liver (half-life of 30–60 minutes), raising the possibility that Apobec-1 binding to AU-rich elements would in turn increase mRNA stability. Cyp7a1 3′UTR conferred RNA instability to a stable reporter construct in a variety of heterologous cells, a direct effect of Apobec-1 in modulating chimeric mRNA stability in these settings could not be established [54]. These findings suggest the possibility that the effects of Apobec-1 are indirect, involving other

mediator(s) and future work is required to address this question. Among the intriguing possibilities is the putative role played by changes in micro RNA processing and target selection, since evidence from A to I RNA editing deaminases has indicated that up to 10% of all micro RNAs are subject to enzymatic modification [56, 57]. In addition, the Apobec-1 family member activation-induced cytidine deaminase (AID) was downregulated by the lymphocyte-specific miR-155 [58], suggesting that there exist a range of mechanisms for regulating the expression of genes with great mutagenic potential.

## Gain-of-function phenotype in Apobec-1 transgenic animals

Forced liver-specific transgenic overexpression of Apobec-1 (in both mice and rabbits) produced hepatic dysplasia and hepatocellular carcinoma [59]. Interestingly, apoB mRNA itself was extensively edited at multiple cytidines downstream of the canonical cytidine 6666 [59], a phenomenon referred to as hyperediting. The presumed basis for the loss of specificity is the altered stoichiometry of Apobec-1:ACF as a result of the forced overexpression of Apobec-1. This presumption was validated in studies demonstrating C to U hyperediting as a result of forced overexpression of Apobec-1, in-vitro [60–62]. Hyperediting in this context revealed cis-acting constraints with a nearest neighbor A or T preference but was independent of the downstream mooring sequence in apoB RNA [60]. The role for auxiliary factors, specifically ACF, in constraining Apobec-1 site selection is yet to be determined experimentally in-vivo. Studies using $Acf^{+/-}$ mice as well as ACF transgenic and conditional $Acf^{-/-}$ deletor mice will be informative in dissecting these issues. As alluded to above, studies in $Acf^{+/-}$ mice revealed an increase in C to U editing of hepatic apoB RNA but no evidence for hyperediting [41], suggesting that there is yet much to learn regarding the stoichiometric proportions of ACF and Apobec-1 within the nuclear C to U editosome. Using liver-specific Apobec-1 transgenic mice, Yamanaka and colleagues identified a novel candidate RNA editing substrate, NAT1 [63] containing multiple C to U editing sites with clusters in proximity to regions showing homology to the apoB RNA mooring sequence. As consequence of C to U RNA hyperediting, nine stop codons were introduced generating a range of truncated forms of NAT1. NAT1 is highly conserved and exhibits homology to the carboxy-terminal portion of eukaryotic translation initiation factor 4G, suggesting that the introduction of these translational stop codons might lead to loss-of-function as a result of C to U RNA editing, although this awaits formal examination. By contrast, $Nat1^{-/-}$ embryonic stem cells failed to differentiate in response to retinoic acid and exhibited impaired expression of the cell cycle inhibitor p21, demonstrating that the null allele is not viable [64].

In considering the mechanism(s) underlying these gain-of-function phenotypes associated with Apobec-1 overexpression, it is worth noting the finding that recombinant Apobec-1, purified from E. Coli, mediates C to U deamination of single stranded DNA as evidenced in an in-vitro assay using uracil-DNA glycosylase [65]. These findings suggest that Apobec-1, like its ancestral founder Activation induced deaminase (AID) [66] is in theory capable of introducing mutations into somatic DNA as a result of cytosine deamination [67]. The functional constraints on such DNA deamination activity and the role (if any) for cofactors identified in the context of C to U RNA editing mediated by Apobec-1 remain unknown.

## Loss-of-function phenotypes following *Acf* deletion and alterations in auxiliary factor expresssion

As detailed above, the major constraints on Apobec-1 mediated C to U RNA editing are exerted through its requisite interactions with the AU-rich RNA binding protein ACF. Studies using recombinant proteins have established unequivocally that ACF is required for Apobec-1 mediated C to U RNA editing of apoB [13, 14]. However, for reasons outlined

below, the physiological function of ACF itself and by implication the effects of alterations in Apobec-1: ACF stoichiometry on RNA metabolism in general and apoB RNA editing in particular have yet to be defined.

Targeted deletion of *Acf* revealed early embryonic lethality: *Acf*$^{-/-}$ embryos developed until the blastocyst stage (day E3.5) but failed to implant and *Acf* $^{-/-}$ blastocysts isolated from the uterine horns failed to form in vitro outgrowths [41]. These observations imply an essential and non-redundant role for ACF in early embryonic development, which is presumably independent of hepatic or intestinal apoB C to U RNA editing, since embryonic development of the liver and small intestine occurs more than 10 days after blastocyst implantation. While the presumed alternative target(s) for ACF are unknown in this early developmental stage, it is worth noting that cytokines containing AU-rich RNAs, including IL-6 and COX-2, are expressed in murine blastocysts [68] and ACF interactions with these candidate RNAs is certainly worthy of consideration. Extending this suggestion, it is tempting to speculate that the role of ACF in complementing Apobec-1 mediated C to U apoB RNA editing represents a functional adaptation rather than a primary function. This is germane to the findings in *Acf*$^{-/-}$blastocysts since no Apobec-1 or apoB RNA is detectable at this developmental stage. A loss-of-function phenotype of ACF was explored using siRNA-mediated gene silencing in human hepatoma HepG2 cells, which revealed increased apoptosis and increased active caspase-3 [41], suggesting that ACF knockdown in somatic cells may be associated with a growth phenotype. Since these studies were undertaken in human liver-derived cells that lack Apobec-1 expression, the findings suggest that ACF itself may function in RNA metabolism independent of Apobec-1. This suggestion will need to be pursued using conditional deletor lines and liver-specific overexpression strategies. Additionally the consequences of these alterations in the intestinal tract—where both ACF and Apobec-1 are normally expressed—will further require the development of appropriate conditional deletor and transgenic lines.

## Modulation of Apobec-1:RNA interaction through the auxiliary protein CUGBP-2

CUGBP-2 is a member of a family of RNA binding proteins that bind CUG repeats and functions in several aspects of RNA metabolism. CUGBP-2 interacts with Apobec-1 in a complex containing apoB mRNA and ACF, leading to inhibition of apoB C to U editing [34]. Follow up studies demonstrated a further role for CUGBP-2, specifically in regulating COX-2 RNA stability and translation [69] in intestinal epithelial cells, associated with increased radiation-induced apoptosis. CUGBP-2 binds AU-rich elements located within the first 60 nucleotides of COX-2 mRNA 3′UTR, increasing COX-2 mRNA stability but paradoxically inhibiting COX-2 mRNA translation by impairment of polysomal RNA loading [69]. These findings are of interest in view of observations that Apobec-1 also binds the first 60 nucleotides of COX-2 RNA, indicating that COX-2 mRNA is targeted by several RNA binding proteins that interact with one another (including CUGBP-2, Apobec-1 and HuR) and also with COX-2 RNA, with either similar or antagonistic effects on COX-2 mRNA metabolism [70]. In this regard, preliminary observations (Sessa, K, Blanc, V and Davidson, NO) indicate that ACF also binds COX-2 RNA within the first 60 nucleotides, further expanding the possibilities for combinatorial interactions in RNA metabolism. The physiological implications of these interactions is underscored by observations that Apobec-1, HuR, ACF and CUGBP-2 all undergo nuclear-cytoplasmic shuttling, suggesting that their subcellular itineraries, distribution and stoichiometry may modulate their interactions with COX-2 mRNA. Further work will be required to understand the dynamic interaction of these different factors, their roles in commune RNA targets metabolism and downstream consequences on carcinogenesis.

## Conclusion and future perspectives

Apobec-1 dependent C to U RNA editing is normally constrained to a single nucleotide in a 14,000 base nuclear RNA. The constraints on aberrant editing specifically and on RNA metabolism in general include stringent cis-acting elements and structural motifs within potential RNA targets as well as physical interactions with a range of auxiliary protein factors, each of which exhibit combinatorial control of tertiary and quarternary interactions and stoichiometry through alterations in abundance and subcellular localization. It will be important to define the role of each of these pathways in the posttranscriptional regulation of AU-rich mRNAs encoding oncoproteins, cytokines and growth factors. Finally, it is noteworthy that Apobec-1 RNA itself is a target for posttranscriptional regulation by the RNA binding protein T-cell intracellular antigen-1 (TIA-1) an RNA binding protein that binds AU-rich elements in the 3′UTR and functions primarily to inhibit translation [71]. TIA-1 regulation of Apobec-1 mRNA expression was demonstrated to be at least partially the result of altered mRNA decay, likely reflecting the presence of an AUUUA motif within a minimal consensus site in the 3′UTR of Apobec-1. These findings collectively imply that there is yet further complexity to the regulation of networks of posttranscriptional RNA metabolism and DNA mutator families.

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