RNA Biology 11:10, 1233–1237; October 2014; © 2014 Taylor & Francis Group, LLC

Re-editing the paradigm of Cytidine (C) to Uridine (U) RNA editing

Nicolas Fossat[1,2,*] and Patrick P L Tam[1,2]

[1]Embryology Unit; Children's Medical Research Institute; Westmead, Australia; [2]Discipline of Medicine; Sydney Medical School; University of Sydney; Sydney, Australia

Cytidine (C) to Uridine (U) RNA editing is a post-trancriptional modification that until recently was known to only affect *Apolipoprotein b* (*Apob*) RNA and minimally require 2 components of the C to U editosome, the deaminase APOBEC1 and the RNA-binding protein A1CF. Our latest work has identified a novel RNA-binding protein, RBM47, as a core component of the editosome, which can substitute A1CF for the editing of *ApoB* mRNA. In addition, new RNA species that are subjected to C to U editing have been identified. Here, we highlight these recent discoveries and discuss how they change our view of the composition of the C to U editing machinery and expand our knowledge of the functional attributes of C to U RNA editing.

Keywords: APOBEC1, *Apolipoprotein b*, A1CF, Intestine, RBM47, RNA editing

*Correspondence to: Nicolas Fossat; Email: nfossat@cmri.org.au

Submitted: 09/10/2014

Accepted: 09/10/2014

http://dx.doi.org/10.1080/15476286.2014.996054

Cytidine (C) to Uridine (U) RNA editing was first reported for *Apolipoprotein b* (*Apob*) in the late 1980s.[1,2] There are 2 major isoforms of APOLIPOPROTEIN B proteins: APOB100 that has a molecular weight of about 500 kDa and is produced in the liver, and a shorter version, APOB48, synthesized in the small intestine. After ruling out the possibilities that these protein isoforms were produced by 2 different genes or that APOB48 was a cleavage product of APOB100, sequence analysis of 14121-nucleotide-long *Apob* messenger (m)RNA revealed that APOB48 was in fact the product of a then new process of post-transcriptional modification. The C at position 6666 of *Apob* mRNA is changed to U, creating a premature UAA stop codon such that the edited transcript codes for APOB48 instead of APOB100 in the small intestine.[1,2] The deaminase APOBEC1 was subsequently discovered and was shown to be responsible for the deamination of C6666 into U.[3-5] Consistent with this role, loss of *Apobec1* function in mutant mice abolishes C to U editing of *Apob* mRNA.[6-8] APOBEC1 is the catalytic subunit of a multi-protein complex referred as the C to U editosome.[9,10] While APOBEC1 can directly bind RNA, in vitro experiments suggest that it is not sufficient to elicit editing. Purified recombinant APOBEC1 is unable to edit a synthetic unedited *Apob* RNA by itself and requires a cofactor for this process.[10-12] Until recently, the RNA binding protein (RBP) A1CF (also known as ACF) was the only factor known to partner with APOBEC1 to mediate C to U RNA editing,[10-16] leading to the concept of the minimal core components of the C to U editosome: APOBEC1 and A1CF for editing of *Apob* RNA. Our recent work has identified a novel RBP, RBM47, that can substitute A1CF in vitro and is essential for C to U RNA editing in vivo.[17] In addition, new RNA targets for APOBEC1 editing have been identified through sequencing analysis of the transcriptome of *Apobec1*-null mutant mice.[18,19] Here, we will discuss how these discoveries call for a revised view of the core components of the editing machinery and open new avenues to study the role of C to U RNA editing.

RBM47, a novel requisite cofactor for C to U RNA editing

Rbm47 was identified in a screen as one of the genes that are differentially expressed in the foregut endoderm of embryonic day (E) 8.5 mouse embryo.[20] In addition to the embryonic foregut endoderm, *Rbm47* is expressed in adult

organs such as the liver, the pancreas, the lung and the small intestine.[17] RBM47 protein is conserved between human and mouse and has 3 RNA recognition motifs (RRM). RBM47 was shown to bind RNA in the human epithelial colorectal adenocarcinoma Caco-2 cell line.[17] Analysis of the ENSEMBL database[21] revealed A1CF as a potential paralogue of RBM47, thus pointing to a possible role of RBM47 for C to U RNA editing. *Rbm47* is co-expressed with *Apobec1* and *A1cf* in the epithelial cells of the intestine. RBM47 colocalises with APOBEC1 and A1CF in the nucleus, where RNA editing takes place.[22] RBM47 binds *Apob* mRNA and can interact with APOBEC1 and A1CF via the non-RRM region.[17] In mouse 3T3 fibroblasts (which are inherently void of C to U RNA editing activity) or in vitro, RBM47 was able to substitute A1CF to mediate APOBEC1-editing of *Apob* RNA.[17] In $Rbm47^{gt/gt}$ mice that are deficient for *Rbm47* due to a gene-trap (gt) mutation, C to U editing of *Apob* RNA is impaired.[17] Taken together, these findings show that RBM47 is a new and essential component of the C to U editing machinery.

A new look for the core components of the C to U editosome

In addition to APOBEC1 and A1CF, the other known components of the editosome are the RBPs KHSRP,[13] HNRNPAB (also known as ABBP1),[23] SYNCRIP (GRY-RBP; HNRNPQ),[15,24] HNRNPC1 [25] and CELF2 (CUGBP2),[16] and the co-chaperones DNAJB11 (ABBP2) [26] and BAG4.[27] They were identified by their ability to interact with APOBEC1 or *Apob* RNA and modulate C to U editing.[12-16,23-27] However, in contrast to APOBEC1 and A1CF, these factors inhibit C to U RNA editing.[28] The discovery of RBM47 has added a new component to the C to U editosome. More importantly, it is a component that is required for editing and is sufficient on its own to mediate APOBEC1-editing activity in vitro,[17] a property that is reputed to be unique to A1CF.[10] RBM47 can substitute A1CF for C to U RNA editing.[17] That either A1CF or RBM47 may fulfil the role of a requisite cofactor suggests that the constitution of the core machinery for C to U RNA editing is less stringent than previously anticipated. Furthermore, the potential existence of 2 different core editosomes raises many questions: Does the binding of RBM47 to *Apob* RNA, like for A1CF,[12] involve the essential 11-nucleotide mooring motif downstream of the editing site? Does RBM47 interact with other factors of the editosome? Are these 2 core editosomes performing redundant, complementary or specific functions? Are they acting on same or different RNA targets? Is there any other cofactor still to be discovered that could substitute for A1CF or RBM47 and constitute another core editosome?

In conjunction with APOBEC1, either RBM47 or A1CF is sufficient to elicit editing of *Apob* mRNA but together they do not produce any additive or synergistic effect, signifying that any interaction between these cofactors is not critical for editing.[17] These findings suggest the possibility of functional redundancy between the 2 cofactors. However, while RBM47 is essential for RNA editing in mouse, the role of A1CF in vivo is unclear.[29] $A1cf^{-/-}$ homozygous mutant mice die early during gestation, which preclude a proper analysis of its function. $A1cf^{+/-}$ heterozygous mice are viable and, contrary to the requirement of A1CF for RNA editing in vitro, genetic haplo-insufficiency leads to an increase, rather than a reduction, in the level of editing of *Apob* RNA in the liver and the kidney (in which C to U RNA editing also takes place in rodents) relative to wild type level.[29] In the small intestine of the $A1cf^{+/-}$ heterozygous mice, almost all *Apob* RNA is edited as in the wild type mice, thus making it impossible to detect any enhancement of the C to U editing activity. *Apob* RNA editing is unchanged or slightly reduced in the small intestine or the liver of the heterozygous $Rbm47^{+/gt}$ mice and is abolished in $Rbm47^{gt/gt}$ homozygous mutant mice ([17] and unpublished data). Therefore, RBM47 is a necessary cofactor for C to U RNA editing in vivo while the role of A1CF remains uncertain. In this context, it is imperative to examine the level of *Apob* mRNA editing in conditional *A1cf* mutant mice that are not inflicted with early embryonic lethality. Similarly, it is necessary to test the role of additional putative candidate for C to U RNA editing as well as estimate the level of *Apob* RNA editing in mice that are mutated for other known components of the editosome in order to fully appreciate the contribution of each factor to this process in vivo.

Other putative factors for C to U RNA editing

The identification of RBM47 as a RNA editing factor stems from the discovery of sequence homology with a known C to U editing factor, A1CF.[17] DND1, another putative paralogue of A1CF, can interact with APOBEC1.[30] $Dnd1^{ter}$ mutant mice develop testicular germ cell tumors (TGCT),[31] the incidence of which is modulated by the dosage of *Apobec1*-null allele.[32] *Apobec1* has been shown to affect TGCT susceptibility in a Mendelian manner, as well as via a parent-of-origin trans-generational epigenetic manner whereby a maternally inherited *Apobec1* mutation can affect the tumorigenic susceptibility of 2 generations of offspring regardless of their *Apobec1* genotype.[32] Non-Mendelian bias in the transmission of the *Apobec1-null* and the $Dnd1^{ter}$ alleles were also observed which is reminiscent of the preponderance of heterozygous $A1cf^{+/-}$ individuals obtained from the crossings of *A1cf* mutant mice.[29] The molecular mechanism underpinning this pattern of inheritance and the involvement of RNA editing in this process is presently unknown but these observations highlight a functional connection between DND1, A1CF and APOBEC1. DND1 therefore appears as an obvious candidate for which it would be interesting to examine the role in C to U RNA editing.

APOBEC1 is part of the APOBEC family that can be divided in 5 sub-groups (AICDA, APOBEC1, APOBEC2, APOBEC3 and APOBEC4) containing 11 members in human and 5 members in mouse that are characterized by the presence of at least one zinc-dependent catalytic domain necessary for cytidine deamination.[33,34] Among them, human APOBEC3G can interact with

HNRNPC1, HNRNPAB, SYNCRIP and HNRNPR.[35,36] In the mouse, APOBEC3 can interact with DND1 to counter its inhibitory activity on miRNA function.[30,37] HNRNPC1, HNRNPAB, SYNCRIP, HNRNPR and DND1 are involved in C to U RNA editing and/or related to A1CF.[10,21] While it is tempting to speculate that APOBEC3 proteins and other paralogues of APOBEC1 may similarly engage with C to U RNA editing, the studies so far have failed to observe such activity for these deaminases.[33,34] However, this may be because this was investigated with *Apob*, until recently the only RNA known to be edited, whereas the deaminases may act on other targets yet to be identified.

C to U editing beyond *Apob* mRNA

Apob is a natural RNA target of APOBEC1 editing, while 2 other RNA species, *Nat1* and *Nf1*, can be edited under non-physiological condition.[38,39] 32 new editing sites in 29 new RNA targets have been identified recently by pinpointing single-nucleotide mismatches in the RNA-sequencing reads of the wild type mice (compared to the reference genome: T instead of C or Adenine [A] instead of Guanine [G] for the negative strand transcripts) that were absent in the reads of the *Apobec1*$^{-/-}$ mutant mice.[18] An APOBEC1-editing sequence pattern was discerned in these new APOBEC1-edited RNA, which was subsequently detected in about 400 locations in the mouse genome. Analysis of some of the transcripts from these locations identified 9 additional C to U edited sites.[18] In another study also of the *Apobec1*$^{-/-}$ mutant mice, more than 40 extra edited sites were identified.[19] We analyzed the editing status of the sites localized in *Sult1d1*, *Serinc1*, *Casp6* and *2010106E10Rik* mRNA in the *Rbm47*$^{gt/gt}$ mutant mice. This revealed that the editing of all of them was impaired, suggesting that RBM47 may have a wide coverage of the transcriptome for APOBEC1-mediated editing.[17] Blanc et al. tested some of these new sites and showed that contrary to *Apob* RNA, recombinant APOBEC1 and A1CF were not sufficient to mediate their editing.[19] It will therefore be interesting to determine if RBM47 can bring about the editing of these new sites.

While these discoveries suggest that the function of C to U RNA editing is not only limited to the control of APOB48 protein expression and the formation of chylomicrons,[40] the functional consequence of the editing of these new sites is not known. Of particular interest though is the finding that almost all of these sites are located in the 3' untranslated region (UTR) of mRNA. An attractive hypothesis is that C to U editing modifies the miRNA binding motif that influences the stability of the mRNA.[18] However, the study by Blanc et al. did not find any association of the editing of the miRNA binding sites and the stability of the mRNA, but showed an effect on mRNA translation instead.[19] As C to U RNA editing takes place concomitantly with splicing and poly-adenylation of the mRNA,[22] another intriguing possibility is that editing could generate a AAUAAA motif,[18] a recognition signal known for initiating cleavage and polyadenylation of pre-mRNA.[41]

A role beyond C to U RNA editing

APOBEC1 can bind AU-rich elements to stabilize RNA (e.g. *IL8* mRNA [42,43]), a function that seems to be independent of its editing activity.[42-45] The association of APOBEC1 with *IL8* mRNA requires SYNCRIP,[43] another factor that interacts with APOBEC1 to modulate its editing activity.[15,24] Interestingly, SYNCRIP codes different protein isoforms and the isoform that modulates C to U RNA editing may be different from the one that stabilises *IL8* mRNA.[43] *Apobec1*$^{-/-}$ mice on certain genetic background or maintained on specific diets show variable susceptibility to intestinal tumors and gallstone formation, which may be related to the ability of APOBEC1 to control the stability of *Cox2* and *Cyp7a1* mRNA.[44,45] A1CF and CELF2, another modulator of C to U editing,[16] also bind the AU-rich region of *Cox2* mRNA, and this leads to the stability of the mRNA in the case of CELF2.[10,46,47] In a similar context, the binding of RBM47 to intron and 3' UTR may modulate splicing and/or stabilize different RNA species, including *IL8* mRNA, to prevent tumor progression.[48] In addition, while RBM47, A1CF and APOBEC1 can interact with each other,[17] their individual loss in mice has different phenotypic effect [6-8,17,29] suggesting that they have different functional attributes.

Conclusion

The identification of novel RNA targets of APOBEC1-mediated editing, and the discovery of RBM47 that can act as a core component of the editosome in place of A1CF have garnered renewed interest in C to U RNA editing. The proposition of the common functionality of the potential paralogues of A1CF and APOBEC1 for this process is especially appealing. Future works will test the possibility that the association with different core components may underpin the target specificity of the editing machinery. At this stage, another important task is to characterize the biological role of the editing of the novel RNA targets. It would also be interesting to find out if the event of C to U RNA editing, like that of Adenine (A) to Inosine (I) editing,[49] can impact on a diverse range of biological processes, e.g., cell-cell signaling, growth and homeostasis, and tumorigenesis.[50]

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

We thank Karin Tourle for critical reading of the manuscript.

Funding

Our work is supported by the Australian Research Council (Grant DP130100779) and Mr James Fairfax. NF is the Sir Norman Gregg Research Fellow of CMRI. PPLT is a NHMRC Senior Principal Research Fellow (Grant 1003100).

References

1. Chen SH, Habib G, Yang CY, Gu ZW, Lee BR, Weng SA, Silberman SR, Cai SJ, Deslypere JP, Rosseneu M, et al. Apolipoprotein B-48 is the product of a messenger RNA with an organ-specific in-frame stop codon. Science 1987; 238:363-6; PMID:3659919; http://dx.doi.org/10.1126/science.3659919
2. Powell LM, Wallis SC, Pease RJ, Edwards YH, Knott TJ, Scott J. A novel form of tissue-specific RNA processing produces apolipoprotein-B48 in intestine. Cell 1987; 50:831-40; PMID:3621347; http://dx.doi.org/10.1016/0092-8674(87)90510-1
3. Teng B, Burant CF, Davidson NO. Molecular cloning of an apolipoprotein B messenger RNA editing protein. Science 1993; 260:1816-9; PMID:8511591; http://dx.doi.org/10.1126/science.8511591
4. Navaratnam N, Morrison JR, Bhattacharya S, Patel D, Funahashi T, Giannoni F, Teng BB, Davidson NO, Scott J. The p27 catalytic subunit of the apolipoprotein B mRNA editing enzyme is a cytidine deaminase. J Biol Chem 1993; 268:20709-12; PMID:8407891
5. Hadjiagapiou C, Giannoni F, Funahashi T, Skarosi SF, Davidson NO. Molecular cloning of a human small intestinal apolipoprotein B mRNA editing protein. Nucleic Acids Res 1994; 22:1874-9; PMID:8208612; http://dx.doi.org/10.1093/nar/22.10.1874
6. Hirano K, Young SG, Farese RV Jr., Ng J, Sande E, Warburton C, Powell-Braxton LM, Davidson NO. Targeted disruption of the mouse apobec-1 gene abolishes apolipoprotein B mRNA editing and eliminates apolipoprotein B48. J Biol Chem 1996; 271:9887-90; PMID:8626621; http://dx.doi.org/10.1074/jbc.271.1.380
7. Morrison JR, Paszty C, Stevens ME, Hughes SD, Forte T, Scott J, Rubin EM. Apolipoprotein B RNA editing enzyme-deficient mice are viable despite alterations in lipoprotein metabolism. Proc Natl Acad Sci U S A 1996; 93:7154-9; PMID:8692961; http://dx.doi.org/10.1073/pnas.93.14.7154
8. Nakamuta M, Chang BH, Zsigmond E, Kobayashi K, Lei H, Ishida BY, Oka K, Li E, Chan L. Complete phenotypic characterization of apobec-1 knockout mice with a wild-type genetic background and a human apolipoprotein B transgenic background, and restoration of apolipoprotein B mRNA editing by somatic gene transfer of Apobec-1. J Biol Chem 1996; 271:25981-8; PMID:8824235; http://dx.doi.org/10.1074/jbc.271.42.25981
9. Sowden MP, Ballatori N, Jensen KL, Reed LH, Smith HC. The editosome for cytidine to uridine mRNA editing has a native complexity of 27S: identification of intracellular domains containing active and inactive editing factors. J Cell Sci 2002; 115:1027-39; PMID:11870221
10. Blanc V, Davidson NO. APOBEC-1-mediated RNA editing. Wiley Interdiscip Rev Syst Biol Med 2010; 2:594-602; PMID:20836050; http://dx.doi.org/10.1002/wsbm.82
11. Mehta A, Banerjee S, Driscoll DM. Apobec-1 interacts with a 65-kDa complementing protein to edit apolipoprotein-B mRNA in vitro. J Biol Chem 1996; 271:28294-9; PMID:8910449; http://dx.doi.org/10.1074/jbc.271.45.28294
12. Mehta A, Kinter MT, Sherman NE, Driscoll DM. Molecular cloning of apobec-1 complementation factor, a novel RNA-binding protein involved in the editing of apolipoprotein B mRNA. Mol Cell Biol 2000; 20:1846-54; PMID:10669759; http://dx.doi.org/10.1128/MCB.20.5.1846-1854.2000
13. Lellek H, Kirsten R, Diehl I, Apostel F, Buck F, Greeve J. Purification and molecular cloning of a novel essential component of the apolipoprotein B mRNA editing enzyme-complex. J Biol Chem 2000; 275:19848-56; PMID:10781591; http://dx.doi.org/10.1074/jbc.M001786200
14. Henderson JO, Blanc V, Davidson NO. Isolation, characterization and developmental regulation of the human apobec-1 complementation factor (ACF) gene. Biochim Biophys Acta 2001; 1522:22-30; PMID:11718896; http://dx.doi.org/10.1016/S0167-4781(01)00295-0
15. Blanc V, Navaratnam N, Henderson JO, Anant S, Kennedy S, Jarmuz A, Scott J, Davidson NO. Identification of GRY-RBP as an apolipoprotein B RNA-binding protein that interacts with both apobec-1 and apobec-1 complementation factor to modulate C to U editing. J Biol Chem 2001; 276:10272-83; PMID:11134005; http://dx.doi.org/10.1074/jbc.M006435200
16. Anant S, Henderson JO, Mukhopadhyay D, Navaratnam N, Kennedy S, Min J, Davidson NO. Novel role for RNA-binding protein CUGBP2 in mammalian RNA editing. CUGBP2 modulates C to U editing of apolipoprotein B mRNA by interacting with apobec-1 and ACF, the apobec-1 complementation factor. J Biol Chem 2001; 276:47338-51; PMID:11577082; http://dx.doi.org/10.1074/jbc.M104911200
17. Fossat N, Tourle K, Radziewic T, Barratt K, Liebhold D, Studdert JB, Power M, Jones V, Loebel DA, Tam PP. C to U RNA editing mediated by APOBEC1 requires RNA-binding protein RBM47. EMBO Rep 2014; 15:903-10; PMID:24916387; http://dx.doi.org/10.15252/embr.201438450
18. Rosenberg BR, Hamilton CE, Mwangi MM, Dewell S, Papavasiliou FN. Transcriptome-wide sequencing reveals numerous APOBEC1 mRNA-editing targets in transcript 3' UTRs. Nat Struct Mol Biol 2011; 18:230-6; PMID:21258325; http://dx.doi.org/10.1038/nsmb.1975
19. Blanc V, Park E, Schaefer S, Miller M, Lin Y, Kennedy S, Billing AM, Ben Hamidane H, Graumann J, Mortazavi A, et al. Genome-wide identification and functional analysis of Apobec-1-mediated C-to-U RNA editing in mouse small intestine and liver. Genome Biol 2014; 15:R79; PMID:24946870; http://dx.doi.org/10.1186/gb-2014-15-6-r79
20. Loebel DA, Studdert JB, Power M, Radziewic T, Jones V, Coultas L, Jackson Y, Rao RS, Steiner K, Fossat N, et al. Rhou maintains the epithelial architecture and facilitates differentiation of the foregut endoderm. Development 2011; 138:4511-22; PMID:21903671; http://dx.doi.org/10.1242/dev.063867
21. Flicek P, Ahmed I, Amode MR, Barrell D, Beal K, Brent S, Carvalho-Silva D, Clapham P, Coates G, Fairley S, et al. Ensembl 2013. Nucleic Acids Res 2013; 41:D48-55; PMID:23203987; http://dx.doi.org/10.1093/nar/gks1236
22. Lau PP, Xiong WJ, Zhu HJ, Chen SH, Chan L. Apolipoprotein B mRNA editing is an intranuclear event that occurs posttranscriptionally coincident with splicing and polyadenylation. J Biol Chem 1991; 266:20550-4; PMID:1939106
23. Lau PP, Zhu HJ, Nakamuta M, Chan L. Cloning of an Apobec-1-binding protein that also interacts with apolipoprotein B mRNA and evidence for its involvement in RNA editing. J Biol Chem 1997; 272:1452-5; PMID:8999813; http://dx.doi.org/10.1074/jbc.272.3.1452
24. Lau PP, Chang BH, Chan L. Two-hybrid cloning identifies an RNA-binding protein, GRY-RBP, as a component of apobec-1 editosome. Biochem Biophys Res Commun 2001; 282:977-83; PMID:11352648; http://dx.doi.org/10.1006/bbrc.2001.4679
25. Greeve J, Lellek H, Rautenberg P, Greten H. Inhibition of the apolipoprotein B mRNA editing enzyme-complex by hnRNP C1 protein and 40S hnRNP complexes. Biol Chem 1998; 379:1063-73; PMID:9792439; http://dx.doi.org/10.1515/bchm.1998.379.8-9.1063
26. Lau PP, Villanueva H, Kobayashi K, Nakamuta M, Chang BH, Chan L. A DnaJ protein, apobec-1-binding protein-2, modulates apolipoprotein B mRNA editing. J Biol Chem 2001; 276:46445-52; PMID:11584023; http://dx.doi.org/10.1074/jbc.M109215200
27. Lau PP, Chan L. Involvement of a chaperone regulator, Bcl2-associated athanogene-4, in apolipoprotein B mRNA editing. J Biol Chem 2003; 278:52988-96; PMID:14559896; http://dx.doi.org/10.1074/jbc.M310153200
28. Chen Z, Eggerman TL, Patterson AP. ApoB mRNA editing is mediated by a coordinated modulation of multiple apoB mRNA editing enzyme components. Am J Physiol Gastrointest Liver Physiol 2007; 292:G53-65; PMID:16920700; http://dx.doi.org/10.1152/ajpgi.00118.2006
29. Blanc V, Henderson JO, Newberry EP, Kennedy S, Luo J, Davidson NO. Targeted deletion of the murine apobec-1 complementation factor (acf) gene results in embryonic lethality. Mol Cell Biol 2005; 25:7260-9; PMID:16055734; http://dx.doi.org/10.1128/MCB.25.16.7260-7269.2005
30. Bhattacharya C, Aggarwal S, Kumar M, Ali A, Matin A. Mouse apolipoprotein B editing complex 3 (APOBEC3) is expressed in germ cells and interacts with dead-end (DND1). PLoS One 2008; 3:e2315; PMID:18509452; http://dx.doi.org/10.1371/journal.pone.0002315
31. Youngren KK, Coveney D, Peng X, Bhattacharya C, Schmidt LS, Nickerson ML, Lamb BT, Deng JM, Behringer RR, Capel B, et al. The Ter mutation in the dead end gene causes germ cell loss and testicular germ cell tumours. Nature 2005; 435:360-4; PMID:15902260; http://dx.doi.org/10.1038/nature03595
32. Nelson VR, Heaney JD, Tesar PJ, Davidson NO, Nadeau JH. Transgenerational epigenetic effects of the Apobec1 cytidine deaminase deficiency on testicular germ cell tumor susceptibility and embryonic viability. Proc Natl Acad Sci U S A 2012; 109:E2766-73; PMID:22923694; http://dx.doi.org/10.1073/pnas.1207169109
33. Prohaska KM, Bennett RP, Salter JD, Smith HC. The multifaceted roles of RNA binding in APOBEC cytidine deaminase functions. Wiley Interdiscip Rev RNA 2014; 5:493-508; PMID:24664896; http://dx.doi.org/10.1002/wrna.1226
34. Smith HC, Bennett RP, Kizilyer A, McDougall WM, Prohaska KM. Functions and regulation of the APOBEC family of proteins. Semin Cell Dev Biol 2012; 23:258-68; PMID:22001110; http://dx.doi.org/10.1016/j.semcdb.2011.10.004
35. Kozak SL, Marin M, Rose KM, Bystrom C, Kabat D. The anti-HIV-1 editing enzyme APOBEC3G binds HIV-1 RNA and messenger RNAs that shuttle between polysomes and stress granules. J Biol Chem 2006; 281:29105-19; PMID:16887808; http://dx.doi.org/10.1074/jbc.M601901200
36. Gallois-Montbrun S, Holmes RK, Swanson CM, Fernandez-Ocana M, Byers HL, Ward MA, Malim MH. Comparison of cellular ribonucleoprotein complexes associated with the APOBEC3F and APOBEC3G antiviral proteins. J Virol 2008; 82:5636-42; PMID:18367521; http://dx.doi.org/10.1128/JVI.00287-08
37. Ali S, Karki N, Bhattacharya C, Zhu R, MacDuff DA, Stenglein MD, Schumacher AJ, Demorest ZL, Harris RS, Matin A, et al. APOBEC3 inhibits DEAD-END function to regulate microRNA activity. BMC Mol Biol 2013; 14:16; PMID:23890083; http://dx.doi.org/10.1186/1471-2199-14-16
38. Yamanaka S, Poksay KS, Arnold KS, Innerarity TL. A novel translational repressor mRNA is edited extensively in livers containing tumors caused by the transgene expression of the apoB mRNA-editing enzyme. Genes Dev 1997; 11:321-33; PMID:9030685; http://dx.doi.org/10.1101/gad.11.3.321
39. Mukhopadhyay D, Anant S, Lee RM, Kennedy S, Viskochil D, Davidson NO. C–>U editing of neurofibromatosis 1 mRNA occurs in tumors that express both the type II transcript and apobec-1, the catalytic subunit of the apolipoprotein B mRNA-editing enzyme. Am J Hum Genet 2002; 70:38-50; PMID:11727199; http://dx.doi.org/10.1086/337952
40. Sniderman A, Couture P, de Graaf J. Diagnosis and treatment of apolipoprotein B dyslipoproteinemias.

Nat Rev Endocrinol 2010; 6:335-46; PMID: 20421882; http://dx.doi.org/10.1038/nrendo.2010.50
41. Beaudoing E, Freier S, Wyatt JR, Claverie JM, Gautheret D. Patterns of variant polyadenylation signal usage in human genes. Genome Res 2000; 10:1001-10; PMID:10899149; http://dx.doi.org/10.1101/gr.10.7.1001
42. Anant S, Murmu N, Houchen CW, Mukhopadhyay D, Riehl TE, Young SG, Morrison AR, Stenson WF, Davidson NO. Apobec-1 protects intestine from radiation injury through posttranscriptional regulation of cyclooxygenase-2 expression. Gastroenterology 2004; 127:1139-49; PMID:15480992; http://dx.doi.org/10.1053/j.gastro.2004.06.022
43. Shimizu Y, Nishitsuji H, Marusawa H, Ujino S, Takaku H, Shimotohno K. The RNA-editing Enzyme APOBEC1 Requires Heterogeneous Nuclear Ribonucleoprotein Q Isoform 6 for Efficient Interaction with Interleukin 8 mRNA. J Biol Chem 2014; 289:26226-38; PMID:25100733; http://dx.doi.org/10.1074/jbc.M114.563221
44. Blanc V, Henderson JO, Newberry RD, Xie Y, Cho SJ, Newberry EP, Kennedy S, Rubin DC, Wang HL, Luo J, et al. Deletion of the AU-rich RNA binding protein Apobec-1 reduces intestinal tumor burden in Apc(min) mice. Cancer Res 2007; 67:8565-73; PMID: 17875695; http://dx.doi.org/10.1158/0008-5472.CAN-07-1593
45. Xie Y, Blanc V, Kerr TA, Kennedy S, Luo J, Newberry EP, Davidson NO. Decreased expression of cholesterol 7alpha-hydroxylase and altered bile acid metabolism in Apobec-1-/- mice lead to increased gallstone susceptibility. J Biol Chem 2009; 284:16860-71; PMID: 19386592; http://dx.doi.org/10.1074/jbc.M109.010173
46. Mukhopadhyay D, Houchen CW, Kennedy S, Dieckgraefe BK, Anant S. Coupled mRNA stabilization and translational silencing of cyclooxygenase-2 by a novel RNA binding protein, CUGBP2. Mol Cell 2003; 11:113-26; PMID:12535526; http://dx.doi.org/10.1016/S1097-2765(03)00012-1
47. Sureban SM, Murmu N, Rodriguez P, May R, Maheshwari R, Dieckgraefe BK, Houchen CW, Anant S. Functional antagonism between RNA binding proteins HuR and CUGBP2 determines the fate of COX-2 mRNA translation. Gastroenterology 2007; 132:1055-65; PMID:17383427; http://dx.doi.org/10.1053/j.gastro.2006.12.031
48. Vanharanta S, Marney CB, Shu W, Valiente M, Zou Y, Mele A, Darnell RB, Massague J. Loss of the multifunctional RNA-binding protein RBM47 as a source of selectable metastatic traits in breast cancer. Elife 2014; 3:e02734; PMID:24898756; http://dx.doi.org/10.7554/eLife.02734
49. Mallela A, Nishikura K. A-to-I editing of protein coding and noncoding RNAs. Crit Rev Biochem Mol Biol 2012; 47:493-501; PMID:22988838; http://dx.doi.org/10.3109/10409238.2012.714350
50. Avesson L, Barry G. The emerging role of RNA and DNA editing in cancer. Biochim Biophys Acta 2014; 1845:308-16; PMID:24607277