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REVIEW

RNA binding to APOBEC deaminases; Not simply a substrate for C to U editing

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ABSTRACT

Apolipoprotein B mRNA Editing Catalytic Polypeptide-like 1 or APOBEC1 was discovered in 1993 as the zinc-dependent cytidine deaminase responsible for the production of an in frame stop codon in *apoB* mRNA through modification of cytidine at nucleotide position 6666 to uridine. At the time of this discovery there was much speculation concerning the mechanism of base modification RNA editing which has been rekindled by the discovery of multiple C to U RNA editing events in the 3′ UTRs of mRNAs and the finding that other members of the APOBEC family while able to bind RNA, have the biological function of being DNA mutating enzymes. Current research is addressing the mechanism for these nucleotide modification events that appear not to adhere to the mooring sequence-dependent model for APOBEC1 involving the assembly of a multi protein containing editosome. This review will summarize our current understanding of the structure and function of APOBEC proteins and examine how RNA binding to them may be a regulatory mechanism.

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ADAR; adenosine deaminase active on RNA; antiviral; APOBEC; apolipoprotein B editing catalytic subunit; ADAT; adenosine deaminase active on tRNA; cancer; cytidine deaminase; DNA mutation; epigenetics; HIV; human immunodeficiency virus; host defense; lncRNA; long noncoding RNA; mRNA; miRNA; microRNA; retrovirus; RNA editing; RNA modification

Historical preface: What if any distinction is there between RNA editing and RNA modification

Throughout the 3 domains of life there are over one hundred ribonucleotide modifications and several deoxyribonucleotide modifications identified in various classes of RNA as well as in genomic and organellar DNAs[1-4] (Fig 1). The identification of RNA modifications and associated phenotypic studies predates the first use of the term RNA editing.[4,5] Rob Benne introduced the term 'RNA editing' in the 1980s in reference to Trypanosome guide-RNA dependent, insertion and deletion of uridines within mitochondrial mRNAs (reviewed in[6]). Editing through numerous U insertions and deletions into mitochondrial transcripts precisely timed during the life cycle of the organism created the initiation codons, sense codons and open reading frames for many mitochondrial proteins and enabled mitochondrial function (reviewed in[6,7]). Subsequently, adenosine to inosine (A to I) and cytidine to uridine (C to U) base transitions through deamination in mRNAs of plants, insects and mammals became known as mRNA editing as these too created translation start codons, sense changes, nonsense codons as well as premRNA splice junctions (reviewed in[8,9]).

Adenosine deaminase active on RNA (ADAR)[10,11] and adenosine deaminase active on tRNA (ADAT)[12] are responsible for A to I editing and have deaminase domains that are structurally related to, but distinct from, those of apolipoprotein B mRNA editing catalytic subunit (APOBEC) family of cytidine deaminases[13,14] responsible for C to U editing.[8] ADAR1 and ADAR2 were first shown to edit mRNAs encoding glutamate and kainate receptor gated ion channels in excitatory tissue.[6,7,15,16] In different excitatory tissues and through the brain mRNAs encoding ion channel subunits may not all be edited, nor are they edited at the same sites. The resulting protein heterogeneity in subunits comprising the multi subunit ion channels for Ca^{2+} and K^{+} enables regional control of plasticity in ion conduction rates and ion gradient recovery rates. APOBEC1 (A1) editing of the mRNA encoding apolipoprotein B created protein variants that are required for serum transport and tissue uptake of fats and cholesterol. ApoB protein variants have markedly different half lives in the blood and therefore have different implications in the production of low density lipoproteins (LDL) and atherogenic diseases.[8,17]

Both ADAR and APOBEC catalytic domains known as the zinc-dependent deaminase domain (ZDD) require a protein fold that coordinates zinc through histidine and cysteine residues and places a glutamic acid for proton shuttling proximal to the adenosine/cytosine targeted for deamination.[13,18-23] The structure of APOBEC3F (A3F) C-terminal deaminase domain in the absence of zinc suggested that metal chelation is not essential for the general fold of the ZDD.[23] ADAR1, ADAR2 and ADAT1 contain one or more double stranded RNA binding domains with selective affinities for imperfect RNA duplexes that contain the target adenosine to be edited; and

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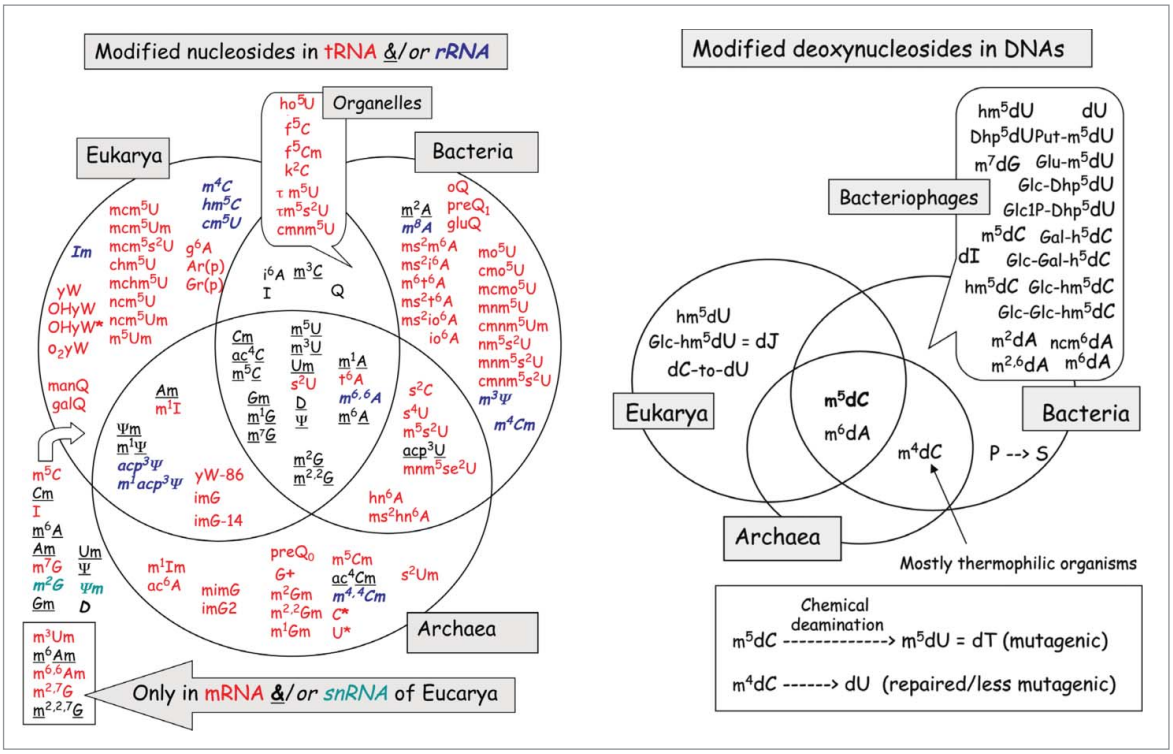

Figure 1. RNA Modifications Unique and Common to the Three Orders of Life. The Venn diagram shows the known modifications of ribonucleotides (indicated by standard abbreviations) found in naturally occurring RNAs in Archea, Bacteria and Eukarya. Nucleotide modifications common to 2 or all orders of life are indicated in the overlapping areas. Abbreviations for the modification are provide in.[4] Figure modified from Figs. 4 and 6 in reference 4 (Landes BioSciences).

hence edit different RNA substrates.[10,11,24] ADAT2 and ADAT3 have no recognizable double-stranded RNA binding domains. In contrast, A1 has weak affinity for RNA[25] and is moored to the RNA editing site through its interaction with the RNA binding protein A1CF that recognizes a cis-acting, 11 nucleotide RNA recognition element (the mooring sequence) 3′ of the edited cytidine[26,27] (reviewed in[14,28]). As will be discussed below, APOBEC deamination of dC in ssDNA may not require auxiliary proteins as they bind ssDNA with nanomolar affinity using residues surrounding catalytic cleft and residues along exposed surfaces adjacent to the catalytic domain.[18,20,29-32]

By 1997 ADARs and A1 became the mammalian paradigms of editing enzymes as a growing list of examples of A to I and C to U mRNA editing sites emerged from studies in plants, protozoa, insects and viruses.[9] Since that time, numerous non-genomically encoded A to I and C to U transitions have been identified through advances in computation biology and RNA and DNA sequencing technology.[33-39] Although the ADAR and APOBEC editing enzymes are likely to be responsible for transcriptome and genome wide A to I and C to U transitions, the functional significance of editing these nucleotides is usually not apparent. Sequence analyses show that under *in vitro* conditions ADAR and APOBEC family members can edit numerous sites within RNAs (and DNA in the case of AID/APOBEC) as long as they satisfy the nearest neighbor nucleotide and/or secondary structure requirements; so called 'hot spots'. And yet the vast majority of sites that qualify as ADAR or APOBEC editing sites are not edited *in vivo*. So while under defined *in vitro* conditions the cis-acting requirements for ADAR and APOBEC editing site selection can be readily described, we do not understand why nucleotides predicted to be editing sites are or are not utilized *in vivo*.

It has become increasingly difficult to think of all of the sites affected by ADAR or APOBEC in the historical strict definition of a nucleic acid editing site; namely as a form of nucleotide modification that enables phenotypic diversity. One might speculate that most of these modifications are determined by random access of the enzymes to RNA or ssDNA regions of the genome made single stranded during RNA transcription and DNA replication. But this cannot entirely be true as the chemical nature and frequency of particular DNA and RNA sequences harboring these nucleotide modifications are known to vary with changes in physiologic or disease states,[16,33,34,40-44] reviewed in.[14] Alternatively, if there is a clear phenotype associated with a modification, then there probably was an underlying regulatory process for modifying that site; hence it may be considered to be an editing event even though the function of other nucleotide modifications that occur simultaneously might not be clearly purposeful.

As case in point, the APOBEC field discovered early on that overexpression of editing enzymes for experimental purposes can lead to high levels of editing at physiologically relevant sites but also hyperediting of multiple RNAs that otherwise would not have been significantly edited[45] and promiscuous editing of multiple cytidines proximal to the native editing site.[46] Activation induced deaminase (AID) in the APOBEC family (described in greater detail below) is responsible for the diversity of antibodies that can be produced as part of the acquired immune system.[47] Upon B lymphocyte activation, AID induces numerous dC to dU transitions within genomic DNA encoding the variable region of the immunoglobulin locus and within the

immunoglobulin class switch region.[47-49] In each activated B cell the deoxycytidines deaminated to deoxyuridine are repaired to any one of the 4 bases. This leads to a large diversity of new functionalities in immunoglobulins expressed within the activated B cell population in germinal centers throughout the body.[47,50-52] While there are potentially numerous nucleotide modifications within some of the activated B cells that do not enable expression of functional immunoglobulins, AID modification of DNA produces diversity in the proteome and therefore arguably is DNA editing. Moreover, despite exquisite regulation of this process, there are numerous mutations within genomic DNA with AID/APOBEC signature nearest neighbor preferences.[33,53] In some instances these 'hyperediting' sites lead to alterations in protein expression and are associated with particular cancers and cancer progression (reviewed in[14,54,55]).

Broadening the inclusivity of the RNA editing nomenclature, the functionality of several tRNAs is enabled by A to I transitions catalyzed by ADAT affecting codon structure, codon usage or tRNA availability.[1,56] In addition, A to I transitions catalyzed by ADARs disrupts base pairing in RNA secondary structure such as those required for recognition and processing of microRNAs (miRNA) by the RISC complex.[24,40,57] Therefore RNA editing also might be an appropriate nomenclature for the reduction of miRNA abundance by ADARs leading to altered gene expression through chromatin modification and condensation[40,58-60] as well as reduction in the capacity of cells to produced miRNA that silence mRNA.[24,40,61] ADAR colocalization with long noncoding (lnc) RNAs and unspliced HIV RNA in nuclear para speckles catalyzes A to I transitions in lncRNA secondary structure. This may be RNA editing as well based on the hypothesis that it is essential for controlling nuclear export of unspliced HIV RNA to the cytoplasm for translation of viral proteins and viral packaging.[62,63] Future research no doubt will show that there are additional instances where nucleotide modifications in RNA (or DNA) lead to a gain or loss of function. Should these nucleic acid modifications be thought of as RNA editing once their functional consequences have been identified? For the moment, the field has taken a 'middle of the road' position in adopting the moniker 'editing and modification' when referring to all of these nucleotide transitions in RNA and DNA.

Development of the APOBEC field through the discovery of new genes and new editing mechanisms

In the decade spanning the discovery of *apoB* mRNA C to U editing and APOBEC1 (A1) as the enzyme responsible for this base modification editing, a question frequently posed by the scientific community was why would an apparently dedicated enzyme like A1 be conserved in mammalian evolution given that it catalyzes a single editing event in only one mRNA? If the truncated protein product expressed from edited mRNA is important, why over time has the C to U change responsible for the nonsense mutation not have been selected in the *apoB* gene? The answer put forth then and still in use today is that editing affords tissue-specific flexibility in protein expression and the ability to regulate the proportion of the ApoB proteins translated from edited and unedited mRNA; and consequently modulate serum lipid transport through metabolic and developmental regulation (reviewed in[8,17]).

A broader role for A1 in regulating protein diversity, mRNA expression and stability was suggested in the discovery of A1-dependent editing of the mRNAs encoding the tumor suppressor NF1[64] and the translation repressor factor eIF4G[45] along with numerous C to U edits within the 3′ UTRs of RNAs[36] (see other predicted mRNA substrates in[65,66]). The biological role of APOBEC proteins has come under the spotlight again following the discovery that A1 is one of 11 proteins in a family of cytidine deaminase active on nucleic acids.[14,67] Many of proteins in the APOBEC family have essential deaminase activity-dependent and deaminase activity-independent functions in determining innate and acquire immunity, host cell antiviral defense[65,68] and if unregulated could become oncogenic[33,34,48,54,55,69,70] or potential reduce cancers by enabling immune surveillance.[71]

The ability to bind to nucleic acids and to catalyze dC to dU base modification on single stranded DNA is a family characteristic that many but not all of the APOBEC family members have in common,[53,67,72,73] reviewed in.[74] The reader is referred to recent reviews for the structures and functions of the APOBEC family[13,14,34] as this review will provide only a brief overview of the APOBEC family for context in establishing the hypothesis that RNA binding to APOBEC proteins regulates their deaminase activity.

There are 11 known members in the human APOBEC family

A1 and AID are both encoded on human chromosome 12. A1 expression is most abundant in mammalian small intestine and liver.[75] Expression of mammalian AID is highly regulated in B lymphocytes within germinal centers in response to foreign antigens. Its tissue-specific expression and ssDNA mutagenic activity of the immunoglobulin gene locus are essential in determining adaptive immunity through class switch recombination (CSR), somatic hypermutation (SMH) and gene conversion.[47-49] Deletion of A1 has a weak phenotype in lipid metabolism in mice[76] but loss of AID function leads to an autosomal recessive, immune disorder known as hyper-IgM syndrome (HIGM2) where IgM accumulates in the blood because class switch recombination cannot be performed.[77] APOBEC2 (A2) and all 7 APOBEC3 proteins (A3A, A3B, A3C, A3D, A3F, A3G and A3H) are encoded on human chromosomes 6 and 22, respectively.[67] A3 proteins have diverse deaminase activities on RNA and ssDNA; mostly related to the control of retroviruses and endogenous retroviral elements ([13,39] and reviewed in[14]). APOBEC4 is encoded on chromosome 1.[78] A2 and APOBEC4 (A4) have no known catalytic functions.[78-80]

AID and A2 may have been the ancestral genes from which all other APOBEC were derived. This may have occurred through gene duplication and divergence over the course of ~500 million years of vertebrate evolution. AID ssDNA deaminase activity emerged with jawed fish and its DNA mutagenic activities would have been selected for in overcoming infections, immune surveillance in controlling cancer cell proliferation and maintaining homeostasis.[53,70,81-84] For the A3 proteins, the leading hypothesis is that the driving force for A3

gene expansion and diversification was selective pressure on the innate immune system through the genotoxic effects resulting from infection with rapidly mutating retroviral genomes and/or transpositions of endogenous retroviral-like elements within the genome,[38,84-92] reviewed in.[14] This is an intriguing hypothesis considering present day diversification within the human APOBEC family, notably polymorphisms in A3C,[93,94] the loss of A3B expression in various human populations[55,93] and the expansion of alternatively spliced variants of AID in the progression of cancer[95,96] and of A3H that have different capacities to suppress HIV infections[88,97,98] or contribute to cancer.[99] The importance of A3 in host cell defense is evident in that HIV-1 and -2 encode the accessory protein known as viral infectivity factor (Vif) whose primary function is to suppress the antiviral activity of A3C, 3D, 3F, 3G and 3H by mediating their ubiquitination and proteosomal degradation.[68,88,94,97,100-102]

APOBEC have a conserved catalytic domain

All APOBEC proteins can be identified through database searches by their signature zinc-coordinating deaminase domain (ZDD) motif (H x E—X_{25-30}—PC X_{2-4} C) (Fig 2).[8] The underlined residues are an absolute requirement for APOBEC binding to and use of zinc as a Lewis acid for a nucleophilic attack of the C4 position of cytidine or deoxycytidine during hydrolytic deamination.[23] The ZDD is found within the tertiary fold comprising the cytidine deaminase catalytic domain that is composed of a 5-stranded mixed β-sheet that is stabilized by α helices packing against both faces of the β sheet due to their sequential arrangement as α1-β1-β2-α2-β3-α3-β4-α4-β5-α5-α6 in the primary sequence (Fig 2). This organization is conserved in the crystal structure of the yeast homolog of AID/A1 known as Cdd1 that has both RNA and ssDNA editing activity[103,104] and with very little variation, is a key structural landmark observed in all known crystal or NMR structures of mammalian APOBEC.[13,19,20,23,30,32,105-108] AID, A1, A2, A3A, A3C, A3H and A4 are single ZDD whereas A3B, D, F and G are dual deaminase domain proteins. With the possible exception of A3B and D, there is only one catalytically active deaminase domain in proteins with 2 ZDD. There is no explanation for the structural or catalytic advantage that single versus dual ZDD-containing proteins have although ssDNA substrates bind to residues in both domains in APOBEC with dual ZDD[23,31,108,109] and both N- and C-terminal ZDD are required for robust ssDNA editing.[109,110] The structure of APOBECs have the greatest divergence within the primary sequence and secondary structure of loop domains outside of the ZDD as well as their quaternary interactions such as homo multimerization, interaction with other cellular or viral proteins and nucleic acid binding that affects APOBEC oligomerization and subcellular distribution.[14,74]

Most APOBEC have deaminase activity on ssDNA substrates

Nucleic acid binding is common to all APOBECs and with the exception of A2 and A4, all APOBEC will support *in vitro* deamination of deoxycytidine (dC) to deoxyuridine (dU) in

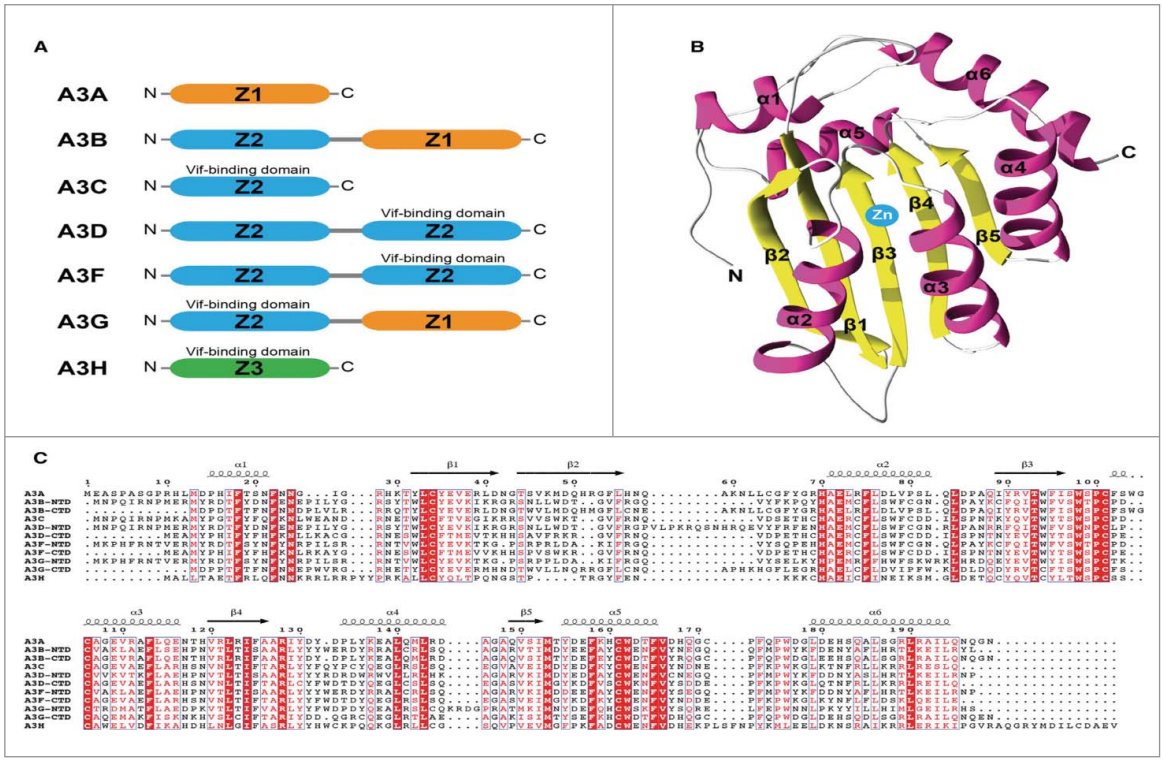

Figure 2. Structural Organization of Zinc Dependent Deaminase Domains and the Catalytic Fold for the APOBEC3 family. (A) Cartoon of the occurrence and position of evolutionarily related ZDD (color coded in orange, blue and green) in APOBEC3 a through H. Regions where the HIV Vif protein binds to A3 proteins is indicated. (B) Three dimensional fold of the A3 Z1 showing the distribution of α helices and β sheets relative to the catalytic zinc atom. (C) Primary amino acid sequence alignment of each individual ZDD domain in the A3 family showing the locations of conserved residues (in red vertical stripes) and homologous residues (in red text). Amino acids sequences forming α helices and β sheets are indicated about the text. Reproduced with permission from reference 13.

ssDNA.[67,72] Within single stranded DNA stretches of 25 nucleotides or longer dC's are targeted and deaminated do dU with apparently very lax nearest neighbor sequence preferences.[111-114] The resultant dU's are repaired, first by rendering them to abasic sites and then through low fidelity of DNA repair converting them to dA, dC, dG or T.[47,48,52] AID mutagenic activity targeting to the variable region and class switch region of transcriptionally active immunoglobulin genes may be facilitated through a mechanism that involves cofactor binding to DNA, AID post-translation modification or DNA structure restrictions.[51,52,115-122]

A3D, F, G and H provide host defense against retroviral infection by hypermutating proviral ssDNA during reverse transcription,[72,101,123,124] reviewed in.[125] Paleo-DNA databases reveal numerous dG to dA mutations throughout primate genomes with nearest neighbor target preferences characteristic of modern day A3 family deaminases.[86,90,92] Evolutionary models predict that A3 proteins, especially A3G and A3F, have served a significant role as antiviral vanguards, in many species, for millions of years by mutating retroviral genomes and impairing their productive replication and retrotransposition.[86,92,100,126-128]

Crystal and NMR structures are only available for single ZDD APOBEC and for individual ZDD from double domain APOBEC. These have been modeled for ssDNA binding to A3B, 3F and 3G along a shallow groove on the protein surface punctuated with patches of positively charged (basic) and aromatic (hydrophobic) residues that respectively accommodate the negative charge on the backbone of nucleic acids backbone and enabling their stacking with the nucleic acid bases.[13,20,29,30,109,129-131] In this regard the first crystal structures of A3B C-terminal half with bound dCMP[130] and A3G N-terminus half with mono and oligo deoxynucleotides bound[108] have begun to suggest the residues required to restrain nucleic acid in proximity to the catalytic site. A3B, 3F and 3G have greater processivity in deaminating multiple dC along ssDNA compared with A3A and this may be the result of a greater number of contacts made with ssDNA by their ZDD.[109,132] Modeling suggests that single deaminase domain A3 such as A3A with fewer contacts with nucleic acid and may bend ssDNA substrates to position the targeted dC into the catalytic pocket.[32] In this regard it is interesting that a rare S188I mutation in A3C expressed in a subset of Africans was shown to increase RNA bridged multimerization of the single domain A3C and activate of the mutant protein's deaminase activity on HIV-1.[94]

Mass spectroscopy of tryptic peptides from full length A3G cross linked to ssDNA 25 nt to 99 nt in length revealed that ssDNA binds to peptides within the C-terminus where the catalytic domain resides as well as to peptides within the N-terminus, containing the pseudo catalytic domain.[31,133] Cross-linking coupled with mass spectroscopy peptide analysis suggested A3 residues that were bound to nucleic acid and corroborated biochemical studies suggesting that residues in the loop domains of both ZDD in dual deaminase domain A3 such as A3F were required for ssDNA binding and robust deaminase activity.[109]

APOBEC proteins commonly form homo multimers

The relative contribution of ssDNA in bridging APOBEC monomeric proteins to one another as higher-order oligomers vs. protein-protein interactions remains to be determined. Protein-protein interactions may alone be sufficient for homodimerization of A1[67,134,135] and A3F and A3G[109,136-138] as these APOBEC bind to ssDNA as such multimers.[109,114,139] Consistent with these data, in-cell fluorescence fluctuation spectroscopy demonstrated that A2, A3A, and A3C were monomeric in cells whereas A3B, A3D, A3F, A3G, as A3H were multimeric.[50] The prerequisite of a homo oligomeric state for AID/APOBEC to recognize target dC and bind to ssDNA remains an area of active research.[94,106,107,140-147] We do not known whether both subunits of a homodimer are directly bound to ssDNA or in fact whether the catalytic activity of holoenzyme complexes require more than one active site; in other words, how many ZDD are engaged to edit a single dC? What is more certain is that full length A3G monomers has approximately >100-fold higher affinity of ssDNA than does the C-terminal ZDD half molecule alone.[29,109,141,148] The date suggest that APOBEC binding to ssDNA, the recognition of dC to be deaminated and movement of APOBEC along the ssDNA to adjacent editing sites requires more than the catalytic ZDD and the interaction with more than one APOBEC protein monomer.[31,112-114,145]

RNAs bound to APOBEC have important functions even when the RNAs are not substrates for deamination

After several years of controversy homomultimeric and heteromeric complexes of AID/APOBEC proteins have been accepted as critical for regulating APOBEC subcellular localization and their activity on nucleic acid substrates (reviewed in[14,74]). Almost every member of the AID/APOBEC family interacts with a variety of RNAs that bridge APOBEC monomers together to form megaDalton sized ribonucleoprotein particles (RNP) that also contain a variety of other RNA binding proteins involved in RNP structure and processing RNAs.[31,94,149-158]

Dual deaminase domain APOCECs were once thought to bind to RNA through their non-catalytic N-terminal CDA[18,128,141,150,155,159-161] based on an early report suggesting that RNA and ssDNA bound to different termini.[110] MS analysis of full length and native A3G cross linked to nucleic acid cross revealed that RNA bound to both N- and C-terminal peptides[31] (Fig 3). RNA bound to the sites within the C-terminus of A3G that ssDNA also bound to. The N-terminal sites in A3G cross-linked exclusively to RNA were part of a continuous groove extending to the C-terminus and proximal to those that bound to both RNA and DNA in the C-terminus (Fig 3). The MS data and model in Fig. 3 were supported by data demonstrating that RNA displaced ssDNA from A3G and inhibited its deaminase activity in an RNA concentration-dependent manner.[31,151] Given that RNA can bind to A3G at sites were ssDNA does not bind, the model suggested that in addition to being a competitive inhibitor, RNA ligands may noncompetitively inhibit ssDNA deaminase activity or have alternative structural or regulatory functions. It remains to be determined whether RNA and ssDNA can bind simultaneously to an APOBEC monomer or multimer.

A1 must interact with RNA binding proteins AC1F[27,162-164] or RBM47[165] for site-specific editing of *apoB* mRNA but A1 itself, has a low affinity for binding to RNA and is nonselective.[25] A1

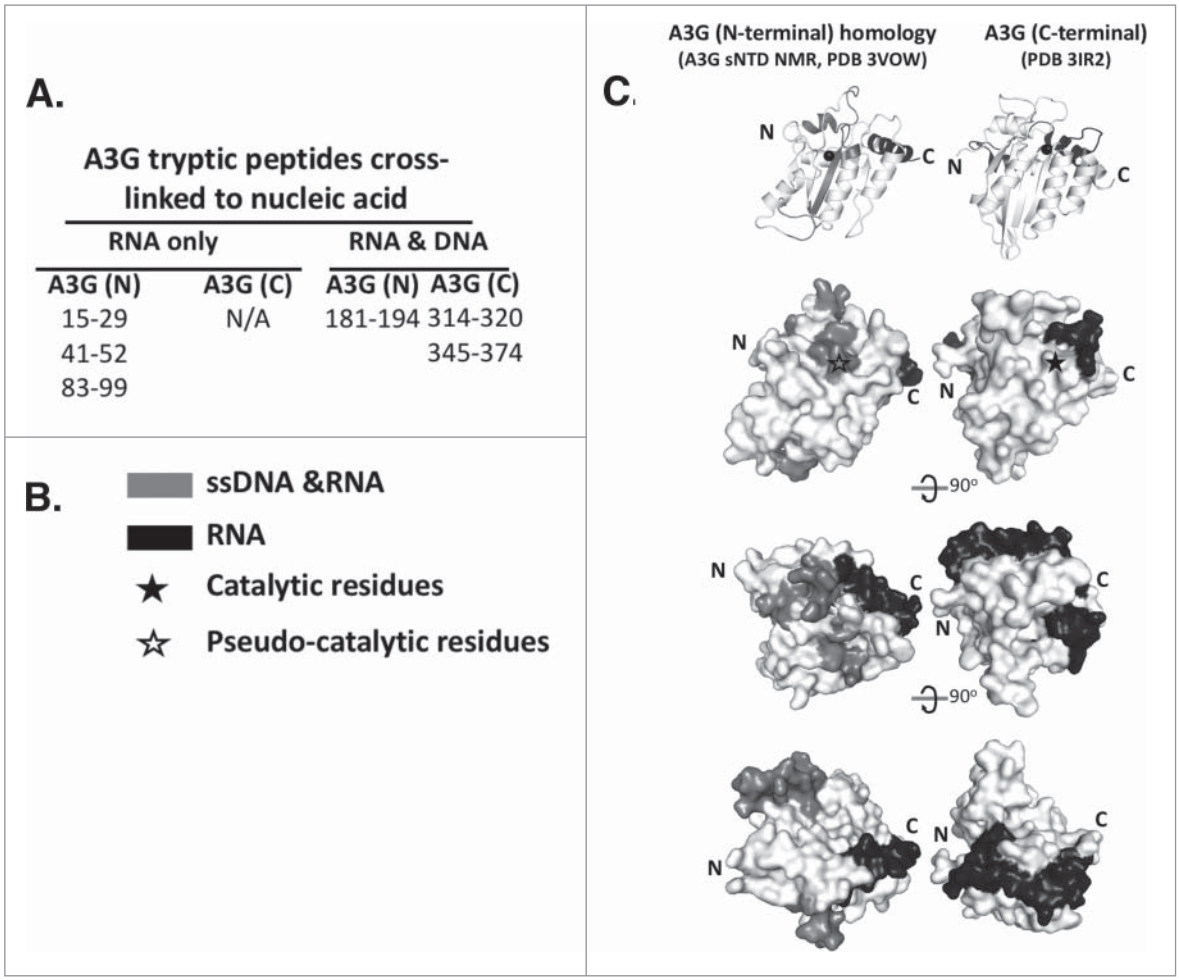

Figure 3. RNA and ssDNA Binding Surfaces on A3G. (A) Tryptic peptides of A3G bound to RNA or ssDNA were identified by mass spectroscopy following cross linking of native and full length A3G to short nucleic acids. (B) Peptides that only bound RNA (black) or bound to both RNA and ssDNA (gray) were mapped relative to the C-terminal ZDD catalytic domain and the N-terminal ZDD catalytically inactive pseudo-catalytic domain. (C) Grey scale coded RNA binding peptides and RNA and ssDNA binding peptides were mapped onto the NMR structure for the N-terminal ZCC and the crystal structure of the C-terminal ZDD of A3G shown as a ribbon diagram (top) and progressively rotated (top to bottom) space filling models. Black star and open star mark the location of the the catalytic and pseudo-catalytic ZDD, respectively. Reproduced with permission from reference 31.

predominantly is a cytoplasmic protein[125,166] sequestered with A1CF and *apoB* mRNA as editing-inactive 60S complexes along the exterior of the rough endoplasmic reticulum.[27] Hormone regulated, reversible phosphorylation of A1CF enables nuclear import of A1[164] and *de novo* assembly of 27S active editing complexes containing A1CF[27] bound to unedited but spliced *apoB* mRNA.[66,167] AID also must be imported to the nucleus for CSR and SHM[125,168-170] and then is rapidly exported and degraded[171,172] to control its mutagenic and potentially oncogenic activity.[53,54,173,174] Regulation of AID occurs at many levels including alternative splicing[173,174] and retention of AID in the cytoplasm through its interactions with HSP90,[168,175] and cytoplasmic RNAs[176] and binding to replication protein A.[120]

A3 proteins also form high molecular mass homo- and hetero-oligomers[94,154,155,157,177-179] within the cytoplasm of cells. A3 complexes bridged by RNA form soon after A3 protein translation.[179] This has led many in the field to conclude that A3 binding to RNAs only serves to inhibit A3 antiviral properties including their deaminase activity and assembly with viral particles.[157,177-181] With additional studies the functional significance of A3 RNP formation became more nuanced. A3 binding to cellular coding and noncoding RNAs is now thought to be critical to maintaining their antiviral activity against HIV.[150,153-156,182,183] Other studies have confirmed these interactions but concluded that A3 binding to HIV genomic RNA alone[94,153,158,184] or with HIV p24 Gag protein[185-188] is the most critical RNP for the assembly of A3D, F, G, and H with nascent viral particles. It remains unclear which residues within the N- and C-terminus bind to RNA but regional selectivity for RNA binding to A3G is supported by data showing that bulk cellular RNA and noncoding hY1 and hY3 RNAs required A3G residues W94 and W127 and to a lesser degree, S28 and Y124 but binding to *Alu* and 7SL RNAs did not require these residues.[128] It is also apparent that A3 interaction with cellular RNAs is dynamic and reversible[177,178] and upon viral infection can become more selective for HIV RNA and noncoding RNAs leading to their redistribution to cellular sites of viral particle assembly.[153]

Prospective on the APOBEC frontier

As the field pushes forward for structural characterization of APOBECs and their interactions with substrates and other macromolecules, an overarching focus has become the search

for regulatory processes that limit or enhance APOBEC expression and their functions (reviewed in[43,52,53,68,101]). Given that the evolutionary forces leading to present day APOBEC proteins may be difficult to prove, a priority will be to understand the function of the present day APOBEC family. If we do come to appreciate the strengths and potential limitations of this family of proteins, there may be opportunities to use these enzymes in cell engineering and for the development of therapeutics for disease intervention.

From this perspective, there is a need to keep in mind what the native and biological context of APOBEC proteins and their enzymology is when inferring their functions from experimental systems. It can be very informative to overexpress cDNAs encoding APOBEC or mutants thereof in cells or animals to assess their maximum potential to deaminate viral or host cell genomic DNAs or bind to RNAs in cells. It is not appropriate to infer a proof of their biological role or activity *in situ* on nucleic acid substrates when the experimental expression of protein far exceeds that observed naturally. Promiscuous and hyperediting of substrates and the induction of neoplasia by overexpressing A1 has been known since 1996. The natural expression of A1 in small intestine is below western blot detection limits but edits 100% of the apoB mRNA produced in enterocytes. Following this analogy, many of the proposed antiviral roles for overexpressed A3 proteins and variants thereof that are naturally expressed at an intracellular abundance much lower than A3F and A3G may have to be reconsidered.

Many laboratories are pursuing computational methods and sequencing of genomic DNA and transcriptomes from cell types where AID/APOBEC are not only expressed but where changes in their expression or alternative *apobec* mRNA splicing correlate with phenotypic changes. These are important studies but beyond cataloging mutations, greater efforts need to be made in quantitative biology. Detecting APOBEC C to U editing in a particular RNA is undoubtedly of interest. What becomes biological significant is going on to quantify the proportion of edited RNAs in the transcriptome, determining whether the function of edited RNA and its translation product is altered and demonstrating how the frequency of editing site utilization varies in response to or drives cell phenotype.

How do APOBEC recognize editing sites in RNA and ssDNA? Other than the mooring sequence for A1 editing of RNA substrates, most of what we know suggests that AID/APOBEC prefer editing cytidine or deoxycytidine within single stranded regions of RNA or DNA with only lax requirements for the sequence immediately flanking the editing site. An area for future research will be to determine what are the intrinsic structural features of AID/APOBEC monomers of multimers that determine the selection of editing sites. We also will need to identify cellular auxiliary proteins, RNAs or post-translational modifications that determine selection of RNA and DNA substrates and editing site preferences. There is ample evidence that what every these control mechanisms are, they can be disrupted, and for AID, A1 and A3 proteins lead to disease-associated promiscuous editing within known targets and hyperediting of novel RNAs and chromosomal sites.

APOBEC enzymology, with few exceptions, is an underdeveloped area of research. The structural features of AID/APOBEC are being cataloged but high resolution structural determination of enzyme-substrate complexes and of full length APOBEC with 2 ZDD has not been achieved. There are conflicting reports as to whether AID/APOBEC monomers or multimers form before or after binding to nucleic acid substrates. An error in the past has been to conclude functionality of monomers or multimers of AID/APOBEC without reassessing the complexes that formed once the proteins had been added to nucleic acid substrates in a test tube. Holoenzyme complexes and the structural constraints they impose on the enzyme-substrate interactions are an important area for future enzymology research. While recent data for most APOBEC, particularly A3, are consistent with homomultimers being required for enhanced deaminase activity on ssDNA, addition studies will be required to determine the role of RNA binding and protein-protein interactions in multimerization.

New opportunities for discoveries exist in the area of the functional significance of RNAs that bind to AID/APOBEC as ligands that are not used as editing substrates. AID/APOBEC bound to a variety of coding and noncoding RNAs may have deaminase-independent functions in regulating endogenous retrovirus-like elements, redistributing A3 to the viral particle assembly process and sequestering RNAs in P-bodies and stress granules during a cellular response to changing environmental signals. Current data suggest that APOBEC interactions with non substrate RNAs inactive catalytic capability. Given that A1 employs an RNA binding protein to 'find' *apoB* mRNA within the vast abundance of cellular RNAs, RNA inhibition of AID/APOBEC may be driven by mass action of cellular RNAs that bind to these proteins but do not have appropriate editing sites.

Recent research has suggested that A3 binding to RNAs may not be nonspecific and that there may be competitive and noncompetitive interactions with RNAs that determine A3 oligomerization, RNP formation and the subcellular redistribution of A3 to sites of retroviral particle assembly. That later interaction with RNA must have been a critical feature of A3 antiviral activity in host cell defense for millennia. High resolution studies coupled to functional studies will be necessary to define the amino acid residues and protein folds of AID/APOBEC that bind to RNA and the RNA sequences that are bound to them. It is apparent from the literature that these interactions are not static and change during cell differential and development and in response to hormone stimulation, cell stress and viral infection. Here again, our understanding of RNA ligand binding to APOBEC will only be complete when the functional consequences of these interactions and their regulation has been revealed.

Conflict of Interest Statement

Dr. HC Smith is a full-time and tenured professor at the University of Rochester School of Medicine and Dentistry. He is the founder and CEO of the University of Rochester spinout company OyaGen, Inc. The company has a financial interest in the development of antiviral and anti-cancer drugs based on APOBEC technology.

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