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Review

Functions and regulation of the APOBEC family of proteins

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ABSTRACT

APOBEC1 is a cytidine deaminase that edits messenger RNAs and was the first enzyme in the APOBEC family to be functionally characterized. Under appropriate conditions APOBEC1 also deaminates deoxycytidine in single-stranded DNA (ssDNA). The other ten members of the APOBEC family have not been fully characterized however several have deoxycytidine deaminase activity on ssDNAs. Despite the nucleic acid substrate preferences of different APOBEC proteins, a common feature appears to be their intrinsic ability to bind to RNA as well as to ssDNA. RNA binding to APOBEC proteins together with protein–protein interactions, post-translation modifications and subcellular localization serve as biological modulators controlling the DNA mutagenic activity of these potentially genotoxic proteins.

Contents

1. Introduction

The purpose of this review is to familiarize the reader with the proteins in the APOBEC family in order to better appreciate differences in their functional roles as well as to describe cellular and viral control mechanisms that determine APOBEC activities. The review begins with Apolipoprotein B Editing Catalytic subunit 1 (APOBEC1 or A1) because it is the founding member of the family [1]. All family members have in common a zinc-dependent cytidine

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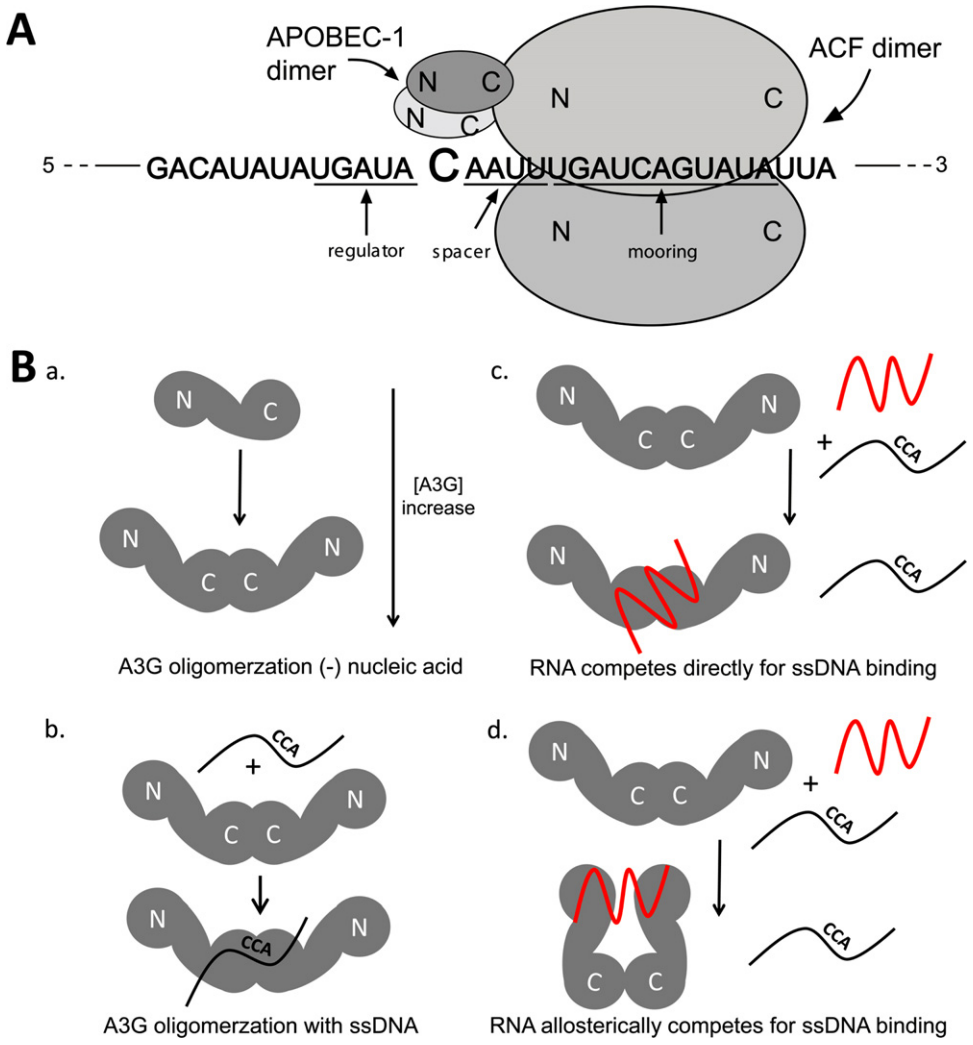

Fig. 1. Models for A1 and A3G complexes with nucleic acids. (A) The tripartite apoB mRNA editing motif consisting of the mooring sequence, and spacer 3′ of the C to be edited and the enhancer element 5′ of the edited C is shown with a cartoon of an editosome assembled upon it. An A1 C-terminal dimer is positioned for site-selective C to U editing by virtue of its association with ACF dimers that are shown bound to the mooring sequence. For the purposes of presentation only one A1 dimer is shown bound to one ACF through C-terminal to N-terminal interactions, respectively (although the precise stoichiometry is unknown). Most of the three RNA recognition motifs comprising the N-terminal half of ACF are required for optimal A1 binding. ACF dimerization requires only the N-terminal half of ACF. (B) (a) An A3G monomer is shown containing an N- and C-terminal ZDD (label as 'N' and 'C'). Nucleic acid deficient A3G forms a heterogeneous mixture of oligomers consisting mostly of dimers in solution and an A3G concentration-dependent small population of monomers and tetramers. (b) A3G dimers to bind ssDNA substrates (black line with the CCA editing site) and must form at minimum a tetramer for enzymatic activity. (c) RNA (red line) competes for ssDNA binding by displacing ssDNA and binding at the same site or (d) RNA competes for ssDNA binding by binding at a distal site and causing an allosteric change in A3G conformation, preventing ssDNA binding.

deaminase domain (ZDD) that is identifiable through its primary amino acid motif and a conserved super-secondary structure.

1.1. Overview of the requirements for apolipoprotein B mRNA editing

Apolipoprotein B (*apoB*) mRNA (C to U editing) and the glutamate receptor mRNA (A to I editing) were the first mRNAs discovered to be edited in mammalian cells circa the late 1980s [2]. Human liver and intestine produced a long and short form of the apolipoprotein B (ApoB) protein and the discovery of *apoB* mRNA editing resulted from research to determine the molecular basis for this polymorphism. Sequencing revealed a single nucleotide difference between mRNA and the genomically encoded sequence which was attributed to post-transcriptional RNA editing [3,4]. The cis-acting sequences required for editing site recognition flanking the cytidine to be edited, in particular the 11 nt 'mooring sequence' (Fig. 1A), had already been completely defined [2] before A1 was discovered [5]. However A1 is a low-affinity RNA-binding protein [6–8] and its ability to edit mRNA could only be realized in cells or cell extracts if they contained the RNA-binding protein APOBEC1 Complementation Factor (ACF) [9–11]. A1 dimers [7,12] and RNA-bridged dimers of ACF [13] make up the minimal composition of the 27S editosome [14,15] (Fig. 1A).

1.2. Site-specific editing

The primary editing site at nt 6666 in *apoB* mRNA is a CAA glutamine codon that is deaminated to a UAA premature stop codon. Unedited and edited mRNAs coexist at varying ratios in editing-competent cells because tissue-specific and metabolically regulated differences in editing efficiency and because edited *apoB* mRNA is stabilized through the ability of ACF to blunt nonsense codon mediated mRNA degradation [16]. The specificity of this editing event is apparent in that *apoB* mRNA contains 3315 cytidines of which 375 are in the correct reading frame and 100 are CAA. The mooring sequence is necessary and sufficient in determining whether a 5′ located cytidine is a candidate for editing [17–21].