RNA editing is the changing of a nucleotide sequence at one or more positions within an RNA transcript. Hence, editing leads to the formation of transcripts, the sequence of which differs from that found in the genome. RNA editing was initially described in the 1980s in a unicellular protozoan (1) and soon thereafter in the mouse (2, 3) and also in a viral pathogen that affects humans (4). The frame-shifted cytochrome oxidase coxII gene transcript of trypanosome mitochondria provided the first example of RNA editing when it was found to contain four inserted uridines that were not encoded by the genomic DNA (1). Subsequently, editing by nucleotide substitution was described for the apolipoprotein B (apoB) transcript in mouse intestine (2) and the glutamate-gated ion channel (GluR-B)1 transcript in mouse brain (3). ApoB mRNA possesses a UAA translational stop codon, at a position where the genomic DNA specifies a CAA glutamine codon (2). The edited GluR-B mRNA possesses a CIG arginine codon (I is recognized as G by decoding ribosomes), whereas unedited mRNA possesses the genome-encoded CAG glutamine codon at the same position (3).

RNA editing now is known to occur in a wide range of eukaryotic organisms and their viruses (5–7), and more examples are likely to be uncovered in the future.

What are the biochemical mechanisms responsible for RNA editing? The two minireviews in this issue focus on the genetic and biochemical aspects of nucleotide substitution RNA editing by deamination, either A-to-I (8) or C-to-U (9). The substrates and enzymes responsible for these editing processes are reviewed, along with the functional roles that representative editing events play in cellular processes. A third minireview that focused on 2'-O-methyl ribose nucleotide modification, uridine to pseudouridine conversion, and RNA-guided editing events mediated by small nucleolar RNA cofactor guides and associated proteins was published recently (10).

In the first minireview, Stefan Maas, Alexander Rich, and Kazuko Nishikura in their article entitled “A-to-I Editing: Recent News and Residual Mysteries” review new developments in the biochemistry and biology of editing by C-6 adenosine deamination (8). Recent advances in understanding the physiologic significance of individual members of the multigene family of adenosine deaminases that act on RNA (ADAR) enzymes, and the biochemical activities associated with the double-stranded RNA binding, Z-DNA binding, and catalytic domains of the ADAR deaminases are described. The enzymatic deamination of adenosine in pre-mRNAs and other structured RNAs is evaluated in the context of the components of the RNA viral genome, differences that correspond to A-to-G and U-to-C substitution mutations (4). RNA editing now is known to occur in a wide range of eukaryotic organisms and their viruses (5–7), and more examples are likely to be uncovered in the future.

Roles of RNA Editing

Edited RNA transcripts (A-to-I; C-to-U) possess sequences different from their unedited transcript counterparts and hence may display functional activities different from that shown by the unedited transcripts. Editing may alter processes including mRNA translation by changing codons and hence coding potential; editing may alter pre-mRNA splicing patterns by changing splice site recognition sequences; editing may affect RNA degradation by modifying RNA sequences involved in nuclease recognition; editing may affect viral RNA genome stability by changing template and hence product sequences during RNA replication; and editing potentially may affect RNA structure-dependent activities that entail binding of RNA by proteins.
editing machinery that carry out deamination editing of the A-to-I variety. The expression of ADAR enzymes is a complex process. This is illustrated by the ADAR1 gene, where alternative promoters including one inducible by interferons together with alternative splicing give rise to different protein isoforms. Information derived from the study of gene disruptions of ADARs has led to important insights into the roles of A-to-I editing. Pre-mRNA substrates encoding glutamate receptor and serotonin 2C receptor proteins provide two examples whereby A-to-I editing gives rise to amino acid substitutions, changes that alter the sequences and hence activities of the encoded proteins.

The second minireview of the series by Valerie Blanc and Nicholas O. Davidson entitled “C-to-U RNA Editing: Mechanisms Leading to Genetic Diversity,” summarizes progress in understanding the biochemical mechanisms and substrate targets for C-to-U RNA editing in mammals (9). Like A-to-I editing, C-to-U RNA editing is catalyzed by a deaminase that acts on the target RNA substrate. However, important differences exist between the biochemistry of C-to-U and A-to-I editing. The known C-to-U editing events involve a single-strand substrate, occur on spliced RNAs in the nucleus, and are mediated by a multicomponent complex that includes one or more associated protein complementation factors in addition to the catalytic deaminase (apobec-1). ApoB and neurofibromatosis type 1 (NF1) mRNA substrates provide two examples whereby C-to-U editing gives rise to translational stop codons that shorten the respective open reading frames and hence coding capacity of the mRNAs.

Altering the information transfer process at the post-transcriptional level of gene expression by nucleotide substitution editing through A or C deamination mechanisms represents an important strategy for amplifying genetic diversity and modifying the functions of products encoded by an organism’s genome (5–7). Some of the established and potential roles that A-to-I and C-to-U RNA editing plays, or may play, in biologic processes are summarized in Fig. 1. These include effects on mRNA translation, pre-mRNA splicing, RNA degradation, RNA replication, and RNA structure that result from A-to-I or C-to-U deaminations (5–9). Site-specific editing may change the coding potential of mRNA transcripts, leading to proteins with altered function due to amino acid substitutions following A-to-I editing, as exemplified by GluR-B and serotonin 2C receptor proteins. Introduction or removal of translation termination codons may also occur, as exemplified by apoB and NF1 mRNAs where C-to-U editing generates UAA and UGA translation stop codons, respectively, and hepatitis delta virus RNA where A-to-I editing converts an amber UAG stop to an UIC tryptophan codon. ADAR2 edits its own transcript to create an alternative splice acceptor site. Additionally, a novel ribonuclease selective for inosine-containing RNAs has been identified, which creates the possibility that A-to-I edited transcripts may be degraded preferentially relative to the unedited transcripts. For some viral RNAs, modifications characteristic of adenosine deamination are seen which, following RNA replication, would be expected under certain conditions to lead to changes in the encapsidated viral genome sequence. Finally, sequence changes resulting from editing may subsequently affect RNA structure and hence function, including altered binding of RNA by proteins (Fig. 1).

Much progress has been made in our understanding of the mechanisms and roles of RNA editing. Identification of additional mRNA substrates that undergo editing by deamination and establishing the functional roles that editing events play in biologic processes, together with further definition of the biochemical and regulatory mechanisms of A-to-I and C-to-U editing, present some of the immediate challenges and opportunities in the RNA editing field.

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