Mammalian C to U editing

Harold C. Smith, Joseph E. Wedekind, Kefang Xie, and Mark P. Sowden

Abstract

The sequencing of genomes from higher organisms demonstrated that the number and complexity of expressed mRNA sequences and proteins exceeds the quantity of predicted genes. This disparity has been attributed to a variety of cellular mechanisms including the use of alternative promoters, mRNA splice sites and/or polyadenylation sites. Additionally, single nucleotide modifications within RNA, and more recently DNA, can generate diversity in protein expression. C to U or dC to dU modification at specific sites within RNA or DNA can arise from targeted editing activities rather than spontaneous mutation and is catalyzed by APOBEC-1 or related zinc-dependent, cytidine deaminases. The function and substrate specificity are known for only five of the ten deaminases in the APOBEC-1 Related Protein family. Hence, exciting discoveries are predicted regarding the role of editing enzymes as modifiers of protein expression in normal physiology, in conferring resistance to invading pathogens, and possibly activities underlying human disease.

1 Introduction

This chapter addresses the function of APOBEC-1 and the family of related mammalian cytidine deaminases. Many of these proteins have the ability to deaminate free nucleosides or nucleotides, as well as the capacity to convert cytidine to uridine in RNA or deoxycytidine to deoxyuridine in DNA. The focus will be on mammalian apolipoprotein B (*apoB*) C to U mRNA editing, a nuclear RNA processing event that mediates cytidine to uridine conversion and which occurs to a limited extent cotranscriptionally but largely coincident with, or subsequent to, pre-mRNA splicing (Lau 1991; Sowden et al. 1996b; Sowden and Smith 2001). The catalytic and auxiliary proteins involved in this process will be described along with a scheme for the regulation of *apoB* mRNA editing. A model for the structure of APOBEC-1 is presented that has predictive value for the structure and function of Activation Induced Deaminase (AID) and APOBEC-3G (CEM15; see Marquet and Dardel, this volume), which are members of the APOBEC-1 Related Protein family whose respective DNA editing activities are required for diversification and expression of immunoglobulins (Reynaud et al. 2003), and disruption of retroviral, e.g. HIV-1, infectivity (Sheehy et al. 2002; Mangeat et al. 2003). The finding that other members of the family (Mian et al.

Topics in Current Genetics, Vol. 12
H. Grosjean (Ed.): Fine-Tuning of RNA Functions by Modification and Editing
DOI 10.1007/b105432 / Published online: 14 December 2004

1998; Jarmuz et al. 2002; Wedekind et al. 2003) exhibit DNA deaminase activity (Harris et al. 2002, 2003; Lecossier et al. 2003; Mangeat et al. 2003; Zhang et al. 2003; Zheng et al. 2004; Wiegand et al. 2004) suggests a broader role for mammalian C to U editing enzymes in biological processes than previously considered.

Although relatively few editing events have been characterized in mammals, they can have profound effects on: the function of transmembrane receptors and ion channels (Reenan 2001), erythropoiesis and inflammation (Beghini et al. 2000; Yang et al. 2003; Hartner et al. 2004), cardiovascular disease (Kozarsky et al. 1996; Yang et al. 2002), cancer (Anant et al. 2002; Harris et al. 2002; Cappione et al. 1997; Okazaki et al. 2003; Machida et al. 2004), and upon the life cycle of viruses (Sheehy et al. 2002; Wong and Lazinski 2002; Harris et al. 2003; Lecossier et al. 2003; Macnaughton et al. 2003; Mangeat et al. 2003; Zhang et al. 2003; Turelli et al. 2004; Yu et al. 2004; Zheng et al. 2004). Editing activity affects protein expression by altering nucleotides that change codon sense or by producing translation initiation or stop codons (reviewed in Gott and Emeson 2000; Keegan et al. 2001, 2004; Reenan 2001; Wedekind et al. 2003) or by modifying the nucleotides necessary for pre-mRNA splice site selection (Rueter et al. 1999; Palladino et al. 2000a; Keegan et al. 2004). For additional information on these topics, the reader is directed to Hoopengardner, this volume.

2 Site-specific *apoB* mRNA editing: the basic facts

ApoB mRNA is edited within the epithelial cells (enterocytes) that line the small intestines of all mammals and in the liver (hepatocytes) of some species (Chen et al. 1987; Powell et al. 1987; Davidson et al. 1988; Greeve et al. 1993). Editing at cytidine 6666 of this mRNA converts a CAA glutamine codon to a UAA stop codon, thereby, enabling both full length (apoB100) and truncated (apoB48) variants of apoB protein to be expressed from a single gene. ApoB48 is stored in the enterocyte and assembled with dietary lipids as the structural protein core of chylomicrons. These are secreted into the lymphatic ducts draining the small intestine and enter the blood stream from which they are rapidly taken up by the liver. Chylomicron derived lipids are reassembled in the liver as very low density lipoproteins (VLDL) on apoB100 protein which are secreted into the circulation for peripheral tissue utilization. In several mammals, *apoB* mRNA editing also occurs in liver (Greeve et al. 1993) where, unlike intestine, *apoB* mRNA editing is regulated to determine the proportion of edited *apoB* mRNA as well as the amount of secreted B48 VLDL (Sparks et al. 1981). Hepatic VLDL are assembled and secreted with apoB100 and apoB48 protein cores. B100 VLDL are digested by peripheral lipases, rendering them to protein and cholesterol rich low density lipoproteins (LDL), whose elevated abundance in blood is an atherosclerotic risk factor (Corsetti et al. 2003). ApoB48 VLDL is cleared from the blood more rapidly than apoB100 VLDL and is not metabolized to LDL (Chan 1992). For this reason, hepatic apoB mRNA editing has been considered as a means of reducing the risk of atherogenic disease.