Mechanisms and functions of RNA-guided RNA modification

Yi-Tao Yu, Rebecca M. Terns, and Michael P. Terns

Abstract

RNA-guided 2'-*O*-methylations and pseudouridylations occur in several different types of RNAs and in a wide range of organisms. Hundreds of the RNAs that guide these modifications have been identified, leading to breakthroughs in our understanding of the mechanisms of RNA-guided RNA modifications and, to some extent, the functions of 2'-*O*-methylated residues and pseudouridines. There are two classes of guide RNAs, namely box C/D and box H/ACA RNAs, which direct 2'-*O*-methylations and pseudouridylations, respectively. The guide RNAs function primarily by binding to complementary regions in the target RNAs. Cellular guide RNAs exist in RNA-protein complexes comprised of one guide RNA and a set of proteins that includes the modifying enzyme (2'-*O*-methylase or pseudouridylase). We are beginning to understand the basis for the importance of the RNA-guided modifications, which are well conserved and clustered in functionally important regions of RNAs. Recent reports indicate that modified nucleotides in rRNAs and spliceosomal snRNAs contribute to protein synthesis and pre-mRNA splicing, respectively.

1 Introduction

Post-transcriptional modifications occur in a large number of cellular RNAs and are an important component of RNA maturation. Modifications can occur within the base, sugar ring (ribose), or both, and thereby increase the diversity and functional potential of RNAs. In fact, a large collection of naturally occurring modified nucleotides has been identified (Motorin and Grosjean 1998). Importantly, modified nucleotides are, in most cases, conserved from species to species and are often clustered in regions of functional importance within RNAs (Massenet et al. 1998; Ofengand and Fournier 1998; Decatur and Fournier 2002). The fact that modified RNA nucleotides are widespread, conserved and located in strategic locations within RNAs leaves little doubt about their functional relevance. Yet despite intense work over many years, the question of what roles the modified nucleotides play in cellular processes remains largely unanswered.

Pseudouridylation and 2'-*O*-methylation are the most abundant internal modifications found in stable RNAs, namely tRNAs (Bjork 1995; Grosjean et al. 1995;

Topics in Current Genetics, Vol. 12
H. Grosjean (Ed.): Fine-Tuning of RNA Functions by Modification and Editing
DOI 10.1007/b105585 / Published online: 14 December 2004
© Springer-Verlag Berlin Heidelberg 2005

Auffinger and Westhof 1998; Sprinzl et al. 1998; Hopper and Phizicky 2003), rRNAs (Maden 1990; Bachellerie and Cavaille 1998; Ofengand and Fournier 1998) and spliceosomal snRNAs (some snoRNAs as well) (Reddy and Busch 1988; Massenet et al. 1998). In fact, these are the predominant modifications found in rRNAs and spliceosomal snRNAs. The mammalian rRNAs contain ~100 pseudouridines (Ψ) and ~100 2'-*O*-methylated residues (Maden 1990; Bachellerie and Cavaille 1998; Ofengand and Fournier 1998), and a total of 30 2'-*O*-methylated residues and 24 pseudouridines have been reported in the major vertebrate spliceosomal snRNAs (including U1, U2, U4, U5, and U6 snRNAs) (Reddy and Busch 1988; Massenet et al. 1998). 2'-*O*-methylation and pseudouridylation are also the predominant modifications in U3, a well-characterized snoRNA (Reddy and Busch 1988). While pseudouridylations and 2'-*O*-methylations may not be the most prevalent modifications in tRNA, they are present in all tRNAs (Bjork 1995; Grosjean et al. 1995; Auffinger and Westhof 1998).

RNA modifications can be categorized as either RNA-dependent or RNA-independent, based on the mechanism by which they are generated. RNA-dependent modifications are introduced by RNA-protein complexes (for example small nucleolar ribonucleoprotein complexes or snoRNPs), in which the RNA component serves as a guide that base-pairs with the target RNA to direct modification at a specific site(s) (Kiss 2001; Bachellerie et al. 2002; Filipowicz and Pogacic 2002; Kiss 2002; Terns and Terns 2002; Decatur and Fournier 2003). RNA-independent modifications are catalyzed by a single protein or a protein complex that recognizes and binds to a specific RNA sequence or structure (Bjork 1995; Alexandrov et al. 2002; Ofengand 2002; Ferre-D'Amare 2003; Ma et al. 2003). While most RNA base modifications are catalyzed by the RNA-independent (protein only) mechanism, 2'-*O*-methylations and pseudouridylations are introduced by both RNA-independent and RNA-dependent mechanisms depending on the RNA type and organism. Computational and experimental evidence indicates that 2'-*O*-methylation and pseudouridylation of eukaryotic and archaeal rRNAs and higher eukaryotic spliceosomal snRNAs are almost exclusively catalyzed by the RNA-dependent mechanism (Dennis et al. 2001; Kiss 2001, 2002; Bachellerie et al. 2002; Terns and Terns 2002; Decatur and Fournier 2003; Omer et al. 2003). 2'-*O*-methylation of archaeal tRNA is also catalyzed by RNA-dependent mechanism (Omer et al. 2000; Clouet d'Orval et al. 2001; Dennis et al. 2001). Recent reports suggest that RNA-guided modifications may occur in certain mRNAs as well (Cavaille et al. 2000; Liang et al. 2002). In this review, we focus on RNA-dependent RNA modifications, including RNA-guided pseudouridylation and 2'-*O*-methylation in various organisms.

2 Discovery of eukaryotic snoRNAs that guide rRNA modifications

The nucleolus of eukaryotic cells harbors, in addition to precursor and mature rRNAs and ribosomal proteins, a huge number of small RNAs (termed small nu-