Modification and editing of RNA: historical overview and important facts to remember

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Abstract

RNA plays a central role in many cellular processes and several peculiarities of RNAs are probably relics of an ancient primordial RNA World. To fulfill their multiple present-day functions, these molecules need more than just four canonical bases. The numerous modified nucleosides that are formed during processing of nascent precursor RNA transcripts clearly serve this purpose. The recent discoveries of RNA-guided RNA modification machineries and of RNA editing processes leading to selected conversions of one base into another in the pre-RNA, add new dimensions to the problems surrounding the biosynthesis and functions of modified and edited nucleosides in RNA. The majority of these so-called minor or edited nucleosides appear to improve the performance of the matured RNA by working more efficiently and accurately in various steps of cellular metabolism. However, their effects can be subtle and not easy to demonstrate either *in vivo* or *in vitro*. Here, we review some basic characteristics of the modified nucleosides and of enzymes leading to such post-transcriptional modifications and editing of RNA

1 Short historical background

1.1 Discovery of modified nucleosides

Figure 1 points out the most important discoveries concerning modified nucleosides in nucleic acids (mostly RNA) and their corresponding enzymes, which span about five decades, while the discovery of the RNA editing process was made more recently, about 20 years ago.

Before 1948, naturally occurring nucleic acid polymers (DNA and RNA) were thought to contain only four canonical nucleosides: the ribo- or deoxyribo-derivatives of adenine, cytidine, guanine and uracil or thymine. Hotchkiss (1948) reported the first evidence for presence of trace amounts of a non-canonical nucleoside in DNA. This nucleoside was identified as deoxy 5-methylcytosine (dm^5C; Wyatt 1950). Soon after, Cohn and Volkin (1951) also detected small amounts of another compound (designated "?"), but in RNA hydrolysates. The structure of that minor compound was identified in 1956 as 5-ribosyluracil, an

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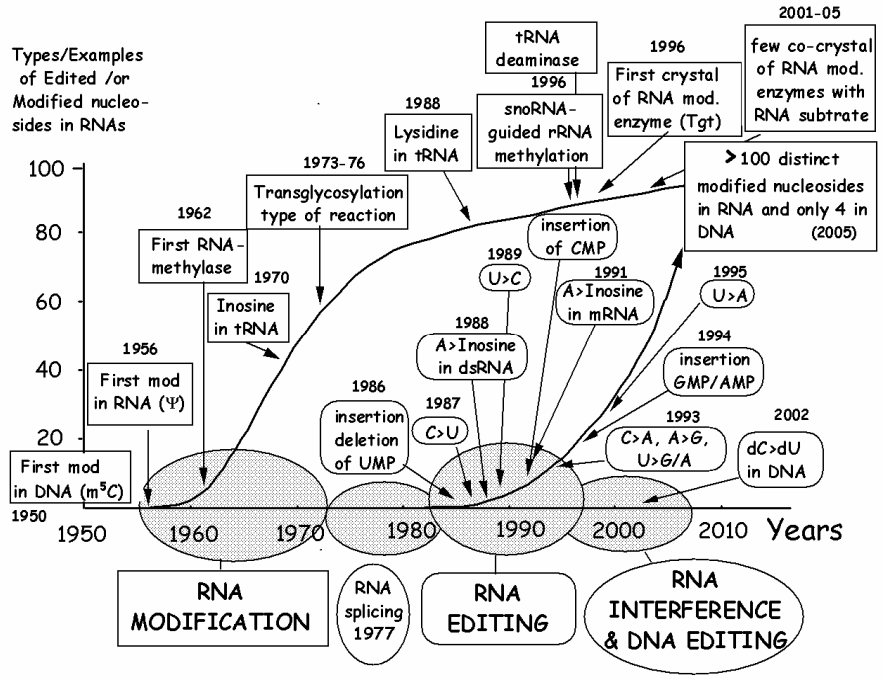

Fig. 1. Milestones discoveries related to post-transcriptional modification, splicing, editing and interference of nucleic acids (DNA and RNA). Gray circles along abscissa correspond to the various periods of the greatest scientific excitements concerning the novelty of the discoveries: 1) the identification of numerous modified nucleosides in RNA hydrolysates and in newly sequenced RNAs (period 1955-1970); 2) the discovery of intron splicing phenomena (period 1975-1985); 3) the RNA Editing phenomena (period 1985-1995), and 4) more recently the discoveries related to RNA interference and DNA editing processes (period 1995 - present). For details, see text and information within the figure

isomer of the canonical 1-ribosyluracil (uridine), thereafter called the "fifth ribonucleoside" (Davis and Allen 1957) and soon after designated pseudouridine (abbreviated in Ψ) (Cohn 1960). This unusual ribonucleoside was present in about 1-2% in "salt-soluble" RNA fractions (in fact tRNA), while the "salt-insoluble" fraction (in fact rRNA) also contained Ψ but less (below 1%). To date, we know that pseudouridine Ψ is indeed present in every isoacceptor tRNA (at least one mole per mole, present at position 55 in the so-called TΨ-loop), in all rRNA molecules and in most sn(o)RNAs. Only mRNA has not been shown to date to contain Ψ, however, an experiment to prove or disprove that possibility has not really been carried out. Pseudouridine results from enzymatic isomerization (internal transglycosylation, see below) of the genetically encoded U into Ψ, catalyzed by RNA:pseudouridine synthases. To date, many distinct RNA:pseudouridine synthases have been identified and several of them (mostly from *Escherichia coli*) have been obtained in crystallized forms (see e.g. Hoang and Ferré d'Amaré 2000;