The Other RNA World

RNA is more than a messenger between genome and protein: Ribosomal RNA has long been recognized as fulfilling a structural role and transfer RNA as fulfilling an adapter role in the conversion of message to protein. The discovery of catalytic RNAs, or ribozymes, in 1981 proved that RNA could catalyze reactions just as proteins do, as well as having the information storage function of DNA. The realization that RNA combines features of proteins and DNA led to the "RNA world" hypothesis for the origin of life. In spite of the many attributes of RNA, there are many fewer so-called noncoding RNAs (ncRNAs) than proteins, the biochemistry of polypeptides being so much more versatile than that of polynucleotides. Nevertheless, their number and importance are increasing as we learn more about them. The growing interest in noncoding RNAs has been fueled in part by two related discoveries: the identification of large numbers of very small RNAs of ~22 nucleotides in length, called microRNAs (miRNAs), in organisms as diverse as the worm *Caenorhabditis elegans* and humans, and the relationship of these miRNAs to intermediates in RNA interference (RNAi), one of a family of eukaryotic RNA silencing mechanisms in which RNA is used to target and destroy homologous mRNA, viral RNA, or other RNAs.

CONTENTS

VIEWPOINTS

1260 **An Expanding Universe of Noncoding RNAs**
G. Storz

1263 **RNA Silencing: The Genome's Immune System**
R. H. A. Plasterk

1265 **Ancient Pathways Programmed by Small RNAs**
P. D. Zamore

REVIEW

1270 **RNA-Dependent RNA Polymerases, Viruses, and RNA Silencing**
P. Ahlquist

See also Science's STKE on p. 1195 and Report on p. 1319.

This special issue surveys some of the recent developments in our understanding of ncRNAs and RNAi. Storz (p. 1260) provides an overview of the diverse family of ncRNA molecules in both prokaryotes and eukaryotes. Our full appreciation of the importance of ncRNAs is very much limited by the lack of data on both functions (for many this is still unknown) and the extent of the "RNome," the RNA equivalent of the proteome. Estimates for the number of ncRNAs range from hundreds to thousands per genome. The roles so far characterized for ncRNAs are as diverse as their structures and range from the purely structural to the purely regulatory.

The newly described eukaryotic miRNAs almost certainly fall into the regulatory class of ncRNAs. Of the tens of miRNA genes characterized in detail, two have a known function: *lin4* and *let7*, the so-called small temporal RNAs (stRNAs). These control developmental timing in the nematode worm *C. elegans* and repress the translation of their target genes by binding to the 3′ untranslated regions of their mRNAs. The stRNAs are cleaved from precursor molecules by the enzyme Dicer (as are other miRNAs) and appear to be structurally very similar to the small intermediate RNAs (siRNAs) that this enzyme generates in its role in the various RNA silencing pathways. The siRNAs are otherwise very different from miRNAs, being derived from "aberrant" RNA and triggering a mechanism for the complete destruction of the target RNA.

RNA silencing systems have been described in numerous organisms: posttranscriptional gene silencing (PTGS) and cosuppression in plants, quelling in fungi, and RNAi in animals. These processes are now known to be mechanistically related at their core, helping to provide a unified view of the field. Nevertheless, each system and each organism shows substantial and often confusing variations on the RNAi theme. Zamore (p. 1265) grapples with some of these outstanding questions. For example, how do the different systems sense "foreign" nucleic acid? Double-stranded RNA (dsRNA) can induce silencing, but what is the signal in single-stranded mRNA detected by PTGS? Perhaps RNA-dependent RNA polymerase (RdRP), required for PTGS, senses target mRNA and copies it to form dsRNA. Ahlquist (p. 1270) discusses the contrasting yet essential roles of RdRPs in the life cycle of RNA viruses and in the RNA silencing pathways that evolved to eliminate such viruses.

It is clear that the function of RNAi-based RNA silencing in plants is to defend the genome against foreign, invading nucleic acids—viruses, transposons, and transgenes. Evidence that small RNAs may play a similar role in animals is bolstered by the Report by Li *et al.* (p. 1319) showing that an animal virus encodes a suppressor protein capable of abrogating RNA silencing in insect cells. Plasterk (p. 1263) draws parallels between the genome-protective function of these RNA silencing pathways and the immune system of vertebrates. Both systems distinguish what is foreign from what is self and are able to amplify an initial response to overwhelm the invader, but using a dramatically different molecular toolkit. –GUY RIDDIHOUGH

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