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Desperately seeking RNAs

Many years ago RNA came in three flavors: messenger RNA, transfer RNA and ribosomal RNA. Now RNA has become the Baskin-Robbins of nucleic acids. Many different flavors of RNA seem to control the majority of processes in the cell and, in many cases, do so in a cell-specific and developmentally controlled manner. How do these RNAs regulate gene expression and cell growth? In most cases, we don't know the details, but two articles on pages 816 and 822 of this issue provide an example of the progress scientists are making toward understanding at least one small non-messenger RNA.

The search for different types of RNA molecules has an exciting history. RNA appeared on the scientific scene in the late 1950s when Crick posited the 'central dogma' in which RNA was an information carrier between DNA and proteins. In 1961, Jacob and Monod extended this hypothesis and predicted that an RNA intermediate, mRNA, would have specific characteristics. As they entered the 1960s, scientists were hard at work looking for mRNA and deciphering the genetic code.

Ten years later, there was a better understanding of the three main types of RNA in the cell (mRNA, tRNA and rRNA), all of which participated in protein synthesis, and of how genes were organized. However, in the early 1970s, it became clear that eukaryotic genes contained introns within their mRNA that were removed before translation. What cellular machinery existed to accomplish this task? In 1979, a RNA–protein complex called small nuclear ribonucleoprotein (snRNP) was identified. This RNP contained uridine-rich RNAs, many of which turned out to be components of one of two spliceosomes. Splicing became the new hot area of RNA research.

It did not escape anyone's notice that most RNAs were associated with proteins. At the time, RNA was considered the glue holding the proteins together in the ribosome. However, in the late 1970s, Noller showed that the rRNA was acting as more than just scaffolding. Furthermore, in the early 1980s, Cech and Altman showed that, like proteins, RNAs can act as catalysts. Within ~25 years, it had become clear that RNA was full of surprises and functioned as more than an information carrier in the cell.

Fast-forward to the 1990s. Small regulatory noncoding RNAs, most of which are found in bacterial intergenic regions and eukaryotic introns, have become all the rage. Regulation by small RNA (sRNA, ~100–200 nucleotides long) has been known for a long time in bacteria (~30 years) but only recently have mechanistic studies enhanced our understanding of how these RNAs function. In prokaryotes, sRNAs regulate such processes as the transition from growth to stationary phase, quorum sensing and virulence. In some cases, the target of the sRNA is known. 6S RNA, for example, binds to the bacterial σ^{70} holoenzyme and modulates promoter use. A major class of sRNAs act by binding to the RNA chaperone Hfq, followed by pairing to specific target mRNA. This pairing results in the stimulation or inhibition of translation and in mRNA decay. However, the targets of the majority of the bacterial sRNAs and their mechanisms of action are not known.

The history of eukaryotic regulatory RNAs began ~11 years ago. The Ambrose lab discovered that *lin-4*, a gene known to control the timing of worm larval development, coded for a pair of small RNAs and not a protein. The Ambros and Ruvkun labs noticed that *lin-4* RNA had complementarity to the 3′ untranslated region of the *lin-14* gene product. These and other data from both labs suggested a model in which *lin-4* RNA pairs with the *lin-14* 3′ untranslated region to repress translation of the *lin-14* message. This repression is part of a regulatory pathway that triggers the timing of larval development. Seven years after the discovery of *lin-4*, a second gene, *let-7*, was also shown to code for an RNA and to function in regulation of development. At the time, these RNAs were named small temporal RNAs and were considered oddities particular to worms. However, it quickly became evident that these RNAs would write the next chapter of the exciting history of RNA.

The last two years have brought significant progress in the identification of new small RNAs, now called microRNAs (miRNAs, ~21–25 nucleotides long). Current estimates for the number of miRNAs from genomic and computational analyses are: *Arabidopsis* (20–40); *Drosophila* (96–124); *Caenorhabditis elegans* (~130, most are validated); *Homo sapiens* (200–255). These estimates represent 1% of the predicted genes in the mammalian genome, similar to the proportion represented by large gene families, such as transcription factors, involved in regulation. What are the targets of miRNAs and how do they regulate gene expression? Computational methods are being used to identify targets with the expectation that the results will provide clues as to the mechanism of action of a particular miRNA. Preliminary results from these methods suggest that the targets are involved in numerous biological processes, and operate at many levels to regulate the expression of diverse genes. Future studies of miRNAs are sure to elucidate the mechanisms by which these small RNAs control cellular processes.

It is clear that miRNAs are not the only noncoding RNAs in the cell. Other examples include the small nucleolar RNAs, which direct the modification of rRNA, tRNA and noncoding RNA, and guide RNAs, which direct insertion or deletion of uridine residues in mRNAs. In this issue, a new, atypical, ~178-nucleotide noncoding RNA is reported. This RNA, called B2, is transcribed from short interspersed repetitive elements (SINEs) found in the genomes of multicellular animals and plants. Goodrich and Kugel show that the SINE-encoded mouse B2 RNA is a *trans*-acting regulator of transcription that binds to RNA polymerase II. B2 inhibits the formation of the preinitiation complex during heat shock. Transcription regulation has long been the realm of proteins, but the Goodrich and Kugel studies and those on other noncoding RNAs, such as 6S, U1, and 7SK, suggest that RNA has the potential to take control of transcription regulation.

So what have we learned about RNA in its short 50-year history? It is far more versatile in both form and function than ever anticipated. We should not underestimate its abilities but instead expect exciting surprises as we write the next chapter in its history. ■