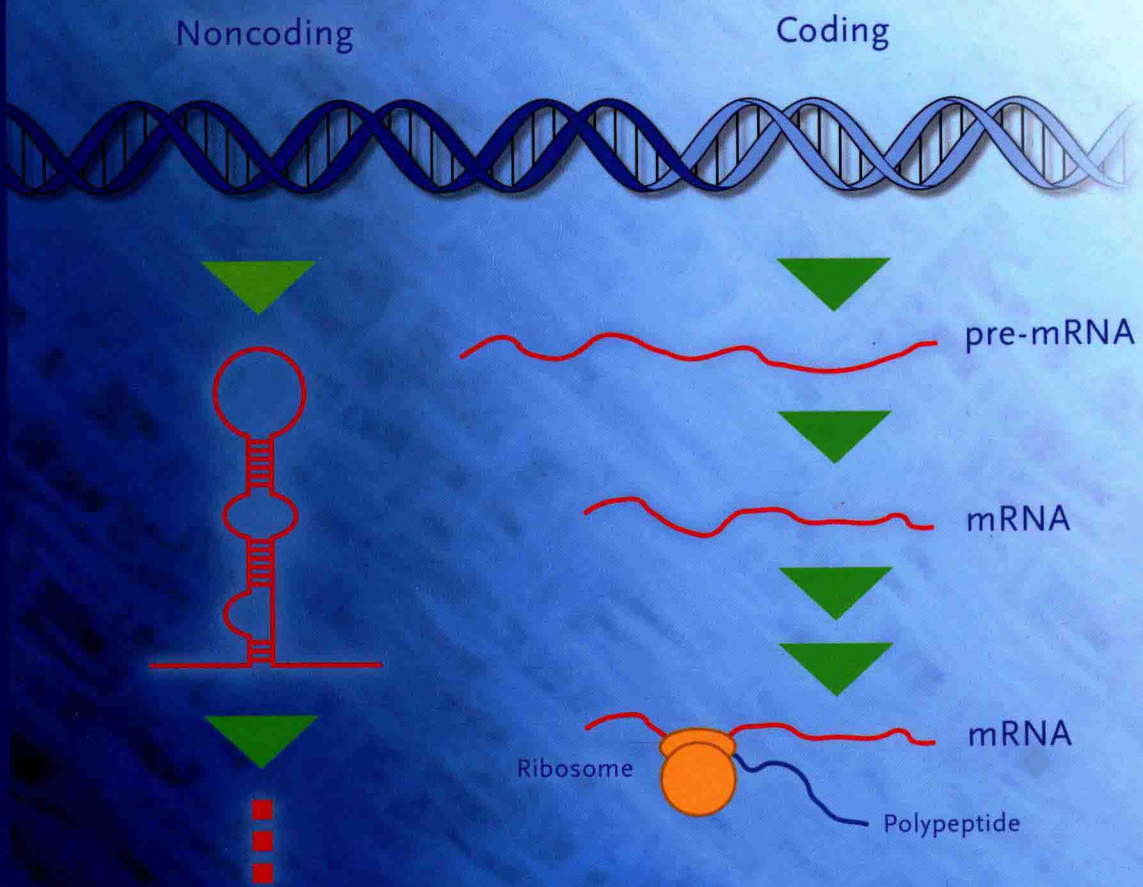
Posttranscriptional Gene Regulation

RNA Processing in Eukaryotes

Edited by Jane Wu



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The Editor

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Cover
Illustrated on the cover is a simplified summary of our current understanding of eukaryotic gene regulation. Most of our knowledge about gene expression and regulation has come from studies of protein coding genes ("Coding"), although nonprotein coding genes ("Noncoding") may account for the vast majority of eukaryotic genomes. Following transcription from DNA (depicted as the double-stranded helix), precursor noncoding RNA gene products (diagrammed as the stem-looped structure) or messenger RNA precursors (pre-mRNAs) undergo multistep posttranscriptional RNA processing before they become functionally active in engaging their target genes or serving as messengers (mRNAs) to direct polypeptide synthesis in the protein synthesis machinery (Ribosomes). Each step of these complex gene expression processes (depicted as green triangles) is under intricate regulation to meet the cell's needs in adapting to its constantly changing environment. (Contributed by Mengxue Yang and Jane Y. Wu.)

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Foreword

RNA is the "working substance" of genetics, a multipart actor playing almost every part in the expression of genetic information. The central dogma of molecular biology places RNA centrally between the cell's genetic library of DNA, and its catalytic engines the proteins, underscoring RNA's key importance in the flux of information. Yet the deceptive simplicity of the original scheme as set out by Crick greatly underrepresents the myriad functions of RNA, and its critical role in orchestrating the almost impossibly complex regulatory networks of the cell.

There are many reasons why RNA plays such a big part in the genetic life of the cell. The chemical nature of DNA has been selected to be relatively immutable to change; it has a rather staid, stay-at-home character. RNA by contrast is its rather racy cousin that is into everything. The 2′-hydroxyl group of RNA adds immeasurably to its chemical reactivity and structural repertoire. Moreover, as a formally single-stranded molecule, RNA can fold up into complex structures that bind ligands with huge selectivity (and there is a whole dimension of genetic regulation that is based on riboswitch function) and even exhibit catalytic activity. These properties were most probably the key to the early evolution of life, and the strongest indicator of this is telegraphed in the catalysis of peptidyl transfer by RNA in the modern ribosome. While most catalysis in the cell is now performed by proteins with their greater chemical flexibility, RNA has taken up most of the remaining genetic functions and run with them. The ancient role of RNA may be one of the reasons why it occupies such a central role in contemporary biology.

These additional functions have revealed themselves over a long period. I am old enough to remember the tremendous surprise we all felt when it transpired that eukaryotic genes were interrupted by introns, requiring splicing processes accurate to the nucleotide and a hugely complex apparatus to achieve that. This machine, the spliceosome, is a dynamic assembly of functional RNA and proteins, yet at its heart is probably at least in part a ribozyme. Unsurprisingly, splicing is precisely and dynamically regulated in a coordinated way in the cell, and alternative splicing events can increase genetic coding power by enabling exon skipping that is important in development.

Another unexpected development was the discovery that specific nucleotides could be chemically changed to "edit" the genetic content of the RNA. The classic example is the deamination of adenosine to generate inosine by the enzyme

adenosine deaminases acting on RNA (ADAR). Of course, the high level of nucleotide modification in the transfer RNAs (tRNAs) should indicate that the chemical alteration of "plain vanilla" RNA is likely to be considerable. In archaea and eukaryotes, RNA is subject to site-specific methylation and pseudouridylation by relatively small RNA–protein machines, the box C/D and H/ACA small nucleolar ribonucleoprotein particles (snoRNPs). These exhibit an ordered assembly that begins with the binding of a protein that stabilizes a ubiquitous structural motif in RNA called the kink turn, and ends when the methylase or uridine isomerase binds to the complex.

Transcription of RNA is tightly regulated but does not have the same checks on accuracy that DNA replication requires. There is no major requirement for repair processes for RNA; it lives by a more throwaway philosophy. And that is just what happens. In nonsense-mediated decay, RNA containing a premature termination codon is selectively degraded. This process is also used to regulate the synthesis of RNA-binding proteins. At the other end of the central dogma, translation is also regulated, and remarkably this can be involved in learning and memory.

Nobody can be unaware of the revolution that has swept through RNA biology with the discovery of gene regulation mediated by small RNA species. While the fraction of the genome that encodes proteins is really quite small, it transpires that much more of the genome encodes regulatory RNAs that are transcribed from untranslated regions and introns. Presumably for decades, RNA investigators were running these species off the ends of their gels, yet these noncoding RNA species have now assumed a vast importance and have become an industry both as a regulatory mechanism and a powerful laboratory tool. They could even yet be the source of therapeutic agents, although as ever the big problem there remains delivery. Regulatory RNA networks of great complexity will ultimately require the methods of systems biology and mathematical modeling to be fully understood.

Given the central importance of RNA in the life of the cell, it is obvious that defects will occur with serious consequences for function. These can lead to important diseases, exemplified by the role of noncoding RNA species in neurodevelopment and neurodegeneration. The role of RNA in disease is a significant issue in human health that we neglect at our peril. I suspect we have only begun to scratch the surface of this topic and await exciting developments.

This book provides a guided tour through the key functions of posttranscriptional gene regulation, that is, pretty much an overview of RNA biology, written by the experts in each area. Importantly, it also covers some aspects of the pathology of RNA when things go wrong. I congratulate Jane Wu in putting this book together–it is a highly valuable resource for many of us who are interested in eukaryotic gene regulation.

Beijing, May 2012
University of Dundee

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