CLINICAL IMPLICATIONS OF BASIC RESEARCH

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Unveiling the RNA World

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The 2018 Lasker–Koshland Special Achievement Award in Medical Science, announced September 11, recognizes Joan A. Steitz, who has made pioneering contributions to the understanding of RNA biology and, as a woman scientist, has led the way as a role model and strong advocate for removing the barriers to welcoming and advancing women and minorities into the scientific community.

Steitz began her scientific training when there were few women scientists, not long after the discovery of the "central dogma" of molecular biology. The central dogma posits that DNA provides the coding information for genes, which are transcribed into messenger RNAs (mRNAs) that are then translated by ribosomes into proteins. As a postdoctoral fellow and young faculty member, she identified the mRNA sequences that ribosomes recognize to begin translation and found that the recognition of the start site relies on base pairing between sequence-constrained sections of DNA located close to the start codon and a complementary sequence in a ribosomal RNA.[1,2]

According to the central dogma, RNA has a passive, intermediary role as messenger, carrying information encoded in DNA to proteins, which are the main structural and enzymatic components of cells. However, since this dogma was first conceptualized, the RNA world has exploded — partly as a consequence of advances in deep sequencing technology — to encompass a diverse universe of RNAs that are modified in hundreds of ways and transported to different locations in the cell and that have myriad functions beyond encoding proteins (Fig. 1). In fact, mRNAs make up only a few percent of cellular RNA. In eukaryotes, the sequences of most mRNA primary transcripts, called pre-mRNAs, contain coding regions (exons) and intervening sequences (introns) that need to be removed before translation in a process called splicing, which occurs as DNA is being transcribed into pre-mRNA. The bulk of cellular RNAs are noncoding RNAs (i.e., RNAs that are not translated into proteins), which range from approximately twenty to thousands of nucleotides in length. These noncoding RNAs are central components of tightly bound RNA- and protein-containing particles (known as ribonucleoproteins) that function as cellular machines to regulate transcription, orchestrate posttranscriptional RNA processing and translation (and other functions), and use nucleic acid base-pairing to other RNAs or DNAs to confer exquisite sequence specificity to their targets. Steitz played a key role in uncovering many functions of small noncoding RNAs, as well as the key steps needed to process their primary transcripts into functioning components of the RNA machinery.[3]

She also uncovered the role of small noncoding RNAs in promoting viral life cycles, and she made important contributions to the understanding of how small noncoding RNAs called microRNAs, which posttranscriptionally suppress the expression of host and viral genes by promoting mRNA decay and blocking protein translation, are processed and regulate gene expression. Although most biologists had previously concentrated on the regulation of transcription (by proteins called transcription factors) as the primary "control" of the expression of protein, it has become increasingly clear that RNA-mediated processes have, in the aggregate, an equally important role. These processes include the regulation of transcription and posttranscriptional regulation of splicing; mRNA modifications, such as methylation and polyadenylation; binding of untranslated mRNA regions to proteins that sequester mRNAs in specialized subcellular sites; and mRNA decay. In fact, the two systems — transcription factors and noncoding RNAs — regulate each other.

The key that unlocked the small noncoding

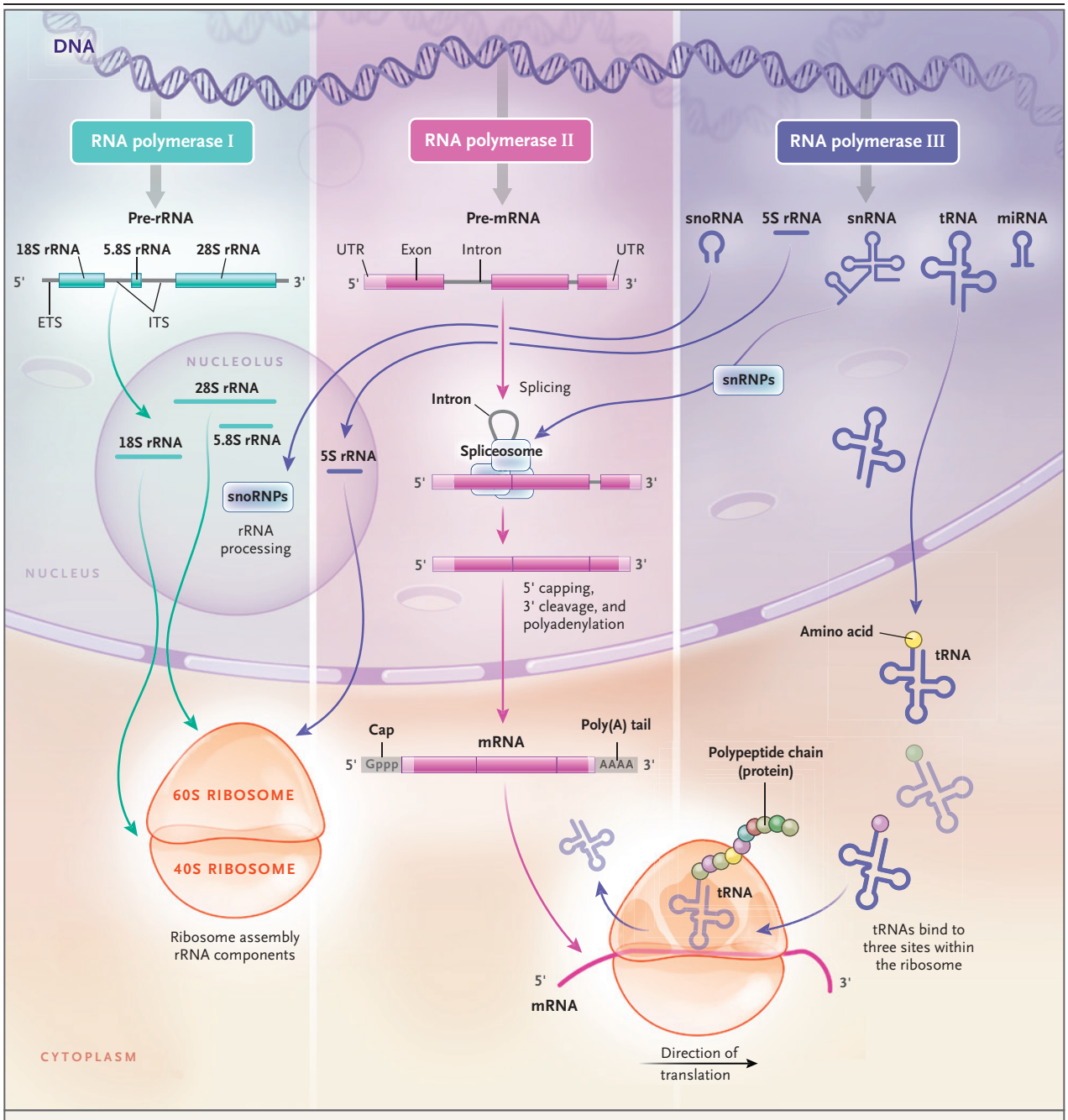

Figure 1. An Abundance of RNA.

DNA is transcribed by three different enzymes — RNA polymerases — into primary transcripts or precursors (pre-RNAs) of messenger RNAs (pre-mRNAs are produced by RNA polymerase II) and small and large noncoding RNAs. The small noncoding RNAs, which come in many varieties, are incorporated into ribonucleoprotein (RNP) machines. Ribosomal RNAs (rRNAs), the RNA components of the ribosome, are critical for translating mRNAs into proteins. The main rRNA transcript, which encodes three of the four rRNAs (5.8S, 18S, and 28S), is synthesized by RNA polymerase I and processed in the nucleolus with the use of the small nucleolar RNPs (snoRNPs). The fourth rRNA (5S) is synthesized by RNA polymerase III. The small noncoding RNAs (snRNAs) synthesized by RNA polymerase III include snRNAs that splice pre-mRNAs within a large and dynamic complex called the spliceosome; small nucleolar RNAs that process rRNAs and other noncoding RNAs; transfer RNAs (tRNAs) that load amino acids onto nascent peptides in the ribosome; and pre-microRNAs. Pre-microRNAs are processed into microRNAs (miRNAs) in the nucleus; miRNAs regulate gene expression by causing the degradation of mRNA or blocking the initiation of its translation in the cytosol. ETS denotes external transcribed spacer, Gppp guanosine triphosphate, ITS internal transcribed spacer, and UTR untranslated region.

RNA world was the discovery by Steitz and one of her graduate students (Michael Lerner) that some antinuclear antibodies, generated in patients with systemic lupus erythematosus and other autoimmune diseases, selectively recognize both protein and RNA components of many of the abundant ribonucleoproteins.[3,4] The Steitz laboratory used autoantibodies to isolate or deplete specific types of ribonucleoproteins to identify their components and dissect their function.

The insights of Steitz's pioneering studies that revealed the small RNA world and how it functions are just now beginning to be translated into new classes of therapeutics.[5] Last year, two antisense oligonucleotide RNA-based drugs, nusinersen and eteplirsen, that alter RNA splicing were approved to treat previously untreatable neurodegenerative diseases (spinal muscular atrophy and Duchenne's muscular dystrophy, respectively). The first drug to harness the microRNA pathway of RNA interference, patisiran, has just been approved to knock down transthyretin RNA for the treatment of a hereditary form of amyloidosis. These are probably just the first examples of a new pharmacopoeia of RNA-based drugs that will expand the universe of drug targets beyond those that are "druggable" with the use of small molecules and biologic agents.

The Lasker–Koshland award also recognizes Steitz's inspiring work as a role model, mentor, and advocate for women in science. When Steitz entered graduate school, there were very few women in science. I entered college at about the same time; there were only two women professors on the entire Faculty of Arts and Sciences at Harvard University. The women who succeeded as scientists had to be exceptionally capable and determined. As Steitz said in a 2001 *New York Times* article, "If a woman is a star [as she was] there aren't that many problems. If she is as good as the rest of the men, it's really pretty awful. A woman is expected to be twice as good for half as much." The situation of women in science has greatly improved since then, so that flagrant discrimination is uncommon. Still, the playing field is far from even, because of unconscious bias against women (by both men and women), underrepresentation of women in positions of leadership and prestige so that colleagues in "old boy" networks are preferentially recommended for promotions and awards, and poor self-esteem among women, as a result of deep and long-standing cultural biases. Steitz has effectively worked to counteract gender-based discrimination, speaking out to intervene in individual cases of discrimination, describing the difficulties that women face, and articulating ways to overcome them.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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