Twenty years of *RNA*: reflections from the RNP world

A. GREGORY MATERA

Department of Biology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3280, USA

As a product of the Boulder and New Haven RNA enclaves, I joined the RNA community at Case Western Reserve in 1994 as a newly-minted Assistant Professor. The very next year, Tim Nilsen and the RNA Society launched the journal that you now hold in your hands ... err, computer. After a dozen years or so, I moved to Chapel Hill. And I watched as a strong community of RNA biologists formed here at UNC, almost organically, without any sort of institutional directive or center. How did that happen? I think it is because RNA has become so incredibly interesting and central to studies of organismal biology that, as an institution of higher learning, you simply ignore this stuff at your own peril. But if you are reading this piece, then you are most likely already part of the choir, so I will stop preaching.

One could certainly argue that RNA has been a hot field ever since Cech's discovery of the *Tetrahymena* ribozyme in the early 1980s. However, there have been a plethora of significant advances in RNA science since the inception of our journal. Nearly everything has changed. But if you ask me what is the major difference between 1995 and 2015? It's this: Non-coding RNAs are cool again.

In order to gain proper perspective on the 1995–2015 time window, we first need to think about RNA science during the previous 20 years. In the first of those two decades (1975–1985), non-coding RNAs held center stage, primarily because only the abundant transcripts (e.g., tRNAs, rRNAs and snRNAs) were really even accessible for study. Following the advent of molecular cloning and PCR, the period from 1985–2000 saw the rise of the messenger RNA. During this time, mRNA was king, and much of the research on mRNA was actually focused on the proteins that carried out their processing, transport, translation and degradation. Interest in the cell biology of RNA was also rekindled, due in large part to advances in digital imaging microscopy and non-radioactive nucleic acid labeling techniques.

And then, circa 2000, an elegant little worm turned the RNA world on its head. Suddenly, there was Biology in those tiny RNAs that we used to dismiss as degradation products and run off the bottoms of our gels. RNAs that we thought were quite small (e.g., U2, 7SK and 5S) turned out to be

rather medium-sized. The ncRNA revolution was upon us, and researchers outside of our field began thinking about—and using—micro and short interfering RNAs on a daily basis. RNA interference really opened up the field of somatic cell genetics, allowing the interrogation of specific gene function in the absence of the appropriate germline mutation. More recently, the discovery that bacteria and archaea have RNA-based adaptive immune systems has given a tremendous boost to the study of small ncRNAs—not to mention the entire field of Genetics. Who would have thought that studying bacteria in yogurt cultures would lead to the development of sophisticated editing tools that can rapidly reshape genomes? The CRISPR/Cas system has firmly planted small ncRNAs in the limelight of the scientific world.

Thus, over the past 20 years, the identification of the RNAi and CRISPR genome defense systems are arguably the most far reaching discoveries. But they are not the only important RNA lessons. What else have we learned? We now appreciate that humans have many fewer protein coding genes than first predicted, but that each gene expresses many more alternative mRNA isoforms than expected previously. We've found that transcription is far more pervasive than previously envisioned, and are beginning to realize that promoters and enhancers are a lot more similar to each other than we first thought, as they both appear to be platforms for transcription initiation events. Moreover, a much clearer picture of the interconnectivity of the various gene expression regulatory steps has emerged. This finding has led to a somewhat cloudier experimental landscape as we try to parse out the contributions associated with each of the individual steps.

Conceptually, we've also learned a lot in the past two decades. We now know that most cellular RNAs are never really naked, rather, they form complexes with partner proteins in ribonucleoprotein (RNP) particles from their birth through to their destruction. Eukaryotic RNPs tend to be assembled in subcellular compartments that are distinct from those in which they are thought to function. Furthermore, the assembly of functional RNPs and delivery to their final destinations often involves progression through a series of intermediate complexes and subcellular locales. For example, we now understand that Cajal bodies are crucibles of ncRNP

Corresponding author: matera@unc.edu

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maturation, concentrating assembly factors to accelerate complicated biochemical reactions. We have learned that mRNPs undergo constant remodeling as they travel from the site of transcription to their ultimate, sometimes very specific, sites of translation in the cytoplasm. The discovery of the exon junction complex that distinguishes newly-minted mRNPs from older ones, and its coupling to downstream processes like nonsense-mediated decay are remarkable illustrations of the concept of RNA surveillance. Similarly, the identification of the Survival Motor Neuron (SMN) protein complex and its role in distinguishing Sm-class spliceosomal snRNAs from the cellular milieu, and chaperoning their assembly into functional snRNPs is another shining example of RNA quality control. These and other findings have led to a much greater appreciation of the importance of riboregulation to human health.

Technological advances have always driven scientific discovery, and the past 20 years are no exception. The depth provided by the massively parallel sequencing techniques available today has propelled RNA and gene expression research to incredible new heights. Where will RNA research take us over the *next* 20 years? I think we will continue to find RNAs and RNPs in strange and unexpected places, both inside the cell and out.

As a biomolecule, RNA has very ancient roots. Consistent with the RNA World hypothesis, RNAs seem to be involved

in nearly every aspect of cellular function. We live in the RNP World now, and proteins have taken over many of RNA's previous jobs. Yet, I find it interesting that RNAs (polynucleotides) do not appear to have many roles in cellular signaling, or membrane/actin cytoskeletal dynamics. Why is that? Do all the negative charges make RNAs somehow incompatible with these processes? Can RNPs function as primary messengers? Recent work has shown that cell-free circulating micro RNAs can be transported between cells; they have been detected in blood serum and other extracellular spaces. Indeed, the importance of extracellular RNAs as a good source of medical biomarkers is only now being realized. Recent appreciation of the pervasiveness of circular RNA transcripts in eukaryotic transcriptomes leads me to speculate that circular RNPs might be good candidates for potent intercellular signaling factors. Given their remarkable stability, and previously unrecognized ubiquity, it would not be surprising if circular RNAs are secreted. Understanding how these potential signals might be received is a challenge for the future.

The next two decades will certainly bring exciting new scientific challenges. Whatever they may be, I am confident that future investigators have been well served by the rigorous training and strong leadership provided by the founding members of our RNA Society. Let's keep up the good work!

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