APRIL 25, 2018
VOLUME 118
NUMBER 8

pubs.acs.org/CR

CHEMICAL REVIEWS

RNA: FROM SINGLE MOLECULES TO MEDICINE

ACS Publications
Most Trusted. Most Cited. Most Read.

www.acs.org

CHEMICAL REVIEWS

Editorial

Cite This: *Chem. Rev.* 2018, 118, 4117−4119

pubs.acs.org/CR

Introduction—RNA: From Single Molecules to Medicine

> *"This is the RNA World. To see how plausible it is, we need to look at why proteins are good at being enzymes but bad at being replicators; at why DNA is good at replicating but bad at being an enzyme; and finally why RNA might just be good enough at both roles to break out of the Catch-22."* — *Richard Dawkins in The Ancestor's Tale: A Pilgrimage to the Dawn of Evolution*

Since these lines were published in 2004, the genome sequencing revolution has revealed that, in many ways, we still live in the RNA World. Not only does RNA uniquely combine properties of both "chicken" and "egg" to resolve the conundrum of life's origin, but a plethora of RNA "chicken" also control much of the "egg" laying process,[1] with important implications for cellular health and disease.[2] Seminal discoveries such as those of RNA splicing, catalysis, and silencing, together with advances in technologies such as single molecule fluorescence and cryo-electron microscopies—often honored with a Nobel Prize (https://www.nobelprize.org)—have both revealed more functions of RNA and allowed us to probe them more deeply.[3] Together, these two waves of progress have propelled the RNA field to ever greater prominence, leading to unexpected scientific revelations that may, like genome editing[4,5] or, more recently, RNA editing using RNA-guided CRISPR-Cas technology,[6] one day give us true control over our destiny, closing the loop on our origins and improving our quality of life.

In this thematic issue, the assembled reviews represent but a limited sampling of the many insights emerging from, and tools important for, the RNA field. Inevitably, our selection of articles was constrained by the availability of authors and our own limits of imagination. As such, our goal was more to inspire future studies than exhaustively cover all that came before, as our collective future as a species may well depend on our ability to fully understand how each single RNA molecule in our body functions so it may be harnessed for personalized medicine and other benefits.

First, Walter and colleagues survey single molecule fluorescence microscopy as a tool that can study virtually any process involving RNA, from catalytic ribozymes and RNA silencing to CRISPR-Cas and pre-mRNA splicing. As long as an RNA, RNA−protein complex, or an entire RNA-guided pathway can be reconstituted *in vitro* with fluorophores attached to one or more components, single molecule fluorescence observation can remove the cloak of ensemble averages, revealing just how diverse and versatile RNA is.

Nagai and colleagues highlight the advances of another single molecule imaging tool, cryo-electron microscopy, in resolving a bevy of functional states of the dynamic spliceosome at near-atomic resolution. These structures unveil strong similarities with the active site of group II introns, suggesting a common evolutionary origin of both the RNA and protein components. These comparisons suggest a path by which evolution over time steadily replaced some RNA components, while retaining the central RNA functions of substrate recognition and catalysis.

In a particularly comprehensive review, Šponer, Bussi, and colleagues remind us how important computational tools can be in discerning RNA structure, dynamics, and function. Simulating single RNA molecules and their protein complexes all the way to the massive ribosome *in silico* reaches time resolutions so fast that experimental tools can rarely achieve them, while both helping interpret existing experimental data and rapidly generating experimentally testable hypotheses. The authors particularly focus on the scope and limitations of molecular dynamics simulations, with the goal to help lower the barrier to their broader adoption outside the specialist community.

Maquat and colleagues emphasize that the cellular steps of RNA metabolism do not happen in a vacuum but represent a continuum under the influence of preceding steps and affecting subsequent ones. This interconnectedness partly reflects the ability of nucleic acid binding proteins to multitask, as exemplified by DNA-binding transcription factors that shape gene expression beyond initiating RNA synthesis by regulating pre-mRNA splicing and, thereby, mRNA isoforms. Looking forward, the authors not only cover mechanistic models already experimentally proven but also call attention to connections that, although currently lacking direct support, are consistent with existing data and ripe for further investigation.

Next, D'Adda di Fagagna and colleagues make the case for the widespread involvement of "smart" nuclear noncoding RNAs in DNA damage signaling and repair, telomere maintenance, and genomic rearrangement. Intracellular single molecule techniques have begun to reveal the spatiotemporal production and recruitment of RNAs at DNA double-strand breaks to help patch them back up, perhaps one reason for the pervasive transcription of RNAs from most of the mammalian genome. They argue that this widespread involvement of RNA in maintaining genome integrity may offer opportunities for therapeutic intervention and lead to new medical therapies.

Complementarily, Siomi and colleagues describe a specific case of genome maintenance in the form of PIWI-interacting RNAs (piRNAs), found to control transposons in the germline to protect future generations. Long ago in evolution, transposons invaded mammalian genomes as parasitic DNA elements aiming to self-replicate, eventually striking a synergistic balance between destroying and diversifying the host's genes. piRNAs silence these transposons in analogy to microRNA-directed gene silencing, by employing their own germline-specific biogenesis and mechanism of action.

Wolin and colleagues close another loop by following the cellular RNAs to their end when they are no longer needed. Numerous surveillance pathways have evolved that degrade unneeded, defective, and potentially harmful noncoding RNAs to protect the cell and recycle its building blocks. The authors summarize and compare the yeast and human machineries that recognize accessible 5′ and 3′ ends on RNAs and feed them to exoribonucleases for degradation.

Finally, lest we forget, Bradrick, Garcia-Blanco, and colleagues remind us that flaviviruses, including the infamous dengue,

Special Issue: RNA: From Single Molecules to Medicine

Published: April 25, 2018

DOI: 10.1021/acs.chemrev.8b00095
Chem. Rev. 2018, 118, 4117−4119

yellow fever, and Zika viruses, are simple RNA−protein machines that carry out basic functions of their life cycle with the help of host factors. The authors discuss the fundamental biochemistry and molecular biology of these viruses, laying the foundation for our ability to combat them.

Writing a review that is equally comprehensive and comprehensible is challenging, so all authors have earned our thanks for making it happen on a timeline, as have Associate Editor Ruma Banerjee and Production Manager Lou Larsen for helping push the entire issue across the finish line. RNA deserves still broader attention, so our hope is that the collection of reviews assembled here may help a growing audience appreciate that RNA not only broke the Catch-22 of early life, needing both enzyme and genome, but stands to powerfully bridge the basic sciences and medicine today.

Nils G. Walter
University of Michigan, Ann Arbor
Lynne E. Maquat
University of Rochester

AUTHOR INFORMATION

Notes

Views expressed in this editorial are those of the authors and not necessarily the views of the ACS.

Biographies

Nils G. Walter is currently the Francis S. Collins Collegiate Professor of Chemistry, Biophysics, and Biological Chemistry in the College of Literature, Science and the Arts of the University of Michigan in Ann Arbor, Michigan. He founded and currently directs the unique Single Molecule Analysis in Real-Time (SMART) Center, as well as cofounded and currently codirects the Center for RNA Biomedicine at Michigan. He started his career by receiving his "Vordiplom" (B.S.) and "Diploma" (Masters) from the Technical University of Darmstadt after performing research with Hans-Günther Gassen on the physiochemical characterization of a protein dehyrogenase enzyme. He earned his Dr. Ing. while studying molecular *in vitro* evolution of DNA and RNA using fluorescence techniques with Nobel laureate Manfred Eigen at the Max-Planck-Institute for Biophysical Chemistry, Göttingen. For his postdoctoral studies, he turned to RNA enzymes under the guidance of John M. Burke at the University of Vermont in Burlington, Vermont. His research interests focus on noncoding RNA through the lens of single molecule techniques. Based on this work, he received the Otto-Hahn medal for Outstanding Researchers of the Max-Planck Society (1995), a Feodor-Lynen Postdoctoral Research Fellowship from the Alexander von Humboldt Foundation (1995), and a Camille Dreyfus Teacher-Scholar Award (2004), was elected a Member of the American Academy of Arts & Sciences (2011), received the Faculty Recognition (2013) and Harold R. Johnson Diversity Service Awards (2015) from the University of Michigan, and became the first RNA Society Mid-Career Award recipient (2017). Photo by Daryl Marshke, Michigan Photography, University of Michigan.

Lynne Elizabeth Maquat is the J. Lowell Orbison Endowed Chair and Professor of Biochemistry & Biophysics in the School of Medicine and Dentistry, Director of the Center for RNA Biology, and Chair of Graduate Women in Science at the University of Rochester, Rochester, NY, USA. After obtaining her Ph.D. in Biochemistry from the University of Wisconsin-Madison and undertaking postdoctoral work at the McArdle Laboratory for Cancer Research, she joined Roswell Park Cancer Institute before moving to the University of Rochester. Lynne discovered nonsense-mediated mRNA decay (NMD) in 1981 and, subsequently, the exon-junction complex (EJC) and how the EJC marks mRNAs for a quality-control "pioneer" round of protein synthesis. She also discovered Staufen-mediated mRNA decay, which mechanistically competes with NMD and, by so doing, new roles for short interspersed elements and long noncoding RNAs. Additional current interests include the influence of 3′UTR short interspersed elements on post-transcriptional gene expression, microRNA decay, functional links between transcription factors and RNA-binding proteins, and molecular mechanisms of particular neurologic disorders. She is an elected Fellow of the American Association for the Advancement of Science (2006) and an elected Member of the American Academy of Arts & Sciences (2006), the National Academy of Sciences (2011), and the National Academy of Medicine (2017). Lynne was a Batsheva de Rothschild Fellow of the Israel Academy of Sciences & Humanities (2012-2013) and has received the William C. Rose Award from the American Society for Biochemistry & Molecular Biology (2014), a Canada Gairdner International Award (2015), the International RNA Society Lifetime Achievement Award (2017), the Vanderbilt Prize in Biomedical Science (2017), the Federation of American Societies for Experimental Biology (FASEB) Excellence in Science Award (2018), and the Wiley Prize in Biomedical Sciences (2018).

REFERENCES

(1) Morris, K. V.; Mattick, J. S. The rise of regulatory RNA. *Nat. Rev. Genet.* **2014**, *15*, 423−437.
(2) Sullenger, B. A.; Nair, S. From the RNA world to the clinic. *Science* **2016**, *352*, 1417−1420.
(3) Walter, N. G. Going viral: riding the RNA wave to discovery. *RNA* **2015**, *21*, 756−757.
(4) Doudna, J. A.; Charpentier, E. Genome editing. The new frontier of genome engineering with CRISPR-Cas9. *Science* **2014**, *346*, 1258096.
(5) Sontheimer, E. J.; Barrangou, R. The Bacterial Origins of the CRISPR Genome-Editing Revolution. *Hum. Gene Ther.* **2015**, *26*, 413−424.

DOI: 10.1021/acs.chemrev.8b00095
Chem. Rev. 2018, 118, 4117−4119

(6) Cox, D. B. T.; Gootenberg, J. S.; Abudayyeh, O. O.; Franklin, B.; Kellner, M. J.; Joung, J.; Zhang, F. RNA editing with CRISPR-Cas13. *Science* **2017**, *358*, 1019−1027.

DOI: 10.1021/acs.chemrev.8b00095
Chem. Rev. 2018, 118, 4117−4119