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Nucleotide-level resolution of RNA folding interactions within peptide-based complex coacervates

MCCAULEY MEYER[1], RYOTA YAMAGAMI[1], SAEHYUN CHOI[1], FATMA PIR-CAKMAK[2], CHRISTINE D KEATING[1] AND PHILIP BEVILACQUA[1]

[1]Penn State University

[2]Massachusetts Institute of Technology

Presenting Author: mxm1357@psu.edu

The RNA World Hypothesis states that RNA or an RNA-like polymer may have acted as both the initial genetic material and the catalyst for the reactions of life. In the 1980s, the first ribozymes were discovered, demonstrating that RNA could act as a catalyst. Since then, it has become apparent that RNA folding is integral to function in a way similar to protein enzyme folding. Because of this, it is important to try to understand RNA folding under prebiotically relevant conditions.

On the early Earth, a problem that would have been faced by the first enzymes was the scarcity of organic material. To overcome this issue, organic material would need to be localized and concentrated on either a mineral surface or in some type of compartment, like a protocell. An ideal protocell candidate should partition molecules required for catalysis such as Mg^{2+}, nucleotides, RNAs, amino acids, and peptides. A model protocell able to do this is one made of complex coacervates.

I will describe our recent work on droplet observation and RNA folding studies within complex coacervate droplets made out of $(Lys)_n$-$(Asp)_n$, and $(Lys)_n$-ATP [1]. $tRNA^{phe}$ from S. cerevisiae was subjected to in-line probing (ILP) in low concentrations of Mg^{2+} to determine its native fold both in solution and inside of $(Lys)_n$-$(Asp)_n$ and $(Lys)_{10}$-ATP coacervates. Under coacervate conditions, the tRNA lost its tertiary contacts and the acceptor stem was unfolded. Upon changing Mg^{2+} conditions and charge-ratio of polyanions to polycations, more native folding of $tRNA^{phe}$ was observed. I will describe ongoing studies evaluating multiple RNAs under differing protocell composition and ionic conditions where we are applying Next-Generation sequencing approaches [2,3]. These experiments provide one of the first detailed views of RNA folding in protocells.

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[2] Ding, Y. et al. (2014), Nature 505, 696-700.

[3] Ritchey, L. E. et al. (2017), Nucleic Acids Res, 45 e135.