Chemistry Virtual Seminar

Local Binding Environment:
A Substrate's View of Protein-RNA Molecular Recognition

SPEAKER: Rodrigo Noriega
Assistant Professor
Physical and Materials Chemistry
University of Utah

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In this talk, we will discuss our group's work to characterize the process of molecular recognition between large biomolecules – specifically, between proteins and RNA. Of particular interest to us is Dicer-2, a large (198 kDa) enzyme whose biochemical activity differentiates between double-stranded RNA substrates with a blunt terminus from those with a 2-nucleotide 3' overhang. This has been posited as a way to target "non-self" entities (i.e., viral dsRNA intermediates) vs. endogenous dsRNAs. Using time-resolved fluorescence spectroscopy, we probed the local binding environment at the dsRNA terminus, which allowed us to identify distinct modes of interaction that are specific to the substrate structure and are regulated by nucleotide and accessory proteins. In this way, we observe a strong, ATP-dependent binding of blunt-end dsRNA by Dicer-2's helicase domain; which stands in contrast to a weaker, ATP-independent binding of 3' overhang dsRNA. Interestingly, these differences are greatly reduced by the accessory protein Loquacious-PD, which we show is due to the modification of the molecular recognition event into a substrate-independent and nucleotide-dependent binding of both kinds of dsRNA substrates by the helicase domain. Our results show that the bifurcation in the mechanism of Dicer-2 function occurs early on, and that the observed differences in biochemical activity follow from this initial termini-specific substrate recognition.