Science at the Edge Seminar Series

Quantitative Biology Graduate Program/ Gene Expression in Development and Disease

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Molecular Recognition and Catalysis in Ribonucleic Acids

RNA plays a central role in many biological processes and is therefore an important target for drug development. In recent years an increasing wealth of structural and functional information about RNA – ligand complexes has been obtained using in vitro selected RNAs (aptamers). However, those studies generally focused on structure and changes of the nucleic acid and mostly considered the ligand as a rigid target. In order to develop a detailed picture of ligand structure and dynamics in RNA – small molecule complexes we have used the Malachite Green binding RNA aptamer as a model system. We determined the solution structure of the MG – RNA complex and have used isotopically labeled ligand to probe the ligand structure in complex with RNA. The surprisingly asymmetric changes in the ^{13}C chemical shift of the ligand methyl groups indicate that the dye undergoes significant changes in its conformation and charge distribution upon binding. We have explored the role of the RNA in this interaction using *ab initio* and molecular dynamics calculations of the complex structure and charge distribution. The results indicate that the charge gradient in the RNA binding pocket provides a major contribution to the driving force of the ligand structural changes. The observation that not only the RNA adapts to the ligand in what is called adaptive binding, but the ligand itself also undergoes conformational changes ("induced fit"), is crucial for the rational design of RNA ligands and for understanding the properties of RNA – ligand complexes. We have used the results from these computational studies to convert the aptamer into a catalyst, i.e. a ribozyme.

Piazza M, Taiakina V, Guillemette SR, Guillemette JG, and Dieckmann T: Solution Structure of Calmodulin bound to the target peptide of Endothelial Nitric Oxide Synthase phosphorylated at Thr495. 2014, *Biochemistry*, in Press.

Da Costa JB, Andreiev AI, and Dieckmann T: Thermodynamics and Kinetics of Adaptive Binding in the Malachite Green RNA Aptamer. 2013, *Biochemistry*, **52**:6575-6583.

Da Costa JB and Dieckmann T: Structure and Thermodynamics of Drug-RNA Aptamer Interactions. 2013, *Mini-Rev Med Chem*, **13**:467-477.

Friday, October 2, 2015 at 11:30a.m.
Room 1400 BPS
Refreshments at 11:15