MAR17-2016-009703

Abstract for an Invited Paper
for the MAR17 Meeting of
the American Physical Society

**Opposing intermolecular tuning of $Ca^{2+}$ affinity for Calmodulin by its target peptides**

MARGARET CHEUNG, University of Houston

We investigated the impact of bound calmodulin (CaM)-target compound structure on the affinity of calcium ($Ca^{2+}$) by integrating coarse-grained models and all-atomistic simulations with non-equilibrium physics. We focused on binding between CaM and two specific targets, $Ca^{2+}$/CaM-dependent protein kinase II (CaMKII) and neurogranin (Ng), as they both regulate CaM-dependent $Ca^{2+}$ signaling pathways in neurons. It was shown experimentally that $Ca^{2+}$/CaM binds to the CaMKII peptide with higher affinity than the Ng peptide. The binding of CaMKII peptide to CaM in return increases the $Ca^{2+}$ affinity for CaM. However, this reciprocal relation was not observed in the Ng peptide, which binds to $Ca^{2+}$-free CaM or $Ca^{2+}$/CaM with similar binding affinity. Unlike CaM-CaMKII peptide that allowed structure determination by crystallography, the structural description of CaM-Ng peptide is unknown due to low binding affinity, therefore, we computationally generated an ensemble of CaM-Ng peptide structures by matching the changes in the chemical shifts of CaM upon Ng peptide binding from nuclear magnetic resonance experiments. We computed the changes in $Ca^{2+}$ affinity for CaM with and without binding targets in atomistic models using Jarzynski's equality. We discovered the molecular underpinnings of lowered affinity of $Ca^{2+}$ for CaM in the presence of Ng by showing that the N-terminal acidic region of Ng peptide pries open the $\beta$-sheet structure between the $Ca^{2+}$ binding loops particularly at C-domain of CaM, enabling $Ca^{2+}$ release. In contrast, CaMKII increases $Ca^{2+}$ affinity for the C-domain of CaM by stabilizing the two $Ca^{2+}$ binding loops.