QCB
Quantitative and Chemical Biology
Indiana University

Ernesto Fuentes

University of Iowa School of Medicine

Host: David Giedroc

Structure, Dynamics and Inhibition of Tiam1 PDZ Domain Complexes

The T-cell lymphoma invasion and metastasis (Tiam) family of proteins are guanine nucleotide exchange factors (GEFs) for the Rho-family GTPase Rac1 crucial for cell-cell adhesion and cell migration. Deregulation of Tiam1/Rac1 signaling leads to various malignancies, including cardiovascular disease and cancer. Tiam proteins contain several protein-protein interaction domains, in particular a PDZ domain. Previously we determined that the Tiam1 and Tiam2 PDZ domains had distinct binding specificities. Intriguingly, four residues in the ligand binding pocket are not conserved between the Tiam1 and Tiam2 PDZ domains. To test the importance of these residues in specificity, we engineered quadruple mutants of the Tiam1 and Tiam2 PDZ domains (QM PDZ), where four residues of one domain were substituted for those in the other. Remarkably, the QM PDZ binding preference was largely swapped. In this seminar, I will focus on the biochemical, structural and dynamic origins for the specificity switch for both the Tiam1 and Tiam2 PDZ domains. One main conclusion is that the data support a model where enhanced protein motions (i.e. dynamics) alters the conformational ensemble of the QM PDZ domain allowing for broader ligand specificity relative to the WT counterpart. If time permits, I will discuss our current work in identifying small-molecule inhibitors of Tiam1 PDZ.

For further details, contact Ms. Jill Campbell at 5-9749

QCB
Seminar Series

Co-hosted by the Department of Chemistry and the Graduate Program in Biochemistry

FRIDAY

MARCH 6

CHEMISTRY

C033

2:30 p.m.