BCHM421/422 - Jia Lab Project #2

Project Outline: The alpha kinase family is a small subgroup of atypical protein kinases and is non-homologous to the hundreds of conventional protein kinases in the human genome yet displays a similar 3D fold alike them. One such alpha kinase is Eukaryotic Elongation Factor 2 Kinase (eEF2K), which phosphorylates Eukaryotic Elongation Factor 2 (eEF2), a GTPase essential for global translation in eukaryotes. eEF2, when phosphorylated by eEF2K, is unable to bind the ribosome, therefore translation is suppressed. eEF2K has 3 domains; a calmodulin binding domain, alpha kinase domain, and eEF2 binding domain, as well as a long linker region known as the 'regulatory loop'. A full construct of eEF2K with all domains has not yet been structurally determined. Our goal is to determine the structure of eEF2K in order to understand the structural basis of regulation between the calmodulin binding domain and the alpha kinase domain. eEF2K as a global translation regulator is the target of many cellular signalling pathways, implicated in diseases such as cancer, neurological disorders like depression or Alzheimer's, and cardiovascular diseases. Structural determination of eEF2K, followed by subsequent structure-based drug design to inhibit eEF2K, is a lucrative opportunity in structural biology that may result in therapeutic advance. Our lab is readily familiar with structural determination of alpha kinases like the Myosin Heavy Chain II Alpha Kinase and is excited regarding this project and student opportunity. Compound eEF2Ks importance in regulating translation, with the fact that it is an atypical alpha kinase, makes it a worthwhile target for selective inhibition and analysis.

Supervisor: Zongchao Jia

Project Title: Structure and functional insights into the alpha-kinase eEF2K and its regulation.

Project Goals: This project aims to determine structural basis of regulation of eEF2K a protein crucial in regulating eukaryotic protein translation. Additionally, knowledge of this regulation will aid in structure-based drug design of a molecule to target eEF2K with high specificity.

Experimental Approaches: X-ray crystallography, protein expression and purification, structure-based drug design, biophysical protein characterization

References:

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