DICKERSON BIOCHEMISTRY SEMINAR SERIES

Midstream Presentation - Spring 2023

Can Aged-Damaged Proteins Be Targeted for Degradation? Early Insights in the Structural and Molecular Characterization of Human Protein-L-Isoaspartate O-Methyltransferase Domain-Containing Protein 1 (PCMTD1)

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L-asparagine and L-aspartate can isomerize into L-isoaspartate which can contribute to decreased functionality of proteins. Because these reactions are spontaneous, the accrual of this damage increases as one ages. Methylation repair activity by protein-L-isoaspartyl (D-aspartyl) O-methyltransferase (PCMT1) was thought to be the only cellular mechanism which combats the accrual of L-isoaspartyl damages. However, an additional mechanism may exist.

Protein carboxyl methyltransferase domain-containing protein 1 (PCMTD1) may be a potential E3 ubiquitin ligase that ubiquitylates proteins harboring isoaspartyl damages for proteasomal degradation. Similar to PCMT1, the N-terminus of PCMTD1 contains L-isoaspartate and S-adenosylmethionine (AdoMet) binding motifs. PCMTD1 also contains SOCS-box recruitment motifs found in substrate receptor proteins which complex into cullin-RING E3 ubiquitin ligases (CRLs). While PCMTD1 is able to bind to the methyltransferase cofactor AdoMet, isoaspartyl repair activity has not yet been demonstrated by PCMTD1. Biochemical, negative stain electron microscopy, and native top-down mass spectrometry suggests PCMTD1 multimerizes with CRL components to form the putative CRL, CRL5-PCMTD1. While further molecular and structural characterization of PCMTD1 is needed to better understand the role of PCMTD1 in this newly proposed preotolytic pathway for aged-damaged proteins, we describe here initial studies of this uncharacterized protein which may ultimately function as an isoaspartyl-residue-specific E3 ubiquitin ligase.

Investigating the role of heme transfer in Corynebacterium diphtheria

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Bacterial pathogens must acquire iron from their host in order to proliferate and mount an infection, as iron is an essential metal cofactor involved in vital cellular processes. However, the concentration of free iron within the body is extremely low because the majority of it is bound to hemoglobin in the form of heme and sequestered within red blood cells. Corynebacterium diphtheriae is the causative agent of diphtheria disease in humans and is a model member of the Actinobacteria phylum. During infection, C. diphtheriae actively procures iron from human hemoglobin, and then uses a network of surface proteins to relay the iron-containing heme prosthetic group across the cell wall to the heme importer hmuTUV. Unpublished data from the Clubb lab shows that the C. diphtheriae bacterial surface proteins HtaA, HtaB, and ChtA utilize heme-binding Conserved Region (CR) domains that associate to rapidly transfer heme between one another in vitro. We aim to define the relative affinity for heme of these different CR domains using mass spec based approaches. We hypothesize that directionality of heme flow is driven by an affinity gradient, and these results could inform on the sequential ordering of heme-binding proteins on the cell surface.

Friday, May 5th at 3:30pm

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