Abstract 1738

Analysis of structural similarities between TAM receptors and other cell surface molecules

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TAM receptors represent a unique non-growth factor associated receptor subfamily of receptor tyrosine kinases (RTKs). These receptors have a vital role in maintaining cellular homeostasis through the clearance of apoptotic cells and control of inflammatory and immune responses. Linked to these important regulatory roles, dysregulation of TAM receptors is implicated in numerous disease states, but little is currently known about the structural changes that are associated with their activation and that underly their role in these various diseases. Furthermore, while there is growing interest in TAM receptors as therapeutic targets, their multiple roles in homeostatic processes create challenges for developing therapeutic strategies. Understanding TAM receptor activation mechanisms is important for further investigation of the potential development of targeted therapies. While these receptors are commonly believed to be activated through classical receptor-induced dimerization, there are no current studies that confirm this activation mechanism applies for TAM receptors and preliminary work suggests alternative mechanisms may be possible. My work utilizes a combination of structural, biophysical and biochemical approaches to investigate TAM oligomerization and cross-talk with other receptors, and here I will present early structural analysis of TAM receptors and intriguing similarities to cell-cell adhesion molecules and receptors that are involved in higher order oligomerization or clustering. Furthermore, my presentation will introduce some of the future goals of my new lab, which officially opens in February of 2023.

This work was funded by a MOSAIC K99/R00 grant from NIGMS (1K99GM144683-01).

104060, https://doi.org/10.1016/j.jbc.2023.104060

Abstract 1754

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 residues can non-enzymatically isomerize into L-isoaspartate residues which can contribute to the decreased functionality of proteins. Because these reactions are spontaneous, the accrual of this damage naturally increases as one ages. Historically, the methylation-induced repair activity initiated 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, recent studies suggest an additional mechanism may exist in which L-isoaspartyl damaged proteins may be preferentially recognized and degraded through the ubiquitin-proteasomal system. Current work suggests protein carboxyl methyltransferase domain-containing protein 1 (PCMTD1) is a potential E3 ubiquitin ligase that ubiquitylates proteins harboring isoaspartyl damages for proteasomal degradation. Similar to PCMT1, the N-terminal domain of PCMTD1 contains L-isoaspartate and S-adenosylmethionine (AdoMet) binding motifs needed for isoaspartyl repair activity. This protein also contains SOCS-box recruitment motifs found in substrate receptor proteins which eventually complex into active multimeric cullin-RING E3 ubiquitin ligases (CRLs). While PCMTD1 is able to bind to the canonical methyltransferase cofactor AdoMet, isoaspartyl repair activity has not yet been demonstrated by PCMTD1. However, PCMTD1 is able to associate with components of the CRL system, Cul5 and Elongins B and C, *in vitro* and in cells. Early work in negative stain electron microscopy and native top-down mass spectrometry to characterize the structural dynamics of PCMTD1 further suggests PCMTD1 multimerizes with CRL components to form the putative E3 ubiquitin ligase, CRL5-PCMTD1. While further molecular and structural characterization of PCMTD1 is needed to better understand this newly proposed preotolytic pathway for aged-damaged proteins and the potential structure-function relationship of PCMTD1, we describe here initial studies of this previously uncharacterized protein which may ultimately function as an isoaspartyl-residue-specific E3 ubiquitin ligase.

This work was supported by the National Science Foundation grant MCB-1714569 and by the NIH NIGMS-funded predoctoral fellowship (T32GM136614).

104061, https://doi.org/10.1016/j.jbc.2023.104061