How Does the O-GlcNAc Transferase Enzyme Choose its Protein Substrates?

Fri, February 10
3:30 pm
Carleton Campus
Anderson Hall
Room 329

Chemistry Seminar at Carleton

O-GlcNAcylation, or the transfer of O-linked beta-N-acetylglucosamine (O-GlcNAc) to serine and threonine residues of nuclear and cytoplasmic proteins, is an essential, metazoan post-translational modification. O-GlcNAc transferase (OGT) is the sole enzyme responsible for this modification and targets over one thousand different substrates involved in almost every cellular process. Misregulation of protein O-GlcNAc levels and O-GlcNAcylation patterns has been implicated in metabolic diseases, cancers, and neurodegenerative diseases. This broad disease activity makes OGT an attractive therapeutic target, however the substrate diversity makes pan inhibition as a therapeutic strategy unfeasible. Rather, a substrate-specific approach to targeting is more advantageous, but how OGT chooses its substrates is poorly understood. It has been shown that OGT uses its noncatalytic, tetratricopeptide repeat (TPR) domain, rather than its catalytic domain, to drive substrate selection. There are two proposed mechanisms for this selection that are thought to coexist: 1) the intrinsic selection mechanism where OGT directly interacts with substrates through the lumenal region of the TPR domain and 2) the adaptor-mediated selection mechanism where OGT interacts with adaptor proteins that are proposed to target protein substrates to OGT and alter OGT's activity. Here, I will present structure-activity relationship studies used to identify key residues in the TPR lumen that drive intrinsic substrate selection that were performed during my postdoctoral training and the current work my lab at St. Olaf is doing to capture OGT-adaptor interactions along the TPR domain to ultimately determine the adaptor-mediated selection mechanism. By understanding these two selection mechanisms, we hope to provide insights into the way to selectively target subsets of OGT's protein substrates.

Cassie Joiner, Ph.D., Assistant Professor of Chemistry, St. Olaf College

I received my Bachelor of Science degree in Chemistry, with a minor in biology, at Madonna University in Livonia, Michigan. I moved to the University of Michigan (Go Blue!) where I received a PhD in Chemistry. There I worked under the supervision of Prof. Anna Mapp to design new photo-activatable unnatural amino acids to capture transient protein-protein interactions in live yeast. After graduate school, I moved to Harvard Medical School to work in Prof. Suzanne Walker's lab for my postdoctoral training where I fell in love with the human O-GlcNAc transferase (OGT) enzyme and worked to determine the mechanisms of intrinsic protein substrate selection. In Fall 2020, I started as an Assistant Professor in the Chemistry Department at St. Olaf College teaching the biochemistry lecture and lab course and the first-year chemistry/biology integrated courses. I officially started my research lab in Spring 2021, and our work focuses on understanding how protein structure and protein-protein interactions govern both the nucleotide-sugar and protein substrate selection mechanisms of nucleocytoplasmic O-glycosyltransferases.