ORGANIC CHEMISTRY SEMINAR

Tuesday, April 9, 2024
4:30 PM, WTHR 104

"Development of Cationic Amphiphilic Polyproline Helices and Coiled-Coil Assemblies for Biological Applications."

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Abstract:

The rise of antimicrobial resistance has contributed to a global health crisis. Many current antibiotics are announced as unviable, and the addition of some bacteria to invade the cell further challenges and limits these current drugs. The Chmielewski group has previously shown that cationic amphiphilic polyproline helices (CAPHs) act as dual agents displaying both cell-penetration and antibiotic activity. To further increase these dual properties, stereochemical modifications were used to synthesize new amino acids and new CAPH peptides. In this presentation, I will discuss the outcomes of these modifications, including cell penetration, subcellular localization, and antibacterial efficacy.

Moreover, considering new interest in biomaterials for drug formulation and delivery, coiled-coil assemblies have emerged as promising candidates. Characterized by facile synthesis, low toxicity, and biocompatibility, coiled-coil assemblies hold a significant potential for drug encapsulation and cellular delivery. Herein, I will discuss the development of a novel nanoscale metal-mediated coiled-coil assembly with tunable assembly properties, presenting a compelling platform for drug encapsulation and targeted cell delivery, thereby addressing critical challenges in modern pharmaceutical science.

PURDUE UNIVERSITY

Department of Chemistry

JOSEPH F. FOSTER MEMORIAL
CHEMICAL BIOLOGY AND BIOCHEMISTRY SEMINAR

Monday, April 1, 2024
3:30 PM, BRWN 4102

"Analysis of the substrate specificity and binding site of the yeast zinc metalloprotease, STE 24."

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Abstract:

The Yeast Zinc Metalloprotease is a unique and ubiquitous enzyme that has been a subject of study for many years. This enzyme is involved in the maturation of the yeast mating pheromone **a**-factor by performing two distinct cleavages in the same substrate. Firstly, Ste24 cleaves the three terminal residues of **a**-factor which is then followed by an upstream N-terminal cleavage. In humans, defects in this metalloprotease or its substrate, Prelamin A, typically result in a range of progeroid disorders. Furthermore, the severity of these diseases has been directly linked to the catalytical activity of the enzyme. Treatments for these diseases are difficult to develop due to the limited knowledge available on the catalysis, substrate recognition and functions of Ste24 and its homolog. As such, this study aims to expound on the substrate specificity and the binding site of Ste24. Identifying the substrate requirements of Ste24 has been an increasingly interesting topic due to the implication of Ste24 in a variety of unrelated functions. Ste24 and its human homolog, ZMPSTE24, have almost identical crystal structures and are both able to cleave the substrate of the other at both cleavage sites. As a result, studies on either homolog are highly applicable to the other. With that in mind, various studies have implicated both Ste24 and ZMPSTE24 in a wide range of newly discovered functions, such as translocon unclogger, ability to defend against viruses, and influencing the synthesis of chitin (a polysaccharide that forms the cell wall of fungi). To perform these varied functions, Ste24 has to have a broader substrate recognition ability than previously believed. To elucidate the substrate specificity of Ste24, short peptide sequences containing varying CaaX sequences were developed and tested for C-terminal activity through a radioactive methyltransferase-coupled diffusion assay. Secondly, we tested the necessity of carboxymethylation for the upstream N-terminal cleavage using 33-mer analogs of **a**-factor, developed to mimic the C-terminally cleaved peptide. Finally, we interrogated the binding site of Ste24 through the use of a radioactive methyltransferase-coupled diffusion assay (C-terminal cleavage), a FRET-based assay (N-terminal cleavage), and photocrosslinking assays (binding). Together, these data presented a clear image of residues necessary for the cleavage and binding of substrates within Ste24.