The Biological and Biomedical Joint Seminar Series

(Hosted by the departments of Molecular & Cellular Biology, Chemistry & Biochemistry, Cellular & Molecular Medicine, and Plant Sciences)

"Enzyme Filamentation: A New Enzyme Regulatory Mechanism and So Much More"

Nancy Horton

Molecular & Cellular Biology
The University of Arizona

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Hosted By: Ted Weinert

Although filament formation by some enzymes in vitro has been known for decades, only recently has it been appreciated that enzyme filamentation is wide-spread and physiologically relevant. Further, the biological role of enzyme filamentation is under active investigation. Using our model system, the sequence specific DNA endonuclease SgrAI, our lab has shown that enzyme filamentation activates its DNA cleavage activity, as well as changes its DNA specificity. By combing structural biology (including x-ray crystallography and cryo-electron microscopy) and biochemical investigations (FRET kinetic assays combined with global model fitting), our lab has uncovered the detailed structural mechanisms of this phenomenon, as well as its full kinetic reaction pathway. The structural work shows how a conformational change in SgrAI when in a filament transforms the active site to result in rapid DNA cleavage, as well as how the DNA structure itself is critical to controlling the change in substrate specificity induced by filamentation. The computational model resulting from global model fitting has allowed for predictions of SgrAI behavior in vivo, as well as comparisons with other, non-filament forming mechanisms of enzyme regulation. Significantly, these comparisons show that the filament mechanism is advantageous in the speed of enzyme activation, as well as in controlling the enzyme substrate specificity to only particular substrates of interest. Therefore the biological significance of the SgrAI filament mechanism is predicted to be in optimizing the anti-phage activity in a bacterial host with an unusually large genome, and to protect the genome from off-target DNA cleavage. Continued work aims to understand the filament mechanism in other enzymes, such as phosphofructokinase-1.

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