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Home Page

Features:

UNM Researchers Tackle Antibiotic Resistance with HPC

Since its discovery more than 70 years ago by Alexander Fleming, penicillin and its analogs have been at the forefront of the fight against bacterial infections. These molecules share a common ring motif called beta-lactam, thus the name beta-lactam antibiotics. They operate by forming a covalent adduct with membrane-bound bacterial transpeptidases, which are also known as penicillin-binding proteins, involved in the biosynthesis of cell walls. These mechanism-based inhibitors prevent the construction of the bacterial cell wall and lead eventually to cell lysis and death.

In the last twenty years, the efficacy of these antibiotics has been overshadowed by the emergence of drug-resistant bacterial strains resulting from their evolutionary responses to widespread overuse and abuse of antibiotics in clinical and agricultural settings. The problem has escalated to a crisis level, posing a serious public-health and economic challenge to modern society. There are many ways that bacteria adopt to resist the antibiotics. The most common and effective strategy is through a bacterial enzyme called beta-lactamase, which inactivates beta-lactam antibiotics by breaking the C-N bond in the lactam ring with a water molecule (hydrolysis). Such a reaction is typically very slow in water solution, but can be greatly accelerated by the enzyme. So, the understanding of how beta-lactamase catalyzes the hydrolysis of beta-lactam antibiotics would help us to design effective drugs to inhibit its activity. In fact, the co-administration of antibiotics and beta-lactamase inhibitors is now a common clinical practice.

Assistant Research Professor D. Xu and Professor H. Guo in the Department of Chemistry at the University of New Mexico (UNM) are using sophisticated computational approaches to understand the catalytic mechanism of a unique class of beta-lactamases. The so-called Class B2 beta-lactamases possess a zinc ion in its active site, which helps to accelerate the hydrolysis of a beta-lactam antibiotic molecule that docks at the active site. Although the Class B2 beta-lactamases are still rare in the clinical setting, an alarming trend in recent years points to a rapid spread of these metallo-enzymes in pathogenic micro-organisms by plasmid-mediated gene exchanges. Their broad substrate spectra and the absence of clinically useful inhibitors render them a dangerous threat to the relatively small arsenal of beta-lactam

antibiotics.

A key step in designing inhibitors is to understand the mode of binding for the antibiotic molecule in the enzyme active site and the structure of the transition state in the slowest step of the catalysis. Unfortunately, the enzyme has so far resisted to yield its secret. This is because the enzyme-catalyzed hydrolysis reaction is so fast that it is not amenable to any existing experimental technique in structure determination. The lack of substrate analogs (inhibitors) for Class B2 beta-lactamases renders it very difficult to determine how the antibiotic molecule binds with the enzyme. Computational approaches can thus be very helpful to unravel the structure and reaction kinetics of the antibiotic-enzyme complex.

In a recent publication in Journal of Medicinal Chemistry, the two UNM researchers reported a computational study of the antibiotic binding dynamics of a third generation beta-lactam antibiotic molecule (biapenem) to a beta-lactamase (CphA) from the bacterium A. hydrophila. Using a state-of-the-art quantum mechanical/molecular mechanical (QM/MM) method, the UNM study identified a unique binding mode that sheds valuable light on the catalytic mechanism of the beta-lactamase. This binding model is unique in that it is consistent with a recently published structure of enzyme-intermediate complex.

It was determined that the antibiotic, biapenem, is engaged in direct metal binding with the zinc co-factor in the enzyme through its 3-carboxylate oxygen. It is further anchored by several hydrogen bonds between the substrate and active-site residues, particularly those made possible by conformational changes of Asn233. An active-site water is poised to attack the carbonyl carbon in the beta-lactam ring of the antibiotic molecule, with the help of either a Histidine or Aspartate residue serving as the general base. Work to elucidate the detailed catalytic mechanism using the QM/MM approach is underway in their laboratory, which is expected to provide helpful guidance to the designing of mechanism-based inhibitors that mimic the transition state structure.

Part of the UNM work was carried out on a recently purchased high performance shared-memory computer -- IBM p570 -- with 16 Power 5 chips and 256 GB of memory. This new addition to UNM's HPC center was made possible by a Major Research Instrumentation grant from the National Science Foundation. As the Principal Investigator of the NSF grant, Professor Guo is very excited about the prospect of scientific computing at UNM. Apart from the beta-lactamase project, the Guo group is also investigating a number of important enzymatic reactions, such as proton transfer, phosphoryl-transfer, hydrolysis, and arginine modification. The insights provided by these computational studies will help us to understand catalytic principles in general and to design new drugs that block the enzyme catalysis when needed.

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Top of Page