Ackert Hall, Room 120
Wednesday, October 16, 2024
4:00 P.M.

Coffee and Cookies
Chalmers Hall, Room 168
3:45 P.M.

Biochemistry & Molecular Biophysics Seminar

Proteins in motion: Understanding the role of dynamics in the function of borrelial immune evasion and regulatory proteins

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In this talk, I will highlight two projects where studying protein dynamics has improved our understanding of the host-pathogen interactions in the borrelial pathogens that cause Lyme disease, relapsing fever, and *Borrelia miyamotoi* disease. *Borrelia* spirochetes are tick-borne infectious agents that encode numerous surface-localized lipoproteins that bind components of the human complement system to evade host immunity. One such borrelial lipoprotein, BBK32, protects the Lyme disease spirochete from complement-mediated attack via an alpha helical C-terminal domain (*i.e.*, BBK32-C) that interacts directly with the initiating protease of the classical complement pathway, C1r. Orthologs of BBK32, termed FbpA, FbpB, and FbpC are found in relapsing fever spirochetes and *Borrelia miyamotoi* and also inhibits C1r. We carried out long-timescale molecular dynamics (MD) simulations of each of these inhibitory proteins which showed that they adopt energetically favored open and closed conformations defined by two functionally critical regions. This study showed how protein dynamics play a pivotal role in borrelial C1r inhibitors and revealed surprising structural plasticity within this family of microbial immune evasion proteins.

A key regulator of the expression of host-associated surface lipoproteins in the Lyme disease spirochete *B. burgdorferi* is the protein BosR (Borrelial Oxidative Stress Regulator). BosR is a FuR family protein that binds directly to DNA and RNA. An accurate structural model of BosR has remained elusive, making it challenging to understand the molecular mechanisms of its transcriptional and post-transcriptional regulatory activity. In this ongoing study, we have used *in silico* modeling and biochemical assays to predict the structure of the BosR dimer and understand the role of zinc in its formation. We then modeled the interaction of the BosR dimer with DNA and RNA and performed MD simulations of BosR in bound and unbound forms. These experiments generated predictions about which residues of BosR were critical in mediating interaction with nucleic acids and guided site-directed mutagenesis. BosR mutants were evaluated using surface plasmon resonance-based binding assays which validated the computational models. Collectively, this study suggests that BosR uses on a flexible C-terminal "arm" to modulate its specificity and affinity for key regulatory elements within the *B. burgdorferi* genome.