Actin Filament Systems in Health and Disease

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Elongating filaments systems, such as actin, are polymerizing motors that drive movement in many biological processes. The actin filament is astonishingly well conserved across a diverse set of eukaryotic species. It has essentially remained unchanged in the billion years that separate yeast, Arabidopsis and man. In contrast, bacterial actin-like proteins have diverged to the extreme, many of which are not readily identified from sequence-based homology searches. My laboratory is particularly interested in understanding how the force generated from polymerization is integrated into different biological processes. Here, I will contrast the properties of eukaryotic and prokaryotic actin filament systems and discuss why mammalian actin is an Achilles' heel for pathogen modulation. I will use the example of *Yersinia pestis*, a human pathogen and the causative agent of the bubonic plague. *Yersinia*'s virulence stems, in part, from its ability to evade the host's immune defense by the injection of *Yersinia* outer proteins (YOPs) into phagocytic cells. One such YOP YopO is a kinase that specifically disables actin polymerization-dependent phagocytosis. The X-ray structure of YopO in complex with actin reveals that YopO sequesters an actin monomer in a manner that precludes association with and actin filament, yet allows interaction with other actin monomer binding proteins. SILAC mass spectrometry and *in vitro* phosphorylation assays confirm that the actin polymerization-inducing proteins are directly sequestered and phosphorylated by YopO. Thus YopO uses actin as a bait to recruit and directly inactivate actin polymerization machineries at the membrane while phosphorylating these proteins for potential release in order to cripple phagocytosis and ensure *Yersinia*'s survival in the human host. Finally, I will describe the non-physiological, yet curious, case of the human homolog of the YopO kinase domain, PAK4, which spontaneously forms crystals inside mammalian cells.