Proteolysis and quality control by the energy dependent protease Lon

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The Lon protease is highly conserved in all bacteria and is crucial for stress responses, damage tolerance, and virulence of pathogens. Because Lon is a protease, loss of Lon results in accumulation of potentially toxic proteins, killing the cell; however, prolific activation of Lon could spuriously destroy essential proteins and also kill the cell. Therefore, both inhibition and activation of proteases could be useful antibiotic strategies. Our lab is interested in understanding how Lon plays a role in normal biological responses as well as identifying chemical mechanisms to manipulate Lon. Despite its discovery decades ago, we still know surprising little about Lon’s role in many bacteria. For example, in E. coli, loss of Lon results in accumulation of a cell division inhibitor SulA, causing cells to filament. Interestingly, in Caulobacter crescentus, loss of Lon also causes cells to filament, but SulA does not exist in Caulobacter. These results beg the question of how convergent phenotypes can arise from deletion of lon given the different bacterial systems. Finally, we have identified positive and negative regulators of the Lon protease, validating their activity in vitro. We are currently working with the UMMS Small Molecule Screening Facility to identify new compounds that may activate or inhibit Lon, with the expectation that these will be excellent leads for new classes of antibiotics.