

Using NMR to study kinase regulation

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Histidine kinases (HKs) are ubiquitous molecular sensors that are used by bacteria to detect and respond to an impressive variety of environmental cues. In recent years, HKs have become attractive antimicrobial targets due to their roles in mediating virulence and antibiotic resistance in bacterial pathogens. Unfortunately, attempts to develop therapeutically useful HK inhibitors have proved unsuccessful, primarily due to our limited understanding of the way HKs function as well as the mechanisms by which their activity is regulated. We have used a variety of NMR methods to probe the way in which kinase function is regulated by both the HK sensor domain as well as endogenous antikinases. Moreover, we have developed a unique NMR-based approach that can be used to: (i) search for the molecular signals that activate or repress HKs; (ii) screen small molecule libraries for ligands that might serve as leads for rational development of HK inhibitors. These NMR methodologies have been developed using a model histidine kinase that regulates sporulation in the soil bacterium *Bacillus subtilis* and its pathogenic relative *Bacillus anthracis*.