Regulation of Morpheein Behavior in B. cenocepacia HMG-CoA Reductase

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The enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase is expressed in members of all three kingdoms of life. Its most well-known role is in the reductive biosynthesis of mevalonate from HMG-CoA as part of the mevalonate pathway for the biosynthesis of isopentenyl diphosphate (IPP) and subsequent isoprenoid derivatives. However, a number of bacteria have been shown to utilize this enzyme in the oxidation of mevalonate to HMG-CoA, presumably as a source of acetyl-CoA. One of these bacteria, *Burkholderia cenocepacia*, has been shown to express an oxidative HMG-CoA reductase but appears to utilize the nonmevalonate pathway for the biosynthesis of isoprenoids. As such, the physiological role of *B. cenocepacia* HMG-CoA reductase (*Bc*HMGR) is not entirely clear. Current evidence from a number of kinetic, spectroscopic and chromatographic techniques strongly suggest that *Bc*HMGR is regulated via the morpheein model of allostery. In this model, nonadditive quaternary forms of different levels of activity interconvert in response to changes in substrate concentration, pH, and enzyme concentration. Evidence of *Bc*HMGR's morpheein characteristics will be presented, including unusual kinetic behavior, the presence of multiple oligomeric states of differing activities, a possible alternate function for the enzyme involving GTP hydrolysis, and reversible aggregation in solution. Emerging crystallographic and molecular dynamics simulation studies will also be presented, suggesting possible mechanisms by which this dynamic shapeshifting enzyme responds to changes in ligand and substrate concentrations.