New structural insight into HMG-CoA reductase mechanism and cofactor specificity

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HMG-CoA reductase (HMGR) uses the cofactor NAD(P)H to reduce HMG-CoA to mevalonate in the biosynthesis of countless metabolites and natural products. HMGR is the sole target for the entire class of statin drugs used to lower blood cholesterol, yet several mechanistic details remain unresolved. Further, the structural basis for the wide range in cofactor specificity for either NADH or NADPH among HMGRs from different organisms is also unknown. We present crystal structures of HMGR from the human pathogen *Streptococcus pneumoniae* (SpHMGR) alongside kinetic data on the enzyme's cofactor specificity. Our structure of SpHMGR bound with its preferred NADPH cofactor indicates how cofactor specificity is achieved. Moreover, our structure of substrate-bound SpHMGR reveals dramatic, previously unknown conformational domain movements that control HMGR substrate binding and enable cofactor exchange without intermediate release during the catalytic cycle. Taken together, this work provides critical new insight into both the HMGR reaction mechanism and the structural basis of cofactor specificity.