Structure of Monomeric NADP-isocitrate Dehydrogenase: an Open Conformation

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Both monomeric and dimeric NADP-dependent isocitrate dehydrogenase (IDH) catalyze the oxidative decarboxylation from 2R,3S-isocitrate to yield 2-oxaloglutarate. Monomeric NADP-specific IDHs have been identified from about 50 different bacteria, whereas, dimeric NADP-dependent IDHs are diversified in both prokaryotes and eukaryotes. We have constructed the phylogenetic tree based on amino acid sequences of all bacterial monomeric NADP-IDHs. This is done to get an idea of evolutionary relationship. It is important to solve the structures of IDH from various species to correlate with its function and evolutionary significance. So far, only two crystal structures of substrate-bound (NADP or isocitrate) NADP-dependent monomeric IDH from *Azotobacter Vinelandii* (AvIDH) have been solved. Here, we are reporting for the first time the substrate free structure of monomeric IDH from *Corynebacterium glutamicum* (CgIDH) in the presence of Mg^{2+}. The 1.75 Ă structure of CgIDH-Mg^{2+} showed distinctly an open conformation in contrast to the closed conformation of Av-IDH-isocitrate/NADP complexes. The changes in fluorescence intensities of CgIDH in the presence of isocitrate or NADP indicate the conformational change. The conformational changes observed in fluorescence studies agree with the structural observation. Fluorescence results also suggest a low energy barrier between CgIDH with isocitrate or NADP resulting into easy access of the other substrate to perform the catalytic reaction. In CgIDH, the amino acids corresponding to the *E. coli* IDH phosphorylation-loop is alpha-helical compared to the more flexible random-coil loop in *E. coli*. This more structured region supports the idea that activation of CgIDH is not controlled by phosphorylation. This research is funded by the NSERC and SSI.

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