

Induced Fit and the Catalytic Mechanism of Isocitrate Dehydrogenase

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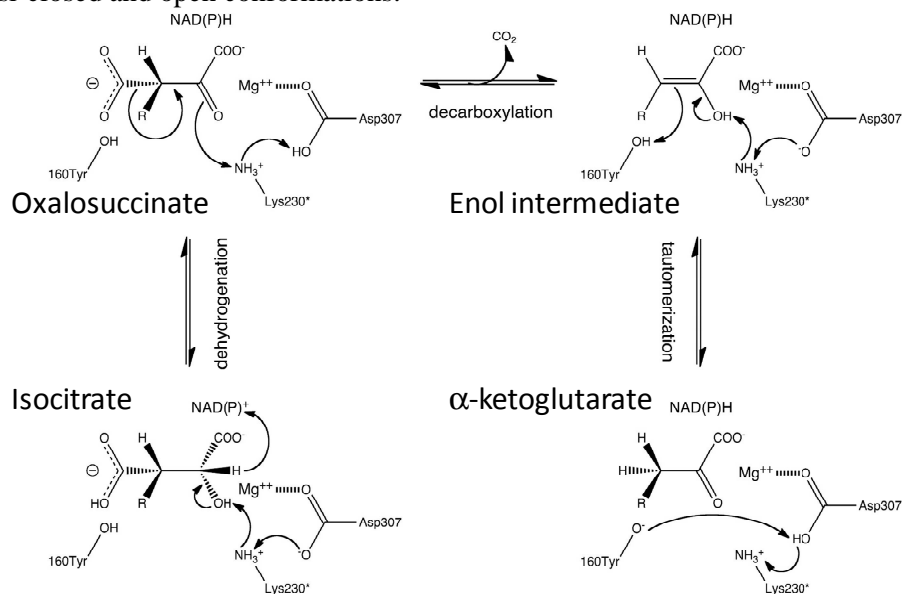
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NADP⁺ dependent isocitrate dehydrogenase isoform 1 (IDH1; EC 1.1.1.42) belongs to a large family of α -hydroxyacid oxidative β -decarboxylases that catalyze similar three-step reactions, with dehydrogenation to an oxaloacid intermediate preceding β -decarboxylation to an enol intermediate followed by tautomerization to the final α -ketone product.

IDH1 is involved in the citric acid (Krebs) cycle and converts 2*R*,3*S*-isocitrate into α -ketoglutarate. A comprehensive view of the induced fit needed for catalysis is revealed on comparing the first fully closed conformations of *Escherichia coli* IDH1 in crystal structures of a pseudo-Michaelis complex of wild-type *E. coli* IDH1 and of a reaction product complex of the K100M mutant with previously obtained quasi-closed and open conformations.



As previously predicted by Aktas and Cook (2009), Lys230* is positioned to deprotonate/reprotonate the α -hydroxyl in two of the reaction steps and Tyr160 moves into position to protonate C3 following β -decarboxylation. A proton relay from the catalytic triad Tyr160-Asp307-Lys230* connects the α -hydroxyl of isocitrate to the bulk solvent to complete the picture of the catalytic mechanism.

References

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