The role of solvent exclusion in the interaction between D124 and the metal site in SOD1 : implications for ALS

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Abstract

Structural changes in the metal site of the copper–zinc superoxide dismutase (SOD1) are involved in the various mechanisms proposed for the pathogenesis of the SOD1-linked familial form of amyotrophic lateral sclerosis (ALS). Elucidating how the metal site of SOD1 can be disrupted by ALS-linked mutations is important for a better understanding of the pathogenesis of the disease and for developing more efficient treatments. Residue D124, a second-sphere ligand of the copper and zinc ions, is known from experimental studies to be essential for the integrity of the metal-site structure. In this work, we used density functional theory calculations and molecular dynamics simulations to elucidate which factors keep D124 attached to the metal site and how structural changes may disrupt the binding between D124 and the metal first-sphere ligands. The calculations show that D124 is kept attached to the metal site in a kinetic trap. The exclusion of solvent molecules by the electrostatic loop of the protein is found to create the binding of D124 to the metal site. The calculations also indicate that changes in the structure of the electrostatic loop of the protein can weaken the D124–metal site interaction, lowering the affinity of the zinc site for the metal. Destabilization of the electrostatic loop of SOD1 has been previously shown to be a common property of ALS-linked variants of the protein, but its role in the pathogenesis of SOD1-linked ALS has not been elucidated..

Keywords

Copper–zinc superoxide dismutase, Amyotrophic lateral sclerosis, Zinc.