

Protein topology determines substrate-binding mechanism in homologous enzymes

Herrera-Morande, A., Castro-Fernández, V., Merino, F., Ramírez-Sarmiento, C. A., Fernández, F. J., Vega, M. C., & Guixé, V. (2018). Protein topology determines substrate-binding mechanism in homologous enzymes. *Biochimica et Biophysica Acta (BBA)-General Subjects*, 1862(12), 2869-2878. <10.1016/j.bbagen.2018.09.007> Accessed 17 Nov 2020.

Abstract

During evolution, some homologs proteins appear with different connectivity between secondary structures (different topology) but conserving the tridimensional arrangement of them (same architecture). These events can produce two types of arrangements; circular permutation or non-cyclic permutations. The first one results in the N and C terminus transferring to a different position on a protein sequence while the second refers to a more complex arrangement of the structural elements. In ribokinase superfamily, two different topologies can be identified, which are related to each other as a non-cyclic permutation occurred during the evolution. Interestingly, this change in topology is correlated with the nucleotide specificity of its members. Thereby, the connectivity of the secondary elements allows us to distinguish an ATP-dependent and an ADP-dependent topology.

Here we address the impact of introducing the topology of a homologous ATP-dependent kinase in an ADP-dependent kinase (*Thermococcus litoralis* glucokinase) in the structure, nucleotide specificity, and substrate binding order of the engineered enzyme. Structural evidence demonstrates that rewiring the topology of TIGK leads to an active and soluble enzyme without modifications on its three-dimensional architecture. The permuted enzyme (PerGK) retains the nucleotide preference of the parent TIGK enzyme but shows a change in the substrate binding order. Our results illustrate how the rearrangement of the protein folding topology during the evolution of the ribokinase superfamily enzymes may have dictated the substrate-binding order in homologous enzymes of this superfamily.

Keywords

ADP-dependent glucokinase; Non-cyclic permutation; Kinetic mechanism; Archaea; Folding topology; Protein evolution; X-ray crystallography; TIGK; *Thermococcus litoralis* glucokinase; PerGK; Permuted ADP dependent; Glucokinase