Tuning of Conformational Dynamics Through Evolution-Based Design Modulates the Catalytic Adaptability of an Extremophilic Kinase

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Abstract

Conformational flexibility plays a critical role in enzyme function and is a key aspect in transitions from an open to a closed state induced by substrate binding and product release. Psychrophilic enzymes display a high catalytic efficiency at low temperatures through the improved flexibility of some regions involved in the catalytic cycle. This flexibility enables an optimal conformational dynamic for the catalytic process, whose conservation in homologous enzymes that perform the same biological function has been highlighted. In this work, we demonstrated that two homologous enzymes adapted to function in niches with different temperatures exhibited different conformational dynamics. The psychrophilic bifunctional ADP-dependent PFK/GK from Methanococcoides burtonii (MbPFK/GK) shows a domain closing/opening dynamic described as a breathing-type, while its mesophilic homologue from Methanococcus maripaludis (MmPFK/GK) shows a twist-type domain closing/opening dynamic. In the psychrophilic MbPFK/GK, these conformational movements are associated with increased structural flexibility of the active site, reflected in the exponential increase of the K-m values with increasing temperature, and a greater H/D exchange of regions flanking the active site. Through sequence alignment between extant and ancestral enzymes, we identified two ion pairs outside the active site that were highly conserved in the mesophilic MmPFK/GK branch of the ADP-dependent sugar kinases family but were absent in the psychrophilic MbPFK/GK branch. Incorporation of these two ionic pairs in the psychrophilic MbPFK/GK modified the conformational dynamics of the domain closing/opening transition, the K-m dependence on temperature, and the H/D exchange, making them similar to those of its mesophilic homologue. We propose that conformational dynamics are responsible for the catalytic adaptability of this enzyme at low temperatures.

Palabras clave

Palabras clave de autor:biocatalysts; evolution-based design; molecular dynamics simulation; conformational dynamics; catalytic adaptability; psychrophilic ADP-dependent kinase enzyme
KeyWords Plus:DIHYDROFOLATE-REDUCTASE; TEMPERATURE-DEPENDENCE; PROTEIN DYNAMICS; ENZYME; FLEXIBILITY; STABILITY; SPECIFICITY; DETERMINES; ADAPTATION; NETWORK

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