Structural flexibility and protein adaptation to temperature of marine molluscs

With the support by the National Natural Science Foundation of China, a collaborative study by Prof. Dong YunWei (董云伟) from the State Key Laboratory of Marine Environmental Science, Xiamen University and Prof. George N. Somero from the Hopkins Marine Station, Stanford University, uncovered the structural flexibility and protein adaptation to temperature of marine molluscs, which was published in *PNAS* (2018, 115: 1276—1279).

Orthologous proteins of species adapted to different temperatures exhibit differences in stability and function that are interpreted to reflect adaptive variation in structural "flexibility". However, quantifying flexibility and comparing flexibility across proteins has remained a challenge. To address this issue, Dong and his co-authors examined temperature effects on cytosolic malate dehydrogenase (cMDH) orthologs from differently thermally adapted congeners of five genera of marine molluscs whose field body temperatures span a range of ~60 ℃. They described consistent patterns of convergent evolution in adaptation of function (temperature effects on K_M of cofactor) and structural stability (rate of heat denaturation of activity). To determine how these differences depend on flexibilities of overall structure and of regions known to be important in binding and catalysis, they performed molecular dynamics simulation (MDS) analyses.

The data support the microstate ensemble model of protein structure which postulates rapid and temperature-sensitive interconversion of conformational microstates and a shift towards an ensemble with fewer ligand-binding-competent microstates with high or low extremes of temperature. It has been conjectured that the intensity of natural selection on proteins evolving at different temperatures may be governed by the types and magnitudes of conformational changes that are necessary for function. If this is the case, then the types of flexibility-modulating adaptations described for cMDHs may be common among many, but possibly not all classes of enzymes. Investigations of other sets of orthologous proteins from species adapted to widely different ranges of temperature seem warranted to test the generality of the observations made in this and earlier studies. *In vitro* and *in silico* studies of these "naturally occurring mutants" could complement studies of laboratory-created mutants and yield deeper insights into the processes of protein evolution across the proteome and provide a better understand of how changes in sequence translate into adaptive modifications of protein function and structure.

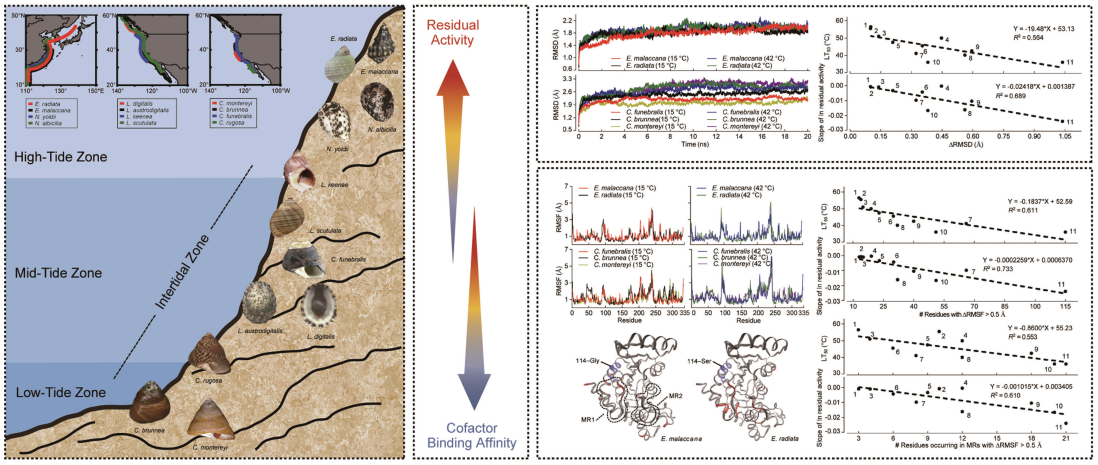

Figure Orthologous proteins of species adapted to different temperatures exhibit differences in stability and function. MDS analysis reveals protein-wide as well as local adaptation in flexibility. Sequence regions involved in binding and catalysis show significant inter-specific, temperature-related differences in flexibility.