MS09 Structural Biology combining methods/High resolution

MS9-03

Probing ligand-binding modes by 'temperature-resolved' macromolecular crystallography

C.Y. Huang [1], S. Aumonier [1], S. Engilberge [2], D. Eris [1], K.M.L. Smith [1], F. Leonarsky [1], J.A. Wojdyla [1], J.H. Beale [1], D. Buntschu [1], A. Pauluhn [1], M.E. Sharpe [1], V. Olieric [1], M. Wang [1]

[1]Paul Scherrer Institut - Villigen PSI (Switzerland), [2]European Synchrotron Radiation Facility - Grenoble (France)

Abstract

Continuous developments of cryogenic X-ray crystallography have provided most of our knowledge in 3D protein structures, which has been further augmented by the revolutionary advances in cryoEM recently. However, a single structure conformation identified at cryogenic temperatures may introduce a misleading interpretation as a result of cryogenic cooling artifacts. This can limit the overview of inherent protein physiological dynamics, which can play a critical role in protein biological functions. We developed an ambient temperature X-ray crystallography method using temperature as a trigger to record movie-like structure snapshots. The method has been used to show how TL00150, a 175.15 Da fragment, undergoes structural changes in its binding modes with the aspartic protease endothiapepsin (EP). We observed a surprising fragment binding discrepancy between the cryocooled and the physiological temperature structures, and captured multiple binding poses and their interplay with DMSO. The observations here open up new promising prospects for structure determination and interpretation at physiological temperatures, their implication in structure-based drug discovery and also providing more accurate starting models for molecular dynamics simulations.

References

Probing ligand binding of endothiapepsin by "temperature-resolved" macromolecular crystallography, Huang *et al.* Acta Cryst. D, under revision

Ligand binding modes of EP upon temperature change