

MS11-1-2 MAXS reveals the conformational changes of intrinsically disordered regions of MAP2K6
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Abstract

Mitogen-activated protein kinase kinase 6 (MAP2K6) plays a crucial role in the MAP2K6/p38 MAP kinase signalling cascade that regulates various stress-induced responses. This cascade is involved in inflammatory responses and apoptosis, and has attracted attention as a drug target for inflammatory and immune system diseases.

Crystal structure analysis of full-length MAP2K6 was solved at 2.6 Å resolution showing the N-terminal 43 residues were disordered¹. The docking domain, which is important for correct recognition and facilitating signal transduction of p38 MAP kinase, is located at this disordered N-terminus. This disordered docking domain is flexible, and therefore, we speculate that it is usually intrinsically disordered, but may transition to an ordered state on binding to the p38 kinases. The structure prediction of MAP2K6 with AlphaFold also strongly suggested that the N-terminus is an intrinsically disordered region^{2, 3}.

If the structure and conformational changes of molecules in solution can be directly visualized, it is possible to confirm that areas of intrinsically disorder region are transitioning to an ordered state by complex formation. X-ray solution scattering experiments are a powerful technique for analysing structures and conformational changes.

In addition, the scattering from the middle range of the resolution region [q values between 0.30 to 0.65 Å⁻¹] contains important information such as the inter-domain distances and inter-secondary structure distances in the molecule. This data allows us to visualize more detailed molecular behaviours and conformational changes. The solution scattering that contains this important middle-angle region information is called mid-angle X-ray scattering (MAXS).

Therefore, we performed MAXS analysis of the MAP2K6/p38 complex and found that the solution structure of MAP2K6/p38 α complex revealed compact state. We also succeeded in observing order state of n-terminus.

In this presentation will discuss solution structure analysis by MAXS and show that is essential to evaluate the conformational changes of intrinsically disordered regions.

References

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