Rate constants and mechanisms of intrinsically disordered proteins binding to structured targets

Huan-Xiang Zhou

Department of Chemistry and Department of Physics, University of Illinois at Chicago, USA

Abstract:

Amyloid Intrinsically disordered proteins (IDPs) play key roles in signaling and regulation. Many IDPs undergo folding upon binding to their targets. We have proposed that coupled folding and binding of IDPs generally follow a dock-and-coalesce mechanism, whereby a segment of the IDP, through diffusion, docks to its cognate subsite and, subsequently, the remaining segments coalesce around their subsites [1]. Parallel dock-and-coalesce pathways (initiated by different docking segments) may exist but one pathway may dominate [2]. By combining experiment and computation, we have determined the precise form of dock-and-coalesce operating in the association between the intrinsically disordered GTPase binding domain (GBD) of the Wiskott-Aldrich Syndrome protein (WASP) and the Cdc42 GTPase [3, 4]. In the major binding pathway, the N-terminal basic region (BR) has been identified as the docking segment whereas the middle CRIB motif and the C-terminal subdomain (Csub) as the coalescing segments. Recently we have designed mutations to alter binding pathways. By slowing down the BR docking rate and accelerating the Csub docking rate, these mutations are able to promote a minor binding pathway into the new major binding pathway. Together, these results demonstrate that the dock-and-coalesce mechanism provides a framework for quantitatively understanding the rate constants and mechanisms of IDP binding and it is now possible to design mutations that enable IDPs to follow specific binding pathways.

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2. X. Pang and H.-X. Zhou (2017). Rate constants and mechanisms of protein-ligand binding. Annu. Rev. Biophys. 46,105-130.
3. X. Pang and H.-X. Zhou (2016). Mechanism and rate constants of the Cdc42 GTPase binding with intrinsically disordered effectors. Proteins 84, 674-685.
4. L. Ou, M. Matthews, X. Pang, and H.-X. Zhou (2017). The dock-and-coalesce mechanism for the association of a WASP disordered region with the Cdc42 GTPase. FEBS. J. 284, 3381-339.

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Room PH 3024 (Seminarroom E22)

Contact: Martin Zacharias, martin.zacharias@mytum.de, phone: +49 89 289 12335