Rate Constants and Mechanisms of Intrinsically Disordered Proteins Binding to Structured Targets

SPEAKER: Huan-Xiang Zhou, University of Illinois at Chicago
TIME: 2:00pm-3:00pm, Tuesday, August 13, 2019
VENUE: Room 264, Geography Building, Zhongbei Campus, ECNU
HOST: John Zhang, NYU Shanghai

ABSTRACT OF THE TALK
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. Parallel dock-and-coalesce pathways (initiated by different docking segments) may exist but one pathway may dominate. 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. 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.

BIOGRAPHY
Huan-Xiang Zhou received his Ph.D. from Drexel University in 1988 and did postdoctoral work at the National Institutes of Health. After faculty appointments at Hong Kong University of Science and Technology, Drexel University, and Florida State University, he moved in 2017 to the University of Illinois at Chicago, where he is Professor of Chemistry and Physics and holds an LAS Endowed Chair in the Natural Sciences. He has served on many grant review panels and journal editorial boards, and was elected as a fellow of the American Association for the Advancement of Science and a fellow of the American Physical Society. His group does theoretical, computational, and experimental research on molecular and cellular biophysics. Current interests include binding kinetics and allostery of structured and disordered proteins, crowding and emergent properties in cellular environments, structures and functional mechanisms of ion channels and other membrane proteins, and structures and mechanisms of peptide self-assembly.