Intradomain interactions in c-SRC revealed by domain specific deuteration and small-angle neutron scattering

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c-Src kinase, belongs to the Src family kinases, is a non-receptor tyrosine kinase that aberrantly phosphorylates several signaling proteins in different cancers. c-Src kinase is a multi-domain protein with an N-terminal disordered SH4UD domain, two regulatory SH3 and SH2 domains, and the C-terminal kinase domain. Previous studies have shown that the SH3 domain interacts dynamically with SH4UD forming a fuzzy complex. However, this important intramolecular interaction involved in c-Src regulation and activity is challenging for structural characterization. We show how segmental labeling of c-Src domains combined with molecular simulations helps resolving the conformations of individual domains during such interactions by using small angle neutron scattering (SANS). Our SANS results show that (SH3-SH2) domains assume extended conformations in the presence of SH4UD and compact conformations in its absence. Based on our Hamiltonian replica exchange molecular dynamics and SANS-restrained Monte Carlo simulations, we find that only SH3, not SH2, domain becomes extended in the presence of SH4UD and the regulatory loop regions of SH3 domain cause this increased flexibility in SH3 domain. In addition, our results support the previous study that SH4UD remain extended in the presence of SH3 and SH2 domains. Our findings suggest that SH4UD makes SH3 domain assume extended and flexible conformations which could make them available for allosteric interactions with binding partners.