O-17.6 Short talk

Exploring Protein Conformational Transitions in the Second Timescale through Multiscale Molecular Dynamics: The Case of SHP2 Activation

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The SHP2 phosphatase is a central node in multiple pathways and contributes to various cancers; inhibiting its activity suppresses tumor growth. SHP2 comprises a catalytic (PTP) and two SH2 domains; the latters mediate its interaction with pY-containing partners and regulate its activity. Under basal conditions, the N-SH2 domain blocks the PTP catalytic, making SHP2 inactive; upon partner binding to the SH2 domains, SHP2 undergoes a major conformational change, leading to activation. Most cancer-causing mutations destabilize the autoinhibited structure.

Although structures exist for both inactive and active states, SHP2 activation remains poorly understood. Simulations could clarify these aspects, but slow interconversion rates (in the order of seconds) challenge standard techniques. This study presents findings from enhanced sampling methods (i.e., REMD and metadynamics) and coarse-grained MD simulations, together with their combinations. Thanks to these approaches, we could identify bona fide activation pathways. Preliminary results on the effects of the topological constraints imparted from bis-phosphorylated peptide binding to both SH2 domains will be presented.

(R. Frankson et al., Cancer Res. 77 (2017) 5701; M. Tartaglia et al., Am. J. Hum. Genet. 78 (2006) 279; P. Calligari et al., Comp Struct Biotech J 19 (2021) 6125;M. Marasco et al., Sci Adv, 6(5):eaay4458, 2020)