Molecular Dynamics investigation on the regulatory mechanism of the SHP-2 protein

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The phosphatase protein SHP2 plays a critical role in the regulation of important signaling pathways in the cell. Activating mutations of SHP2 have been associated with developmental pathologies such as Noonan syndrome and are found in multiple cancer types [1]. Recently, it has been shown that RTK-driven cancer cells depend on SHP2 for survival [2]. This evidence has led to an enormous increase in the interest for SHP2 in the last years. The structure of SHP2 includes two Src homology 2 domains (N-SH2 and C-SH2), followed by a protein tyrosine phosphatase (PTP) domain, containing the catalytic site, and a C-terminal tail. Under basal conditions, SHP2 is auto-inhibited, as a loop of the N-SH2 domain blocks the PTP active site (closed conformation). SHP2 activation is mediated by the association between its SH2 domains and partners containing amino acid motifs comprising phosphortyrosine residues. This event is coupled with a rearrangement of the domains, whose final effect is a greater accessibility of the active site on the PTP domain (open conformation) [3].

In the talk, I will discuss our studies aimed at characterizing the SHP2 active state. Very recently, two different structures have been proposed for the SHP2 open state, obtained from X-ray and SAXS/NMR experiments, respectively [4,5]. However, the question whether the proposed structures are truly representative of the SHP2 active state in solution remains open. The N-SH2 domain assumes different positions in the two structures. Furthermore, a great number of the gain of function pathological substitutions affecting the SHP2 amino acids are located at the interface between the PTP and the N-SH2 domains in the closed state but only a few mutations affect the residues at the interface between the same domains in the proposed open structures. I will present preliminary data from both Replica Exchange Molecular Dynamics (REMD) and metadynamics simulations, showing that the open state seems to be better characterized by an ensemble of different accessible conformations.

In the second part of my talk, I will discuss our studies aimed at the design of a novel pharmacological strategy to fight the pathological “gain of function” amino acid substitutions affecting SHP2 residues. Many of these substitutions act by favoring the “open” state. Different lines of evidence show that more than a simple inhibition of the SHP2 activity, an efficient inhibition of the interaction of SHP2 with its binding partners could be a good strategy to reduce the pathological effects of SHP2 mutants. In this context, we have designed a peptide-based inhibitors of SHP2 protein-protein interactions. We evaluated the binding free energy between different phosphopeptides and the N-SH2 domain of SHP2 by using umbrella sampling molecular dynamics (US-MD). Thanks to these data, we obtained a lead peptide sequence. Experimental data confirmed the high binding affinity of the designed peptide, with a sub nM dissociation constant.

We carried out these studies thanks to computational resources made available by a PRACE project (No. 2017174118). The techniques we used (e.g, PMF profile from US-MD and REMD simulations) take advantage of parallel computing, overcoming the problems related with the low scalability usually observed in conventional MD simulations.

Reference

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2. Chen et al., Nature 2016, 535:148.
4. Bocchinfuso et al., Proteins 2007, 66:963.
5. LaRochelle et al. Nat Commun 2018; 9:4508;
6. Pádua et al. Nat Commun 2018; 9:4507