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Characteritzation of pathological mutations affecting protein-protein interactions for drug discovery

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I. Extended Abstract

Pathogenic single nucleotide variants (SNV) can affect binding affinity or change the specificity of a protein-protein interaction (PPI). It is a known fact that modulating PPIs with small molecules is a long sought strategy in drug discovery. We face three major problems: i) the lack of available structures for the majority of PPIs in human; ii) the absence of natural cavities in protein-protein interfaces that could be used to identify small molecules as in standard enzyme inhibitor discovery; and iii) how a small molecule can compete with a large protein interface. We have developed a strategy for identifying small molecule inhibitors of PPIs when complex structure is not available, based on the integration of molecular dynamics with Amber for the generation of transient cavities, FPocket for the identification of such cavities [1], and computational docking calculations and hot-spot predictions with pyDock to select the best cavities for PPI modulation[2,3].

However, estimating the effects of a given single nucleotide variant on a PPI is extremely challenging. We aim to apply this methodology to known pathological variants from Humsavar and ClinVar databases that affect PPIs. There are very few experimental data for the effect on binding affinity of these SNVs (according to SKEMPI database)[4,5]. Thus, in order to estimate this effect, we initially mapped these structural variants on protein-protein complex structures included in the Protein-Protein Docking Benchmark 5 (formed by complexes with available structure for the complex as well as for the unbound components)[6]. The effect of these SNV on binding affinity is predicted with mCSM[7], pyDock and FoldX[8]. Then, for the protein-protein interactions that are stabilized by pathological variants, we will test on the unbound components of the Docking Benchmark the identification of cavities suitable to find possible small molecule inhibitors.

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References

[1] Le Guilloux V, Schmidtke P, Tuffery P. Fpocket: an open source platform for ligand pocket detection. BMC Bioinformatics. 2009;10:168.

[2] Grosdidier S, Fernández-Recio J. Identification of hot-spot residues in protein-protein interactions by computational docking. BMC Bioinformatics. 2008;9:447.

[3] Cheng TM, Blundell TL, Fernández-Recio J. pyDock: electrostatics and desolvation for effective scoring of rigid-body proteinprotein docking. Proteins. 2007;68:503515.

[4] Moal IH, Fernández-Recio J. SKEMPI: a structural kinetic and energetic database of mutant protein interactions and its use in empirical models. Bioinformatics. 2012;28:26002607.

[5] David A, Sternberg MJE. The contribution of missense mutations in core and rim residues of protein-protein interfaces to human disease. J Mol Biol. 2015;427:28862898.

[6] Vreven, T., Moal, I. H., Vangone, A., Pierce, B. G., Kastritis, P. L., Torchala, M., et al. Updates to the integrated proteinprotein interaction benchmarks: Docking benchmark version 5 and affinity benchmark version 2. Journal of Molecular Biology. 2015, 427(19), 30313041.

[7] Pires DEV, Ascher DB, Blundell TL. mCSM: predicting the effects of mutations in proteins using graph-based signatures. L.Bioinformatics. 2014,30(3):335-342.

[8] Schymkowitz J, Borg J, Stricher F, Nys R, Rousseau F, Serrano L. The FoldX web server: an online force field. Nucleic Acids Research. 2005,33(Web Server issue): W382W388.

Mireia Rosell is a PhD student at the Protein Interactions and Docking Group in the Barcelona Supercomputing Center, lead by Juan Fernández-Recio. She did a B.Sc. In Biochemistry at Universitat Autónoma de Barcelona and afterwards she obtained an interuniversity M.Sc. in Bioinformatics for Health Sciences by Universitat Pompeu Fabra and Universitat de Barcelona. Her research is focused on the development of a new methodology for the high-throughput structural annotation of sequence variants involved in protein interactions.