UNIVERSITÀ DEGLI STUDI DI MILANO-BICOCCA

DOTTORATO DI RICERCA IN TECNOLOGIE CONVERGENTI PER I SISTEMI BIOMOLECOLARI - TeCSBi

Project Supervisor: Dott. Renata Tisi

Project Title: Integrating Molecular and Computational approaches for Structural-Functional studies

Possible support for Phd students w/o a University fellowship: no

A collaborative network of geneticians, molecular biologists, computational chemists, biochemists is applying an integrated approach on the study of different research topics. The main line of research are at the moment the MRN/X complex, involved in DNA double strand break repair, and Neurofibromin I, a RasGAP which when mutated can cause neurofibromatosis type I, a severe tumour-prone syndrome.

The evolutionarily conserved Mre11-Rad50-Xrs2 (MRX) complex plays a central role in the cellular response to DSBs, as it is implicated in controlling end resection, a critical process for discriminating between homology-dependent and end-joining repair of DSBs, and in maintaining the DSB ends tethered to each other. This projects aims at exploiting computational biology (i.e. homology modeling and structural-functional insights from different organisms homologs) and computational chemistry (i.e. molecular dynamics applied on MRX complex single components or sub-complexes), with the aim of understanding the molecular determinants of MRX-driven regulatory events hypothesized to finely pace the DSBs repair process. Both Mre11 and Rad50 MRX-core components structures have been modeled, and the effect of different mutations will be studied by extended molecular dynamics simulations. Novel mutations will be designed in order to gain desired functions.

Besides its well-known activity as a Ras GTPase activating protein (GAP), NF1 plays a critical role in several other signalling pathways, such as cAMP signalling, with effects on learning abilities and memory, and regulation of actin cytoskeletal reorganization, with effects on cell motility and adhesion. Beyond the RasGAP domain (GRD), several other domains/motifs have been identified within neurofibromin, including a tubulin-binding domain (TBD), a cysteine/serine-rich domain (CSRD), a Sec14-homology domain (Sec14), a pleckstrin homology domain (PH) and a nuclear localization sequence (NLS). However, their role in regulating neurofibromin functions is still unclear. Starting from fold-recognition 3D structural prediction, a woking model is under construction to gain insights on the effect of pathogenic mutations on the main function of the protein.

The approach spans from data mining and concept maps preparation for mathematical modeling, to molecular and cell biology techniques, to homology modeling and molecular dynamics analysis.

References

Gobbini E, Cassani C, Villa M, Bonetti D, Longhese MP (2016). Functions and regulation of the MRX complex at DNA double-strand breaks. Microb Cell 3(8):329-337.

Lee MJ, Cho JH, Galas DJ, Wang K. The systems biology of neurofibromatosis type 1--critical roles for microRNA. Exp Neurol. 2012 Jun;235(2):464-468.