Using Molecular Dynamics to study the conformational changes of the LDL-r LA5 module upon mutation

Vladimir Espinosa Angarica[1,2], Santiago Cuesta-López[3], Jorge Estrada[1,2] and Javier Sancho[1,2]

[1]Departamento de Bioquímica y Biología Molecular y Celular, Facultad de Ciencias, Universidad de Zaragoza. Pedro Cerbuna 12, Zaragoza 50009, España

[2]Instituto de Biocomputación y Física de Sistemas Complejos, Universidad de Zaragoza. Corona de Aragón 42 Edificio Cervantes, Zaragoza 50009, España

[3]Laboratoire de Physique, Ecole Normale Supérieure de Lyon, Lyon, France

Protein folding is one of the most important processes in cell. As the 3D structure finally determines the biological function, the study of protein folding pathways is an important goal. Increasing our knowledge of the structural mechanisms leading to correct folding or misfolding would give us elements to understand many natural and disease-related phenotypes, and would also be of great importance in the development of therapeutic strategies to modify those phenotypes. Here we report a computational study of the consequences of single point mutations (SNP) in the folding of the fifth module of the Low Density Lipoprotein Receptor (LDL-r) using short-range molecular dynamics (MD). Our idea is to establish theoretical criteria to make anticipated computational diagnosis of Familial Hypercholesterolemia (FH) phenotypes, an important human disease caused by conformational problems in the aforementioned receptor affecting 0.2% of human population. Recent reports from our own group have proven that mutants bearing SNPs reported to produce FH and related to critical residues at the ion binding site of module LA5 or involving residues of the interlobular hydrogen bond network, are still able to fold and to bind calcium when expressed in culture cells. These preliminary achievements establish the basis to try to develop a strategy to improve genetic diagnosis, as well as to gain insights into the molecular basis of conformational disorders. In this regard we are mapping all possible SNPs of the LDL-A locus using short-range MD to set up a methodology that uses different analysis techniques to predict possible missfolding of this module caused by mutations.