

[P20] Computational studies of the Androgen Receptor Ligand-binding Domain (AR-LBD)

Bruno Simões de Almeida, Annick Dejaegere, Roland H. Stote

Integrative Structural Biology Dept. IGBMC - CNRS UMR 7104 - Inserm U 964, rue Laurent Fries, BP 10142, 67404 Illkirch CEDEX France

Androgen receptor (AR) is part of the steroid receptor subfamily of the nuclear hormone receptor (NR) super family, which function as a ligand-induced gene transcription factors. It is vital for the development of both male and female reproductive organs and homeostasis. Dysfunction of this receptor is responsible for several diseases, including prostate cancer, which remains one of the major causes of death among men. AR shares the canonical modular structure of NRs, which consists of well-conserved DNA- and ligand-binding domains. Following the recent determination of the 2.15 Å resolution crystal structure of the AR-LBD homodimer, normal-modes analysis and molecular dynamic simulations of a monomer unit and of the core dimer were done to study the effects of ligand binding and single point mutations on the AR-LBD structure and dynamics. Correlation maps were obtained in order to characterize their effects on long-range correlated motions, which are related to the allosteric character of the LBD. Ligand-binding did not have a great influence on the correlation map for the monomer unit, but it was more apparent for the core dimer. Correlated motions were observed between the ligand-binding pocket (LBP) region and the dimer interface. The results found that a disease-related mutation, R840G, falls in a region of the protein that shows a high degree of involvement in correlated motions. These results suggest that the introduction of a point mutation could have an influence on the long-range collective motions of the androgen LBD and thus affect the equilibrium dynamics wild-type protein, which in turn affects the physiological function of the protein.