Πανεπιστήμιο Κύπρου

The Department of Physics at the University of Cyprus
is organizing a seminar on

Thursday, 14 April 2016, time 5:30p.m.

Room B229, Building 13, New Campus

Speaker:

Professor Annick Dejaegere
Institute de Génetique et Biologie Moléculaire et Cellulaire (IGBMC)
Strasbourg University, France

"Structural Dynamics and Signaling Mechanisms in Nuclear Retinoid Receptors"

Nuclear Retinoic Acid receptors (RARs) are ligand-dependent transcriptional regulators that form heterodimers with Retinoid X receptors (RXRs). They mediate the effects of retinoic acid (RA), the active metabolite of Vitamin A, and regulate many physiological processes such as embryonic development, organogenesis, homeostasis, vision, immune functions and reproduction. The regulation of RARs occurs through the binding of retinoic acid (RA) to the ligand binding domain (LBD), which triggers conformational changes in the receptor that lead to the formation of interfaces for the binding of co-activator proteins. Aside from this classical mechanism of genomic nuclear receptor activation, recent studies showed that RA also integrates non-genomic ones, such as the activation of the p38MAPK/MSK1-signaling pathway, which also targets RARs.

Structural information concerning the molecular mechanism underlying RAR's response to RA has been collected largely by crystallographic studies of the LBD. However, the interplay between receptor phosphorylation and their structural dynamics, the association/dissociation of co-regulators and RAR binding to RAREs are still poorly understood. Here we use molecular dynamics simulations to study the changes in receptor structure and dynamics that occur upon phosphorylation. In particular, we studied two phosphorylation events that occur in RAR as a consequence of the action of RA, the first concerns the phosphorylation of the RAR ligand binding domain and the second that of the receptor's N-terminal domain (NTD). It has been shown experimentally that phosphorylation of the LBD gives rise to enhanced affinity for the protein cyclin H, part of the TFIIH transcription factor complex and that upon phosphorylation of the NTD, there is a decrease in binding affinity for the co-repressor protein vinexinβ. Our numerical simulations provide original information on the structural changes of RAR that occur upon phosphorylation and how these changes may affect the binding affinity for different co-regulatory proteins. The simulations are highly complementary to experimental information and provide original mechanistic interpretations for the phospho-regulation, and allosteric communication in nuclear receptors.

For more information please contact:
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