Deciphering the signal transduction pathway in the vitamin D receptor

Deciphering the signal transduction pathway in the vitamin D receptor

***S. Volkenandt and P. Imhof**, Institute for Theoretical Physics, Freie Universität Berlin*

In Short

- Protein-DNA interaction
- Vitamin D
- Communication networks

Nuclear receptors (NRs) regulate gene expression as transcription factors and thus play a crucial role in many physiological processes and their malfunction can lead to severe diseases, e.g. Alzheimer's and psychiatric disorders [1]. They are activated by their cognate ligands (hormones) and bind inside the cell typically as homo- or heterodimers to a response element (RE) which is a specific DNA sequence within the promoter of a gene (see schematic representation of a heterodimer in Figure 1[2].

NRs are composed of several domains: a variable N-terminal domain, a highly conserved DNA binding domain (DBD) which is linked to the moderately conserved ligand binding domain (LBD) via a flexible and variable hinge region, and a variable C-terminal domain (see Figure 1).

The DBD is responsible for the receptor finding its response elements while the LBD binds ligands and recruits coactivators. Both domains can contribute to dimerisation.

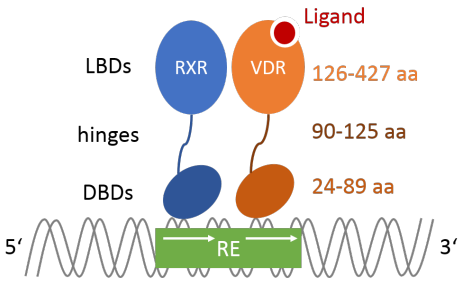

***Figure 1:** Schematic binding structure of the RXR-VDR heterodimer in complex with a direct repeat response element. The numbers of amino acids of the vitamin D receptor are indicated.*

The vitamin D receptor is found in prostate, ovary, breast, skin, brain, heart, pancreas, kidney, intestine, and colon. Ligand binding to it regulates various biological functions. In order to understand the mechanisms underlying ligand and DNA binding and find new target sites for drugs, it is crucial to determine and understand the structure-function relationship as well as the allosteric pathways of VDR-DNA complexes.

The aim of this project is to elucidate the allosteric regulation pathways inside the receptor-DNA complex and how they can be influenced by identifying crucial residues for communication. Therefore, in silico experiments, i.e Molecular Dynamics simulations in combination with communication network techniques, will be employed.

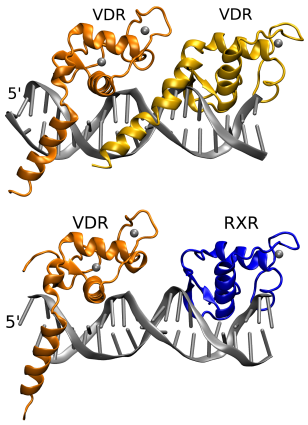

***Figure 2:** Structure of the DNA binding domain of the vitamin D receptor, bound in head-to-tail fashion [3,4].*

An interesting point in the interaction and hence communication between the protein and the DNA is the possible orientation of the two protein moonomers on the DNA and the consequence for recognition of a particular DNA sequence, a response element. Structures have been solved for a homodimer bound to the DNA in so-called head to teail fashion (see Figure 2 left) and of a hetero-dimer, composed of two different subdomains, orientated in head-to-head fashion (see Figure 2). These different scenarios and the associated differences in protein-DNA and protein-protein interaction will be investigated in this project, based o atomic-detail mmolecular simulations.

Possible signal transduction pathways will be explored by the construction and analysis of a communication network In such a network different parts (typically residues) of the protein-DNA complex form the nodes of the network. The edges/connections are defined by an interaction between nodes and the corresponding strengtzh which can be computed from the simulation data. On the network shortest communication paths, regions important for commu-

nication, and a partitioning into parts that communicate more with each other than with the outside can be obtained.

More Information

[1] E. J. Fernandez, V. Gahlot, C. Rodriguez, and J. Amburn, “DNA-induced unfolding of the thyroid hormone receptor α A/B domain through allostery,” *FEBS open bio*, vol. 7, no. 6, pp. 854–864, 2017.

[2] C. Helsen and F. Claessens, “Looking at nuclear receptors from a new angle,” *Molecular and cellular endocrinology*, vol. 382, no. 1, pp. 97–106, 2014.

[3] P. L. Shaffer and D. T. Gewirth, “Structural basis of VDR-DNA interactions on direct repeat response elements,” *The EMBO journal*, vol. 21, no. 9, pp. 2242–2252, 2002.

[4] P. L. Shaffer and D. T. Gewirth, “Structural analysis of RXR-VDR interactions on DR3 DNA,” *The Journal of steroid biochemistry and molecular biology*, vol. 89-90, no. 1-5, pp. 215–219, 2004.