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CCOMP/MSITE-programs for tracking the structure-function relationship (SFR) of liganded vitamin D receptor complexes

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Abstract

The vitamin D receptor (VDR) is a ligand-activated transcription factor sharing its 3D fold with other nuclear receptors. VDR's natural hormone, (1,25D) regulates over 200 genes associated with calcium/phosphorus homeostasis, immune responses and cellular growth, differentiation or apoptosis. During the last ten years many VDR complexes have been successfully crystallized in the absence/presence of peptides which mimic the coactivator sequences. Superimposition of those complexes shows that, even when the ligands differ drastically in their biological potency, vitamin D analogs anchor to the receptor cavity in a similar fashion to 1,25D. To facilitate structure comparison of VDR complexes we developed two programs suited for tracking structure changes due to ligand-protein interactions [http://www.biocomp.chem.uw.edu.pl]. CCOMP identifies differently oriented amino acids, whereas MSITE tracks how structure changes are transmitted from the binding pocket to the protein surface. Comprehensive CCOMP/MSITE analysis of VDR crystal structures shows that 1,25D analogs predominantly change side chain orientation of amino acids residing far away from the VDR binding cavity. Many of those residues are exposed to the protein's surface and are known to interact with cofactors modulating VDR functions. We believe that residues identified by sequential CCOMP-MSITE analysis determine specific action of 1,25D analogs.

Biography

Wanda Sicinska and Dominik Gront are members of Laboratory of Theory of Biopolymers (LTB). The laboratory research interest revolves around computer aided drug design, computer modeling of protein folding pathway simulations, software for large scale molecular modeling and computational analysis of experimental data on biomacromolecules, bioinformatics and biological statistics.