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Allosteric control of transcription regulation by nuclear receptors: An integrative structural biology approach

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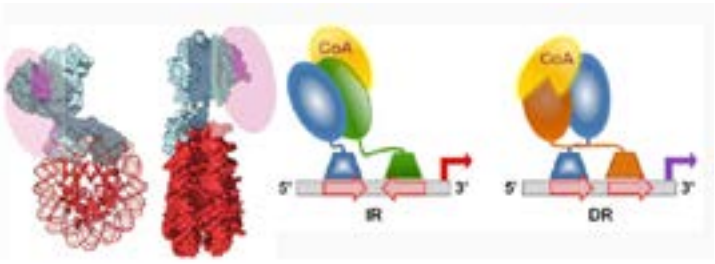
Nuclear hormone receptors interact with corepressors, coactivators and other protein cofactors to regulate signal transduction of the basal transcriptional machinery. Most NRs are known to function as dimers and except for the group of oxosteroid receptors (AR, GR, MR, PR) all structural data point to a conserved interface for the ligand binding domains (LBDs) dimers. Allosteric mechanisms control the sequential and ordered binding of nuclear receptors to the various protein effectors and target DNA. The binding of ligands induces structural transitions in the LBDs leading to the release of the corepressors and their replacement by cofactors. The LBD swallows the ligand and shields it from the solvent by closing the pocket with the C-terminal peptide. The agonist/antagonist character of the ligand is then essentially controlled by the position of helix H12 and the stability of the complex. Ligands are modulators of the activation process, their potency being defined by the fraction of time spent in the active conformation. Crystal structures of DNA binding domains (DBDs) bound to different response elements also support the proposal of DNA being an allosteric effector. The architectures of full length receptors bound to DNA fragments and cofactors have been determined by crystallography and in solution using integrative approaches. The later combine structural small angle diffraction methods by X-Rays (SAXS) and neutrons (SANS), optical techniques like FRET with labelled molecules and single particle electron microscopy (cryo-EM). Some common features emerge that rationalize the key role of DNA. The recent advances in cryo-EM allow solution structures determination at near atomic resolution. Conformational equilibrium of NRs in complex with various cofactors are also accessible.



Left: model of NRs heterodimer bound to its DNA target on a nucleosome (from ref 2).
Right: Schematic representation of the LBDs inversion between Inverted and Direct Repeats-bound complexes, illustrating the strong DNA-dependent allostery (from ref 3).

Biography

Dino Moras has completed his Graduation in Chemistry at the University of Strasbourg. While pursuing Post-doc with M G Rossmann, he has contributed to the concept of nucleotide binding domain known as the 'Rossmann fold'. His main scientific contributions are in structural biology, related to the expression of the genetic information: translation of the genetic code by aminoacyl-tRNA synthetases: discovery of the partition of aaRS in two classes and first crystal structure of a class II tRNA-aaRS complex and transcription regulation by Nuclear Receptors: the first crystal structures of the ligand binding domains of two NRs (RXR and RAR) in their apo and liganded form respectively. Presently, his focus is on the molecular mechanisms of regulation using integrative structural biology approaches.

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