Biophysical studies of the Retinoid X Receptor Interaction with differents DNA Hormone Responsive Elements

Lima, L.H.F..[1]; Portugal, RV[2]; Figueira, ACM[1] ; Silva, LMTR[3]; Skaf, MS[4]; Polikarpov, I[1]

[1]Grupo de Cristalografia, IFSC, USP, SP, Brazil;
[2]Imperial College, London, UK;
Faculdade de Farmácia, UFRJ, RJ, Brazil;
Instituto de Química, UNICAMP, SP, Brazil.

The retinoid X nuclear receptor (RXR) is a ligand responsive transcription factor, fundamental for the genetic regulation in major eukariotes. The physiological agonist for this receptor is a vitamin A metabolite, the 9-cis-retinóic ácid (9-cRA). The pleiotropic effects of this ligand are crucial for the metabolism, development and homeostasis. Under the influence of natural and synthetic agonists, this receptor enhance the transcription in target genes by the interaction with specific DNA sequences, based in direct repeats of the archetipical half site: AGGTCA. These sequences are named hormone responsive elements (HRE). The α isophorm of this receptor, in the homodimeric form, recognize preferentially direct repeats spaced by one base pair (DR1). However, this same isophorm present some recognition and gene activation in other direct repeats, like DR4. In this study, the affinities of binding of the α isophorm of this receptor to differents HREs were studied by the fluorescence anisotropy technique. The results indicate that the RXR bind to differents HREs in different oligomeric states, binding to the most physiologically responsive elements like dimmers. The binding to palindromic repeats were also checked, and the results showed an expected low affinity to a non spaced palindrome (PAL), but a surprising high affinity to an inverted palindrome (F2). The ligand addition, however, inhibited the r binding to F2. Parallel to these experimental studies, some molecular dynamic (MD) simulations have been made, in order to better understand the molecular mechanism of sequence discrimination.

Key words: *Retinoid X Receptor, Hormone Responsive Elements, Fluorescence Anisotropy, Molecular Dynamics.*
Supported by: CAPES and FAPESP.