NEW INSIGHTS ON THE THYROID HORMONE RECEPTOR AND COACTIVATOR COMPLEX.

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The thyroid hormone (T3) regulates several functions in endocrine system through interaction with its receptor (thyroid hormone receptor – TR). In the presence of T3, TR undergoes conformational changes that allow the interaction with coactivators proteins, like GRIP1. The association between TR and coactivators proteins assists chromatin opening through histones acetylation recruitment, resulting in the activation of several genes, mainly associated with the production of basal metabolism proteins. This project aims to study the TR:RXR-coactivator complex, whereas the RXR, also a nuclear receptor, is a natural partner of TR, trying to map the interfaces of interaction for a better understanding about this complex formation and function. For that, some experiments were performed to study: complex stoichiometry, protein binding affinity and the activity of the corresponding ligands in the complex, applying biophysics technique such as circular dichroism (CD), dynamic light scattering (DLS) and analytical ultracentrifugation (AUC). To study the mechanism of action of RXR’s ligand (9C) were made fluorescence anisotropy and cell transactivation assays. The fluorescence anisotropy experiment also gave information about the binding affinity between NRs and the coactivator GRIP1. Our results showed that the interaction between TR:RXR-GRIP1 are more stable in less truncated constructions, indicating that there are more interfaces of interaction between these proteins than the well-established LXXLL CoA motif to NR-LBD. Other information obtained from these results is that 9C can act in NR-CoA complex contributing to corepressor dissociation which could facilitate CoA binding. To summarize, our results altogether indicated that more completed constructions of NRs and CoA present additional contact interfaces besides the well-known ones, which demand further studies on the complex structure that can gives more information about their mechanism of action. ACKNOWLEDGEMENTS: Fundação de Amparo a Pesquisa, FAPESP; Centro Nacional de Pesquisa em Energia e Materiais. KEY WORDS: Nuclear Receptor, TR, NR-CoA complex.