Determination of Three-Dimensional Structures of the Thyroid Hormone Receptor Complexes using Crosslinking Constraints and Bioinformatics

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Introduction

Thyroid gland is one of the largest endocrine glands in the human body, which secretes two thyroid hormones: thyroxine (3,5,3',5'-tetraiodo-L-thyronine, known as T4) and triiodothyronine (3,5,3'-triiodo-L-thyronine, known as T3). The T3 hormone act in complex and specialized systems through of the interaction with its receptor, thyroid hormone receptor (TR), and regulates the transcription of specific human genes.[1]

There are several pathologies associated with disorders caused by thyroid hormones, including the Grave's disease, Hashimoto's syndrome, cretinism, hyperthyroidism, and hypothyroidism,[1] so understanding how the TR interact with T3, with other nuclear receptors (for example, Retinoid X Receptor – RXR), and coregulators (as Glucocorticoid Receptor-Interacting Protein 1 - GRIP1) is relevant to combat these disorders. Therefore, structural dynamics of TR*β*-RXR*α*-GST_GRIP1_LBD complexes, with and without ligands, were analysed via chemical crosslinking method using disuccinimidyl suberate (DSS) and "bottom-up approach" strategy[2] by mass spectrometry. The distance constraints are been used in bioinformatics to determinate the three-dimensional structures of these protein complexes.

Results and Discussion

Spectra of fragment ions of the intra- and intermolecular lysine and serine cross-linked peptides (Lys-Lys, Ser-Ser, and Lys-Ser) were identified by Mascot Server and SIM-XL program. These data revealed the presence of interactions in different regions of TR*β*-RXR*α*-GST_GRIP1_LBD complexes, with and without the 9-*cis*-retinoic acid.

Based on these distance constraints of the intramolecular cross-linked peptides was possible to obtain five molecular models for each individual protein of the complexes by PyMOL, I-TASSER, and Xwalk software, suggesting a likely structure for each protein due to constraints (Fig. 1).

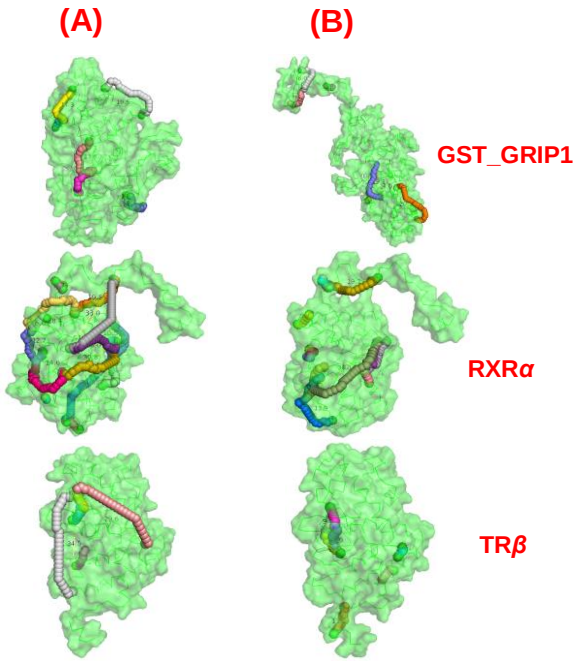

Figure 1. Protein structures are shown in green color in ribbon representation and atoms of disuccinimidyl suberate are shown as colored spheres. (A) Absence and (B) presence of 9-*cis*-retinoic acid in the TR*β*-RXR*α*-GST_GRIP1_LBD complexes.

Conclusions

These results demonstrate a conformational dynamic of the protein complexes and help to understand the system of TR activation. Now, these data will be evaluated by Rosetta modeling software for a more precise structural prediction of these macromolecular complexes.

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