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Roles of the low population structure of transcriptional co-activator SRC1 in the binding to PPARγ

Shin-ichiro Ito[1], Naoya Tochio[2], Naohiro Nakashima [1], and Shin-ichi Tate[1,2]

[1] Department of Mathematical and Life Sciences, Graduate School of Science, Hiroshima University

[2] Research Center for the Mathematics on Chromatin Live Dynamics (RcMcD), Hiroshima University

Steroid Receptor Coactivator-1 (SRC1) interacts with a nuclear receptor, Peroxisome proliferator activated receptor γ (PPARγ), in a ligand-dependent manner and regulates the transcriptional activation. SRC1 is known to be an intrinsically disordered protein, while PPARγ binding sites of SRC1 is also known to adopt the helical structure upon PPARγ binding. PPARγ binding sites in this coactivator shares the similar sequence motif comprising of LxxLL sequence; x means any amino acid.

Our previous study demonstrated that PPARγ binding site of SRC1 showed about 10% helix structural probability even in the absence of PPARγ, and we also reported possibility that this low population structure is concerned with recruit regulation of SRC1[1)]. However, it has been unclear how the low-probability structural components contribute to PPARγ-binding. To explore the functional significance of the low population structures of the binding site, we prepared five mutants of the second PPARγ binding site in SRC1 to change its low population structure. Those showed the distinct secondary structural probabilities evaluated by δ2D[1)] method using the backbone NMR chemical shifts. In addition, we examined the PPARγ binding-affinity of each mutant using Time-Resolved Förster Resonance Energy Transfer (TR-FRET) method, and we compared their affinities with the low population structures determined by NMR. Our results showed that the transient structural stability of SRC1 was engaged in PPARγ binding affinity, which will be presented in the talk.

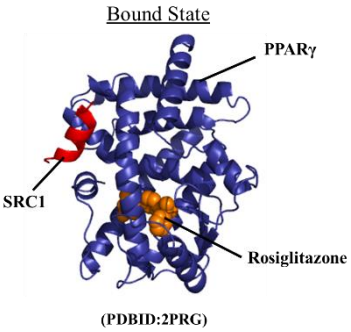

Fig. 1. Complex assembly of PPARγ - SRC1

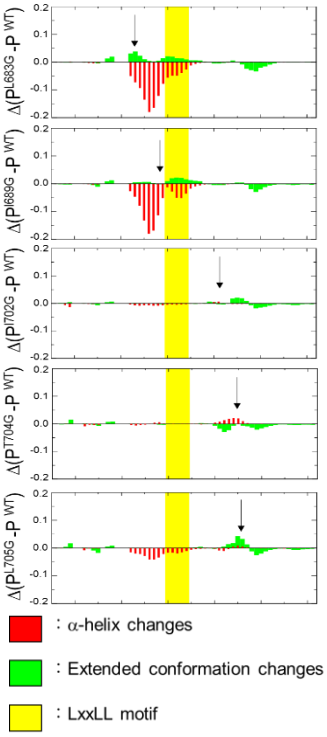

Fig. 2. Secondary structural probability changes between mutants to Wild-type

Keywords

Intrinsically Disordered Protein (IDP), Low population structure, Backbone NMR chemical shifts, TR-FRET, Binding affinity

References

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