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Low population structure in the intrinsically disordered region (IDR) of transcriptional coactivator regulates its binding to nuclear receptor PPARγ

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Nuclear receptor PPARγ recruits various types of coactivator depending on chemical structure of ligands to regulate transcriptions in adipocyte differentiation. Coactivators generally harbor multiple PPARγ-binding sites having LxxLL motif. The binding sites are in the intrinsically disordered regions (IDRs) that do not keep stable structures but transiently fold to give low population structures. Although the binding sites are unstructured in free state, they become folded to α-helix upon binding to PPARγ (Figure 1). We previously reported the two binding sites in coactivator SRC1 have different helix populations and the transient structural properties in the sites were proposed to be functionally relevant.

In this study, we constructed six protein fragments from four different coactivators, each of which contains 60–80 residues and has only one binding site to PPARγ. Nuclear magnetic resonance (NMR) experiments to characterize the transient structures of the fragments revealed that each binding site has different secondary structure population. With time-resolved fluorescence resonance energy transfer (TR-FRET) experiments, we determined the affinities of each fragment to the PPARγ in the complex with Rosiglitazone. Based on the collected data, we found the correlation between the population of the transiently formed helical structure of the binding sites and the affinities to PPARγ bound with Rosiglitazone.

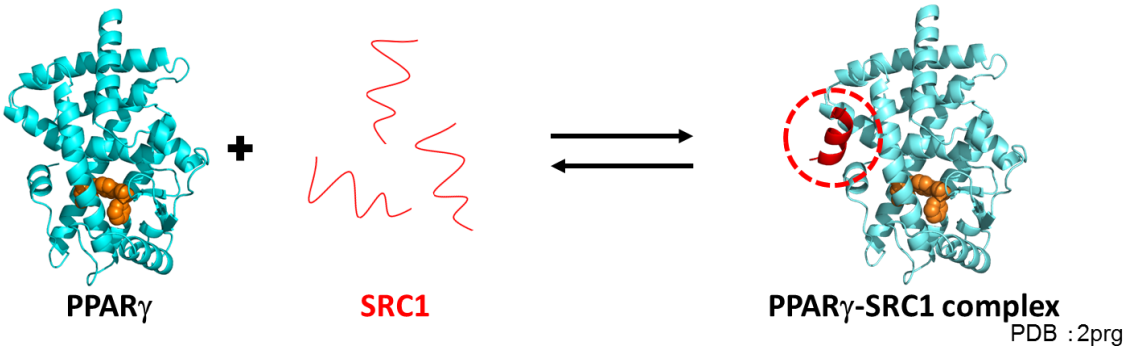

Figure 1. Reaction of PPARγ and steroid receptor coactivator 1 (SRC1). SRC1 is one of the coactivators. SRC1 has IDR in binding sites with PPARγ, but they conform such a helical structure in the presence of PPARγ.