

SELECTIVE ANDROGEN RECEPTOR MODULATOR (SARM) BINDING INITIATES UNIQUE SURFACE TOPOLOGY OF ANDROGEN RECEPTOR AF2 REGION THAT ALTERS N/C INTERACTION AND CO-ACTIVATOR RECRUITMENT

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DHT binding initiates N-terminal/C-terminal interaction of the androgen receptor (AR). The activation function 2 (AF2) in the ligand binding domain (LBD) serves as the interface for this N/C interaction. The unique surface topology of the AF2 region upon DHT binding favors interaction with an N-terminal 'FQNLF' motif as compared to an 'LxxLL' motif from transcriptional co-activators. Nonsteroidal SARMs act as potent and efficacious agonists in transcriptional activation assays using an MMTV-Luc reporter gene. However, it is not clear if SARM binding initiates a similar conformational change in the AR as steroidal agonists. For example, SARM does not stimulate N/C interaction of the AR as shown in both mammalian two-hybrid and GST-pull down assays. On the other hand, SARM-bound AR-LBD does not appear to interact with co-activators containing an LxxLL motif (e.g., Src1 and GRIP1). The lack of interactions between SARM-bound AR LBD and AR NTD and co-activators suggests that SARM binding might introduce a unique surface topology of the AF2 region of the LBD, and affect subsequent protein-protein interactions. Although co-activators do not seem to interact with SARM-bound LBD, both Src1 and GRIP1 greatly enhanced AR regulated transcription activation of reporter genes in the presence of either DHT or SARM, which suggests that co-activator recruitment by SARM-bound AR was more likely mediated through the NTD of the receptor, considering no N/C interaction is present during SARM binding. The unique surface topology of AF2 region in SARM-bound LBD will be further characterized in our laboratory.