REGULATION OF TRANSCRIPTION BY THE ANDROGEN RECEPTOR HINGE DOMAIN

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The Androgen Receptor (AR) hinge domain (amino acids 623-663) is a linker between the DNA binding domain (DBD) and the ligand binding domain (LBD) required for optimal AR action. The sequence is a target for prostate cancer mutations which usually modify AR activity. We created mutants to analyze the hinge in AR action by testing their effects in transfection assays. Deletion or mutation of a lysine rich sequence (KRKK, amino acids 629-633) inhibits or enhances AR action according the context. The AR containing only the Activation Function 1 is super active in the same contexts as AR KRKK mutations. AR KRKK mutants exhibit reduced binding to UBC9, a protein that catalyzes modification of two lysine residues (K385, K517) in the AR N-terminus by small ubiquitin-like modifier (SUMO) groups. Mutations in both lysine residues exhibit similar phenotypes to AR KRKK mutants and do not synergize with KRKK mutants suggesting that they affect the same pathway. AR hinge may inhibit AF-1 by catalyzing SUMOlation of the NTD. Other regions of the hinge modulate AF-2 activity. We suggest that the hinge modulates AR by recruiting factors that influence the activity of associated AR activation functions, and that alteration in the balance of recruitment of these factors could influence AR activity in prostate cancer.