Structure of the homodimeric androgen receptor ligand-binding domain

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The androgen receptor (AR) plays a crucial role in normal physiology, development and metabolism as well as in the aetiology and treatment of diverse pathologies such as androgen insensitivity syndromes (AIS), male infertility, neurodegeneration and prostate cancer (PCa). We have shown that dimerization of AR ligand-binding domain (LBD) is induced by receptor agonists but not by antagonists. The 2.15-Å crystal structure of homodimeric, agonist- and coactivator peptide-bound AR-LBD unveils a 1,000-$Å^2$ large dimerization surface, which harbours over 40 previously unexplained AIS- and PCa-associated point mutations. An AIS mutation in the self-association interface (P767A) disrupts dimer formation *in vivo*, and has a detrimental effect on the transactivating properties of full-length AR, despite retained hormone-binding capacity. The conservation of essential residues suggests that the unveiled dimerization mechanism might be shared by other human nuclear receptors. Our work defines AR-LBD homodimerization as an essential step in the proper functioning of this important transcription factor and opens novel and unexplored therapeutic avenues to design personalized drugs against castration resistant prostate cancer.