REVIEW

Differential Induction of the Androgen Receptor Transcriptional Activity by Selective Androgen Receptor Coactivators

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Abstract. Several new androgen receptor (AR) cofactors, associated to the ligand binding domain of AR, have been identified by our group and named AR associated protein (ARA)70, ARA55, and ARA54. Our previous reports have suggested that the cofactor ARA70 can confer the androgenic effect from 17 β-estradiol (E2) and antiandrogen to AR. It is of interest for us to compare and determine if the specificity of sex hormones and antiandrogens could be modulated by different coactivators. Our results indicate that ARA70 is the best coactivator to confer the androgenic activity on E2. Only ARA70 and ARA55 could increase significantly the androgenic activity of hydroxyflutamide, a widely used antiandrogen for the treatment of prostate cancer. Furthermore, as compared to the relative specificity of these coactivators to AR in the prostate cancer DU145 cells, our results suggest that ARA70 has a relatively higher specificity. Together, our data suggest that the specificity of sex hormones and antiandrogens can be modulated by some selective AR coactivators. These findings may not only help us to better understand the specificity of the sex hormones and antiandrogens, but also to facilitate the development of better antiandrogens or androgens to fight the androgen-related diseases, such as prostate cancer. (Keio J Med 48 (2): 87–92, June 1999)

Key words: ARA70, ARA55, ARA54, Rb, SRC-1

Introduction

As a member of the steroid receptor (SR) superfamily, the androgen receptor (AR) functions primarily as a ligand activated transcription factor that may play critical roles in prostate cancer growth and libido.[1,2] AR regulates the androgen target genes by binding to androgen response elements that may involve coregulators.[3]

In general, most of the steroid receptors have a N-terminus transactivation domain, a DNA binding domain, a hinge region, and a C-terminal ligand binding domain (LBD). The crystal structures of the LBD of several receptors reveal that the ligand is almost entirely buried within the conserved core of the helices 3, 7, and 10.[4] A conserved carboxyl-terminal helix, referred to as the activation function (AF)-2 domain, required for the ligand-dependent gene activation, becomes folded against the LBD of agonist-bound nuclear hormone receptor structure.

We and others have demonstrated that receptors may utilize a group of coactivators to effectively stimulate gene transcription, which would depend on allosteric alterations in the AF-2 helical domain. These cofactors would regulate the SR's function through the transactivation process and may function as a bridge

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