Functional domain and motif analysis of androgen receptor coregulator ARA70 and its differential expression in prostate cancer

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摘要

Abstract

Androgen receptor (AR)-associated coregulator 70 (ARA70) was the first identified AR coregulator. However, its molecular mechanism and biological relevance to prostate cancer remain unclear. Here we show that ARA70 interacts with and promotes AR activity via the consensus FXXLF motif within the ARA70-N2 domain (amino acids 176-401). However, it does not promote AR activity via the classic LXXLL motif located at amino acids 92-96, although this classic LXXLL motif is important for ARA70 to interact with other receptors, such as PPAR γ . The molecular mechanisms by which ARA70 enhances AR transactivation involve the increase of AR expression, protein stability, and nuclear translocation. Furthermore, ARA70 protein is more frequently detected in prostate cancer specimens (91.74%) than in benign tissues (64.64%, $p < 0.0001$). ARA70 expression is also increased in high-grade prostate cancer tissues as well as the hormone-refractory LNCaP xenografts and prostate cancer cell lines. Because ARA70 can promote the antiandrogen hydroxyflutamide (HF)-enhanced AR transactivation, the increased ARA70 expression in hormone-refractory prostate tumors may confer the development of HF withdrawal syndrome, commonly diagnosed in patients with the later stages of prostate cancer. Because ARA70-N2 containing the AR-interacting FXXLF motif without coactivation function can suppress HF-enhanced AR transactivation in the hormone-refractory LNCaP cells, using the ARA70-N2 inhibitory peptide at the hormone refractory stage to battle the HF withdrawal syndrome may become an alternative strategy to treat prostate cancer.