Androgen Receptor Signaling Promotes YAP1 Nuclear Localization

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Abstract

The transcriptional coactivator YAP1 (yes-associated protein 1) is a critical nuclear effector of the Hippo pathway. The serine/threonine protein kinases STK3/4 and LATS1/2, core components of the Hippo pathway, phosphorylate and inhibit YAP1 nuclear localization. Previously, we reported that the interaction of nuclear YAP1 with androgen receptor (AR) might play a critical role in prostate cancer progression and therapeutic relapse (Kuser-Abali et al., Nat. Commun. 2015). Here, we investigated the regulation of YAP1 by androgens in isogenic, androgen-responsive LNCaP and androgen non-responsive C4-2 prostate cancer cell models. We demonstrated that androgen suppressed the inhibitory phospho-Ser127 site on YAP1 in LNCaP cells, but the effects of androgen on phospho-Ser127 was modest in C4-2 cells. In agreement with this observation, androgen increased the presence of nuclear YAP1 in LNCaP cells, whereas regardless of androgen exposure the YAP1 protein was primarily expressed in C4-2 cell nuclei. We also demonstrated that androgen exposure suppressed the levels of phospho-Ser127 induced by okadaic acid, which is a potent inhibitor of the Ser/Thr phosphatases PP1 and PP2A. Moreover, the pharmacological inhibition of androgen receptor (AR) signaling by enzalutamide reversed the inhibitory effects of androgen on phospho-Ser127, which coincided with the inhibition of YAP1 nuclear localization. Similarly, the genetic inhibition of AR signaling by small interfering RNA (siRNA) reduced phospho-Ser127 levels. Additionally, the silencing of the STK3/4 and LATS1/2 signaling by siRNA resulted in increases in YAP1 protein levels. Furthermore, our analysis of the TCGA (The Cancer Genome Atlas) prostate adenocarcinoma data set indicates that the levels of YAP1 and AR mRNA expression were positively correlated in prostate cancer clinical samples. These observations suggest that AR signaling promotes YAP1 nuclear localization by suppressing phospho-Ser127, possibly through the protein phosphatases PP1 and PP2A, and supporting a new mechanism of YAP1 regulation and YAP1-mediated cancer cell growth and survival.

Acknowledgments: This study is supported by the NIH/NIGMS/RISE Grant #5R25GM060414 and NIH/NIMHD/RCMI grant #5G12MD007590, NSF-MCB #1832022.