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The Hippo effector YAP1 biochemically and functionally interacts with the nuclear factor-kappa B/RELA transcription factor

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Abstract

The transcriptional co-activator YAP1 (yes-associated protein 1) is a critical nuclear effector of the Hippo pathway. The Hippo pathway regulates cell growth, cell motility, cell migration, and carcinogenesis, but poorly defined mechanism. We investigated biochemical and functional interactions between YAP1 and the nuclear factor (NF)-kappa B/RELA subunit in prostate cancer cell models. We demonstrated that endogenous YAP1 and RELA form protein complexes in the cell, as revealed by co-immunoprecipitation and western blotting. Compared with control, we found that combined treatment of cells with androgen and SDF-1a (stromal cell-derived factor-1 alpha) or RANKL (receptor activator of NF-kappa B ligand) enhanced the protein-protein interaction between YAP1 and RELA, as showed by proximity ligation assay. Our confocal microscopy experiment further showed that combined SDF-1a and androgen treatment promoted the YAP1 and RELA colocalization instead of single-agent treatment. Moreover, our promoter-reporter and RNAi experiments showed that knockdown of YAP1 or TEAD, a key mediator of the YAP transcription, significantly reduced the NF-Kappa B promoter-reporter gene activity. Also, disruption of YAP1 activity attenuated the TEAD-RELA interaction. Furthermore, controlled expression of MST1/STK4, a potent inhibitor of YAP1, attenuated the NF-Kappa B-promoter reporter activity. Additionally, our unbiased bioinformatics analysis of the exiting ChIP-seq (chromatin immunoprecipitation-sequencing) data sets identified several genes that are likely co-regulated by the YAP1/TEAD

and NF-Kappa B transcription factor. These findings suggest that cooperative androgen and cytokine signaling regulates Hippo/YAP and NF-Kappa B interaction. The YAP1/TEAD and NF-Kappa B interaction may have critical roles in cellular biology and human diseases.