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The Hippo Pathway Effector YAP/TEAD Regulates EPHA3 Expression and Functions

Marwah Al-Mathkour,Abdulrahman Dwead,Esma Alp,Ava Boston,Jazzmin Owens,Bekir Cinar

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Abstract

Cell-cell interaction is critical for tissue development and repair, immunological responses, and cancer cell metastasis. The tyrosine kinase EPHA3 (erythropoietin-producing hepatocellular carcinoma cell surface type-A receptor 3) regulates cell-cell interaction, cell differentiation, and cancer cell survival. Previously, our published study indicated that the STK4-encoded MST1 signaling, a core kinase component of the Hippo pathway, suppressed EPHA3 expression in the prostate cancer cell models. However, the mechanism is unknown. Here, we have demonstrated that the YAP1 and TEAD1 proteins, critical nuclear effectors of the Hippo pathway, mediate EPHA3 expression. First, we showed that AR-positive cell lines express the highest levels of EPHA3 and its ligand ephrin-A5 transcripts compared with other EPH family members. Second, we demonstrated that the induction of MST1/STK4 attenuated the EPHA3 protein and transcripts, consistent with our initial observation. Next, we demonstrated that knockdown of YAP1 by siRNA suppressed EPHA3 protein and mRNA expression. Similarly, the silencing of the TEAD1-4 proteins, critical mediators of YAP1-dependent gene transcription, revealed that the TEAD1 is a crucial inducer of EPHA3 expression. Moreover, bioinformatics tools allowed the identification of three putative TEAD binding sites ($p<0.001$) in the promoter region of the EPHA3 gene. Furthermore, CRISPER/Cas9-aided EPHA3 knockout significantly ($p<0.01$), decreased cell growth in

monolayer and sphere formation in 3D cultures and caused androgen-independent cells to become sensitive to enzalutamide, a potent direct inhibitor of AR activity. These observations suggest that the YAP/TEAD1 transcriptionally regulates EPHA3 and its cellular biology.