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Ku70 binding to YAP to regulate Genome stability and Tumorigenesis

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YAP/TAZ are central players in cancer development extending beyond their recognized role in cell growth regulation. Their involvement in genome instability and the DNA damage response adds a new layer of significance. Our study uncovers that Ku70 engages in a dynamic competition with TEAD4 for binding to YAP, establishing Ku70 as a critical regulator of YAP's transcriptional activity. Depletion of Ku70 disrupts the Ku70/YAP complex, enhancing YAP's interaction with TEAD4 and boosting its transcriptional capacity. Consequently, Ku70 loss activates YAP, propelling tumorigenesis in colon cancer and hepatocellular carcinoma (HCC) in vivo. Additionally, our investigation delves into the intricate post-DNA damage regulatory mechanisms within YAP's purview. We reveal that YAP orchestrates PARP1 degradation through the SMURF2-mediated ubiquitin-proteasome pathway, impeding DNA damage repair processes mediated by PARP1 during the DNA damage response. This inhibition leads to elevated genome instability, a critical factor in cancer initiation and progression. Importantly, our findings establish a link between YAP activity, PARP1 expression, and genome instability in HCC patients. In conclusion, our research offers a mechanistic understanding of YAP's role in tumorigenesis, highlighting the Ku70-YAP-SMURF2-PARP1 axis as a regulator of the DNA damage response. This introduces a perspective on YAP's multifaceted influence on genome stability in the context of cancer.

Collaboration (if any)

Primary authors: Ms SHU, Yinyin (soochow university); Prof. CHANG, lei (Soochow university)

Presenter: Prof. CHANG, lei (Soochow university)

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