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Yap Functions Via TEAD Mediated Transcriptional Activation in Hepatoblastoma Pathogenesis

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Hepatoblastoma (HB) is the most common pediatric liver tumor. Activation of Wnt/β-catenin pathway is considered to be the driver genetic event in HB. In addition to Wnt/β-catenin, activation of Yap is found in a majority of HBs, and high Yap transcriptional activity was recently found to be associated with high risk HB. Importantly, our studies demonstrated the coordinated activation of β-catenin and Yap led to HB formation in mice. However, how Yap functions to promote HB formation remains unknown. Yap has been shown to have transcriptional activity as well as non-transcriptional based functions. Here we investigated whether TEAD mediated transcription is the major mechanism by which Yap promotes HB formation. Specifically, we blocked Yap transcriptional activity via dominant negative form of TEAD2 (dnTEAD2). We found that overexpression of dnTEAD2 inhibited HB cell growth in culture and blocked Yap/β-catenin induced HB formation in mice. We generated TEAD2-VP16 fusion construct which allows TEAD dependent transcriptional activation independent of Yap. When TEAD2-VP16 was co-expressed with activated β-catenin into mice, it led to HB formation. Further analysis demonstrated that TEAD2-VP16/β-catenin HBs shared similar molecular features with Yap/β-catenin tumors. As there are multiple TEADs (TEAD1, 2, 3 and 4) which share redundant functions, we tested the contribution of each TEAD in regulating Yap activity in HB cells. We found that silencing of TEAD4 consistently reduced Yap downstream gene expression, supporting that TEAD4 may be the major Yap partner in HB development. In summary, our studies support that Yap predominantly regulates HB development via TEAD4 mediated transcriptional activation,

and blocking Yap/TEAD interaction may represent a novel therapeutic strategy against HB.

Keywords: Hepatoblastoma (HB); Yap; TEAD2-VP16; TEAD4