IDENTIFICATION OF HRB27C AS A NOVEL REGULATOR OF THE HIPPO PATHWAY USING A *DROSOPHILA* GENETIC SCREEN

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Introduction: Cancer is one of the leadings causes of human death across all countries of the world despite all recent advances in global medicine. Thus, identification of new genetic factors that contribute to cancer initiation and progression is an important issue for the development of new therapeutic strategies. The YAP and TAZ oncogenes have been recently identified as important drivers of several types of human cancer, including liver cancer. YAP and TAZ in mammals and Yorkie (Yki) in *Drosophila* are the effectors of the Hippo tumor suppressor pathway, a key component of animal organ growth control. However, mutations in the known Hippo pathway components are rare and cannot explain the widely observed hyperactivation of YAP and TAZ in human cancers.

Method: In order to identify new regulators of YAP and TAZ activity, we used the fruit fly *Drosophila melanogaster* to screen for suppressors of tissue overgrowth and Yki activation.

Results: In our screen, we identified mutations in the hnRNP (heterogeneous nuclear Ribonucleoprotein) Hrb27C that strongly suppressed the tissue defects induced by ectopic expression of aPKC. We discovered that the mechanism of this suppression is due to the requirement of Hrb27C in regulating Yki activity and ultimately cell proliferation. We conclude from our genetic studies that Hrb27C is a new regulator of the Hippo signaling pathway and that it is required for Yki-driven overgrowth.

Conclusion: Our findings are both novel and significant. First, neither Hrb27C nor its human homolog DAZAP1 have been linked to the Hippo pathway before. Second, DAZAP1 is implicated in oncogenesis through a process called alternative splicing. Third, the expression levels of DAZAP1 correlate with poor prognosis in liver cancer patients. Further investigation of the interaction between DAZAP1 and YAP and TAZ would shed new light on the mechanisms behind the hyperactivation of YAP and TAZ in cancers and has a potential to promote the development of novel anti-cancer therapy.