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Glypican-3 and CD81 Promote Development Of Hepatocellular Carcinoma And Hepatoblastoma Through Negative Selection.

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Glypican3 (GPC3) is highly over-expressed in hepatocellular carcinomas (HCC). Loss-of-function mutations of Glypican-3 cause organomegaly (Simpson-Golabi-Behmel syndrome). GPC3 also down-regulates nuclear Yap and binds to CD81. Activation of CD81 by agonistic antibody is associated with activation of spleen kinase (Syk) and phosphorylation of Ezrin, a regulator of Hippo pathway. The purpose of this study is to explore the role of CD81 and GPC3 protein in regulation of the Hippo pathway and Yap and to investigate why does GPC3 over-expression fail to cause decrease in Yap in HCC, most of which have elevated levels of Yap. In cultures of normal hepatocytes, CD81 agonistic antibody led to enhanced phosphorylation of Ezrin and increase in nuclear Yap. Forced expression of CD81 in a GPC3–expressing HCC cell line caused activation of Hippo, decrease in Ezrin phosphorylation and decrease in Yap. Overexpression of CD81 associated Syk kinase in the same cell line caused inactivation Hippo, increase in Ezrin phosphorylation and increase in Yap. HCC tissue microarray revealed lack of expression of CD81 in most HCC. Hepatoblastoma tissue microarray also show that CD81 loss membrane expression in 56% of cases.

Conclusions: Activation of CD81 by agonistic antibody results in Hippo pathway suppression and increase in nuclear Yap. GPC3 is likely to enhance hepatic neoplasia by acting as negative selection “promoter” of growth of early CD81-negative neoplastic hepatocytes or hepatoblasts which are resistant to GPC inhibition effect and thus have a proliferative advantage to clonally expand as they participate in the required maintenance of 100% of liver weight (“hepatostat”).