2017

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Abstract

AKT/mTOR and Wnt/β-catenin cascades are frequently deregulated in human tumors. And we established a mouse model by co-expression of AKT and β-catenin mutants (S33Y, S45Y) in mouse liver using the sleeping beauty transposon/transposase system via hydrodynamic tail vein injection. The mice showed large liver tumors at 14-15 weeks post injection for the AKT/S45Y-β-catenin group, and 16 weeks for the AKT/S33Y-β-catenin group. All tumors displayed notable lipid accumulation in hepatocytes.

The molecular signal pathway changed in the model including p-ERK, p-AKT, and mTORC1/mTORC2 related gene Raptor, Rictor, p-4ebp1, PS6.IHC staining and western blot showed beta-catenin and its downstream target gene GS, CCND1 were upregulated in the model. Meanwhile, myc was increased in the tumor groups compared to the normal mice. To demonstrate their relative contribution in the HCC model, we sub-cloned shRNA against various downstream targets and co-delivered with AKT and β-catenin mutants by hydrodynamic tail vein injection, including shRaptor, shRictor, shMYC, shYap, shTAZ. Suppression of key target genes of yap, myc and raptor notably affected tumorigenesis in AKT/beta-catenin s45y group, but only shYap and shRaptor could inhibit tumor development in AKT/beta-catenin s33y group. Such results showed there exist difference tumorigenesis function of beta-catenin s33y and beta-catenin s45y when they cross-talk with other oncogene. Another study showed that when we blocked downstream target binding protein of beta-catenin in vivo, namely co-deliver AKT/beta-catenin mutation and dnTCF4 to the mice liver, there were no tumors around 21 weeks post hydrodynamic tail vein injection, the results showed TCF4 is required for the tumor development in the model.

Thus, while differences in β-catenin mutations can lead to differing extents of β-catenin activation, β-catenin does cooperate with AKT to induce HCC with lipogenic phenotype. Yap and mTORC1 pathway is indispensable for AKT/beta-catenin mutant induced HCC, and these dysregulated target gene might be used for precise therapy with the model.

Keywords: β-catenin; AKT; Lipogenic HCC