DYSREGULATED FERMENTATION OF SOLUBLE FIBER MAY INDUCE LIVER CANCER

The gut microbiota benefits the host in part via metabolism of dietary fiber into valuable nutrients. Insoluble fiber resists fermentation, but soluble fiber (such as inulin) is fermented into short-chain fatty acids (SCFA), which have a beneficial metabolic effect. Disruption of the gut microbiota can lead to chronic inflammation, and mice lacking toll-like receptor 5 (TLR5) are at increased risk for developing microbiota-dependent colitis and inflammation-associated metabolic syndrome. Singh, Yeoh, Chassaing, and colleagues aimed to determine if soluble fiber might ameliorate the microbiota dysbiosis and metabolic syndrome associated with TLR5 deficiency. Unexpectedly, enriching the diet of the mice with inulin induced hepatocellular carcinoma (HCC) in these innate immune-deficient mice despite improving glycemic control and reducing adiposity. The inulin diet–induced HCC was associated with hepatic inflammation and was not specific to TLR5 deficiency, but was triggered in other innate immune-dysregulated mice (including TLR4– and lipocalin-2–deficient mice). Other soluble fibers (such as pectin and fructooligosaccharides) had a similar HCC-promoting effect, but nonfermentable or insoluble fiber did not promote HCC. HCC development in TLR5-deficient mice was associated with alterations in gut microbiota (dysbiosis), with an increase in fiber-fermenting species. The susceptibility of TLR5-deficient mice to inulin-induced HCC was dependent on dysbiotic microbiota. Microbial transfer from TLR5-deficient mice rendered wild-type mice susceptible to HCC, whereas microbial ablation with broad-spectrum antibiotics prevented HCC development. Inulin-induced tumorigenesis was initiated by early-onset cholestasis that resulted in hepatocyte apoptosis, neutrophil infiltration, and liver inflammation. Tumorigenesis could be blocked by inhibition of fermentation, which resulted in reduced intestinal SCFA. Collectively, these findings suggest that enriching processed foods with fermentable fiber may increase the risk of HCC.


THE SWI/SNF COMPLEX BINDS TO AND INHIBITS YAP/TAZ

ARID1A and other components of the SWI/SNF chromatin remodeling complex are frequently inactivated by genetic alterations in cancer. However, the mechanism by which the SWI/SNF complex suppresses tumorigenesis remains poorly understood. Chang and colleagues found that ARID1A binds to and inhibits the oncogenic transcriptional coactivators YAP and TAZ, resulting in reduced expression YAP/TAZ target genes. Inhibiting YAP/TAZ promoted proliferation and liver tumorigenesis in Arid1a-deficient cells. SWI/SNF has been previously shown to associate with F-actin, and mechanical cell stress increased the association between nuclear F-actin and ARID1A-SWI/SNF, thereby reducing the association between ARID1A and YAP/TAZ. YAP/TAZ binds to the DNA-binding platform TEAD to drive transcription, and ARID1A competed with TEAD for binding to YAP/TAZ. Thus, under high mechanical stress F-actin blocked YAP/TAZ from binding to ARID1A, promoting increased association between YAP/TAZ and TEAD. In contrast, conditions of low mechanical stress favored the interaction between ARID1A and YAP/TAZ. Consistent with these findings, YAP-expressing neurons formed neurospheres more efficiently on stiff extracellular matrix (ECM) than on soft ECM, and depletion of Arid1a rescued the ability to form neurospheres on stiff ECM by enhancing the YAP/TAZ–TEAD interaction independent of mechanostress. Taken together, these findings suggest that full activation of YAP/TAZ requires nuclear accumulation of YAP/TAZ and inhibition of ARID1A-SWI/SNF.

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