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MiR-22 silenced cyclin A expression in colon and liver cancer cells is regulated by bile acid receptor

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Due to the significant tumor suppressive role of microRNA-22 (miR-22), the current study was designed to understand the regulation of miR-22 and to identify additional downstream miR-22 targets in liver and colon cells. The data showed miR-22 was transcriptionally regulated by bile acid receptor farnesoid X receptor (FXR) through direct binding to an invert repeat-1 (IR-1) motif located at 1012 to 1025 bp upstream from miR-22. Among the studied primary and secondary bile acids, chenodeoxycholic acid (CDCA), which has the highest binding affinity to FXR, induced miR-22 level in both Huh7 liver and HCT116 colon cells in a dose dependent manner. In addition, Cyclin A2 (CCNA2) was identified as a miR-22 novel target in liver and colon cancer cells. The sequence of miR-22, which is conserved in mice, rats, humans and other mammals, aligns with the sequence of 3' UTR of CCNA2. CDCA treatment and miR-22 mimics reduced CCNA2 protein and increased the number of G0/G1 Huh7 and HCT116 cells. In FXR knockout (KO) mice, reduction of miR-22 was accompanied by elevated hepatic and ileal CCNA2 protein as well as increased number of hepatic and colonic Ki-67-positive cells. In humans, the expression levels of miR-22 and CCNA2 are inversely correlated in liver and colon cancers. Taken together, our data showed that bile acid activated FXR stimulates miR-22 silenced CCNA2, a novel pathway for FXR to exert its protective effect in the gastrointestinal tract.

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Metabolic reprogramming is a very early event in HCC development

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Warburg metabolism is associated with cancer, but remains unclear whether it characterizes early phases of tumorigenesis. Here, we performed a metabolic characterization by assessing expression level, activity and modulation of several enzymes with key roles in glycolysis, pentose phosphate pathway (PPP) and oxidative phosphorylation. Preneoplastic hepatic lesions and hepatocellular carcinomas (HCC) were induced in rats by a single dose of diethylnitrosamine (DEN) followed by 2-acetylaminofluorene (2-AAF) and partial hepatectomy. Expression of metabolic genes was also analysed in macrodissected preneoplastic nodules and HCC cells obtained by perfusion of HCC-bearing rats and in two different cohorts of human patients carrying HCC. A switch from OXPHOS to PPP was observed in very early preneoplastic lesions generated 10 weeks after DEN treatment. This metabolic reprogramming was observed only in the most aggressive preneoplastic lesions positive for CK-19. PPP induction shown by increased glucose 6-phosphate dehydrogenase (G6PD) was associated with inhibition of succinate dehydrogenase by the chaperone TRAP1 and increased expression and activity of citrate synthase. Activation of the NRF2/KEAP1 pathway and down-regulation of miR-1 accompanied the metabolic reprogramming in CK-19+ preneoplastic lesions. Accordingly, NRF2 silencing decreases G6PD and increases miR1 expression, consequently inhibiting PPP, while forced expression of miR1 downregulated G6PD expression in HCC cells. Finally, an inverse correlation between miR1 and its target gene G6PD was found in human HCCs. The results demonstrate that metabolic reprogramming takes place at early stages of hepatocarcinogenesis and is likely the consequence of the concomitant activation/increase of the NRF2-KEAP1 pathway and TRAP1.

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