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Deficiency in key transcription factor Brf1 of RNA Pol III genes results in protein synthesis obstacle and phenotypic alteration

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Our early studies have demonstrated that deregulation of Pol III genes (RNA polymerase III-dependent genes), tRNAs and 5S rRNAs tightly links to cell transformation and tumor development. Brf1 is a key transcription factor of Pol III genes. Both Brf1 and its target genes (Pol III genes) take part in protein synthesis and are epigenetically mediated by phosphorylated histone H3. To explore changes in obstacle of protein synthesis and consequences under deficiency in Brf1, we have developed a Tamoxifen (Tam)-inducible conditional knockout Brf1 mouse (ckBrf1) to investigate its phenotypes. All of mice will die after Tam injection a week. The livers of ckBrf1 appear pale, shrinking and collapsing. There was plenty of ascites in abdominal cavity. Biochemistry analysis indicates that knockout Brf1 dramatically decreases the levels of albumin and total proteins of sera, while activities of ALT, AST AKP and bilirubin are sharply increased. It indicates that deficiency in Brf1 causes protein synthesis obstacle, liver dysfunction and acute failure. Electron microscope further indicates that glycogens losses in ckBrf1 liver cells. In contrast, there are numbers of lipid drops deposited in the liver cells. In addition, nuclei shapes appear irregular and deformity. Mitochondria sizes of ckBrf1 liver cells become smaller than control liver. The study, for the first time demonstrates that deficiency in Brf1 results in repression of Pol III gene transcription to loss the capacity of protein synthesis, reduce colloid osmotic-pressure, and bring about plenty of ascites. Consequently, deficiency in Brf1 causes acute liver failure and dead of mice.

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