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Niemann-Pick type C2 protein regulates liver cancer progression via modulating ERK1/2 pathway: Clinicopathological correlations and therapeutical implications.

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Abstract

Primary hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide and the third leading cause of **cancer**-related death. It is important to identify new targets for early diagnosis and treatment of HCC. **Niemann-Pick type C2** (NPC2) plays an important role in the regulation of intracellular cholesterol homeostasis **via** direct binding with free cholesterol. However, little is known about the significance of NPC2 in HCC tumorigenesis. In this study, we showed that NPC2 is abundantly expressed in normal **liver**, but is downregulated in human HCC tissues. The patients with NPC2 downregulation expressed much higher α-fetoprotein, multiple tumor **type**, vascular invasion, later pathological stage and shorter survival rate. Knockdown NPC2 in **liver cancer** cell lines promote cell proliferation, migration and xenograft tumorigenesis. In contrast, NPC2 overexpression inhibits HuH7 promoted tumor growth. Furthermore, administration of hepatotropic adeno-associated virus 8 (AAV8) delivered NPC2 decreased the inflammatory infiltration, the expression of two early HCC markers-glypican 3 and survivin and suppressed the spontaneous HCC development in mice. To identify the NPC2-dependent mechanism, we emphasized on the status of MAPK/ERK signaling. MEK1/**2** inhibitor treatment demonstrated that the expression of NPC2 affected the activation of **ERK1**/**2** but not MEK1/**2**. In addition, cholesterol trafficking inhibitor treatment did not alter the cell proliferation and the activation of MEK/ERK. In conclusion, our study demonstrates that NPC2 may play an important role in negatively regulate cell proliferation and **ERK1**/**2** activation that were independent of cholesterol accumulation. AAV-NPC2 may thus represent a new treatment strategy for **liver cancer**.

KEYWORDS: Adeno-associated virus 8; **ERK1**/**2**; **Niemann-Pick type C2**; hepatocellular carcinoma; proliferation

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