

学位論文抄録

Evaluation of DHCR24 in prognosis of hepatitis C: possible link with risk of liver cancer

(DHCR24のC型肝炎病態進行における役割：肝がん発症との関連に関する研究)

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Abstract of the Thesis

Background and Purpose: Liver cancer is one of the most prevalent forms of cancer. Hepatitis C virus (HCV) infection is a critical etiologic factor for hepatocellular carcinoma (HCC). We recently reported that DHCR24 is induced by HCV infection. In addition, upregulation of DHCR24 impaired p53 activity. We are investigating the possibility that antibody against DHCR24 and genomic polymorphism in DHCR24 promoter sequence might have a potential for prognosis of HCC.

Methods: We established monoclonal antibody 2-152a by immunization of HCV-expressing cells. We developed expression system of DHCR24 gene as Glutathione S transferase (GST)-fused DHCR24 protein. We applied recombinant DHCR24 protein for the antigen of ELISA. Antibody against DHCR24 was measured in Egyptian people (n=27) with high GOT/GPT and normal GOT/GPT, and HCC patients (n=18).

The genomic promoter sequence of DHCR24 was characterized and nucleotide substitutions were observed in hepatoma (HuH-7) cells at nucleotide number -1453; G to A, -1420, G to T, -488, A to C, and -200 G to C.

Results and Discussion: The 2-152a recognized DHCR24. We found the induction of DHCR24 expression by HCV and frequent overexpression in HCV positive HCC patients. We detected antibodies against DHCR24 in Egyptian people (n=27) and significantly higher amount of anti DHCR24 antibody was detected in high GOT/GPT group ($57.8 \pm 3.1 \mu\text{g/ml}$) than normal GOT/GPT group ($26.9 \pm 5.2 \mu\text{g/ml}$). We detected higher amount of anti-DHCR24 antibody in 18 HCC patients ($523 \pm 58.7 \mu\text{g/ml}$).

In human HuH-7 cells, level of DHCR24 expression was higher than normal hepatic cell lines (**WRL68**). Four HCV positive patient tissues with cirrhosis or HCC (#1, 2, 3, 5) possessed **HuH-7** cell type promoter sequences. Interestingly, one liver cirrhosis (LC) patient (#4) possessed **WRL68** type, was infected with HCV and became HCV negative after 17 years of interferon therapy. We next examined the efficacy of HCV infection to these polymorphisms in humanized chimeric mouse liver and HuH-7 cells. The human hepatocytes possess **WRL68** cell type and did not show the nucleotide substitution after HCV infection. The HCV-replicon was removed by interferon treatment to establish the cured K4 cells and they possessed **HuH-7** cell type sequences

The mutations from **HuH-7** cell types to normal hepatocyte types suppressed DHCR24 promoter activity. Thus, DHCR24 antibody or promoter sequences might be a prognostic marker in hepatitis C.