論　文　内　容　要　旨

Heterophile carbohydrate antigen *N*-glycolylneuraminic acid as a potential biomarker in patients with hepatocellular carcinoma

（肝細胞癌患者における異好性糖鎖抗原Ｎグリコリルノイラミン酸のバイオマーカーとしての可能性）

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Background and Objectives

Hepatocellular carcinoma (HCC) has a high recurrence rate even after radical hepatectomy. No optimal biomarker can predict the recurrence and prognosis of HCC. N-glycolylneuraminic acid (NeuGc) is widely expressed in most mammals but not in normal human tissues. The NeuGc deficiency in human is caused by exon deletion in the gene coding for cytidine-5'-monophospho (CMP)-NeuAc hydroxylase (CMAH). The human CMAH gene, also known as CMAH pseudogene (CMAHP), was pseudogenized and inactivated by the deletion event. Recently, NeuGc antigen (Ag) was discovered to be expressed in lung, breast, colon cancer, melanoma, retinoblastoma, and HCC patients. However, no studies have analyzed the oncological effects of NeuGc Ag expression and anti-NeuGc antibody (Ab) to predict HCCprognosis. Thus, we aimed to determine whether the NeuGc Ag expression in hepatectomized tissues and anti-NeuGc Ab titers in the serum may affect HCC prognosis separately for initial and recurrent hepatectomized patients.

Methods

We investigated whether the oncological properties of NeuGc can participate in the prognosis of HCC. We evaluated the NeuGc Ag expression in the HCC tissues and measured the preoperative anti-NeuGc IgG Ab in the sera of the patients with HCC. We compared the clinical characteristics and survival rate in the hepatectomized patients (initial; n = 66, recurrent; n = 34) with and without the NeuGc Ag or Abs. And we evaluated CMAHP mRNA expression normalized against β-actin in the normal and tumor portions of the resected liver tissues from the hepatectomized HCC patients (n = 100).

Results

Multivariate analyses showed positive expression of NeuGc Ag in HCC tissues (Odds ratio; initial = 6.3, recurrent = 14.0) and higher titers of preoperative anti-NeuGc Ab (Odds ratio; initial = 4.9; recurrent = 3.8), which could be the predictive factors related to early recurrence. Both the NeuGc Ag-positive and Ab-positive groups in the initial hepatectomized patients exhibited significantly shorter recurrent free survival compared to those in the negative groups. And the anti-NeuGc Ab-positive group exhibited a significantly reduced overall survival compared with the negative group. On the other hand, RT-qPCR results revealed that the tumor tissues exhibited significantly higher CMAHP mRNA expression than the normal tissues. And we compared the relative CMAHP mRNA expression in the initial and recurrent HCC patient group. The NeuGc Ag-positive group exhibited a significantly higher CMAHP mRNA expression in the tumor tissues than that in the normal tissues. The CMAHP mRNA expression in the anti-NeuGc Ab-positive group was also significantly higher in the tumor tissues than in the normal tissues.

Discussion

In the present study, we identified the expression of NeuGc Ag in most HCC tissues and the expression of CMAHP mRNA in the NeuGc Ag-positive tissues. CMAHP amplification in NeuGc Ag-expressing HCC tissues likely indicates that either CMAHP is transformed into a functional CMAH that biosynthesizes NeuGc or CMAHP is mutated; however, such hypotheses remain speculative. Further studies on the biology of CMAHP and NeuGc Ag-expression in HCC tissues and circulating anti-NeuGc Abs are required to completely elucidate the mechanism of HCC carcinogenesis. Regardless of the mechanism, the intra-tumoral expression of NeuGc Ag was associated with postoperative recurrence and prognosis in the HCC patient groups. Hence, examining NeuGc Ag expression and relative CMAHP mRNA levels in HCC tissues may be useful in identifying high-risk groups for HCC recurrence and prognosis. However, as liver tissues are only available after surgery, no way is available to determine the risk of postoperative recurrence before surgery. As a factor that can predict the risk of postoperative recurrence preoperatively, which is valuable information for determining surgical indications, we investigated the effect of anti-NeuGc Ab titers in the preoperative sera of the HCC patients, which were well correlated with NeuGc Ag expression or CMAHP mRNA level, on prognosis. The analysis of oncological characteristics showed a significant difference between the anti-NeuGc Ab-positive and -negative groups of the HCC patients who underwent hepatectomy with early recurrence within 2 years. These results indicated that the serum anti-NeuGc Ab can be used as a risk factor for predicting HCC recurrence at an early stage after hepatectomy; however, its potential benefit as a tumor marker monitored regularly after surgery for speculating HCC recurrence remains entirely unknown. The higher anti-NeuGc Ab titer in the sera of patients with HCC and positive NeuGc Ag expression appears to indicate that humoral immunity, a biological defense mechanism, targets cancer antigens, leading to the prevention of HCC recurrence.

Conclusions

Our findings suggested that preoperative anti-NeuGc Ab titers and positive NeuGc Ag expression in resected HCC tissues can predict the early recurrence and prognosis of HCC after the initial hepatectomy. Therefore, these factors may serve as potential predictive factors for future studies on improving HCC prognosis and therapeutics.