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Research on Golgi Protein 73 and Its Corpora Heterogenium

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Abstract: **Hepatocellular carcinoma (HCC) is one of the most frequent malignancies, so early diagnosis is crucial to HCC. In recent years, with the rapid development of proteomics and glycomics, new various serum markers related hepatocellular carcinoma were found in succession. Although it is reported that golgi protein 73 (GP73) and its corpora heterogenium (Fucosylated gp73, Fuc-gp73) can be the serum marker used to the diagnosis of HCC, there is certain limitation in current study. Therefore, our study combined with the current domestic and foreign literature, to conduct a review about research progress of GP73 and Fuc - GP73.**

Keywords: GP73; Fuc - GP73; HCC

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1. Introduction

Hepatocellular carcinoma (HCC) is one of the most frequent malignancies, and the pathogenesis of HCC is concealed. As the prognosis is often poor due to diagnosis too late, so early diagnosis is crucial to HCC. At present, histologic examination is still the gold standard in the diagnosis of HCC, but it also exist some shortcoming such as traumatic, high risk and so on. In noninvasive examination, although serum alpha-fetoprotein (AFP) level and ultrasound scans are the most common monitoring method, AFP has a low degree of sensitivity and specific [1]. Some research [2] revealed that the serum AFP level more than 500ug/L was related to tumor size, but around 80% of small hepatocellular carcinoma did not found serum AFP level rising. However, other study found that some cirrhotic or hepatitis patients without HCC has a high level of serum AFP [3]. Therefore, looking for the serum diagnostic index with higher degree of sensitivity and specific has an important significance to improve the early diagnostic rate of HCC. In recent years, it is reported that golgi protein 73 (GP73) can be the serum marker used to the diagnosis of HCC. Glycosylation segments of GP73 is the GP73 heterogeneity, also known as fucus glycosylation golgi protein 73 (Fuc - GP73), it has a great potential value in the early diagnosis of HCC. Therefore, our study combined with the current

domestic and foreign literature, to conduct a review about research progress of GP73 and Fuc - GP73.

2. Genetic Structure and Biological Characteristics of GP73

GP73 is also called type Ⅱ golgi membrane protein (GOLPH2) or GOML1. Kladney et al[4] conducted a search for the etiology of acute adult cytomegalovirus hepatitis, discovered that a sequence was consistent with the gene sequence which was identified in cultured amniotic cells in response to infection with the Newcastle disease virus. In vitro transcription–translation studies indicate that GP73 is an integral membrane protein, and immunolocalization experiments using epitope-tagged GP73 demonstrated that the protein is localized to the Golgi apparatus. It's already known that the GP73 gene located on the Long Arm of Chromosome 9 comprises 3042 bp, which contains a single open reading frame of 1200~1400bp and would yield proteins of 402 amino acids.

3. GP73 Protein Production and Distribution

The results show that multiple tissue and organs of normal body have expressed GP73, but the expression has a great difference. The GP73 mRNA is low or no expression in the lymphoid tissue, muscle, and white blood cells, but it is high expression in the stomach, colon and prostate, indicated that some cells and organization may exist the specific regulatory mechanism. The expression of GP73 mainly concentrated in the epithelial cells, such as differentiated colon cells, renal distal convoluted tubule, collecting duct cells and bronchial columnar epithelial cells. Studies have reported that GP73 expression can lead to changes in host cell function, influenced viral replication, nuclear damage of viral protein and variation of viral particle.

4. The Relationship Between GP73 Expression and Benign Liver Diseases

The abnormal expression of GP73 is associated

with a variety of liver diseases. In 2000, Kladney et al. [4] reported that GP73 mRNA and protein are overexpressed in highly differentiated HepG2 hepatoma cells after infection with adenovirus in vitro, the expression of GP73 mRNA and protein also increased in multinucleated hepatocytes, but no expression in normal liver cells. In 2002, Kladney et al [5]also showed that GP73 protein levels, as measured by densitometric quantitation of Western blot, were an increase of up to 70-fold in the liver disease than that in the normal liver. In 2004, Iftikhar et al [6]also found that hepatocyte GP73 expression was increased in patients with acute and autoimmune hepatitis, increased levels of GP73 expression were also noted in chronic HCV infection and alcoholic liver disease. Under these conditions, GP73 levels were correlated with disease stage but not grade. It also revealed that GP73 immunoreactivity was occasionally detected in alpha-SMA-positive, sinusoidal lining cells, suggesting activated stellate cells as a potential source of GP73.

5. The Relationship Between GP73 Expression and HCC

A large number of studies found that the abnormal GP73 levels are closely related to HCC. In 2005, Block et al [7] applied to disease-related samples by using the woodchuck model of HBV-induced HCC, as a method of glycoproteomic analysis, found that the serum GP73 level of HCC group was obviously higher than that in normal group, suggesting the abnormal GP73 levels may be associated with HCC. Marrero et al[8] found that higher levels of GP73 can be found in the serum of patients with HCC than of those without by using Western blot. When the optimal cutoff point of 10 relative units, GP73 had a sensitivity of 69% and a specificity of 75%. GP73 levels had significantly higher sensitivity (62%) than AFP (25%) for diagnosing early HCC. Moreover, GP73 levels were elevated in the serum of 57% (32/56) of individuals with HCC who had serum AFP levels less than 20 ng/ml. The study suggested GP73 was better than AFP for the diagnosis of early HCC. Schwegler et al[9] assessed the use of surface enhanced laser desorption/ionization time-of-flight mass spectrometry to identify GP73 for detection of liver disease progression to HCC, reported that GP73 had a sensitivity of 95% and a specificity of 74%, which had been better than AFP and abnormal prothrombin for the diagnosis of early HCC. In recent years, the reports about the relationship between abnormal GP73 expression and HCC are increasing in the domestic. In 2009, Li et al [10]detected the expression of GP73 in 45 PHC and tumor-adjacent specimens and 14 normal liver specimens by immunohistochemistry, reported that GP73 is highly expressed in primary liver cancer. Meanwhile, Tan et al[11] performed to detect the level of serum GP73 in 470 samples (150 cases of HCC, 120 cases of benign liver disease and 200 cases of control) by sandwich enzyme-linked immunosorbent assay (ELISA), showed that GP73 had a sensitivity of 43.3% and a specificity of 77.8%. When removing 120 cases of benign liver disease, The sensitivity and specificity of GP73 risen to 44.5% and 82.0%, respectively. It suggested that the detection of serum GP73 has a certain value in the diagnosis of liver cancer, but the sensitivity and specificity of GP73 were not satisfactory. In 2010, Mao et al [12] reported that serum GP73 was compared in a total of 4217 human subjects in this multicentre study, including 1690 healthy adults, 337 hepatitis B virus (HBV) carriers, 512 patients with cirrhosis, 789 patients with HCC, 61 patients with other malignant liver lesions, 206 patients with benign liver lesions and 622 patients with 14 different kinds of non-liver cancers. This study found that the sensitivity and specificity of serum GP73 for HCC were 74.6% and 97.4% by using 8.5 relative units as a cut-off value, which considered that GP73 is an accurate serum marker for the detection of HCC and its recurrence after surgery. However, it remains controversial whether GP73 replaces AFP as a serum marker for the detection of HCC. The reasons are as follows: First, the method of ELISA widely used in current researches will be affected by serum GP73 autoantibody, leaded to some error of detection results[13]. Second, some researches[14] showed that GP73 is highly expressed in some benign liver diseases, while decreased in HCC, affected the specificity of GP73 in the diagnosis of early HCC. Third, it is not clear that the relationship between serum GP73 level and clinical features of HCC. More studies are needed to solve these problems.

6. The Relationship Between GP73 Abnormal Glycosylation and HCC

Glycosylation is one of the most common way of post-translational modification, and more than half of proteins are glycoproteins[15]. It plays an important role in protein folding, transport, positioning and functional form. Some researches[16] showed that glycoproteins have taken place different degrees of glycosylation in the process of the occurrence and development of many diseases. Most glycoproteins exist core fucose. Core fucosylated is the terminal reactive of protein sugar chain synthesis, which could compose some sugar chain structure of adhesion molecule. In the effect ofαl,6-fucosyl transforase, core fucose transfer fucose to the innermost of n-acetyl glucosamine in sugar chains, which can specifically combined with some plant lectins. The researches showed that the activity of αl,6-fucosyl transforase has a significant change in the serum and HCC tissue, which could affect the modification process of sugar chain, resulting in abnormal glycoprotein. This mechanism provides an

important reference value in diagnosis and monitor of HCC. In recent years, results[17] showed that a variety of protein have occurred core fucosylated accompanying the occurrence and development of HCC. The proteins occurred core fucosylated is usually called corpora heterogenium, the AFP core fucosylated (AFP-L3) is the typicalness among them. AFP-L3 showed a higher specificity than AFP in the clinical application, which is suitable for early warning of HCC and a better evaluation of the surgical treatment effect[18]. Meanwhile, Willyard et al. [19] reported that GP73 resembled other proteins occurred core fucosylated in the occurrence and development of HCC, incidated that GP73 core fucosylated is related to HCC. In 2008, Norton et al. [20] established that three quarters of the GP73 secreted from a cell line derived from HCC is fucosylated by using conventional lectin affinity chromatography. In one study including 80 HCC patients[21], Fuc-gp73 had a sensitivity of 90% and a specificity of 100% for the diagnosis of HCC by using mass spectrometry. At present, researches about the molecular biological characteristics of Fuc-gp73 are less, many problems associated with it needed to be solved. First, whether Fuc-gp73 resembled AFP could be divided into different subtypes according to the different affinity appetency to plant lectins [22]; Second, whether it exists fucus glycosylation GP73 antibody to establish a method for detection of serum Fuc - GP73 rapidly. Third, whether blocking the expression of Fuc-gp73 for the treatment of HCC.

7. Summary and Expectation

The biological characteristics of HCC are complex. At present, AFP as serological index of HCC is widely used to census, diagnosis and detection of recurrence. But there is certain limitation in sensitivity and specificity of HCC. A large number of researches showed that GP73 and its corpora heterogenium have a high degree of sensitivity and specificity for the early diagnosis of HCC, and tthere were reports that GP73 and its corpora heterogenium has increased in other tumors. Whether GP73 and its corpora heterogenium were applied to the clinical diagnosis of HCC, it needs more studies and clinical data to confirm.

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