International Journal of Chemical and Biochemical Sciences
(ISSN 2226-9614)

Journal Home page: www.iscientific.org/Journal.html

Role of Glypican-3 in Hepatocellular Carcinoma

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Abstract

Liver cancer is the second leading cause of cancer-related deaths, and hepatocellular carcinoma (HCC) is the most common type. Therefore, molecular targets are urgently required for the early detection of HCC and the development of novel therapeutic approaches. Glypican-3 (GPC3), an oncofetal proteoglycan anchored to the cell membrane, is normally detected in the fetal liver but not in the healthy adult liver. However, in HCC patients, GPC3 is overexpressed at both the gene and protein levels, and its expression predicts a poor prognosis. Mechanistic studies have revealed that GPC3 functions in HCC progression by binding to molecules such as Wnt signaling proteins and growth factors. Moreover, GPC3 has been used as a target for molecular imaging and therapeutic intervention in HCC. To date, GPC3-targeted magnetic resonance imaging, positron emission tomography, and near-infrared imaging have been investigated for early HCC detection, and various immunotherapeutic protocols targeting GPC3 have been developed, including the use of humanized anti-GPC3 cytotoxic antibodies, treatment with peptide/DNA vaccines, immunotoxin therapies, and genetic therapies. In this review, we summarize the current knowledge regarding the structure, function, and biology of GPC3 with a focus on its clinical potential as a diagnostic molecule and a therapeutic target in HCC immunotherapy.

Keywords: Glypican-3 in Hepatocellular Carcinoma, HCC.

Mini review article **Corresponding Author*: e-mail: drsaada2019@gmail.com

1. Introduction

Glypican-3 (GPC3) is a type of glycosylphosphatidylinositol-anchored cell-surface heparin-sulfate proteoglycan HSPGs, that has been repeatedly reported to be highly and selectively expressed in HCC patients. An increasing number of studies have suggested that GPC3 plays vital roles in cell proliferation and tumor suppression, contributing to progression and metastasis of HCC patients. It has been shown that GPC3 stimulated growth of HCC cells and regulated migration, adhesion in tumor cells. Recently, there is a growing interest in the possible prognostic utility of GPC3 in HCC, but the results of different studies with regard to disease-free survival (DFS) and overall survival (OS) are still controversial [1]. Glypicans, a family of proteins classified as HSPGs, and shown to interact with some growth factors(GFs) and modulate thier activity and are linked to the extra cellular side of cell- membrane by a glycosylphos-phatidyl inositol (GPI) anchor [2]. Glypicans have a core protein size of ~60 to70 kDa and express an N-terminal secretory signal polypeptide along with a hydrophobic domain that is used for the addition of GPI anchor at C-terminus. All glypicans have the location of the insertion sites for heparin-sulfate chains (HSC), which appears to be restricted to last 50 amino acids in C terminus, placing chains close to cell-membrane. Furthermore, position of 14-cysteine residues is conserved, further strengthening structural correlation of polypeptides within family [3-6].

Diagnostic Accuracy of GPC3 for HCC

Among the twenty-two studies, eighteen of them have demonstrated that GPC3 level in serum is higher in HCC patients than that in control subjects, which include healthy individuals and patients with hepatitis or liver cirrhosis.

Whereas four studies have claimed that GPC3 is not a diagnostic marker for HCC because sGPC3 level is lower in patients with HCC than that in patients with liver cirrhosis [7]. The sensitivity and specificity of the studies were plotted in a hierarchical summary receiver operating characteristic graph (SROC). The sensitivity of using GPC3 for HCC diagnosis ranged from 36 to 100%, and the specificity ranged from 42 to 100%. The average sensitivity and specificity were 69% (95% CI was 55–80%) and 93% (95% CI was 85–97%), respectively. The overall diagnostic odds ratio (DOR) and the area under SROC were 31 (95% CI was 11–92) and 0.89 (95% CI was 0.86–0.91), respectively. -square values of sensitivity and specificity were 90.71 and 97.30, respectively, indicating that substantial heterogeneity existed among the eligible studies [4]. GPC-3 as a serum biomarker for HCC early detection. GPC-3 may be a potential serum TM in diseases such as HCC in which over expression of GPC-3 is detected [3]. Serum GPC-3 expression using immunohistochemistry and ELISA in HCC patients, as well as in healthy donors and hepatitis, cirrhosis patients. sGPC-3 was high levels in HCC patients, but not in healthy persons. sGPC-3 levels were significantly raised in patients with HCC, but not in healthy and hepatitis patients [8]. Also , GPC-3 was recognized as a novel diagnostic TM for melanoma it its early stages, however, it isnot found in healthy subject , or those with benign skin lesions [9].

GPC-3 is more specific than s-AFP because of its peculiar expression in liver cells, which is the main advantage for its use in detection of HCC. Furthermore , it represents an ideal target for antibody therapeutic techniques Consequent to its expression in pre-neoplastic hepatocytes, this offers the unique benefit of permitting an early and specific therapeutic techniques [3]. Moudi et al., [10] demonstrated an association between HSP70, GPC3 and GS expressions and HBV-related HCC in our population. It was concluded that GPC3 expression could be a useful biomarker for increasing the specificity and sensitivity of HCC diagnosis to acceptable level [10].

GPC-3 expression and stages of HCC

The correlation between liver GPC-3 expression and staging of HCC. According to IUAC staging criteria of HCC, there was 11 cases at staging I (16%, 11 of 69), 19 at II (28%, 19 of 69), and 39 at I I I & I V (57%, 39 of 69) among total 69 tumor tissues. The incidences of high or low GPC-3 expression in HCC tissues were 45.5% (5 of 11) or 54.5% (6 of 11) at I staging, 53% (10 of 19) or 47% (9 of 19) at II staging, 100% (39 of 39) or 0% (0 of 39) at III & IV staging, respectively. The brown GPC-3 expressions were gradually increasing in different staging with very strength staining at advanced stage [5].

GPC-3 as a therapeutic target for HCC

Therapeutic targets are mainly important in treatment of various kinds of malignancy. GC33 which is a monoclonal antibody can bind human-GPC-3. It was detected to have antitumor behviours and targets GPC3 specially. It was noted that GC-33 was well tolerated in end stages HCC and provided some benefit in the treatment [1, 11]. Furthermore, GC33 and YP7 antibodies that also target GPC3 are under different stages of clinical development and could also aid in treatment of liver cancer. Finally, nano-particles are also under development to target and bind GPC3 in cells that could offer valuable for further imaging and targeting of GPC3 [12]. nother therapeutic target on GPC3 is mir-717, a mi-RNA, which is located on intron 3 of GPC-3 on X-chromosome. It has a regulatory role in renal osmoregulation [13].

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