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Concise review

Possible roles of Golgi protein-73 in liver diseases

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ABSTRACT

Golgi protein 73 (also known as GP73 or GOLPH2) is a transmembrane glycoprotein present in the Golgi apparatus. In diseased states, GP73 is expressed by hepatocytes rather than by bile duct epithelial cells. Many studies have reported that serum GP73 (sGP73) is a marker for hepatocellular carcinoma (HCC). For HCC diagnosis, the sensitivities of sGP73 were higher than that of other markers but the specificities were lower. Considering that the concentration of GP73 is consistent with the stage of liver fibrosis and cirrhosis, some studies have implied that GP73 may be a marker for liver fibrosis and cirrhosis. Increased sGP73 levels may result from hepatic inflammatory activity. During liver inflammation, GP73 facilitates liver tissue regeneration. By summarizing the studies on GP73 in liver diseases, we wish to focus on the mechanism of GP73 in diseases.

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1. Introduction

Golgi protein 73 (GP73) is a type II Golgi membrane protein with a molecular weight of 73 kDa that was first identified by Kladney et al. It is mainly expressed by bile duct epithelial cells in the normal liver [1]. Aberrant hepatocyte GP73 expression has been demonstrated in chronic liver diseases such as viral and non-viral hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) [1–2]. GP73 is related to the transforming growth factor- β (TGF- β)/Smad and PIK3-AKT signaling pathways in HCC [3–4] and is involved in the outcomes of patients with HCC [5]. Immune checkpoint inhibitors (ICIs) have the potential to treat biliary tract cancer and HCC [6]. However, without any other agents, ICI performs well in a very small group. This encourages the combination

of immunotherapy with anti-angiogenic agents, which requires biomarker guidance. Hence, some emerging biomarkers got attention, including programmed death-1 and tumor mutation burden [7–8].

Serum GP73 (sGP73) is a component of GP73. In the diseased state, the C-terminus of GP73 is released into circulation [9]. Increased sGP73 was first found in HCC and has been regarded as a promising biomarker for HCC [10]. Considering that HCC is induced by viral infection or hepatitis, some scholars believe that GP73 alone may not be specific for diagnosing HCC [11–14]. It has been found that GP73 increases in prostate cancer [15–16], breast cancer [17] and bladder cancer [18]. Tissue GP73 is upregulated in prostate and bladder cancers, while sGP73 is upregulated in breast tumor [16–18]. sGP73 expression is significantly elevated in patients with acute hepatitis, but this elevation is reversible after disease remission [19]. Regardless of the cause of the injury, there is an increase in sGP73 [12]. Therefore, it is important to investigate the regulation of GP73.

2. Structure of GP73

The coding gene for human GP73 is located on chromosome 9p21.33. It has a full-length sequence of 3080 bp, which includes a 1200 bp open reading frame. Human GP73 encodes 401 amino acids. It mainly contains an N-terminal domain, a transmembrane domain (TMD), and a coiled-coil domain. For GP73 transportation, the N-terminal domain and TMD are important, while the TMD also determines its localization [9]. The length of the TMD is a determinant of

Abbreviations: GP73, Golgi protein 73; sGP73, serum GP73; HCC, hepatocellular carcinoma; TGF- β , transforming growth factor- β ; ICIs, immune checkpoint inhibitors; TMD, transmembrane domain; ER, endoplasmic reticulum; GRP78, glucose-regulated protein 78; UPR, unfolded protein response; HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, non-alcoholic fatty liver disease; MAVS, mitochondrial antiviral signaling protein; TRAF6, tumor necrosis factor receptor-associated factor 6; IL-6, Interleukin 6; HSCs, hepatic stellate cells; AFP, alpha-fetoprotein; GGT-II, glutamyl transferase isoenzyme II; MMPs, metalloproteinases; EMT, epithelial–mesenchymal transition; miRNA, microRNA; APRI, aspartate transaminase to platelet ratio index

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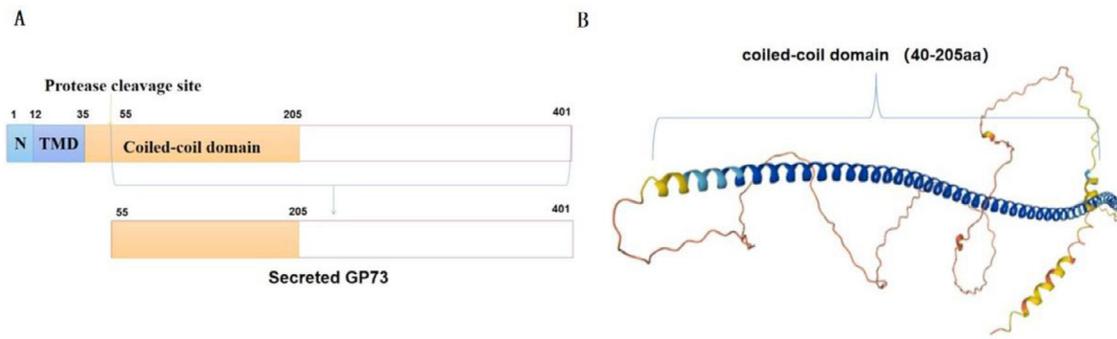


Fig. 1. Structure of GP73. A: Some regions of GP73. B: Prediction tertiary structure of GP73.

localization, and a 19–26 aa long TMD is sufficient to support Golgi localization, while a longer TMD facilitates transport to the plasma membrane. The shorter TMD of GP73 prevents it from entering. The coiled-coil domain not only facilitates transport to the plasma membrane but also mediates dimerization of GP73 [9]. Figure 1A shows the N-terminal, TMD, and coiled-coil domain. Based on the amino sequences of GP73, its tertiary structure was predicted and the coiled-coil domain was marked (Fig. 1B). The biochemical functions of GP73 remain unknown, and some studies have addressed the regulation of its expression. The coiled-coil structural domain is essential for binding, docking, and trafficking [20]. Therefore, focusing on the coiled-coil domain provides new insights into how GP73 enters the serum during disease.

3. Secretion and transportation of GP73

Under normal conditions, the N-terminus of GP73 is cleaved by proteases and then transported to the plasma membrane, eventually returning to the Golgi via the late endosomal pathway [21]. The amino acid site at position R⁵²VRR⁵⁵ of GP73 contains a recognition site for preproteases, such as furin. In the presence of inflammatory factors, GP73 is cleaved by furin and transported from cis-Golgi to trans-Golgi [21]. Its C-terminal fragment is transported to the

cytoplasm via vesicles and is eventually released extracellularly to produce sGP73 [9, 21] (Fig. 2). In response to endoplasmic reticulum (ER) stress, full-length GP73 and cleaved sGP73 are secreted into the extracellular space as signaling molecules, and then they interact with glucose-regulated protein 78 (GRP78) outside the cell surface of neighboring macrophages to activate ER stress signaling and induce the release of factors from macrophages [22]. This provides insights into the function of extracellular GP73 in the regulation of unfolded protein response (UPR)-triggered intercellular communication and identifies GRP78, which belongs to the UPR family, as its cellular receptor for intracellular signal transduction.

4. Homology of GP73

GP73 has no apparent sequence homology or structural similarity to any known nucleotides. We compared the cytoplasmic tails and transmembrane structural domains of GP73 in six model organisms, including human, mouse, rattus, *Xenopus*, *Canis lupus familiaris*, and gallus. Residues in the cytoplasmic tail were identical (Fig. 3A). The human TMD (residues 13–35) includes 13 identical residues, nine highly conserved amino acid residues, no semi-conserved residues, and one relatively variable residue compared to the cytoplasmic tail of GP73 in the other five model organisms (Fig. 3B).

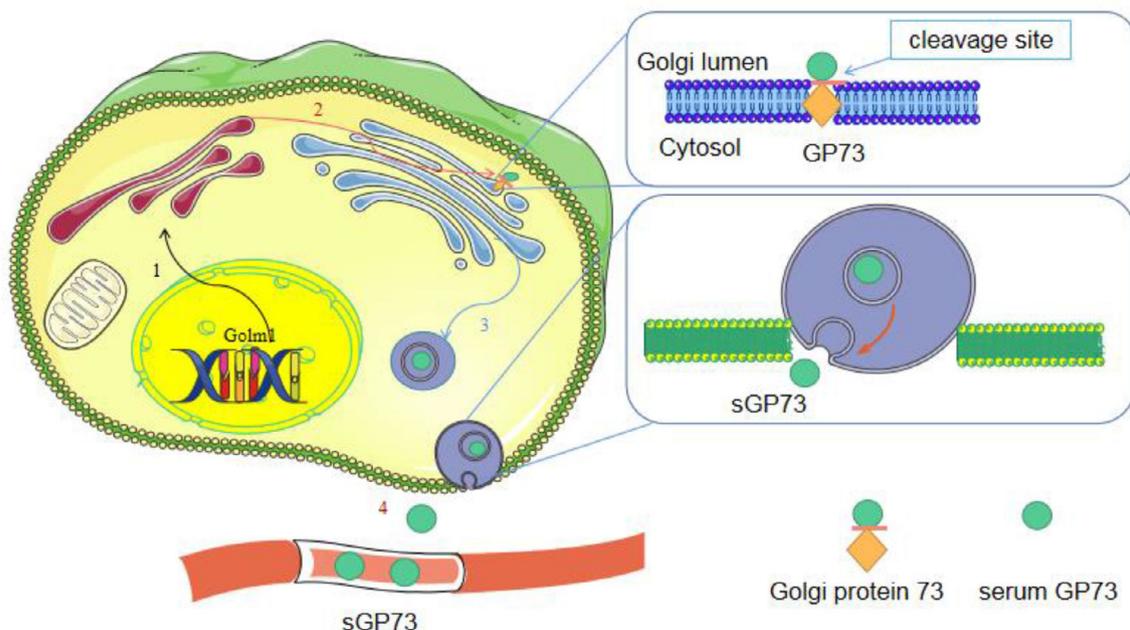


Fig. 2. Synthesis and the actions of sGP73. 1: The coding gene directs the synthesis of Golgi protein; 2: GP73 presents on the Golgi apparatus; 3: Under diseased state, GP73 is cleaved. Vesicular transports sGP73 out of the cell; 4: sGP73 enters the serum.

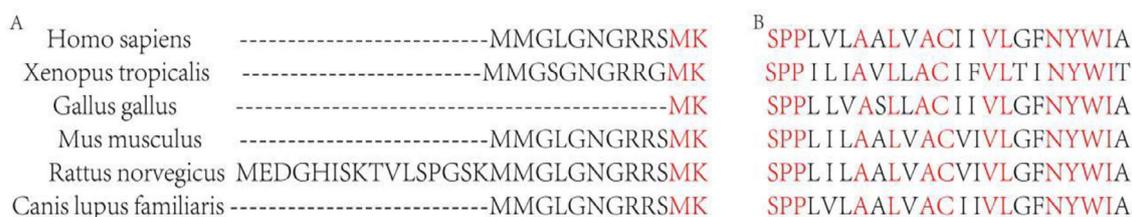


Fig. 3. Homology of GP73 in six model organisms. A: Cytoplasmic tails of GP73 in six model organisms (1–12 aa). B: TMD of GP73 in six model organisms (13–35 aa).

5. GP73 is related to inflammation and liver regeneration

5.1. GP73 is related to inflammation

GP73 levels increase in many diseases, including hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, non-alcoholic fatty liver disease (NAFLD), and other liver diseases. HCV is a chronic liver disease. Without treatment, the liver tends to be damaged. Upregulation of GP73 is observed in HCV [23–25]. In HCV, the coiled-coil domain plays an important role in the secretion of HCV, as it promotes HCV secretion. GP73 increases and interacts with lipoprotein E, a host factor for HCV secretion [24]. This evidence provides new insights into antiviral strategies. Zhang et al. [26–27] first demonstrated that overexpression of GP73 promotes the degradation of mitochondrial antiviral signaling protein (MAVS) and tumor necrosis factor receptor-associated factor 6 (TRAF6) through a protease-dependent pathway, resulting in the suppression of intrinsic host immunity and promotion of HCV infection. There may be some relationship between GP73 and inflammation, but there is no specific conclusion that explains the mechanism of GP73 regulation in an inflammatory environment. Interleukin 6 (IL-6) has been reported to be involved in this process.

IL-6 is an acute-phase response protein induced by acute inflammatory injury. IL-6 is not only involved in hepatocyte injury and repair but also promotes the proliferation of HSCs (hepatic stellate cells) [28]. Consistent with previous reports, IL-6 promoted GP73 expression in HepG2 cells in vitro. IL-6 promotes the transcription of GP73 and preprotein convertase furin by binding to the IL-6 receptor to activate the JAK/STAT3 signaling pathway, and then the GP73 is freed from the Golgi membrane by cleavage [29]. Clinical evidence shows that IL-6 levels progressively increase in HBV patients during disease progression [29], and the connection between GP73 and HBV has also been reported [14, 30]. Additionally, sGP73 levels are increased in patients with HBV [30]. Moreover, it has been suggested that GP73 promotes HBV infection by hindering the immune response [14]. Taken together, these results suggest that GP73 interacts with IL-6 to induce hepatitis development.

In patients with NAFLD, the expression level of GP73 was increased. GP73 weakens the export of very-low-density lipoprotein-apolipoprotein B from intrahepatic to extrahepatic tissues through its GTPase-activating protein activity, thus blocking the extrahepatic transport of triglycerides, cholesterol, and other lipids from the liver, thereby contributing to the development of NAFLD [31]. Iftikhar et al. detected GP73 expression in patients with liver diseases such as alcoholic liver disease and chronic hepatitis. It was found that GP73 levels in hepatocytes from alcoholic liver disease and chronic hepatitis were correlated with disease stages instead of grades [19]. GP73 expression in α -smooth muscle actin positive cells during liver injury suggests that GP73 originates from activated hepatic stellate cells (HSCs) [19]. It has been shown that the main triggers of GP73 expression are the inflammatory activities in acute liver diseases and hepatic fibrosis [32]. Increased sGP73 levels have been reported to be triggered under inflammatory conditions [33]. sGP73 positively correlates with liver disease progression [12–13, 34]. These findings suggested that hepatic inflammatory activity may be a major driver of increased sGP73 levels.

5.2. GP73 is related to liver regeneration

Regardless of the etiology, there is overwhelming evidence linking GP73 to cell proliferation [35–37]. Thus, it is reasonable to speculate that GP73 may play an active role in liver regeneration. Wang et al. [38] reported that regenerating livers from GP73 knockout mice exhibited a less pro-inflammatory environment when performing partial liver resection. In the early stages of liver regeneration after partial liver resection, GP73 deletion inhibited residual hepatocyte proliferation and liver inflammation, however, the liver mass recovered more rapidly. This difference in recovery was mainly due to compensatory hypertrophy of hepatocytes, in which the mTOR signaling pathway plays an important role. Regenerating livers from GP73^{-/-} mice exhibited a less pro-inflammatory environment than GP73^{+/+} mice because of the low expression of inflammatory cytokines in GP73^{-/-} mice [38]. This study revealed a novel function of GP73 in liver regeneration, in which GP73 facilitates the regeneration of liver tissue and inflammation during the process. After partial hepatectomy, the absence of GP73 promoted hepatocyte hypertrophy through the activation of the mTOR signaling pathway.

5.3. GP73 is bound with HCC

GP73 has been considered a promising biomarker for HCC since its upregulation was discovered in HCC patients [39–42]. Before the discovery of GP73, alpha-fetoprotein (AFP) was regarded as a useful marker for HCC. Serum AFP levels and abdominal ultrasound have been widely used for the diagnosis and surveillance of HCC [43]. GP73 increases the secretion of AFP through direct binding to AFP both in vivo and in vitro, thereby promoting the proliferation and metastasis of HCC cells that express AFP and its receptor. Extracellular secretion of GP73 is required for this process [44]. GP73 is used as a screening tool for the detection of HCC, with a higher diagnostic performance than AFP [41]. The diagnostic sensitivities for HCC, as detected using time-resolved fluorescence immunological assays of GP73, AFP, and γ -glutamyl transferase isoenzyme II (GGT-II), were 73.4, 55.6 and 68.4%, respectively, and the specificities were 80.0, 86.7 and 97.1%, respectively. The combination of these markers increased the diagnostic sensitivity to 96.3% for HCC [45]. It has been shown that GP73 interacts with the TGF- β /Smad signaling pathway [4], metalloproteinases (MMPs) [35–36], CD44 [46], c-Myc [35] and other factors in HCC and plays a role in the development of HCC; for example, GP73 partially regulates epithelial mesenchymal transition (EMT) and metastasis in HCC by targeting TGF- β 1/Smad2 signaling [4, 37]. In HepG2 cells, GP73 decreased the expression of the epithelial marker E-cadherin and increased the expression of mesenchymal markers, such as N-cadherin and Vimentin. Apart from TGF- β 1/Smad signaling, GP73 may be involved in regulating other EMT pathways [37]. Furthermore, Chen et al. have shown that mTOR promotes HCC development by stimulating the expression of GP73, which is possibly involved in the PIK3-AKT signaling pathway [3]. GP73 enhances the invasion of HCC cells by upregulating MMP-13 [36]. GP73 promotes tumor progression through a combination of multiple factors in multiple pathways. As shown in Figure 4, some studies involved in the interactions between GP73 and other factors were illustrated.

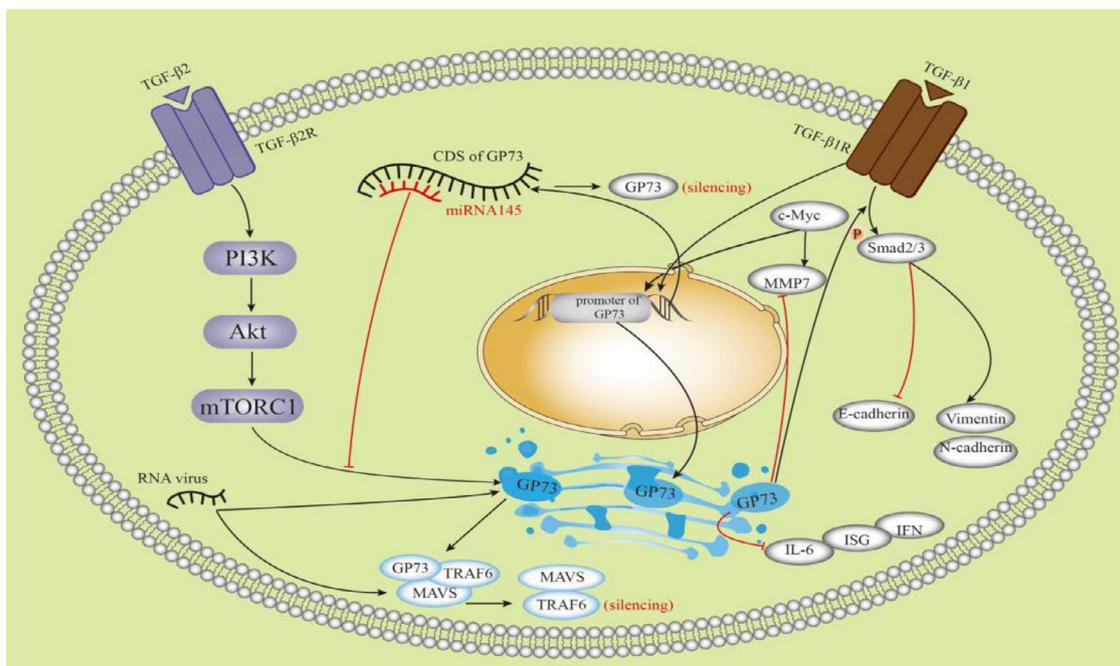


Fig. 4. Schematic diagram showing the multiple factors connected with GP73. TGF- β 1, transforming growth factor- β 1; TGF- β 2, transforming growth factor- β 2; mTORC1, mTOR complex 1; MMP 7, matrix metalloproteinase-7; CDS, coding sequence; MAVS, mitochondrial antiviral signaling protein; TRAF6, TNF receptor-associated factor 6; IL-6, interleukin 6; ISG, IFN-stimulated gene.

GP73 is a transcriptional target of the TGF- β 1/Smad signaling pathway, which directly activates p-Smad3 and upregulates GP73 [37]. Second, mTOR complex 1 upregulates GP73 expression [3]. Third, upregulation of c-Myc promotes transactivation of GP73. However, GP73 overexpression reduces MMP7 [35]. microRNA (miRNA)-145 directly targeted the coding sequence region of GP73 and then abolished GP73 [47]. Overexpression of GP73 promotes degradation of MAVS and TRAF6 and downregulates interferon- β , interferon- λ 1, IL-6, and immune serum globulin 56 [26–27]. High levels of sGP73 are associated with aggressive tumor behavior and poor disease-free survival and overall survival [48]. It has been suggested that sGP73 has important prognostic value for HCC. GP73 has been shown to promote proliferation, migration, invasion, and metastasis of HCC cell lines and xenograft tumors in mice [3].

The differential expression of miRNAs in HCC suggests that miRNAs can be used as new potential targets, either as carcinogens or tumor suppressors. Gai et al. found that miR-145 inhibits HCC development and metastasis by binding to GP73 mRNA [47]. Zhao et al. [49] revealed that miR-493-5p inhibited HCC cell proliferation and induced cell cycle arrest and apoptosis by directly targeting GP73. Hou et al. [50] proposed that miR-141-3p inhibits EMT in HCC cells by promoting mesenchymal-to-epithelial transition through GP73. Overall, some miRNAs were involved in the expression of GP73. Therefore, miRNA expression may be crucial in HCC. However, the mechanism by which GP73 promotes tumor progression remains unclear. Upregulation of sGP73 expression occurs not only in patients with HCC but also in patients with prostate cancer [15], bladder cancer [18], breast cancer [17] and gastric cancer [51]. Thus, as a serum marker for diagnosing other cancers, the levels of GP73 expression and other biomarkers should be considered.

5.4. GP73 is linked with cirrhosis and hepatic fibrosis

As some HCC cases are accompanied by cirrhosis, research suggests that sGP73 may be unsuitable for diagnosing HCC [11, 32, 52]. Cirrhosis is an end-stage manifestation of diffuse liver injury. Usually, it occurs by two mechanisms: (1) the formation of regenerated

nodules of hepatocytes. (2) proliferation of fibrous tissue and reconstruction of liver circulation [53]. It is a long and complex pathological process with the development of hepatitis to hepatic fibrosis, cirrhosis, and HCC. In the course of chronic liver disease due to different etiologies, sGP73 levels gradually increase with the progression of liver fibrosis and development of cirrhosis. A previous study reported that the concentration of GP73 was consistent with the stage of liver fibrosis and cirrhosis [54]. Through case review analysis, it has been demonstrated that GP73 alone is an effective marker of cirrhosis. It is superior to the aspartate transaminase to platelet ratio index (APRI) assay. Its diagnostic performance was further improved when used in combination with the APRI [55]. Although the function of GP73 remains unclear, it has been reported that GP73 expression represents the degree of liver fibrosis because of its expression in activated HSCs [19].

Hepatic fibrosis is a reversible wound healing response characterized by the accumulation of extracellular matrix or “scar,” that follows chronic but not self-limited liver disease. Activation of HSCs is the central event in liver fibrosis [56–57]. Other liver-specific biomarkers, such as hyaluronic acid, laminin, and collagen type III, have also been reported to be positively correlated with GP73, indicating their potential roles in liver fibrosis [55]. During the regression of liver fibrosis, upregulation of GP73 is reversible [19], implying that sGP73 may be a promising marker for monitoring the progression of liver fibrosis.

As mentioned above, for HCC diagnosis, the sensitivity of sGP73 is higher than the sensitivities of AFP and GGT-II but the specificity is lower. Combining sGP73 and AFP with GGT-II can improve the sensitivity [45]. Therefore, sGP73 alone may be unsuitable for HCC treatment. Although sGP73 is better than APRI for diagnosing cirrhosis, its combination improves significantly [55]. Thus, altogether, sGP73 is beneficial in identifying patients at a high risk of disease progression.

6. Conclusions

Clinically, GP73 is widely used to aid the early diagnosis and post-operative monitoring of HCC. Therefore, most of the current studies

of GP73 upregulation are devoted to HCC. The application of GP73 as a serum marker of liver disease is promising. An increasing number of studies have demonstrated its close association with liver fibrosis, cirrhosis, and HCC. However, it is not ideal if GP73 is not associated with other serum markers for diagnosing these diseases.

This review summarizes the recent studies on GP73 in HCC and alternative diseases, including hepatitis, liver fibrosis, and cirrhosis. Here, we conclude with existing reports on GP73 regulation, offering a preliminary understanding of this hot spot. We hope that this will provide some help for the foundation of GP73 function in different diseases. As it may originate from HSCs, it is speculated that GP73 could play a key role in liver fibrosis. Thus far, studies on GP73 in liver fibrosis and cirrhosis are scarce and not well elucidated.

Most of these reports focused on the correlation between upregulation of sGP73 and the occurrence or severity of diseases, but only a few studies have investigated the underlying mechanisms by which GP73 contributes to diseases. Although the related signaling pathways have not been fully discovered, studies on GP73 and the PI3K-Akt signaling and TGF- β /Smad signaling pathways may provide an entry point to investigate the mechanism of GP73 in diseases. However, the mechanisms of GP73 regulation and secretion are not well established, and those of inflammation and liver regeneration remain to be explored. Addressing these issues may provide new directions for the diagnosis and treatment of liver disease.

Authors' contribution

JFW and RTZ contributed to the conception and design of the study. MYL and LH contributed to drafting the article or revising it critically for important intellectual content. WBA and HBZ contributed to final approval of the version to be submitted.

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Declaration Conflicts of interest

None.

References

- [1] Kladney RD, Bulla GA, Guo L, Mason AL, Tollefson AE, Simon DJ, et al. GP73, a novel Golgi-localized protein upregulated by viral infection. *Gene* 2000;249(1-2):53-65.
- [2] Kladney RD, Cui X, Bulla GA, Brunt EM, Fimmel CJ. Expression of GP73, a resident Golgi membrane protein, in viral and nonviral liver disease. *Hepatology* 2002;35(6):1431-40.
- [3] Chen X, Wang Y, Tao J, Shi Y, Gai X, Huang F, et al. mTORC1 Up-Regulates GP73 to Promote Proliferation and Migration of Hepatocellular Carcinoma Cells and Growth of Xenograft Tumors in Mice. *Gastroenterology* 2015;149(3):741-52.
- [4] Yang X, Wei C, Liu N, Wu F, Chen J, Wang C, et al. GP73, a novel TGF-beta target gene, provides selective regulation on Smad and non-Smad signaling pathways. *Biochim Biophys Acta Mol Cell Res* 2019;1866(4):588-97.
- [5] Shan SG, Gao YT, Xu YJ, Huang Y, Zhang Q, Zhai DK, et al. Gradually increased Golgi protein 73 expression in the progression of benign liver diseases to precancerous lesions and hepatocellular carcinoma correlates with prognosis of patients. *Hepato Res* 2013;43(11):1199-210.
- [6] De Lorenzo S, Tovoli F, Barbera MA, Garuti F, Palloni A, Frega G, et al. Metronomic capecitabine vs. best supportive care in Child-Pugh B hepatocellular carcinoma: a proof of concept. *Sci Rep* 2018;8(1):9997.
- [7] Rizzo A, Brandi G. Biochemical predictors of response to immune checkpoint inhibitors in unresectable hepatocellular carcinoma. *Cancer Treat Res Commun* 2021;27:100328.
- [8] Rizzo A, Ricci AD, Brandi G. Recent advances of immunotherapy for biliary tract cancer. *Expert Rev Gastroenterol Hepatol* 2021;15(5):527-36.
- [9] Hu L, Li L, Xie H, Gu Y, Peng T. The Golgi localization of GOLPH2 (GP73/GOLM1) is determined by the transmembrane and cytoplasmic sequences. *Plos One* 2011;6(11):e28207.
- [10] Marrero JA, Romano PR, Nikolaeva O, Steel L, Mehta A, Fimmel CJ, et al. GP73, a resident Golgi glycoprotein, is a novel serum marker for hepatocellular carcinoma. *J Hepatol* 2005;43(6):1007-12.
- [11] Gatselis NK, Tornai T, Shums Z, Zachou K, Saitis A, Gabeta S, et al. Golgi protein-73: a biomarker for assessing cirrhosis and prognosis of liver disease patients. *World J Gastroenterol* 2020;26(34):5130-45.
- [12] Qian X, Zheng S, Wang L, Yao M, Guan G, Wen X, et al. Exploring the diagnostic potential of serum golgi protein 73 for hepatic necroinflammation and fibrosis in chronic HCV infection with different stages of liver injuries. *Dis Markers* 2019;2019:3862024.
- [13] Qiao Y, Chen J, Li X, Wei H, Xiao F, Chang L, et al. Serum gp73 is also a biomarker for diagnosing cirrhosis in population with chronic HBV infection. *Clin Biochem* 2014;47(16-17):216-22.
- [14] Liu L, Zhu J, Yang J, Li X, Yuan J, Wu J, et al. GP73 facilitates hepatitis B virus replication by repressing the NF-kappaB signaling pathway. *J Med Virol* 2020.
- [15] Ying C, Xiao BD, Qin Y, Wang BR, Liu XY, Wang RW, et al. GOLPH2-regulated oncolytic adenovirus, GD55, exerts strong killing effect on human prostate cancer stem-like cells in vitro and in vivo. *Acta Pharmacol Sin* 2018;39(3):405-14.
- [16] Kristiansen G, Fritzsche FR, Wassermann K, Jager C, Tolls A, Lein M, et al. GOLPH2 protein expression as a novel tissue biomarker for prostate cancer: implications for tissue-based diagnostics. *Br J Cancer* 2008;99(6):939-48.
- [17] Zhang A, Cao B. Generation and characterization of an anti-GP73 monoclonal antibody for immunoblotting and sandwich ELISA. *J Biomed Res* 2012;26(6):467-73.
- [18] Yang HJ, Liu GL, Liu B, Liu T. GP73 promotes invasion and metastasis of bladder cancer by regulating the epithelial-mesenchymal transition through the TGF-beta1/Smad2 signalling pathway. *J Cell Mol Med* 2018;22(3):1650-65.
- [19] Iftikhar R, Kladney RD, Havlioglu N, Schmitt-Graff A, Gasmirovic I, Solomon H, et al. Disease- and cell-specific expression of GP73 in human liver disease. *Am J Gastroenterol* 2004;99(6):1087-95.
- [20] Zhou Y, Li L, Hu L, Peng T. Golgi phosphoprotein 2 (GOLPH2/GP73/GOLM1) interacts with secretory clusterin. *Mol Biol Rep* 2011;38(3):1457-62.
- [21] Bachert C, Fimmel C, Linstedt AD. Endosomal trafficking and proprotein convertase cleavage of cis Golgi protein GP73 produces marker for hepatocellular carcinoma. *Traffic* 2007;8(10):1415-23.
- [22] Wei C, Yang X, Liu N, Geng J, Tai Y, Sun Z, et al. Tumor microenvironment regulation by the endoplasmic reticulum stress transmission mediator golgi protein 73 in Mice. *Hepatology* 2019;70(3):851-70.
- [23] Liu L, Al-Dhamin Z, Yuan X, Cui L, Yang Y, Zhao W, et al. Plasma Golgi protein 73 levels predict prognosis of HCV-related hepatic fibrosis. *Histol Histopathol* 2020;35(11):1309-18.
- [24] Hu L, Yao W, Wang F, Rong X, Peng T. GP73 is upregulated by hepatitis C virus (HCV) infection and enhances HCV secretion. *Plos One* 2014;9(3):e90553.
- [25] Liu Y, Zou Z, Zhu B, Hu Z, Zeng P. CXCL10 decreases GP73 expression in hepatoma cells at the early stage of hepatitis C virus (HCV) infection. *Int J Mol Sci* 2013;14(12):24230-41.
- [26] Zhang X, Zhu C, Wang T, Jiang H, Ren Y, Zhang Q, et al. GP73 represses host innate immune response to promote virus replication by facilitating MAVS and TRAF6 degradation. *Plos Pathog* 2017;13(4):e1006321.
- [27] Zhang X, Zhu C, Wang T, Jiang H, Ren Y, Zhang Q, et al. Correction: GP73 represses host innate immune response to promote virus replication by facilitating MAVS and TRAF6 degradation. *Plos Pathog* 2018;14(3):e1006938.
- [28] Xiang DM, Sun W, Ning BF, Zhou TF, Li XF, Zhong W, et al. The HLF/IL-6/STAT3 feedforward circuit drives hepatic stellate cell activation to promote liver fibrosis. *Gut* 2018;67(9):1704-15.
- [29] Wu ZB, Zheng YB, Wang K, Mo ZS, Zhen X, Yan Y, et al. Plasma Interleukin-6 Level: A Potential Prognostic Indicator of Emergent HBV-Associated ACLF. *Can J Gastroenterol Hepatol* 2021;2021:5545181.
- [30] Cao Z, Li Z, Wang H, Liu Y, Xu Y, Mo R, et al. Algorithm of golgi protein 73 and liver stiffness accurately diagnoses significant fibrosis in chronic HBV infection. *Liver Int* 2017;37(11):1612-21.
- [31] Peng Y, Zeng Q, Wan L, Ma E, Li H, Yang X, et al. GP73 is a TBC-domain Rab GTPase-activating protein contributing to the pathogenesis of non-alcoholic fatty liver disease without obesity. *Nat Commun* 2021;12(1):7004.
- [32] Yao M, Wang L, Leung P, Li Y, Liu S, Wang L, et al. The clinical significance of GP73 in immunologically mediated chronic liver diseases: experimental data and literature review. *Clin Rev Allergy Immunol* 2018;54(2):282-94.
- [33] Wei M, Xu Z, Pan X, Zhang X, Liu L, Yang B, et al. Serum GP73 - an additional biochemical marker for liver inflammation in chronic HBV infected patients with normal or slightly raised ALT. *Sci Rep* 2019;9(1):1170.
- [34] Ke MY, Wu XN, Zhang Y, Wang S, Lv Y, Dong J. Serum GP73 predicts posthepatectomy outcomes in patients with hepatocellular carcinoma. *J Transl Med* 2019;17(1):140.
- [35] Liu Y, Zhou S, Shi J, Zhang X, Shentu L, Chen Z, et al. c-Myc transactivates GP73 and promotes metastasis of hepatocellular carcinoma cells through GP73-mediated MMP-7 trafficking in a mildly hypoxic microenvironment. *Oncogenesis* 2019;8(10):58.
- [36] Jin D, Tao J, Li D, Wang Y, Li L, Hu Z, et al. Golgi protein 73 activation of MMP-13 promotes hepatocellular carcinoma cell invasion. *Oncotarget* 2015;6(32):33523-33.
- [37] Yang Y, Liu Q, Li Z, Zhang R, Jia C, Yang Z, et al. GP73 promotes epithelial-mesenchymal transition and invasion partly by activating TGF-beta1/Smad2 signaling in hepatocellular carcinoma. *Carcinogenesis* 2018;39(7):900-10.

- [38] Wang J, Ning J, Qian X, Zhang T, Yao M, Wang J, et al. Deletion of Golgi protein 73 delayed hepatocyte proliferation of mouse in the early stages of liver regeneration. *J Gastroenterol Hepatol* 2021;36(5):1346–56.
- [39] Dong M, Chen ZH, Li X, Li XY, Wen JY, Lin Q, et al. Serum Golgi protein 73 is a prognostic rather than diagnostic marker in hepatocellular carcinoma. *Oncol Lett* 2017;14(5):6277–84.
- [40] Ba MC, Long H, Tang YQ, Cui SZ. GP73 expression and its significance in the diagnosis of hepatocellular carcinoma: a review. *Int J Clin Exp Pathol* 2012;5(9):874–81.
- [41] Ali OM, El AH, Sharkawy YL, Mohamed AA, Kholef E, Elsewify W. Golgi protein 73 versus alpha-fetoprotein as a new biomarker in early diagnosis of hepatocellular carcinoma. *Int J Gen Med* 2020;13:193–200.
- [42] Farag R, Al AD, Alsaleh KA, Kwon HJ, El-Ansary A, Dawoud EA. Studying the impact of Golgi protein 73 serving as a candidate biomarker in early diagnosis for hepatocellular carcinoma among Saudi patients. *Asian Pac J Cancer Prev* 2019;20(1):215–20.
- [43] Ahmed MH, Roberts LR. Should AFP (or any biomarkers) be used for HCC surveillance? *Curr Hepatol Rep* 2017;16(2):137–45.
- [44] Liu Y, Wang J, Yang R, Cheng Y, Zhou Y, Li H, et al. GP73-mediated secretion of AFP and GP73 promotes proliferation and metastasis of hepatocellular carcinoma cells. *Oncogenesis* 2021;10(10):69.
- [45] Hou SC, Xiao MB, Ni RZ, Ni WK, Jiang F, Li XY, et al. Serum GP73 is complementary to AFP and GGT-II for the diagnosis of hepatocellular carcinoma. *Oncol Lett* 2013;6(4):1152–8.
- [46] Yuan Y, Shi L, Wang S. Expression and correlation of CD44 and GP73 in cerebroma tissues. *Oncol Lett* 2018;15(4):4958–62.
- [47] Gai X, Tang B, Liu F, Wu Y, Wang F, Jing Y, et al. mTOR/miR-145-regulated exosomal GOLM1 promotes hepatocellular carcinoma through augmented GSK-3beta/MMPs. *J Genet Genomics* 2019;46(5):235–45.
- [48] Zhang J, Zhang M, Ma H, Song X, He L, Ye X, et al. A meta-analysis of the prognostic significance of Golgi protein 73 in hepatocellular carcinoma in Chinese patients. *Arch Med Sci* 2020;16(5):1104–10.
- [49] Zhao J, Xu T, Wang F, Cai W, Chen L. miR-493-5p suppresses hepatocellular carcinoma cell proliferation through targeting GP73. *Biomed Pharmacother* 2017;90:744–51.
- [50] Hou X, Yang L, Jiang X, Liu Z, Li X, Xie S, et al. Role of microRNA-141-3p in the progression and metastasis of hepatocellular carcinoma cell. *Int J Biol Macromol* 2019;128:331–9.
- [51] Chen LG, Wang HJ, Yao HB, Guan TP, Wu F, He XJ, et al. GP73 is down-regulated in gastric cancer and associated with tumor differentiation. *World J Surg Oncol* 2013;11:132.
- [52] Gatselis NK, Zachou K, Giannoulis G, Gabeta S, Norman GL, Dalekos GN. Serum cartilage oligomeric matrix protein and Golgi protein-73: new diagnostic and predictive tools for liver fibrosis and hepatocellular cancer? *Cancers (Basel)* 2021;13(14).
- [53] Gines P, Krag A, Abralde JG, Sola E, Fabrellas N, Kamath PS. Liver cirrhosis. *Lancet* 2021;398(10308):1359–76.
- [54] Weiskirchen R, Tacke F. Combining GP73 with liver stiffness measurements: A proof-of-concept for non-invasive fibrosis assessment in antiviral-naive HBV patients. *Liver Int* 2017;37(11):1605–7.
- [55] Liu L, Wang J, Feng J, Yao M, Hao C, You Y, et al. Serum Golgi protein 73 is a marker comparable to APRI for diagnosing significant fibrosis in children with liver disease. *Sci Rep* 2018;8(1):16730.
- [56] Dawood RM, El-Meguid MA, Salum GM, El AM. Key players of hepatic fibrosis. *J Interferon Cytokine Res* 2020;40(10):472–89.
- [57] Ezhilarasan D, Sokal E, Najimi M. Hepatic fibrosis: it is time to go with hepatic stellate cell-specific therapeutic targets. *Hepatobiliary Pancreat Dis Int* 2018;17(3):192–7.