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Role of Mac 2 Binding Protein Glycan Isomer in Hepatic and Diabetic Patients

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Abstract:

Mac-2 binding protein glycosylation isomer (M2BPGI) or Wisteria Floribunda agglutinin-positive Mac-2 binding protein (WFA+-M2BP) is the glycoprotein M2BP conjugated with N-glycan residues and bound by WFA. M2BPGI is released during the process of fibrogenesis from various cells, including hepatocytes, and has been developed as a novel serological marker of liver fibrosis.

Keywords: Mac 2 Binding Protein Glycan Isomer, liver, Diabetes.

Introduction:

Glycoproteins are one of the main types of proteins found in the human body. They are proteins with glycan branching on their surface. Its branching shape and sugar composition are known to be highly specific to cell pathogenic alterations or differentiation stages. Thus, it has already been utilized in laboratory tests such as Hemoglobin A1c for measuring blood sugar levels or transferrin low in carbohydrates for prolonged alcohol consumption, as glycoprotein-based biomarkers (glycol-biomarkers) **[1].**

M2BP, or Mac-2 binding protein, is a highly glycosylated, secreted protein that consists of 90 kDa subunits, containing sialylated multibranched N-glycans, and also acts as a ligand to galectin-3 (Mac-2). When extensively glycosylated, the M2BP becomes M2BPGi, or also known as hyperglycosylated Wisteria floribunda agglutinin (WFA)-positive Mac-2 binding protein (WFA^+-M2BP). WFA is an optimal lectin substance used to detect a specific fibrosis-related glycoalteration. Therefore, both M2BPGi and WFA^+-M2BP were considered the same. but using the name M2BPGi, rather than WFA^+-M2BP is favourable [**2].**

As the ligand of galectin-3, M2BPGi will communicate with Mac-2-positive cells to induce several biological activities, including cell adhesion, growth regulation, cytokine production, T-cell apoptosis and immune response. Therefore, M2BPGi would act as the juxtacrine-acting messenger for the activation of hepatic stellate cells (HSCs) during the progression of liver fibrosis **[3].**

Glycoprotein-based biomarkers have been introduced as novel biomarkers for detection of liver cell activities, such as cell adhesion mediation and fibrosis promotion, using M2BPi **[3].**

M2BPGI is one of the blood biomarkers for liver fibrosis that was just commercially released and introduced into labs. After being discovered in 2013 and used as a Glycosylation isomer of serum Mac-2 binding protein (M2BPGI) as a diagnostic sign for liver fibrosis is being extensively utilized, primarily in Asia due to its simplicity of detection in the serum **[4].**

Role of M2BPGi in Liver diseases:

1) NAFLD and liver injury:

M2BPGi is produced by HSCs, it will act as a messenger from them to Kupffer cells, promoting fibrogenesis [**2].** Any injuries, such as infections, may cause inflammation and further activate the Kupffer cells and hepatocytes to release cytokines. Activated HSCs may release M2BPGi along with other ECM, including TIMP-1, PIIINP and hyaluronic acid, which will cause dysfunction of hepatic sinusoidal epithelial cells, leading to the progression of liver fibrosis **[5].** The sugar chain structure of M2BP would change in response to the progression of hepatic fibrosis [**2]**.

In chronic liver diseases, such as liver fibrosis, the WFA will recognize the N-acetyl galactosamine residue of N- and O-glycans on the M2BP, only modified by a fibrosis-specific sugar chain. Thus, the larger the fibrosis area, the higher the M2BPGi levels **[5].**

M2BPGi is representative of hepatic fibrosis and abnormal M2BPGi category with diabetes should be suspected to have a higher fibrosis incidence **[6].**

M2BPGi level was significantly increased in the fibrotic NASH and NASH patients compared to healthy controls **[7].** Moreover , The performance of M2BPGi in predicting disease severity in NAFLD showed a clear association between WFA^+ -M2BP level and the stage of fibrosis with an area under the ROC curve of 0.876 for predicting fibrosis ≥ stage2 **[8].**

HSCs are sensitive to stimuli generated during hepatitis, inflammation or the tissue injury process **[9]**. M2BPGi itself could also be a stimulus for activating and inducing HSCs to change from their dormant form into a myofibrillar form that expresses proliferative, migratory and invasive properties **[10]**. The level of M2BPGi will be expected to increase, and their increase of M2BPGi level reflects the activation of HSCs **[11].**

2) Chronic Hepaitis B Virus (HBV):

The ongoing process during HBV infection would affect the production of M2BPGi through HSCs activation, further affecting the probability of HCC development. The patients treated for hepatitis B had significantly lower serum levels of M2BPGi after the treatment, indicating that suppressing the infection process will decrease M2BPGi production **[12].**

HBV may also contribute to the M2BPGi level by having a direct effect on HSCs **[13].** Hepatitis B protein-X activates the HSCs to express fibrotic properties. HBe-antigen may prevent the apoptosis of HSCs **[13]**.

HBV infection activates the mTOR pathway, but through the PI3K/Akt/mTOR signaling mechanism, which is used to regulate the viral life cycle **[14].** mTOR signaling normally serves in the regulation of cellular lipid metabolism, growth, motility and survival, and after HBV infection the pathway is associated with more aggressive HCC tumor progression and survival**[15].**

During HBV infection, M2BPGi may promote HCC through activation of HSC or through enhancement of mTOR signaling. However, high levels of M2BPGi may not always reflect liver fibrosis, as elevated levels of M2BPGi are also found during acute liver injury **[16].**

3).Chronic Hepatitis C Virus (HCV):

The chronic hepatitis serum C (HCV) patients was utilized to generate the biomarker M2BPGi, which is used to diagnose liver fibrosis in HCV patients **[17].**

With direct-acting antiviral (DAA) therapy, sustained virological response was attained in a number of patients. M2BPGi has a mild correlation with ALT and inflammation in addition to a substantial correlation

with liver fibrosis. As a result, M2BPGi rapidly drops with DAA treatment in accordance with an improvement in ALT levels or inflammation. Acute liver damage also causes an increase in M2BPGi **[18].**

It was contrasted that the M2BPGi's diagnostic accuracy with a liver biopsy's. At stages of histopathological fibrosis 1, 2, 3, and 4, the mean values of M2BPGi were positively correlated with the fibrosis stage **[19].** The prognosis for HCV is likewise correlated with high M2BPGi levels **[20].**

4).Cirrhosis

M2BPGi level increases when compensated cirrhosis develops to decompensated cirrhosis. Therefore, in patients with cirrhosis, high M2BPGi levels indicate a poor prognosis. M2BPGi is reportedly useful as a predictive marker for liver failure and complications after hepatectomy or transcatheter arterial chemoembolization **[21**].

M2BPGi level is associated with recurrence and prognosis after hepatectomy and can be used for follow-up after HCC therapy. Sarcopenia has recently attracted attention as a complication of cirrhosis. M2BPGi level is correlated with muscle mass and is useful as a predictive marker for sarcopenia **[22]**.

5) Hepatocellular Carcinoma (HCC):

M2BPGi could activate dormant HSC via M2BP/galectin-3 and Kupffer cells **[10]**. Activated HSC also may promote HCC tumorgenesis through the production of growth actors, cytokines, angiogenesis signals, and immune suppression **[9].**

The serum level of M2BPGi increased significantly along with liver fibrosis progression. It may also reflect the activation of HBV-related oncogenic factors, given its properties as the ligand of galectin-3. M2BPGi may bind and express galectin-3, thus activating the mTOR signaling that promotes HCC malignancy **[23]**.

The cancer also progresses further because of mitogen-activated protein kinase (MAPK) signaling, which enhances the mTOR signaling pathway from M2BPGi-induced galectin-3. So serum M2BPGi levels had been associated with the risk of HCC **[23].**

M2BPGi can further enhance HCC malignancy through inducing M2BP/galectin-3 expression on Kupffer cells and HCC, activating the mTOR pathway through galectin-3 signaling, as galectin-3 knockdown reduced the effect of M2BPGi on HCC **[24].**

M2BPGi does not reflect HCC severity or disease stage, implying that its use may be limited to serving as an early HCC detection tool **[25].**

6) Liver Transplantation:

Once a cirrhotic liver is replaced with a new liver by liver transplantation, activated stellate cells and activated Kupffer cells in the cirrhotic liver are also replaced with inactivated stellate cells and inactivated Kupffer cells both of which reside in the new liver, which may cause the dramatic decrease of M2BPGi after liver transplantation. When a grafted liver is damaged by some reasons that lead to SFSS, hepatic stellate cells, the source of M2BPGi, might be activated by some of the contributory mechanisms of SFSS. Then, that mutual interrelationship between hepatic stellate cells and Kupffer cells may be strengthened again and, as a result, the levels of M2BPGi might re-rise **[10]**.

7) Other Liver Diseases:

M2BPGi can also be a useful tool for diagnosing several diseases, such as biliary atresia, primary biliary sclerosis, autoimmune hepatitis, primary sclerosing cholangitis, and even interstitial pulmonary fibrosis **[26].**

The role of M2BPGi in diabetes and diabetic complications:

Higher serum M2BPGi levels were associated with high levels of fasting plasma glucose and HbA_1c and higher prevalence of individuals with abnormal glucose metabolism **[27].**

Serum high-sensitivity c-reactive protein (hs-CRP) and homeostatic model assessment for insulin resistance (HOMA-IR), which are indicators of inflammation and insulin resistance, respectively, were positively correlated with serum M2BPGi concentrations **[28].**

Higher serum M2BPGi concentrations were significantly associated with higher risk of type 2 diabetes in Japanese community **[28].**

A cross-sectional study has shown that individuals with fatty liver determined by abdominal ultrasound examination had higher levels of serum M2BPGi than individuals without fatty liver, possibly suggesting that an elevation in serum M2BPGi concentrations reflects the accumulation of fat in the liver and subsequent insulin resistance **[29].**

Insulin resistance itself promotes liver inflammation and liver fibrosis **[30].** Hence, a close relationship exists between liver fibrosis, inflammation, and insulin resistance. Since serum M2BPGi is a biomarker of liver fibrosis, it may reflect the degree of liver fibrosis supporting that high serum M2BPGi would be caused by inflammation and insulin resistance **[28].**

Both liver fibrosis and diabetic microangiopathy or macroangiopathy are associated with chronic inflammation, including tumor necrosis factor-α (TNF-α), the renin angiotensin aldosterone system (RAAS), and intercellular adhesion molecule-1. In patients with liver fibrosis, the expression of TNF-α is increased. TNF-α induces renal damage through several mechanisms. The cytotoxicity induced by TNF-α stimulates apoptosis of glomerular cells and, consequently, results in the progression of albuminuria and cardiovascular disease (CVD) **[31].** Moreover, activation of the RAAS promotes inflammation through enhanced production of reactive oxygen species leading to hypertrophy and renal fibrosis **[32].**

In addition, TNF-α is associated with diabetic retinopathy through reduced adherence of leukocytes to retinal blood vessels, blood-retinal barrier breakdown, and apoptosis of retinal cells **[33].**

Intercellular adhesion molecule-1 is associated with liver fibrosis **[34]**, and diabetic microangiopathy **[35]** and macroangiopathy **[36]** Thus, M2BPGi, which is a surrogate marker of liver fibrosis, has a close association with diabetic microangiopathy and macroangiopathy **[37].**

History of CVD, duration of diabetes, severity of microangiopathy, systolic blood pressure, HDL-cholesterol, and BMI were associated with the serum levels of M2BPGi. These metabolic parameters are associated with an increase of M2BPGi **[38].**

Role in other diseases:

It has been reported that M2BPGi was upregulated in patients with chronic heart failure, idiopathic pulmonary fibrosis **[39]**, chronic pancreatitis **[40]**, or atherosclerosis **[27]**. It was suggested that the M2BPGi level may be associated with cell adhesion, growth regulation, cytokine production, and T cell apoptosis **[3]**. There is a suggested association between M2BPGi levels and the polarization of macrophages **[41]**.

M2BPGi titers were elevated in patients presenting with non-liver-related diseases, such as leukemia, rheumatoid arthritis, hypertension, breast cancer, and hyperlipidemia. These diseases may be associated with macrophage activation and may cause higher M2BPGi titers even without liver fibrosis **[42].**

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