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EDITORIAL

Orosomucoid in liver diseases

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Abstract

In this editorial, the roles of orosomucoid (ORM) in the diagnoses and follow-up assessments of both nonneoplastic diseases and liver tumors are discussed with respect to the publication by Zhu *et al* presented in the previous issue of *World Journal of Gastroenterology* (2020; 26(8): 840-817). ORM, or alpha-1 acid glycoprotein (AGP), is an acute-phase protein that constitutes 1% to 3% of plasma proteins in humans and is mainly synthesized in the liver. ORM exists in serum as two variants: ORM1 and ORM2. Although the variants share 89.6% sequence identity and have similar biological properties, ORM1 constitutes the main component of serum ORM. An interesting feature of ORM is that its biological effects differ according to variations in glycosylation patterns. This variable feature makes ORM an attractive target for diagnosing and monitoring many diseases, including those of the liver. Recent findings suggest that a sharp decrease in ORM level is an important marker for HBV-associated acute liver failure (ALF), and ORM1 plays an important role in liver regeneration. In viral hepatitis, increases in both ORM and its fucosylated forms and the correlation of these increases with fibrosis progression suggest that this glycoprotein can be used with other markers as a noninvasive method in the follow-up assessment of diseases. In addition, similar findings regarding the level of the asialylated form of ORM, called asialo-AGP (AsAGP), have been reported in a follow-up assessment of fibrosis in chronic liver disease. An increase in ORM in serum has also been shown to improve hepatocellular carcinoma (HCC) diagnosis performance when combined with other markers. In addition, determination of the ORM level has been useful in the diagnosis of HCC with AFP concentrations less than 500 ng/mL. For monitoring patients with AFP-negative HCC, a unique trifucosylated tetra-antennary glycan of ORM may also be used as a new potential marker. The fact that there are very few studies investigating the expression of this glycoprotein and its variants in liver tissues constitutes a potential limitation, especially in terms of revealing all the effects of ORM on carcinogenesis and tumor behavior. Current findings indicate that ORM2 expression is decreased in tumors, and this is related to the aggressive course of the disease. Parallel to this finding, in HCC cell lines, ORM2 decreases HCC cell migration and invasion, supporting reports of its tumor suppressor role. In conclusion, the levels of ORM and its different glycosylated

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variants are promising additional biomarkers for identifying ALF, for monitoring fibrosis in viral hepatitis, and for diagnosing early HCC. Although there is evidence that the loss of ORM2 expression in HCC is associated with poor prognosis, further studies are needed to support these findings. Additionally, investigations of ORM expression in borderline dysplastic nodules and hepatocellular adenomas, which pose diagnostic problems in the differential diagnosis of HCC, especially in biopsy samples, may shed light on whether ORM can be used in histopathological differential diagnosis.

Key Words: Orosomucoid; Alpha-1-acid glycoprotein; Viral hepatitis; cirrhosis; Hepatocellular carcinoma; Downregulation

Core Tip: Orosomucoid (ORM) has been suggested as a noninvasive marker in the diagnosis and follow-up of liver diseases. Currently, the results support the hypothesis that ORM can be used together with other markers to diagnose acute liver failure, monitor the development of cirrhosis, and detect early hepatocellular carcinoma (HCC). Although its role in carcinogenesis has not been entirely determined, the fact that decreased ORM2 expression is associated with carcinogenesis and poor prognosis warrants further study with the aim of better understanding the role of ORM in tumor behavior. The use of ORM expression to distinguish HCC from other neoplastic lesions and its role in differential diagnosis await investigation.

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INTRODUCTION

Orosomucoid (ORM), also known as alpha-1 acid glycoprotein (AGP), is an unusual protein with a carbohydrate content of 45% and a very low pI (2.8-3.8) that was identified more than a century ago[1]. Its variation in molecular weight between 37 and 54 kDa is closely related to the differences in its glycosylation content. Although the level of ORM varies according to species, it constitutes 1% to 3% of plasma proteins in humans[2]. This level is slightly higher for men than for women[3]. It is mainly synthesized in the liver; hence, it is also considered a hepatokine. However, smaller amounts can also be produced by breast epithelial cells, type II alveolar epithelial cells, endothelial cells, granulocytes, monocytes, and macrophages[2].

As the name implies, ORM is mainly composed of polypeptide chains and carbohydrate segments. The structures of genes encoding the polypeptide chain of ORM can vary within a broad spectrum. It is located in a cluster of 3 neighboring genes located on the long arm of the 9th chromosome in humans[4]. These neighboring genes are known as AGP-A, AGP-B, and AGP-B'. Among these, AGP-A, which has 3 different alleles (ORM1 * S, ORM1 * F, and ORM1 * F2), encodes ORM-1, and the distribution in the frequency of these alleles in humans may differ according to geographical region[3,5]. AGP-B and AGP-B' encode ORM2. Therefore, ORM exists in human serum as two variants: ORM1 and ORM2[4]. Notably, most individuals carry a mixture of these variants. Although these variants are reported to share 89.6% sequence identity and similar biological properties, ORM1 is the main component of serum ORM, as it is present in plasma at a fivefold higher concentration than ORM2[6,7]. ORM contains 5 N-linked glycans linked to the polypeptide structure, each of which can be a bi-, tri-, or tetra-antennary glycan and can exhibit varying degrees of fucosylation and sialylation and branching[8]. These different glycosylation sites change the protein's biological properties.

ORM is one of the major acute-phase proteins in humans, and its levels increase 2-fold to 6-fold in plasma in most disease states, including inflammation and cancer. Although the biological role of ORM remains unclear, it can regulate immunity and

play roles in both pro- and anti-inflammatory responses, can bind to endogenous ligands such as steroids, and has the ability to bind and transport large numbers of basic and neutral lipophilic drugs[2,8]. Recent studies have shown evidence that it can affect muscle tissue through glycogen metabolism, act as an adipokine in adipose tissue, and be involved in bile metabolism[9-11]. The general properties of ORM are summarized in Table 1.

Because ORM levels vary in many diseases and since their biological effects depend on the glycosylation pattern, this glycoprotein is an attractive target for use in diagnosis and treatment[3]. Accordingly, many current studies are exploring different organs, including the liver, with the aim of using ORM as a potential biomarker for the diagnosis and monitoring of diseases and of revealing its roles in carcinogenesis and tumor behavior.

In this article, the role of ORM in the diagnosis and follow-up of liver diseases is presented.

ORM IN ACUTE LIVER DAMAGE AND REGENERATION

Loss of liver function caused by viral hepatitis, cirrhosis, alcohol, and drug-induced liver damage is a life-threatening condition. Therefore, many studies have been conducted to better understand liver regeneration mechanisms, mainly to shed light on possible clinical applications, such as in the treatment of acute liver failure (ALF), which is a lethal disease characterized by sudden hepatic metabolic and immunological function loss. Liver regeneration is a complicated but coordinated multistep process that is mediated by the integration of multiple factors. Among these factors, proliferation plays a crucial role in the initiation of regeneration, as suggested by a large amount of data on the activation of the cell cycle and the proliferation of quiescent hepatocytes[12,13]. Therefore, eliminating arrest-promoting mechanisms affects the growth of differentiated hepatocytes; in other words, proliferation plays a key role in overcoming liver failure. Although some mitogens, such as growth factors, have been shown to affect proliferation, in recent years, paracrine mediators and nonmitogenic cytokines, including ORM1, have also been shown to participate in the control of this process in a coordinated manner[14]. Indeed, ORM1 expression increases during regeneration following liver resection in both humans and mice[15].

Moreover, the knockdown of ORM1 downregulates the signaling pathways controlling chromatin replication, supporting the notion that ORM1 plays a role in the cell proliferation involved in liver regeneration[16]. This finding is also in line with previous findings related to STAT-3, which is one of the transcription factors involved in liver injury and is associated with proliferation, that show that ORM synthesis is induced in liver injury due to the use of drugs that cause oxidative stress[17,18]. In proteomic analyses, it has been suggested that the sharp decrease in serum ORM levels in HBV-induced ALF (HBV-ALF) patients, as indicated by comparisons between liver tissue samples obtained from HBV-ALF and healthy individuals, may be a valuable biomarker in the diagnosis of ALF in patients with chronic liver disease[19]. Parallel to these findings, the results from a recent study on HBV-ALF showed the downregulation of four genes involved in the immune response and the complement and coagulation cascades, including ORM1 and ORM2; this suggests that both can be potential treatment targets for ALF[20]. However, the tissue expression level of ORM in the liver of patients with HBV-ALF was found to be 4.595-fold higher than that in the liver of healthy patients[21]. This finding is partially explained by the hypothesis that blood ORM accumulates in the liver in response to ALF.

Although further studies that involve a large number of patients and analyze both the blood and tissue levels in the same patients are needed to clarify the role of ORM in the diagnosis and treatment of ALF, current evidence indicates that ORM can be a useful marker in the diagnosis of this lethal disease.

ORM AND NONNEOPLASTIC LIVER DISEASES

As an acute-phase reactant, the ORM level in plasma, which is normally between 4% and 6%, can vary in many inflammatory diseases, including that of the liver. Recently, Oguz *et al*[22] showed that patients with HCV hepatitis have higher ORM levels than healthy individuals. Moreover, evidence has shown that the ORM level fluctuates with fibrosis progression and increases with the development of cirrhosis. Regarding the treatment of HCV hepatitis, no significant difference was found in the responding

Table 1 A brief overview of the general properties of orosomucoid protein

General properties of orosomucoid protein		
Chromosome location	9	
Genes	AGP-A	AGP-B and AGP-B′
Product	ORM1	ORM2
Alleles	ORM1*S, ORM*F, ORM*F2	Monomorphic, except in Japan
Structure		
Polypeptide chain	Single, 183 amino acids with disulfide bonds; There are 22 amino acid differences between ORM 1 and ORM2	
Carbohydrate parts	Five N-linked potential glycosylation sites: Sialic acid, neutral hexoses, mannose, fructose, galactose and hexosamine. Alterations in fucosylation, sialylation, and branching affect its biological properties	
Synthesis	Predominantly by hepatocytes and parenchymal cells. Extrahepatic secretion is rare (breast, endothelial cells, and tumor cells)	
Secretion		
Inflammatory mediators	Glucocorticoids, TNF-α, Interleukins: 1, 6, 8, 11	
Exogenous factors	Phenobarbital, Rifampicin, Retinoic acid, Macrolides	
Biological activities		
Acute-phase reactant	Concentration is elevated 1-10 times during several pathological conditions. Infection, inflammation, tumor, surgery, tissue injury, sepsis, and necrosis	
Immunomodulation	Inhibit leukocyte rolling/adhesion and migration and lymphocyte proliferation. Vitamin D-mediated macrophage deactivation. Agalacto/asialo derivative suppresses the immune response. ORM1 contributes to both anti- and proinflammatory signals to mediate mechanisms activated by the acute-phase response	
Transporting protein	Drug-binding and transporting in the serum. The existence of two forms in the blood also has an influence the binding affinity. ORM1 binds warfarin, prazosin, imatinib, quinidine, and dipyridamole. ORM2 binds methadone, disopyramide, propafenone, and amitriptyline	
Endothelial functions	Maintain the barrier function of capillaries. Regulate injury-induced angiogenesis. Enhance blood-brain barrier functional integrity. Beneficial effect on the glomerular barrier	
Metabolism	ORM1 increases glucose uptake activity in adipocytes. A potential biomarker in distinguishing obese women with metabolic syndrome from those without metabolic disturbances	

ORM: Orosomucoid; TNF-α: Tumor necrosis factor alpha.

group and the nonresponding group, suggesting that ORM levels can only be used as adjuvants to monitor early treatment response. Although not significant, the remarkable increase observed in the early phase of treatment has been attributed to the association of ORM with IFN. In contrast to these findings, another study found that the ORM level in HCV hepatitis was lower than that in healthy subjects and was significantly increased with fibrosis progression[23]. It has been suggested that this decrease may be due to HCV proteins suppressing C3 synthesis. Additionally, variations in the level of ORM were associated with neither necroinflammatory activity nor viral genotype.

High levels of ORM have also been reported in HBV hepatitis and associated cirrhosis[19-21]. In contrast, ORM levels were observed to be within normal limits in NASH and chronic alcoholic liver disease[24,25].

Since the glycosylation pattern of ORM can be modified throughout diseases, these alterations were analyzed for any correlation with the severity of liver diseases to determine the use of ORM as a surrogate marker of fibrosis. In recent years, the fucosylated form of ORM has been observed at a higher level in patients with both HBV and HCV hepatitis than in healthy individuals[26-29]. Moreover, it was emphasized that the fucosylated ORM might be useful in monitoring fibrosis because of it increased with the progression of fibrosis toward cirrhosis[27]. Another interesting finding indicates that during this progression, the increase in ORM fucosylation is associated with a concordant decrease in sialylation. These results support the idea that its glycosylation is modified by the severity of fibrosis and might be useful in disease monitoring[30].

In light of the accumulated data on the modification of the sialylation content of ORM, a few recent studies have been performed to evaluate the diagnostic performance of asialo-AGP (AsAGP) in the detection of cirrhosis in patients with chronic

liver disease. Increasing serum levels of AsAGP were correlated with the degree of fibrosis, and this level was highest in cirrhosis[31,32]. There have also been findings indicating that an increased level of AsAGP shows an inverse correlation with albumin but a positive correlation with the stage of fibrosis, and it may be a positive predictor of cirrhosis[31]. However, in these studies, similar results were not found in comparisons with liver stiffness, a noninvasive method for detecting fibrosis. Thus, further studies are warranted.

ORM IN LIVER TUMORS

Hepatocellular carcinoma (HCC) continues to be one of the major causes of cancer deaths worldwide due to its lack of specific clinical findings at the early stages and the lack of efficient screening methods[33]. To prevent HCC from being diagnosed in advanced stages where treatment options are limited, many efforts have been made to identify new diagnostic and screening methods. For this purpose, several tumor markers have been proposed for use in HCC diagnosis. Because evidence has established that ORM is associated with carcinogenesis and behavior in many organs, changes in the ORM serum level in HCC have been investigated as diagnostic markers. The results of many studies have indicated that the ORM level is increased in patients with HCC and is significantly higher than that in patients with chronic hepatitis and cirrhosis[34-37]. ORM has also been shown to improve HCC diagnostic performance when combined with other markers, such as des-g-carboxy prothrombin (DCP)[38].

Furthermore, determination of the ORM level has been observed to be useful in the diagnosis of HCC in which the AFP values are less than 500 ng/mL[39]. In light of these data, it can be concluded that monitoring ORM levels together with AFP and/or other biomarker levels may be useful in the early detection of HCC. Additionally, it has recently been shown that the combination of urinary ORM-1 levels with urinary AFP levels has a high sensitivity (85%) in the diagnosis of HCC and that this noninvasive method can also be used[40].

Few studies have evaluated the role of ORM in the evolution and prognosis of cholangiocarcinoma (CCC). An experimental study showed that the ORM2 Level increases before tumor onset and tends to be upregulated during tumor progression [41]. The levels of ORM2 were also investigated in patients with CCA. The sensitivity and specificity of ORM2 in distinguishing CCC patients from healthy individuals were 92.86% and 73.68%, respectively[42].

It has been proposed that alterations in the glycosylation pattern of ORM can be used to detect the progression and metastasis of many types of cancer[43]. Indeed, the aberrant glycosylation of ORM in liver cancer progression has received considerable attention in biomarker studies. Previous studies revealed that although there was an increase in the ORM levels of patients with liver cirrhosis and HCC compared to healthy controls, different degrees of fucosylation may distinguish HCC cases from cirrhosis cases[44-47]. Performing an elegant study, Liang *et al*[48] demonstrated a unique trifucosylated tetra-antennary glycan of ORM predominantly identified in HCCs. However, this glycan was absent in both healthy subjects and the majority of cirrhosis patients, as determined by matrix-assisted laser desorption ionization-mass spectrometry, providing a new potential marker for monitoring AFP-negative HCC patients. Although the level of fucosylated ORM differs significantly in advanced stages, determining whether these markers can be used to determine HCC behavior requires further studies in large series.

Similar to nonneoplastic diseases of the liver, the efficacy of AsAGP in the diagnosis of HCC has been investigated in some studies. The AsAGP level is higher in cirrhosis and HCC[49,50]. Kim *et al*[50] revealed that these increases in both cirrhosis and HCC might be related to damaged asialoglycoprotein receptors on the hepatic cell surface, as demonstrated in human and animal studies. The release of extra neuraminidase into the circulation during cellular transformation and the production of incomplete asialoglycoproteins in hepatic cells are also hypothesized to explain the increase in AsAGP in these patients.

In liver diseases, the vast majority of studies addressing ORM were performed in body fluids. However, there are very few studies that investigated ORM expression at the tissue level that have yielded significant results. Although ORM1 and ORM2 are mostly observed in liver tumors compared to other organ cancers, their expression levels are significantly decreased compared with those in neighboring liver tissue, suggesting that ORM genes are downregulated in liver tumors[37,51,52]. The down-

regulation of ORM2 inversely correlates with intrahepatic metastasis and histological grade; in other words, ORM2 is negatively correlated with aggressive tumor behavior [51]. Parallel to these findings, studies using HCC cell lines showed that ORM2 decreased HCC cell migration and invasion, supporting its tumor suppressor role[52]. In addition, Zhu *et al*[52] observed that the prognosis of patients with low ORM2 expression was worse than that of patients with higher ORM2 expression. Therefore, it has been suggested that ORM2 may be a new prognostic factor for liver cancer patients. Moreover, in this study, the inverse association between downregulated ORM2 expression and pathways involved in hepatocarcinogenesis, such as the G2/M checkpoint, E2F target signaling, Wnt/β-catenin, and hedgehog signaling pathways, also supported the use of ORM2 as a marker of liver cancer[51]. The observation of the involvement of ORM2 in tumor-associated macrophage infiltration and the T-cell mediated checkpoint in liver tumor tissue also suggested that its downregulation may be another marker for efficiently predicting the need to apply immune checkpoint therapy. It should be noted that since none of the three current guidelines on the management of HCC include the use of ORM in diagnosis, further studies are needed before recommending its use as a diagnostic marker[53-55]. Moreover, these findings should also be supported by further studies in not only HCC but also CCC. In addition to the relationship of ORM with the immune checkpoint, its relationships with other pathways that may be potential therapeutic targets need to be investigated more comprehensively. The role of ORM expression in differential diagnosis, especially in biopsy samples, to distinguish other neoplastic lesions, such as borderline dysplastic nodules and adenomas, from HCC has not been reported. Furthermore, considering that metastatic tumors of the liver are more common than primary tumors, the role of ORM in these tumors is unknown.

CONCLUSION

In addition to being an acute-phase reactant, ORM is a potential biomarker that can be used with other liver markers for the diagnosis of ALF in the follow-up assessment of fibrosis in viral hepatitis. Similarly, it can be used together with other noninvasive methods to detect early stages of HCC. Recent studies suggest that ORM expression may be useful in determining the behavior of HCC and tumor progression.

However, in HCC, the relationship of ORM with other pathways targeted for treatment in addition to immune checkpoint pathways should be clarified.

Furthermore, the relationship between metastatic tumors and ORM expression, if any, and its role in the histopathological differential diagnosis of HCC require further investigation.

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