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Review

Asialoglycoprotein receptor (ASGPR) as target autoantigen in liver autoimmunity: Lost and found

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ABSTRACT

Asialoglycoprotein receptor (ASGPR) has attracted the attention of liver immunologists for many years. This liver-specific lectin was found to be a major B and T cell autoantigenic target in patients with autoimmune liver diseases, and in particular in autoimmune hepatitis (AIH). This review discusses the biological significance of ASGPR and its relevance to the pathogenesis of autoimmune and virus-triggered liver diseases. We also discuss emerging data on the diagnostic and clinical relevance of anti-ASGPR antibodies in light of recent reports based on commercially available anti-ASGPR enzyme-linked immunosorbent assays. Finally, we critically revisit the data reporting on disease-specific cellular immune responses against ASGPR and their relevance in relation to the pathogenesis of AIH.

Contents

Abbreviations: ANA, anti-nuclear antibody; ASGPR, asialoglycoprotein receptor; AIH, autoimmune hepatitis; DIC, disseminated intravascular coagulation; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; GlcNAc, *N*-acetylglucosamine; HAV, hepatitis A virus; HBV, hepatitis B virus; HepG2, hepatocellular carcinoma cell line; HCV, hepatitis C virus; LSP, liver-specific proteins; LMA, liver membrane antibodies; IIF, indirect immunoflourescence; IL, interleukin; LSP, liver-specific proteins; OD, optical density; RIA, radioimmunoassay; SDS-PAGE, sodium dodecyl sulphate polyacrylamide gel electrophoresis; TNF, tumor necrosis factor; vWF, von Willebrand factor.

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1. Introduction

Asialoglycoprotein receptor (ASGPR) [1] was the first animal lectin to be identified. ASGPR, which is also known as the hepatic galactose/*N*-acetylglucosamine (GlcNAc) receptor [1], the Ashwell receptor or the Ashwell–Morell receptor, is a hepatic C-type lectin. C-type lectins are dependent on Ca^{2+} for ligand binding and disulfide bonds in carbohydrate recognition domains [2,3]. Under normal conditions, ASGPR is expressed primarily on the sinusoidal surface of the hepatocytes [4]. Physiologically, the penultimate galactose residues of glycoproteins are capped by terminal sialic acid moieties [4]. Asialoglycoproteins are endogenous glycoproteins where the sialic acid has been removed by sialidase enzyme activity. The removal of sialic acid (N-acetylneuraminic acid) renders the now terminal galactose residues as recognition determinants for ASGPR [4]. Though the aim of this review is to discuss the current knowledge of the immunobiology of ASGPR and its role as an autoantigenic target in liver diseases, we will also review the current knowledge regarding the involvement of this receptor in the homeostatis of the circulation of glycoproteins and the potential interplay of ASGPR with immunologically significant ligands.

2. The discovery of ASGPR: historical notes

The first investigation for a mammalian lectin was initiated over a dinner between friends in New York City [5]. These investigators, Gilbert Ashwell and Anatol Morell, had different research backgrounds and interests and worked in different laboratories [1]. Morell was at the Albert Einstein College of Medicine and studied the physical and chemical properties of ceruloplasmin, a copper-carrying glycoprotein. Ashwell's research interests surrounded carbohydrates and the turnover of glycoproteins from circulation. During his 1965–1966 sabbatical at Columbia University, Ashwell was a frequent dinner guest at the Morell household, at which point Morell mentioned that he had problems in determining the half-life of ceruloplasmin [5]. Ashwell suggested that they could label a terminal galactose with a long-lasting tritium isotope to calculate ceruloplasmins' serum half-life [5]. From this hypothesis, and knowing that these proteins contained the terminal sequence sialic acid-galactose-GlcNAc, Ashwell and Morell devised a labeling procedure for serum glycoproteins which involved the removal of the glycoproteins' sialic acid residues exposing galactose [6]. This involved either the enzymatic oxidation of the 6-position of galactose residues after removing the outer sialic acid residues, or mild periodate oxidation of sialic acid side chains which left the rest of the sialic acid molecule intact. A dramatic difference between the circulation half-lives of these two preparations was found [7]. The molecules which retained labeled sialic acids remained longer in circulation compared to those that had lost them [7]. These latter labeled asialoglycoproteins rapidly disappeared from the blood stream, and were eventually located in the liver parenchyma [7], predominantly in hepatocyte lysosomes [8]. Remarkably, *in vitro* resialylation or β-galactosidase glycoprotein treatment partially restored circulation stability and, thus, confirmed the importance of the terminal β-linked galactose residues for rapid removal of glycoproteins by the liver [7]. In support of these findings, clearance of enzymatically desialylated and radiolabeled ceruloplasmin was found to be dependent on exposure of its galactose residues, and galactose removal or modification improved retention in circulation [9]. In summary, these observations confirmed the assumption that sialic acid removal allowed the liver to identify and clear defective molecules from the blood. Further investigations led to the identification of asialoglycoprotein receptor (ASGPR) as the responsible receptor for asialoglycoprotein binding [10].

ASGPR consists of two subunits, a major 48 kDa subunit (ASGPR-1) and a minor 40 kDa subunit (ASGPR-2) [11–13], and specifically recognizes terminal β-linked galactose or GlcNAc on circulating glycoproteins or cells. The purified rabbit hepatocyte ASGPR agglutinated desialylated human and rabbit erythrocytes, and it was also able to induce mitogenesis in desialylated lymphocytes isolated from blood [8]. This was the first study to demonstrate that a lectin has a metabolic role. GlcNAc and to a lesser extent galactose inhibited the binding of rabbit hepatic lectin to cells.

Several years later, Ashwell and Kawasaki [14] isolated an avian equivalent of ASGPR and described the similarities and differences between the avian and rabbit hepatic lectins in terms of structure and binding activity. These studies created the basis for the discovery of a series of carbohydrate-specific cell-surface receptors forming what is currently known as the family of lectins. Also, the discovery of ASGPR has led to the appreciation that many pituitary glycoprotein hormones and parasite-derived glycoproteins contain terminal β-linked *N*-acetylgalactosamine residues, which may be recognized by ASGPR. The implications of these findings were apparent early on, as the hepatic sequestration of desialylated hormones allows for drug delivery specifically to the liver [5].

3. Expression and physiological role of ASGPR

3.1. The function of ASGPR

The primary physiological role of ASGPR has been considered to be the binding, internalization, and subsequent clearance from the circulation of glycoproteins that contain terminal galactose or GlcNAc residues [11,12,15]. As mentioned above, its identification has been the final result of seminal studies demonstrating that the asialoglycoproteins' uptake is exerted by hepatic parenchymal cells [7]. Interestingly, further investigations have demonstrated that ASGPR is a multifunctional membrane receptor which is also involved in the removal of apoptotic cells [12], the disposal of cellular fibronectin [16], and the clearance of IgA from circulation [17–20]. ASGPR has been considered to carry a possible binding site for low-density lipoprotein (LDL) and chylomicron remnants, and to be responsible for their removal [21,22]. It also appears that hepatotropic viruses [23–27] can utilize ASGPR as a site of entry. More recent studies have raised convincing data to suggest that ASGPR has immunomodulatory properties [28] and can facilitate the trapping and elimination of activated lymphocytes [29].

Interestingly, ASGPR is a known target of organ-specific B- and T cell autoreactive responses in patients with autoimmune liver disease. The latter feature of ASGPR will be the focus of the current review and will be discussed in greater detail. In order to comprehend