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Review

Lipoprotein lipase transporter GPIHBP1 and triglyceride-rich lipoprotein metabolism

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ABSTRACT

Increased plasma triglyceride serves as an independent risk factor for cardiovascular disease (CVD). Lipoprotein lipase (LPL), which hydrolyzes circulating triglyceride, plays a crucial role in normal lipid metabolism and energy balance. Hypertriglyceridemia is possibly caused by gene mutations resulting in LPL dysfunction. There are many factors that both positively and negatively interact with LPL thereby impacting TG lipolysis. Glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1), a newly identified factor, appears essential for transporting LPL to the luminal side of the blood vessel and offering a platform for TG hydrolysis. Numerous lines of evidence indicate that GPIHBP1 exerts distinct functions and plays diverse roles in human triglyceride-rich lipoprotein (TRL) metabolism. In this review, we discuss the GPIHBP1 gene, protein, its expression and function and subsequently focus on its regulation and provide critical evidence supporting its role in TRL metabolism. Underlying mechanisms of action are highlighted, additional studies discussed and potential therapeutic targets reviewed.

1. Introduction

When blood triglyceride (TG) fails to be hydrolyzed, overall plasma TG concentration increases and the plasma may even appear “milky”, a well-characterized condition known as hypertriglyceridemia. Increased plasma TG initiates proatherogenic systemic disturbances, including changes in lipid, lipoprotein and glucose metabolism as well as the development of insulin resistance, systemic inflammation and oxidative stress [1]. In most cases, hypertriglyceridemia results from the interaction of several common polymorphisms, like the mutations in some novel genes engaged in TG hydrolysis, such as LPL, a key enzyme hydrolyzing plasma TG, and glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1 (GPIHBP1), a key molecule that transports LPL from the capillary basolateral side to the apical side where LPL functions [2]. LPL in the capillary lumen is a potent enzyme hydrolyzing the TG within the core of TG-rich lipoproteins (TRLs), including chylomicrons (CMs) and very low-density lipoproteins (vLDLs). Although LPL is synthesized and secreted by parenchymal cells, the site for its action is on the luminal side of capillary endothelium [3]. How LPL enters the luminal side of the capillary has long been a focus of research. It is known that LPL mislocalization caused by the deficiency of GPIHBP1 leads to severe hypertriglyceridaemia [4,5]. Recent studies also indicated that LPL secreted by parenchymal cells is bound by GPIHBP1 in the interstitial spaces and then transported across the cells into the capillary lumen to embark on its hydrolytic process [6,7]. GPIHBP1, therefore, plays an important role in lipolysis. This review article is to highlight the role of GPIHBP1 in TRL metabolism and lipid metabolism related diseases caused by GPIHBP1 deficiency.

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2. GPIHBP1 expression pattern

GPIHBP1 is a 28-kDa glycosylphosphatidylinositol-anchored glycoprotein, with its gene located on chromosome 8q24.3, stretching a span of 4 kb with 4 exons. It was reported that lipolysis of TRLs by LPL is largely regulated at the metabolic demand in heart, brown adipose tissue and skeletal muscle, and GPIHBP1 is expressed exclusively in the capillary endothelial cells of those tissues [8], suggesting that GPIHBP1 expression profile may be tissue-specific with involvement of energy balance, lipid metabolism and lipoprotein utilization.

Beigneux et al. showed that Gpihbp1 is expressed highly in the capillary endothelial cells of 'lipolytic tissues' such as heart and adipose tissue [8]. However, Gpihbp1 is unable to be detected in such endothelial cell lines as rat heart microvascular endothelial cells, human umbilical vein endothelial cells and bovine aortic endothelial cells. What's more, it's also reported that primary endothelial cells from white adipose tissue expressed normal Gpihbp1 but after a single passage the expression was almost lost, possibly because Gpihbp1 expression may depend on stromal factors and is affected by the ambient parenchymal cells [9].

Gpihbp1 expression is not detected in undifferentiated mouse embryonic stem cells but in embryoid bodies after differentiation induction these cells into embryoid bodies. In embryoid bodies, GPIHBP1 is especially found in CD31-positive endothelial cells around beating cardiomyocytes [9].

LPL is mainly responsible for the production of free fatty acid (FFA), and its activity is regulated by feeding status. A previous study indicated that LPL activity in adipose tissue was predominantly higher 6 h after the first meal than that in the fasting state [10]. As a key cofactor of LPL, GPIHBP1 expression pattern is similar to that of LPL. GPIHBP1 expression is also influenced by metabolism status. It has been confirmed that the expression of these two partners is both largely influenced by the nutritional state [8]. In cardiac muscle, when glucose uptake and oxidation are impaired as a result of diabetes, the heart is compelled to use FFA nearly exclusively for ATP, leading to the increase in both the expressions of LPL and GPIHBP1 [11]. Interestingly, in rodent adipose tissue, the expression of GPIHBP1 increased while LPL activity decreased in mice with food deprivation. Once the fasted mice were re-fed, the expression of GPIHBP1 decreased, while LPL activity increased [12]. Those findings above are somewhat unexpected, because GPIHBP1 is considered as "an LPL-controlling protein" [12]. In addition to transporting LPL to the luminal side of the endothelium under certain circumstances, such as fasting, GPIHBP1 may predominantly transport LPL in the opposite direction, resulting in the inactivation or degradation of LPL within the tissue, suggesting that LPL can be transported bidirectionally within endothelial cells [13]. All the phenomena were observed in the experiments conducted in mice, but what happens to human GPIHBP1 is still not completely understood. Moreover, GPIHBP1 expression plays a critical role in the regulation of lipolysis. The studies of human heterozygotes implicate that half amount of normal GPIHBP1 does not result in the failure of triglyceride hydrolysis [14,15], suggesting that human heterozygous GPIHBP1 with normal function and distribution is potent enough to undergo intravascular TRL lipolysis.

3. GPIHBP1 structure and biological function

3.1. Structure

Some proteins that are anchored on the cell membrane by binding to the oligosaccharide attached to phosphatidylinositol (PI) located in the outer lipid bilayer are named glycosylphosphatidylinositol (GPI)-linked proteins and have the potent mobility on the membrane and the ability to combine with extracellular signaling molecules. GPI family members are widely distributed *in vivo* and include more or less 100 types, such as a hydrolase, immunoglobulin, cell adhesion molecule, membrane receptor.

GPIHBP1, a member of the lymphocyte antigen 6 (Ly6) family, contains the same novel conserved Ly6 motifs as other Ly6 genes previously studied [4,16–20]. What the Ly6 proteins have in common is the presence of N-terminal signal peptide region, the Ly6 domain and a highly hydrophobic C-terminal helical sequence. The N-terminal signal peptide region is removed in the ER. The Ly6 domain contains all disulfide-bonded 10 cysteines. The C-terminal helical sequence embarks on the addition of a GPI anchor, which has an ending motif of hydrophobic amino acids and is cleaved in the ER then substituted by a GPI anchor [21,22]. It is worth mentioning that GPIHBP1 is distinguished from the other Ly6 members due to the presence of a high acidic domain consisting of 21 aspartates or glutamates, locating directly about a length of 12 amino acids before the Ly6 motif [23], as is shown in Fig. 2 [24].

Two of these domains, acidic domain and the Ly6 domain, are reported to be crucial in the interaction of GPIHBP1 with LPL as evidenced by deletion, mutation, or replacement of one or two domains, which greatly inhibit the ability of GPIHBP1 to complex with LPL and result in chylomicronemia [23]. It was ever recognized that the GPIHBP1 acidic domain plays a novel role in binding LPL [23]. However, the recent studies with more refined cell-based and cell-free binding assays indicated that the contribution of the acidic domain to LPL binding was not dominant and that the Ly6 domain was fundamentally responsible for LPL binding [25,26]. Surface plasmon resonance (SPR) studies with purified proteins implicated that Ly6 domain of GPIHBP1 is required for high-affinity interactions with LPL, while the acidic domain only facilitating the binding and stabilizes LPL activity [27]. The two domains of GPIHBP1 interact independently with LPL. The functionality of LPL depends on its localization on GPIHBP1. The Ly6 domain is responsible for capturing and binding LPL, and only LPL that binds to the acidic domain of GPIHBP1 can hydrolyze lipoproteins [28]. However, it is unclear which one of the two domains is the decisive factor for LPL hydrolytic function and whether the Ly6 domain participates in submitting LPL to the acidic domain.

Recently, other studies demonstrate that the *N*-terminal domain binds to LPL with high affinity at physiological salt concentrations, indicating this domain may contribute to the formation of the LPL/GPIHBP1 complex [29].

3.2. Biological function

3.2.1. Transporting and stabilizing LPL

It was once reported that the VLDL receptor (VLDLR) is likely engaged in the transport of LPL across the capillaries [30], but pace-chasing studies showed that VLDLR deficiency does not result in hypertriglyceridemia [31]. However, it was found that *gpihbp1* knockout mice even on a low-fat chow diet were linked with milky plasma and severe chylomicronemia because TRLs failed to be hydrolyzed and were accumulated in the capillary [32], further confirming that GPIHBP1 plays a key role in transporting LPL to the lumen. On the one hand, GPIHBP1 can form an LPL-GPIHBP1 complex that serves as a platform for lipid hydrolysis after binding HSPG-fixed LPL in the interstitial spaces of tissue [33], and shuttling it into the capillary lumen [3,6]. On the other hand, GPIHBP1 contributes to the stabilization of LPL by reducing the spontaneously inactivated unfolding of the LPL catalytic domain and functions as a regulator to prevent its inhibition by ANGPTL3 and ANGPTL4 which can catalyze the unfolding of LPL [27,34]. This is because LPL is an unstable enzyme that is active in its homodimer form and inactive in monomer/dimer form and the spontaneous conversion from active to inactive forms is irreversible [35–37].

3.2.2. Establishing a platform for lipolysis

GPIHBP1 can also bind to chylomicrons mediated by LPL or apoAV, reconfirming the motion that GPIHBP1 serves as a platform for lipolysis