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Review

GPI-anchor remodeling: Potential functions of GPI-anchors in intracellular trafficking and membrane dynamics ☆

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ABSTRACT

Glycosylphosphatidylinositol (GPI) anchoring of proteins is a conserved post-translational modification in eukaryotes. GPI is synthesized and transferred to proteins in the endoplasmic reticulum. GPI-anchored proteins are then transported from the endoplasmic reticulum to the plasma membrane through the Golgi apparatus. GPI-anchor functions as a sorting signal for transport of GPI-anchored proteins in the secretory and endocytic pathways. After GPI attachment to proteins, the structure of the GPI-anchor is remodeled, which regulates the trafficking and localization of GPI-anchored proteins. Recently, genes required for GPI remodeling were identified in yeast and mammalian cells. Here, we describe the structural remodeling and function of GPI-anchors, and discuss how GPI-anchors regulate protein sorting, trafficking, and dynamics. This article is part of a Special Issue entitled Lipids and Vesicular Transport.

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1. Introduction

Several types of membrane-bound proteins, including transmembrane proteins, peripheral proteins, and lipidated proteins, exist on the plasma membrane. In addition, certain proteins are anchored by glycosylphosphatidylinositol (GPI) on the cell surface. GPI anchoring of proteins is a conserved post-translational modification among all eukaryotes. The GPI core structure, consisting of a phosphatidylinositol (PI) moiety, a glucosamine (GlcN) moiety, three mannoses (Mans), an ethanolamine-phosphate (EtNP) moiety, is highly conserved among species [1]. GPI is synthesized and transferred to proteins on the endoplasmic reticulum (ER) membrane involving at least 10 reactions. To date, more than 20 genes involved in these reactions have been identified (Fig. 1) [2,3]. PI is modified by the stepwise addition of sugars, a fatty acid, and EtNPs, forming a complete precursor lipid. The complete GPI precursor is transferred by GPI-transamidase to proteins containing a GPI attachment signal sequence at their C-terminus.

Biogenesis of GPI-anchored proteins (GPI-APs) is essential for viability in yeast, for virulence/survival in host of parasitic protozoa, and for the development of shoots, root meristems, and pollen tube growth in plants [4–7]. In mammalian cells, more than 150 proteins, including receptors, adhesion molecules, and enzymes, have been reported to exist as GPI-APs. Biogenesis of GPI-APs is essential for embryogenesis, neurogenesis, immune responses, and fertilization [8–13]. Several human diseases are known to be caused by mutations in genes involved in GPI biosynthesis. In hematopoietic stem cells, somatic mutation in *PIG-A*, which encodes the first enzyme of GPI biosynthesis (Fig. 1), results in paroxysmal nocturnal hemoglobinuria (PNH), an acquired hemolytic disease [14,15]. In addition, autosomal recessive mutations in *PIG-M*, *PIG-V*, and *PIG-N* have been reported to cause inherited GPI deficiency [8,16,17].

It has been proposed that GPI-anchors function as sorting signals for selective targeting of GPI-APs to secretory and endocytic pathways. In yeast, GPI-APs are sorted and transported from the ER to the Golgi apparatus in vesicles that are distinct from other secretory proteins [18,19]. Most GPI-APs are transported to the apical membranes in many epithelial cells [20,21], whereas several exceptions have been reported [22,23]. GPI-APs are selectively internalized by a unique pathway involving clathrin-independent vesicles [24]. The sorting of GPI-APs to the secretory and endocytic pathways seems to be correlated with their associations with specialized lipid domains called lipid rafts [25,26]. Whereas there is still controversy about the definition, size, and stability of lipid rafts, specific lipids such as sphingolipids and cholesterol form membrane microdomains that function

Abbreviations: ACE, angiotensin-converting enzyme; CLIC, clathrin-independent carrier; COPII, coat protein complex II; DRM, detergent-resistant membrane; ER, endoplasmic reticulum; ERES, ER-exit sites; EtNP, ethanolamine-phosphate; GalNAc, *N*-acetylgalactosamine; GEEC, GPI-APs enriched early endosomal compartment; GlcN, glucosamine; GPI, glycosylphosphatidylinositol; GPI-AP, GPI-anchored protein; Lo, liquid order; Man, mannose; MBOAT, membrane-bound *O*-acyltransferase; PE, phosphatidylethanolamine; PI, phosphatidylinositol; PNH, paroxysmal nocturnal hemoglobinuria; STALL, stimulation-induced temporary arrest of lateral diffusion; tER, transitional ER; TGN, trans-Golgi network; VacA, vacuolating cytotoxin

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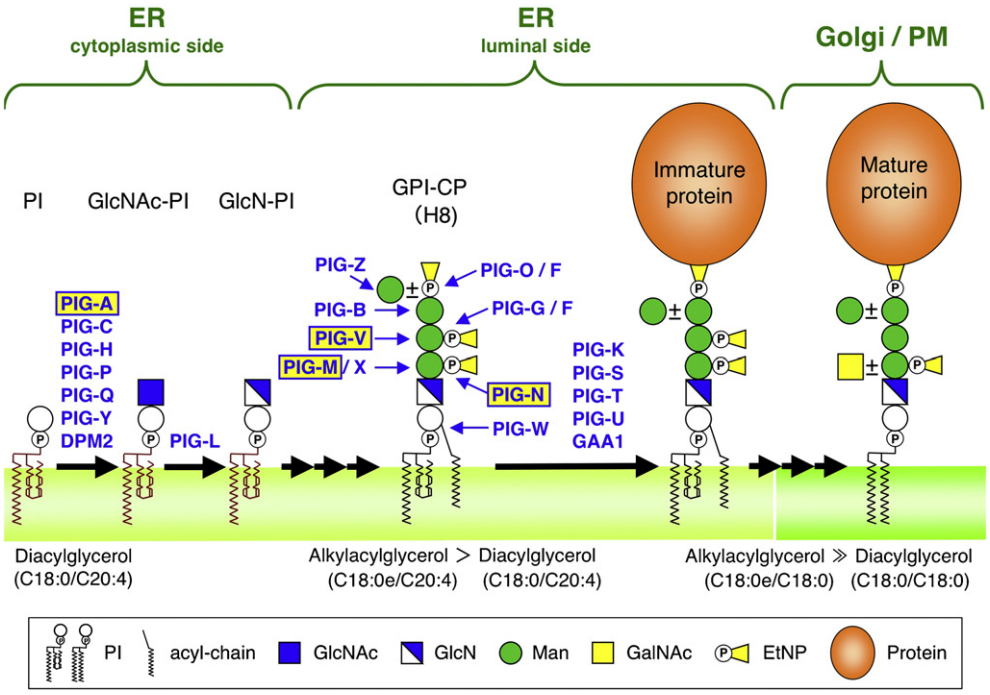

Fig. 1. Biosynthesis and structure of mammalian GPI-APs. Biosynthesis of GPI is carried out in the ER through an enzymatic reaction pathway consisting of at least ten steps [3]. It is initiated by transfer of GlcNAc to PI. The first two steps occur on the cytoplasmic side of the ER, whereas the later steps occur on the luminal side of the ER. PI used for GPI biosynthesis is predominantly 1-stearoyl-2-arachidonyl PI, whereas 1-alkyl-2-acyl PI is dominant in mammalian GPI-APs. The change from diacyl to 1-alkyl-2-acyl would occur in GlcN-(acyl)PI during biosynthesis [59]. About fifty to sixty percent of GlcN-(acyl)PI intermediates contain 1-alkyl-2-acyl forms (shown in Figure as '>'), whereas more than ninety percent of GPI-APs have 1-alkyl-2-acyl forms (shown in Figure as '≫'), suggesting that enrichment of alkyl-containing GPI intermediates occurs during the late steps of the GPI biosynthesis. Proteins required for GPI biosynthesis are indicated. Somatic mutations in *PIG-A* lead to paroxysmal nocturnal hemoglobinuria [15]. Autosomal recessive mutations in *PIG-M*, *PIG-V*, and *PIG-N* have been reported to cause inherited GPI deficiency [8,16,17]. GPI-CP (H8), GPI complete precursor; PI, phosphatidylinositol; GlcNAc, *N*-acetylglucosamine; GlcN, glucosamine; Man, mannose; GalNAc, *N*-acetylgalactosamine; EtNP, ethanolamine-phosphate.

as platforms for protein trafficking and intracellular signaling. During the delivery of GPI-APs to the plasma membranes, the structures of GPI-anchors are dynamically remodeled [2,27]. The remodeling confers on GPI-APs the property to associate with detergent-resistant membranes (DRMs), which is thought to reflect the association of GPI-APs with specialized membrane domains. In this review, we describe (1) the GPI remodeling reactions in mammalian cells and yeast; (2) the selective sorting mechanisms of GPI-APs at the ER; (3) similarities and differences in trafficking of GPI-APs from the ER between mammalian cells and yeast; (4) the late secretory and the endocytic pathways of GPI-APs; and (5) the behavior of GPI-APs at the plasma membrane.

2. Remodeling of GPI-anchors

2.1. Structural differences between GPI in the ER and on the cell surface in mammalian cells

The structures of GPI-anchors are different in several ways between the GPI precursor before attachment to proteins in the ER and mature GPI-APs on the cell surface. In mammalian cells, there are at least four differences between GPI precursors and mature GPI-APs (Fig. 1). First, GPI precursors have an acyl-chain (usually palmitic acid (C16:0)) linked to the 2-position of the inositol ring. Second, GPI precursors have an unsaturated fatty acid (mainly arachidonic acid (C20:4)) at the *sn*-2 position of the lipid. Third, a side-chain EtNP is attached to the 6-position of the second Man in GPI precursors. By contrast, the inositol moiety of the mature GPI-APs on the plasma membrane is not acylated (except in human erythrocytes). The lipid of the GPI-APs contains saturated fatty acid (stearic acid (C18:0)) at the *sn*-2 position and most GPI-APs on the surface lack a side-chain EtNP on the second Man. Fourth, a β-*N*-acetylgalactosamine (β-GalNAc) residue may be linked to the 4-postion of the first Man in some GPI-APs [1]. The GalNAc residue may be further modified by galactose and sialic acid. Therefore, GPI-anchors change their structure during their transport.

2.2. Inositol acylation and deacylation

In an early step of GPI biosynthesis, an acyl-chain is transferred to the inositol ring of the GlcN-PI by mammalian PIG-W (yeast Gwt1p), generating GlcN-(acyl)PI [28,29]. This reaction is required for the efficient completion of later steps in GPI biosynthesis, particularly for the addition of terminal EtNP, which is used for attachment to proteins. The acylation of inositol marks the boundary of the GPI biosynthetic pathway from the cytoplasmic phase to the luminal phase on the ER membrane. Recently, topological analysis of yeast Gwt1p revealed that essential amino acids are located on the luminal side of the ER, suggesting that inositol acylation occurs in the ER lumen [30].

The acyl-chain linked to inositol is a transient structure during GPI biosynthesis, i.e., it is removed soon after GPI is attached to proteins (Fig. 2). The reaction is carried out by mammalian PGAP1 (yeast Bst1p) [31]. PGAP1 is a multispanning membrane protein localized at the ER. On the luminal side, it possesses a lipase motif (GxSxG). A defect in PGAP1 causes a delayed transport of GPI-APs from the ER to the Golgi (as described below); however, the cell surface expression of GPI-APs at the steady state was normal. Nevertheless, the knockout of *Pgap1* in mice results in severe defects in development and fertilization [12]. Most *Pgap1*-knockout mice died soon after birth, and most of them showed otocephaly, a developmental defect exhibiting severely disturbed face and jaw shaping. Interestingly, it has been reported that the gene responsible for the phenotype of *Oto* mice, which show otocephaly, was *Pgap1* itself [32]. The precise

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