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Critical Review

Emerging New Roles of GM130, a *cis*-Golgi Matrix Protein, in Higher Order Cell Functions

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Abstract. GM130 is a peripheral membrane protein strongly attached to the Golgi membrane and is isolated from the detergent and salt resistant Golgi matrix. GM130 is rich in coiled-coil structures and predicted to take a rod-like shape. Together with p115, giantin, and GRASP65, GM130 facilitates vesicle fusion to the Golgi membrane as a vesicle "tethering factor". GM130 is also involved in the maintenance of the Golgi structure and plays a major role in the disassembly and reassembly of the Golgi apparatus during mitosis. Emerging evidence suggests that GM130 is involved in the control of glycosylation, cell cycle progression, and higher order cell functions such as cell polarization and directed cell migration. This creates the potential for novel Golgi-targeted drugs and treatments for various diseases including glycosylation defects, immune diseases, and cancer.

Keywords: vesicular transport, membrane, organelle inheritance, golgin, congenital disorder of glycosylation

1. Introduction

The Golgi apparatus is a central organelle in the secretory pathway. It receives almost all newly synthesized secretory proteins and transmembrane proteins from the endoplasmic reticulum (ER) and processes, sorts, and sends them out to their final destinations. Soon after its discovery by Camiro Golgi, the Golgi apparatus was thought to function in the secretory pathway (1, 2). However, the existence and identity of the Golgi apparatus was under debate until it was confirmed to be an organelle with a characteristic flattened and stacked cisternal structure under electron microscopy in the 1950s (3). Many investigators have been fascinated by the unique structure of the Golgi apparatus and therefore have been trying to understand its molecular basis and physiological roles. The mechanisms of Golgi biogenesis and structural maintenance began to be revealed in the late 1980s, concomitant with progress in the study of vesicular transport machinery.

To date, significant progress has been made in the understanding of the vesicular transport machinery that connects the Golgi apparatus and upstream (ER) or downstream (endosome, lysosome, and plasma membrane) compartments. For example, the mechanisms of standard transport vesicle formation by cytosolic coat proteins (coatomer protein I [COPI], COPII, and clathrin) and their associated factors have been extensively described (4 – 6). Cytosolic coat proteins are recruited and assembled on specific sites of the membrane by activated small G proteins (ADP-ribosylation factor [ARF] for COPI and clathrin, Sar1p for COPII). The assembled coat deforms the membrane and eventually pinches off the membrane to produce a transport vesicle loaded with luminal and membrane embedded cargo molecules. The vesicle coats are then disassembled to enable the fusion of the vesicle with a target membrane. Vesicle fusion is mediated by SNARE (soluble *N*-ethyl maleimide-sensitive-factor attachment protein receptor) proteins that are on both sides of the fusing membranes (7, 8). SNARE proteins are tail-anchored trans-membrane proteins with cytoplasmic coiled-coil domains (some exceptions are

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anchored by a covalently attached lipid). A specific subset of SNARE proteins exists on transport vesicles and target membranes. A SNARE on a transport vesicle (v-SNARE, providing one coiled-coil strand) specifically recognizes and binds a pair complex of SNAREs on a target membrane (t-SNARE, providing three coiled-coil strands) and forms a bundle of four coiled-coil strands, called SNAREpin (7, 9). SNAREpin formation is thought to bring two apposed membranes in close proximity and promote membrane fusion.

The Golgi apparatus disassembles during mitosis and reassembles at the onset of interphase. Warren and colleagues studied the molecular mechanism of Golgi disassembly and reassembly during cell division (10 – 12). During the course of their study, in which I was also involved, GM130 was identified as the first candidate molecule that maintains the structure of the Golgi apparatus (13). GM130 rapidly became a popular Golgi marker and has become a founding member of the "golgins", proteins that are rich in coiled-coil structures and specifically localize to the Golgi apparatus (14, 15). Here, I overview the function of GM130 in the vesicular transport pathway and emerging new roles in the control of glycosylation, cell cycle progression, and higher order cell functions such as cell polarization and directed cell migration.

2. GM130 as a component of the Golgi matrix

The Golgi apparatus consists of a stack of flattened cisternae. It is known that there are proteinaceous links that hold apposed cisternae together (16). The Golgi matrix is a detergent and salt resistant complex that is easily isolated from purified rat liver Golgi membranes (17). The Golgi matrix specifically binds the cytosolic region of Golgi resident transmembrane proteins, so it is supposed to contain intercisternal structural components that support the flattened and stacked cisternal structure. GM130 was identified from the Golgi matrix fraction as a candidate intercisternal structural component (13). Rat GM130 is a homologue of human golgin95, which was identified as an autoantigen of an auto-immune disease, Sjögren's syndrome (13, 18). Accumulating genomic and mRNA sequence data now indicate that golgin95 is a partial fragment of GM130 that lacks the N-terminal region (refer to NCBI gene database GOLGA2: GeneID: 2801). Golgin95 may be a product of an alternatively spliced variant, although this possibility has not been explored. GM130 is conserved in vertebrates including *Xenopus laevis* and *Danio rerio*. A homologue has also been identified in *Drosophila melanogaster*, showing its broad conservation among metazoans (19). On the other hand, no homologue has been identified in unicellular eukaryotes including the budding yeast, *Saccharomyces cerevisiae*. Therefore, it is suggested that GM130 has roles specific for multicellular organisms.

GM130 is predicted to take a coiled-coil structure for most of the molecule with short non-coil N-terminal and C-terminal segments (Fig. 1) (13). The coiled-coil nature suggests that GM130 takes a rod-like shape that is suitable for a structural component or a vesicle-tethering factor (see below). GM130 is a peripheral membrane protein strongly attached to the Golgi membrane and localized mainly at the *cis*-side of the Golgi stack (13).

3. Intercisternal transport and dynamics of GM130

The Golgi stack is polarized in *cis* (an entry face) and *trans* (an exit face). Exocytic materials arrive at the *cis*-cisterna from the ER, serially pass through the cisternae from *cis* to *trans*, and are exported to their final destinations from the *trans*-cisterna (3). It remains controversial whether exocytic cargo molecules are transported by transport vesicles budding from Golgi cisternae (vesicular transport model) or by being retained in a maturing cisterna (cisternal maturation model) (Fig. 2) (20 – 22). In the vesicular transport model, the Golgi stack is assumed to be a stable structure in which Golgi resident enzymes are permanently localized, and exocytic materials are segregated from Golgi residents, concentrated, and exported by budding transport vesicles to the downstream cisternae. In the cisternal maturation model, the Golgi stack is assumed to be a dynamic structure in which a new cisterna is continuously assembled at the *cis*-side and an old cisterna is continuously disassembled at the *trans*-side. A *cis*-cisterna moves in a *cis* to *trans* direction in an escalator-like fashion and eventually "matures" to become a *trans*-cisterna by continuous subtraction or retrieval of Golgi resident enzymes back to the upstream cisternae by retrograde transport vesicles. Real-time fluorescent microscopy studies have shown that the Golgi apparatus actually matures in budding yeast (23, 24). However, the Golgi apparatus does not form a stacked cisternal structure but a cluster of interconnected vesicles in budding yeast (25). Therefore, it remains questionable whether Golgi cisternae also mature in vertebrate cells. Adding complexity, a third model (the direct connection model) has been proposed in which cisternae are directly connected in a transient fashion enabling the transport of the cisternal content (26, 27).

In the vesicular transport model or the direct connection model, GM130 is expected to stably associate with the *cis*-cisterna and not be actively transported elsewhere once it localizes there. In contrast, GM130 is actively and continuously retrieved back to the *cis*-cisterna from a maturing cisterna in the cisternal maturation model.

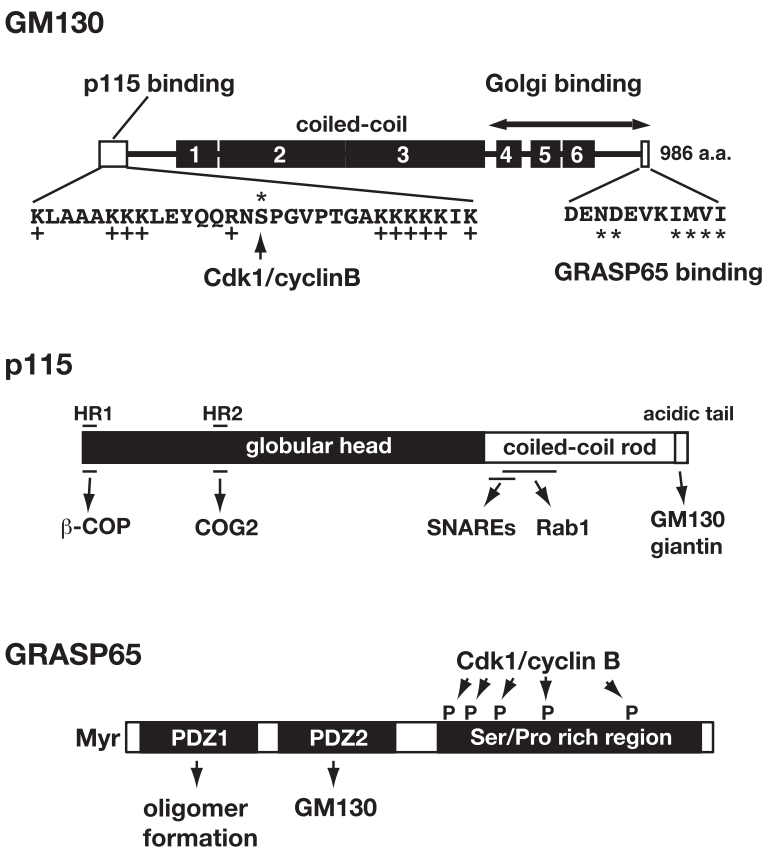

Fig. 1. Structure of GM130, p115, and GRASP65. Top: The structure of GM130 is schematically presented with parts of the amino acid sequence. GM130 consists of 6 major coiled-coil regions in the middle domains of the molecule (solid boxes with numbers) with N-terminal and C-terminal non-coil regions. The N-terminal region is positively charged (indicated by "+") and binds to p115 (open box at the left end). During mitosis, cdk1/cyclinB phosphorylates serine 25 and inhibits p115 binding (asterisks on the bottom). The region from the fourth coiled-coiled domain to the C-terminal end is necessary for Golgi membrane binding (indicated on the top left). The C-terminal end with its bulky hydrophobic residues binds the second PDZ-like domain of GRASP65 (open box at the right end). The residues necessary for GRASP65 binding are indicated by asterisks. Middle: p115 consist of an N-terminal globular head domain (solid box) and C-terminal coiled-coil rod (open box) domain with an acidic tail (open box at the right end). The HR1 and HR2 regions of the N-terminal globular head domain are highly conserved among eukaryotes, including the budding yeast homologue Uso1p. HR1 interacts with β-COP and HR2 interacts with COG2. The C-terminal neck region binds SNAREs and is followed by the overlapping rab1 binding region. The acidic tail binds to GM130. Bottom: GRASP65 has two N-terminal PDZ-like domains and a C-terminal serine/proline-rich region. The second PDZ-like domain binds to GM130. The serine/proline-rich region is heavily phosphorylated by cdk1/cyclin B during mitosis and promotes the disassembly of GRASP65 oligomers, resulting in cisternal unstacking. The first PDZ domain is necessary for GRASP65 oligomerization. Myr: N-terminal myristoylation.

GM130 is not exported from the Golgi cisternae by COPI transport vesicles and remains in remnant Golgi vesicles in the in vitro COPI budding assays or in cells with blocked ER-to-Golgi transport (28, 29). The stable residence of GM130 in the Golgi cisternae fits well with the vesicular transport model. In contrast, GM130 has to be retrieved back to the *cis*-cisterna by an unknown COPI-independent mechanism under the cisternal maturation model. It is possible that GM130 is transferred to the *cis*-cisterna by dissociating from the maturing cisternal membranes. Alternatively, GM130 is retrieved back to the upstream compartment by tubular elements emanating from the Golgi cisternae. Supporting the latter possibility, it has been shown that GM130 recycles between the upstream ER-Golgi intermediate compartment (ERGIC) and the Golgi apparatus by tubular structural elements (30). These possibilities remain to be substantiated.

4. GM130 interacting proteins

GM130 is involved in the regulation of ER-to-Golgi transport and also in the maintenance of the Golgi structure together with its interacting partner proteins, including p115, giantin, GRASP65, and Rab GTPases.

4.1. p115

p115 is the most important partner protein of GM130. It was originally found as a peripheral membrane protein required for intercisternal transport in the Golgi stack and also for transcytosis (31 – 33). p115 is a mammalian homologue of budding yeast Uso1p, which is involved in ER-to-Golgi transport at the vesicle fusion step (34 – 38). In mammalian cells, p115 has been shown to be involved in a similar step of ER-to-Golgi transport (39 – 41). p115 forms a dimer with two N-terminal globular head domains bundled by a coiled-coil rod domain with a C-terminal acidic tail (Fig. 1) (32). The C-terminal acidic tail of p115 interacts with the N-terminal positively charged region of GM130 (42, 43). At the onset of mitosis, the N-terminal positively charged region of GM130 is phosphorylated by cdk1/cyclinB, and the binding of p115 to GM130 is inhibited (42, 44). As a result, COPI vesicle fusion to the Golgi cisternae is reduced, leading to the disassembly of the Golgi apparatus during mitosis (45, 46).

p115 also binds giantin at its C-terminus (Fig. 1) (28, 47). Giantin is a tail-anchored trans-membrane protein

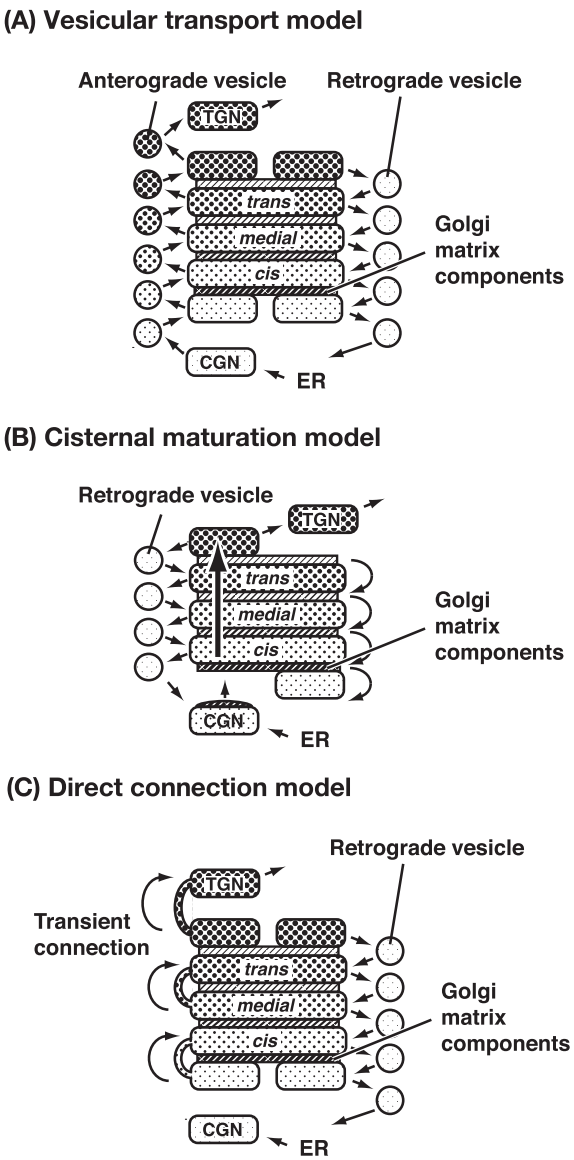

Fig. 2. Intercisternal transport and dynamics of Golgi matrix components. A: In the vesicular transport model, anterograde cargo molecules are transported on transport vesicles budding from the Golgi cisternae in a *cis* to *trans* direction. Golgi resident proteins are retained in stable cisternae and do not move *per se*. Golgi cisternae and Golgi matrix components including GM130 are stably associated. Leaked upstream materials are retrieved back by retrograde transport vesicles. B: In the cisternal maturation model, anterograde cargo molecules are transported in maturing cisternae. Golgi resident proteins are continuously retrieved back to upstream compartments by retrograde transport vesicles. Golgi matrix components are also continuously retrieved back. C: In the direct connection model, the dynamics of the cisternae and Golgi matrix components are similar to the vesicular transport model, except anterograde cargo molecules are transported through transient direct connections between cisternae.

with a large (350 – 380 kDa) N-terminal cytoplasmic region, most of which is predicted to take a coiled-coil structure. Giantin is localized mostly at the rims of Golgi cisternae, suggesting a role in COPI vesicle formation or fusion (48, 49). In vitro vesicle budding assays have shown that GM130 is segregated from COPI vesicles and concentrated in the remaining Golgi cisternal remnant vesicles, while giantin is enriched in COPI vesicles (28). Furthermore, COPI vesicles specifically dock to Golgi remnant vesicles dependent on p115, GM130, and giantin (28). Therefore, the ternary giantin–p115–GM130 complex tethers COPI vesicles to the Golgi cisternae and facilitates vesicle fusion during intercisternal transport (Fig. 3).

p115 interacts with t-SNARE (syntaxin5) and its partner v-SNARE (GOS28) and promotes the assembly of a SNAREpin and subsequent vesicle fusion (50). Therefore, p115 appears to not only increase the probability of SNAREpin formation by constraining a transport vesicle near a target membrane (tethering), but also kinetically enhance the rate of SNAREpin formation, accelerating vesicle fusion to the Golgi cisternae. In addition, while syntaxin5 also binds to GM130, the binding of p115 to GM130 inhibits syntaxin5 binding to GM130 (51). Syntaxin5 is thus most likely transferred from GM130 to p115 after p115–GM130 tethers formation, facilitating SNAREpin formation (Fig. 3).

As described above, p115 and GM130 are now known to function in ER-to-Golgi transport as tethering factors for transporting vesicles to the Golgi cisternae (40, 41, 52 – 59). Concepts such as “vesicle tethering” and “tethering factor” have been rapidly accepted to describe the pre-docking step of transport vesicle targeting in ER-to-Golgi transport and other vesicular transport pathways including endosomal traffic (60, 61). Generally, vesicle tethering is defined as transient long distance docking of a vesicle to a target membrane. A transport vesicle is specifically tethered to a target membrane for a certain amount of time, allowing the proper v- and t-SNARE to meet and proceed to short distance docking by SNAREpin formation. If the proper SNAREpin cannot be produced, a vesicle is released to meet another target membrane. Tethering factors therefore not only facilitate but also add another layer of specificity for vesicle docking and fusion. To date, several classes of tethering factors have been identified, including the p115–GM130–giantin tether. Among these, the conserved oligomeric Golgi (COG) complex and transport protein particle (TRAPP) complex have been shown to function in ER-to-Golgi transport. These other classes of tethering factors may also cooperate with the p115–GM130–giantin tether to support ER-to-Golgi transport (58, 61, 62).

4.2. GRASP65

GRASP65 (Golgi reassembly stacking protein) is the

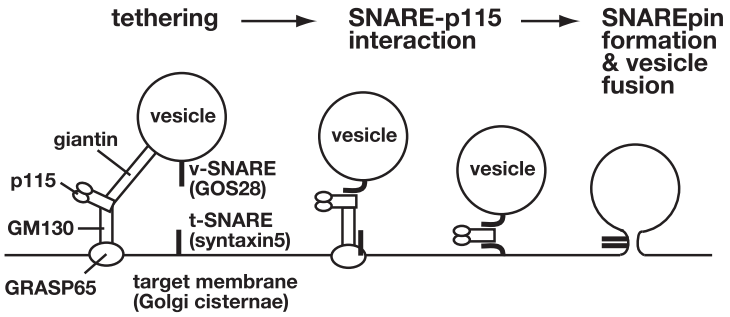

Fig. 3. Vesicle tethering facilitates SNAREpin formation and vesicle fusion. Left: A transport vesicle is tethered to a target membrane (Golgi cisternae) by the formation of the giantin–p115–GM130 ternary complex. Middle left: v-SNARE (GOS28) binds to p115, while t-SNARE (syntaxin5) binds to GM130. Middle right: t-SNARE (syntaxin5) is transferred to p115. Right: p115 facilitates SNAREpin formation and the following vesicle fusion.

second important binding partner for GM130. It is a peripheral membrane protein tightly attached to the Golgi membrane and is involved in cisternal stacking (63). GRASP65 is concentrated together with GM130 at the *cis*-side of the Golgi stack and also at the intercisternal space (64). GRASP65 is N-terminally myristoylated and has two PDZ (a common protein binding domain found in post synaptic density 95 [PSD95], disk large tumor suppressor [Dlg], and zomula occludens protein 1 [ZO-1])–like domains at the N-terminal region (Fig. 1). GRASP65 binds to the Golgi membrane and forms a homo-oligomer. Therefore, GRASP65 has been proposed to bridge two apposed cisternal membranes and promote cisternal stacking (65). The C-terminal part of GRASP65 is rich in serine and threonine and heavily phosphorylated by cdk1/cyclinB during mitosis (Fig. 3). The phosphorylation of this region inhibits the oligomerization of GRASP65 and promotes cisternal unstacking during mitosis (66). The first PDZ-like domain also plays an essential role for oligomer formation (67). GM130 binds to the second PDZ-like domain of GRASP65, and bulky hydrophobic residues at the C-terminal end of GM130 are necessary for this binding (Fig. 1) (63). An in vitro binding experiment indicated that GRASP65 is the receptor for GM130 on the Golgi membrane (68). On the other hand, the myristoylation and binding to GM130 are necessary for the targeting of GRASP65 to the Golgi membrane, suggesting that GM130 and GRASP65 cooperate and depend on each other for Golgi membrane binding. (69). Therefore, GM130 is thought to function in cisternal stacking together with GRASP65.

GRASP55 is a paralogue of GRASP65 conserved in most vertebrates. GRASP55 has a similar overall structure with GRASP65 and is localized to the Golgi apparatus (64). Compared to GRASP65, which is concentrated at the *cis*-cisterna, GRASP55 is distributed broadly in all cisternae from *cis* to *trans* and binds golgin45, a coiled-coil protein similar to GM130 (70). GRASP55 is reported to function in cisternal stacking and Golgi ribbon formation (64, 71). Like GRASP65, GRASP55 is phosphorylated during mitosis, which is thought to promote Golgi disassembly during mitosis (72, 73). Simultaneous knockdown of GRASP65 and GRASP55 completely disassembles the Golgi apparatus, while single knockdown of either GRASP65 or GRASP55 does not largely affect the structure of the Golgi apparatus (71, 74 – 76). Therefore, GM130–GRASP65 and golgin45–GRASP55 are thought to have complimentary functions for cisternal stacking and maintenance of the Golgi structure.

GRASP65 and GRASP55 directly interact with C-terminal valine motifs of membrane cargo proteins including CD8α and Frizzled4 receptor and promote effective transport of cargo proteins through the ERGIC and the Golgi apparatus (discussed later) (77).

4.3. Rab GTPases

Rab proteins are a family of small GTPases that belong to the Ras superfamily and are thought to control various steps of vesicular transport, especially vesicle docking and fusion (15, 62, 78 – 81). More than 60 Rab proteins have been identified in mammalian cells, and detailed localization of these members has been extensively described (82). Generally, a Rab protein binds to a vesicle membrane in its GTP-bound form and recruits effector protein(s) to the membrane for exerting its regulatory functions.

Rab1 and Rab33b bind GM130 and regulate the docking of ER-derived vesicles to the Golgi membranes, although the precise roles of Rab1 and Rab33b remain to be described (83 – 85). Interestingly, binding of Rab1 to GM130 is inhibited by binding of p115 to GM130 (51). On the other hand, Rab1 binds to p115 as well (Fig. 1) (86). As binding of p115 to GM130 promotes vesicle tethering and the subsequent assembly of SNAREpin (Fig. 3) (50, 51), it is probable that rab1 regulates the binding of p115 and GM130 and the subsequent assembly of SNAREpin and vesicle fusion.

5. Function of GM130

5.1. Vesicular transport and Golgi structure

The inhibition of p115 and GM130 binding in vivo

slows but does not completely stop ER-to-Golgi transport or Golgi-to-plasma membrane transport (40, 54, 59). GM130 knockdown by RNA interference also results in a similar partial inhibition or delay of ER-to-Golgi transport (51), although the extent of inhibition is somewhat controversial (74). In addition, a mutant CHO cell line (*ldl*G), which lacks GM130, is viable while it shows certain glycosylation defects and temperature sensitivity for cell growth (87). It is possible that another molecule(s) with an overlapping function compensates the loss of GM130 function. Since the function of GRASP65, a partner protein of GM130, is complemented by GRASP55, it is reasonable to assume that the golgin45–GRASP55 tether has a complementary role for the GM130–GRASP65 tether for the maintenance of the Golgi structure and efficient ER-to-Golgi and intra-Golgi transport (76). Alternatively, GM130 functions not in general ER-to-Golgi or intra-Golgi transport but in transport of a subset of cargo molecules. Supporting this possibility, it has been shown that GM130 and its partner protein GRASP65 promote efficient transport of membrane proteins with C-terminal valine motifs, including CD8α and Frizzled4 receptor, but not the general cargo transport (77).

As described above, vesicle tethering is understood to enhance or fine-tune SNARE promoted vesicle fusion. Therefore, it is reasonable to assume that tethering factors including GM130 play roles in quality control of ER-to-Golgi or intra-Golgi transport that are essential for higher order cell functions.

5.2. Glycosylation

Knockdown of GM130 inhibits the lateral fusion of Golgi stacks and disturbs a uniform distribution of Golgi enzymes affecting proper glycosylation of membrane and secretory proteins (74). Therefore, a deficiency of vesicle tethering is predicted to affect proper glycosylation of proteins and lipids. Consistent with this idea, mutations of subunits of the COG complex, another tethering factor functioning in the Golgi apparatus, cause glycosylation defects leading to a subtype of congenital disorder of glycosylation (CDG), which manifests as a severe childhood disease including perinatal death (88, 89). While the p115–GM130 tether is proposed to function in anterograde ER-to-Golgi transport, the COG complex is proposed to function in retrograde transport in the Golgi apparatus (90). Interestingly, the COG complex interacts with p115 (Fig. 1) (58), suggesting that the p115–GM130 tether cooperates with the COG complex for proper organization of glycosylation machinery at the Golgi apparatus.

Glycans attached to proteins and lipids have important roles in the development and physiology of multicellular organisms (91). Therefore, it is possible that GM130 has some roles in these higher order cell functions by providing a proper glycosylation environment in the Golgi apparatus (Fig. 3).

5.3. Cell cycle, cell polarity, and directed cell migration

Emerging evidence has indicated that GM130 has unexpected roles in the control of cell division, polarization, and directed cell migration. First, GM130 binds yeast Sps1/Ste20–related kinase 1 (YSK1), which is a mammalian homologue of Ste20 kinase involved in signal transduction, and promotes cell movement and invasion into the collagen matrix (92). Second, GM130 appears to control centrosome organization by binding to Tuba, a guanine nucleotide exchange factor for cdc42 (93). Accordingly, knockdown of GM130 causes abnormal multiplication of centrosomes and multi-polar spindle formation, leading to a defect in proper cell division (94). Finally, GM130 recruits A-kinase anchoring protein 450, also known as centrosome- and Golgi-localized PKN (protein kinase N)–associated protein (AKAP450/CG-NAP), which interacts with γ-tubulin complexes, to the Golgi apparatus and nucleate microtubules from the Golgi apparatus (95). The nucleated microtubules from the Golgi apparatus have a role in Golgi ribbon formation and establishing cell polarization and directed cell migration (96).

Interestingly, GRASP65, a GM130 partner protein, is also involved in these processes. First, phosphorylation of GRASP65 plays a critical role in the regulation of entry into mitosis. It is proposed that the fragmentation of the Golgi apparatus is necessary for entry into mitosis (the existence of a "Golgi checkpoint" for mitotic entry), and this is controlled by the phosphorylation of GRASP65 (97, 98). GRASP65 is phosphorylated by cdk1/cyclinB and extracellular signal–regulated kinase (ERK), and the phosphorylation promotes Polo-like kinase 1 (Plk1) binding and further phosphorylation of GRASP65 by Plk1 (98, 99). Therefore, GRASP65 is thought to be actively involved in the regulation of cell cycle control as a scaffold or a switch of the signal transduction pathway. Second, GRASP65 has been shown to be involved in spindle dynamics directly but not via Golgi disassembly (100). As GM130 is involved in the control of centrosome organization (93, 94), the GM130–GRASP65 complex may play a critical role in the regulation of centrosome organization and spindle dynamics independent of their function in the regulation of the Golgi structure. Alternatively, the regulatory mechanism of the Golgi structure can be integrated with that of centrosome organization and spindle dynamics. Finally, and supporting the above possibilities, the phosphorylation of GRASP65 plays a

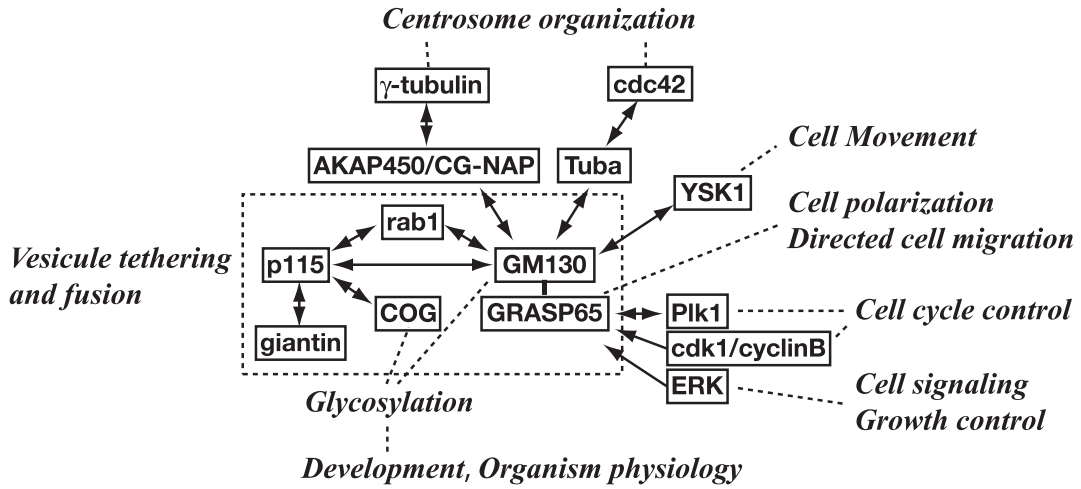

Fig. 4. Proposed functions of GM130. GM130 and GRASP65 are involved in vesicle tethering and fusion together with p115, giantin, and rab1 (indicated by the box). GM130 participates in centrosome organization by an interaction with AKAP450/CG-NAP and Tuba and in the control of cell movement by an interaction with YSK1. GM130 also plays a role in the control of glycosylation directly or indirectly by an interaction with the COG complex via p115. Through phosphorylation of its partner protein, GRASP65, GM130 is involved in cell cycle control, cell signaling, growth control, cell polarization, and the directed cell migration.

critical role in the reorganization of the Golgi apparatus during directed cell migration (101). Strikingly, the reorganization of the Golgi apparatus appears to be necessary for the reorientation of centrioles toward the direction of cellular movement (101).

Evidence suggests that GM130 and GRASP65 play active roles in the control of the cell cycle, cell polarization, and directed cell migration in addition to their classical roles in vesicle tethering and the maintenance of the Golgi structure (Fig. 4).

6. Future perspectives

Significant progress has been made in understanding the molecular mechanisms of the structural maintenance of the Golgi apparatus. However, details of the mechanisms and the dynamics of the component molecules are still largely unknown. On the other hand, there is growing evidence indicating that the Golgi apparatus has roles in the control of cell cycle progression, cell polarization, and directed cell migration in addition to its classical roles in the secretory pathway and glycosylation. GM130 and its partner proteins appear to have important roles in these higher order cellular functions and are involved in various diseases and the physiology of multicellular organisms. Future work will pave the way for developing new Golgi-targeted drugs and treatments of various diseases, including glycosylation defects, immune diseases, and cancer.

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