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Unlocking Golgi: Why Does Morphology Matter?

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Abstract

The mammalian Golgi apparatus is a highly dynamic organelle, which is normally localized in the juxtanuclear space and plays an essential role in the regulation of cellular homeostasis. While posttranslational modification of cargo is mediated by the resident enzymes (glycosyltransferases, glycosidases, and kinases), the ribbon structure of Golgi and its cisternal stacking mostly rely on the cooperation of coiled-coil matrix golgins. Among them, giantin, GM130, and GRASPs are unique, because they form a tripartite complex and serve as Golgi docking sites for cargo delivered from the endoplasmic reticulum (ER). Golgi undergoes significant disorganization in many pathologies associated with a block of the ER-to-Golgi or intra-Golgi transport, including cancer, different neurological diseases, alcoholic liver damage, ischemic stress, viral infections, etc. In addition, Golgi fragments during apoptosis and mitosis. Here, we summarize and analyze clinically relevant observations indicating that Golgi fragmentation is associated with the selective loss of Golgi residency for some enzymes and, conversely, with the relocation of some cytoplasmic proteins to the Golgi. The central concept is that ER and Golgi stresses impair giantin docking site but have no impact on the GM130–GRASP65 complex, thus inducing mislocalization of giantin-sensitive enzymes only. This cardinally changes the processing of proteins by eliminating the pathways controlled by the missing enzymes and by activating the processes now driven by the GM130–GRASP65-dependent proteins. This type of Golgi disorganization is different from the one induced by the cytoskeleton alteration, which despite Golgi de-centralization, neither impairs function of golgins nor alters trafficking.

Keywords

Golgi morphology; golgins; giantin; GM130; GRASP65; Golgi-resident enzymes; ER stress; cancer

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Over the past three decades, the structure and function of the Golgi apparatus have attracted ever-increasing attention in the biomedical research. The Golgi is the central sorting and transportation station for the posttranslational modification of cargo molecules, which is provided by resident proteins represented by different families of glycosyltransferases, glycosidases, and kinases. Under normal physiological conditions, the Golgi localizes within the juxtanuclear area and forms a ribbon-like, convoluted structure composed of a stack of cisterns and associated vesicles. However, it has become clear that, besides processing of proteins, Golgi is also involved in various integrated cellular processes and responses, such as mitosis, apoptosis, stress, autophagy, and carcinogenesis [1-5]. Many of these intracellular events are associated with the rearrangements of Golgi morphology, from mild enlargement to severe fragmentation and unstacking. For example, as we described previously [6], treatment of VA-13 cells (HepG2 cells expressing alcohol dehydrogenase) with ethanol results in the expansion of Golgi membranes after 24 h and Golgi conversion to the fragmented phenotype after 72 h (Fig. 1). The determination of the extent of Golgi fragmentation is based on simple calculations, which we have employed previously [7] and used here to analyze the data presented by other groups. Briefly, the entire cell was divided into three areas: nuclear (A), perinuclear (B), and cytoplasmic (C). After subtraction of the nuclear region, the cytoplasm is considered as two-third of (B + C), while one-third of this sum is denoted as the perinuclear area, where the Golgi is located. We consider the Golgi fragmented if separate Golgi membranes are detected beyond the perinuclear area. This type of Golgi disorganization is described by some authors as a peripheral fragmentation, contrary to the central Golgi fragmentation when membranes lose stacking but still concentrate in the perinuclear area [8, 9]. In this review, we will mostly highlight the evidence of abnormal distribution of cytoplasmic and Golgi resident proteins in cells, whose Golgi is experiencing peripheral fragmentation.

GOLGINS: MORE THAN A SCAFFOLD

Several Golgi matrix proteins, referred to as *golgins,* form the structural scaffold of the Golgi. Most of these proteins are predicted to form coiled-coil dimers, whose *C*-terminals mediate attachment to Golgi membranes, and *N*-terminals project into the cytoplasm for up to 400 nm [10]. The function of golgins is coordinated by the Golgi reassembly stacking proteins (GRASPs) [11]. Among these proteins, giantin, GM130, and GRASP65 have been the most studied. Giantin is the highest-molecular-weight (376 kDa) Golgi matrix dimeric protein with a large (⩾350 kDa) A-terminal cytoplasmic region [12]. It is distributed throughout the Golgi stack, with predominant positioning in the medial cisternae [13, 14]. GM130 is a *cis*-Golgi-localized, segmented coiled-coil dimer that binds to Golgi membranes through its *C*-terminal region via preferential interactions with GRASP65 [15, 16] (Fig. 2a). The functioning of both golgins and GRASPs is tightly linked to the fidelity of glycan processing [16-20]; however, the detailed molecular processes are not well understood. The clue comes from the mounting evidence indicating that golgins serve as the docking sites for different types of Golgi-targeting vesicles [21-24], implying that transportation of the Golgi resident enzymes to their location sites relies on their cooperation with Golgi matrix proteins. This concept has been gaining momentum since the early observation by the Warren group, indicating that isolated rat liver Golgi matrix contains both α-mannosidase II

(Man-II) and mannosyl-(α-1,3)-glycoprotein β-1,2-N-acetylglucosaminyltransferase (MGAT1) in the remnants of Golgi cisternae, which can be removed by the treatment with low salt. Washout of salt restores the binding of these enzymes to the membranes; however, re-binding is abolished in the presence of proteinase K, signifying that the protein complexes between the cisternae represent critical docking sites for Golgi enzymes [25].

GIANTIN AND GM130–GRASP65: TOGETHER OR SEPARATE?

Despite the obvious importance of golgins for Golgi architecture, individual silencing of related genes does not substantially change visible positioning of this organelle. Indeed, depletion of *cis*-Golgi proteins (GPP130, GRASP65, GM130, or golgin-160 [16, 18, 26, 27]), *medial*-Golgi proteins (golgin-84 and giantin [16, 28]), and *trans*-Golgi proteins (golgin-97, p230, GCC185, and TMF [29-32]) may affect the Golgi ribbon and induce central Golgi fragmentation, but it has no significant effect on the perinuclear location of Golgi. Moreover, in the mouse model of GRASP65 or giantin knockouts, Golgi still appeared juxtanuclear, and no significant alterations in the development of these animals have been reported [33, 34]. The most probable explanation of this phenomenon is the exchangeability of golgins, where the lack of one matrix protein can be compensated by the overexpression of others. For example, the knockdown of GRASP65 gene induces an increase in the GM130 and giantin content [16]. Meanwhile, knockdown of GRASP65 does not affect the intra-Golgi position of GM130 [16, 18, 20], since GM130 can be tethered to the Golgi via giantin [16]. In advanced prostate cancer (PCa) cells, Golgi undergoes fragmentation, which is associated with a reduction of giantin levels and its de-dimerization [20] (Fig. 2b). In these cells, depletion of GRASP65 reduces the GM130 levels and GM130 association with Golgi [20], confirming the importance of both giantin dimer and GRASP65 for the GM130 tethering to Golgi.

One may assume that polarization of Golgi is primarily determined by the cytoskeleton [35]. Certainly, treatment with cytochalasin D (actin destabilization agent) [36] or nocodazole (microtubule depolymerization agent) [37] results in extensive Golgi fragmentation. However, concurrent lack of different golgins can itself cause significant alterations in the Golgi structure. For instance, during apoptotic Golgi disorganization, caspase-mediated cleavage of several golgins preceded major changes in the organization of both actin and tubulin cytoskeletons [38-41]. In our observations [42], codepletion of giantin and GM130 was sufficient to induce peripheral fragmentation of Golgi.

It has been postulated that giantin cooperates with GM130 via interactions with the vesicle docking protein p115, suggesting a common contribution to the trafficking of coatomer protein complex I (COPI) vesicles [43]. However, this model fails to explain intra-Golgi transportation of COPI in intra-*medial*- and *medial*-*trans*-Golgi directions because, contrary to giantin, distribution of GM130–GRASP65 is restricted to cis-Golgi only [44]. This implies that giantin may interfere with intra-Golgi trafficking independently from GM130–GRASP65. Also, further studies revealed that the response of giantin to different cellular perturbations is distinct from that of GM130 and GRASP65. It is known that the dysfunction of GTPases involved in endoplasmic reticulum (ER)-to-Golgi or intra-Golgi trafficking results in ER stress, loss of Golgi integrity, and collapse of its membranes into the ER [45].

For instance, in cells overexpressing a GTP-restricted mutant of Sarlp (H79G) or treated with different inhibitors of ARF1, brefeldin A (BFA) and AMF-26, most of Golgi resident proteins (including golgin-45, GRASP55, and giantin) relocate partially to the ER. However, both GM130 and GRASP65 are completely retained in the punctate cytoplasmic structures, namely Golgi remnants [46, 47]. A similar effect was observed in cells treated with an inhibitor of GBF1 (guanine nucleotide exchange factor for ARF1), golgicide A [45]. Next, Golgi membranes undergo fusion with ER elements in BFA-treated cells [48]; however, co-treatment with BFA and 50 μM H-89, the protein kinase inhibitor, results in the appearance of only tubular structures toward the ER, where GM130-, GRASP65-, GRASP55-, and p115-positive elements are segregated from giantin-specific tubules [49]. Finally, depletion of GM130 disrupts the association of GRASP65 with the Golgi and reduces its expression; however, it is dispensable for giantin localization and has no impact on cargo transport [16, 18, 50]. Further, the work from our laboratory indicates that the specific vesicular complexes carrying Golgi-resident glycosyltransferases are COPI- and COPII-independent and employ two separate recruitment sites at the Golgi: giantin and the complex of GM130 and GRASP65 [16] (Fig. 2, a and b).

Most of the Golgi-resident proteins are type II membrane proteins consisting of a short cytoplasmic tail at the *N*-terminus, which is followed by a transmembrane domain, a short stem, and a large catalytic region [51]. The cytoplasmic tail of glycosyltransferases is involved in every intracellular trafficking step, including ER exit [52], Golgi targeting [16], Golgi retention [53-58], and recycling [59]. Different research groups, including ours, have clearly demonstrated that Golgi localization of several resident enzymes requires giantin [16, 20, 34, 60, 61]. On the other hand, other Golgi proteins appear to be GM 130-sensitive [16, 42, 62-65]. Our screening of known giantin-sensitive enzymes revealed the dibasic KK, RR, or KR motifs in their cytoplasmic domain (Fig. 3, left, bold/underlined); however, the *N*-terminal tail of the GM130–GRASP65-dependent enzymes primarily contains different combinations of hydrophobic motifs (Fig. 3, right, bold/underlined). The only exception was found in α-1,2-mannosidase I (Man-I), whose cytoplasmic domain contains both a strong hydrophobic region and one RR motif; however, giantin depletion has no significant effect on the intra-Golgi position of Man-I [42]. Interestingly, direct interaction with both GRASP65 and GRASP55 was essential for Golgi docking of several members of the p24 family. Importantly, p24a has two *C*-terminal valine residues that are required for this interaction [66], again confirming the importance of hydrophobic interactions for docking to either GRASPs or GM130 and implying that this phenomenon is applicable not only for Golgi resident enzymes but also for other proteins.

MISLOCALIZATION OF CELLULAR ENZYMES OR “THERE AND BACK AGAIN”

In summary here, it appears that the combination of giantin, GM130, and GRASP65 is critical for Golgi homeostasis, and dysfunction of either protein inevitably results in selective mislocalization of resident enzymes, depending on their specificity. In hepatic cells treated with ethanol, the loss of dimeric giantin is associated with the redistribution of MGAT1 to the cytoplasm [42]. For the same reason, in advanced PCa cells, core 2 N-acetyl-

glucosaminyltransferase-L (C2GnT-L) was found to be mislocalized, which results in the domination of alternative “pro-metastatic” O-glycosylation via β-galactoside-α-2,3-sialyltransferase-1 (ST3Gal1), which uses GM130–GRASP65 as the Golgi docking site [20]. Furthermore, both *in vitro* and *in vivo* data indicate that ethanol-induced fragmentation of Golgi in PCa cells is accompanied by mislocalization of an “anti-metastatic” Golgi enzyme, N-acetylglucosaminyltransferase-III (MGAT3), thus inducing activation of a “pro-oncogenic” Golgi glycosyltransferase, N-acetylglucosaminyltransferase-V (MGAT5), which still remains in the fragmented Golgi membranes [67]. In recent years, multiple observations describe the redistribution of Golgi proteins to different intracellular structures. Nevertheless, the underlying translocation mechanisms are not yet understood, and the Golgi-docking partners for most of the resident enzymes still need to be identified. For example, neutralization of pH in the Golgi results only in the enlargement of the stack, but it does not affect its perinuclear position. Still, it causes a redistribution of different Golgi glycosyltransferases to the ER [68, 69]. Disialoganglioside 3 (GD3) synthase converts ceramide to the ganglioside in the Golgi. This enzyme has been shown to translocate to the mitochondria during apoptosis, where it triggers the swelling of mitochondria, as well as the release of cytochrome *c,* apoptosis-inducing factor, and caspase 9 [70]. Trip230, a coactivator of the thyroid hormone receptor, is localized predominantly to the vicinity of the Golgi; however, during the cell cycle, it translocates to the nucleus [71]. Conversely, some proteins can be shifted in the opposite, ER-to-Golgi direction. CerS1, one of a family of enzymes responsible for the *de novo* synthesis of ceramide, is a typical ER-resident that translocates to the fragmented Golgi upon UV light-or dithiothreitol-induced stress [72].

Similar behavior was observed for the Golgi-localized kinases. In PCa cells, ethanol-induced Golgi disorganization induces a shift of giantin-sensitive glycogen synthase kinase 3β (GSK3β) from Golgi to the cytoplasm [61], which results in the downstream activation of cytoplasmic histone deacetylase 6 (HDAC6) and subsequent transactivation of androgen receptor (AR), the driver of prostate tumor cell proliferation. Additionally, under normal conditions, cAMP-dependent protein kinase (cAMP-dPK II) resides in the Golgi, but stimulation of adenylate cyclase by forskolin leads to Golgi disorganization and redistribution of this enzyme to the nucleus. Interestingly, forskolin removal reverses Golgi morphology and restores the intra-Golgi positioning of cAMP-dPK II [73]. Similarly, SOK1, a Ste20 protein kinase of the germinal center kinase (GCK) family, is localized to the Golgi, where it functions in a signaling pathway required for cell migration and polarization. SOK1 drives the apoptotic response to reactive oxygen species (ROS) and chemical anoxia, a model of ischemia characterized by marked ROS production and severe ATP depletion. Importantly, this activation is associated, again, with Golgi disorganization and translocation of SOK1 to the nucleus [74]. Treatment of colon cancer cells with the bile-specific deoxycholic acid alters Golgi structure, induces partial translocation of protein kinase Cη (PKCη) from Golgi to the cytoplasm, and reduces protein secretion [75]. The extracellular signal-regulated kinase 8 (ERK8) localizes to the Golgi but, upon growth factor stimulation, it is segregated from the enlarged Golgi membranes [76]. The same study indicates that depletion of phosphatidylinositol (PI) 4-kinase (PI4KA) results in cytoplasmic Golgi and redistribution of GalNAc-transferase from Golgi to the ER. Similarly, serine/threonine-

protein kinase 16 (STK16) resides in the Golgi and regulates actin dynamics, but the depletion or inhibition of STK16 causes Golgi fragmentation [77].

Therefore, kinases may directly interfere with Golgi positioning and localization of various resident proteins. Translocation of the βγ subunit of G-protein-coupled receptors from the plasma membrane to the Golgi is associated with Golgi disorganization and is triggered by protein kinase D (PKD) [78]. This finding is reminiscent of the effects of butanol on Golgi, which are characterized by fragmentation and loss of βIII spectrin in the *trans*-Golgi, as well as its phosphorylation, presumably by the c-Src kinase [79, 80]. Activation of Src kinase per se has a profound effect on Golgi morphology [81], with the same study showing that pancreatic, tumor-derived cells have a fragmented Golgi phenotype that can be reversed via inhibition of Src. Finally, oxidative stress can induce Golgi scattering [1] and cause phosphorylation of the calcium-dependent phospholipid-binding protein annexin II by the Lyn, a member of the Src kinases, leading to the translocation of annexin II from the Golgi to the ER [82].

On the other hand, growing evidence indicates that different cytoplasmic kinases may dislocate to the Golgi upon disturbance of its ribbon organization. During mitosis-specific Golgi fragmentation, cyclin-dependent kinase 1 (Cdk1–cyclin B) phosphorylates GRASP65, which, in turn, serves as a docking site for the Polo-like kinase 1 (Plk1) [83]. Additionally, GRASP65 can be phosphorylated by ERK, which results in the loss of GRASP65 oligomerization and Golgi cisternal unstacking [84]. Similarly, the timing of the appearance of activated mitogen-activated protein kinase kinase 1 (MEK1) in the Golgi also coincides with the initiation of its mitotic fragmentation [85]. Treatment of cells with the platelet-activating factor stimulates translocation of protein kinase Ca (PKCa) to the Golgi; however, this was not the case in cells with Golgi collapsed by pre-treatment with BFA [86].

GOLGI RESIDENT PROTEINS: ARE THEY THE POWER BEHIND THE THRONE?

At this time, an important question has arisen: what influence do other resident enzymes have on Golgi morphology? In some instances, the silencing of genes for Golgi proteins has little effect on the Golgi morphology. For example, out of 70 human Rab GTPases, 20 proteins showed Golgi localization [87] but, to the best of our knowledge, only Rab1, Rab6a, Rab18, and Rab41 are required for compact and perinuclear Golgi [20, 88, 89]. However, many independent studies have shown that depletion of different Golgi-associated proteins drastically affects Golgi organization, resulting in the loss of ribbon formation and scattering of Golgi elements throughout the cell [90-92]. Nevertheless, these data need to be interpreted tentatively, as not every case of Golgi disorganization induced by the downregulation of its resident proteins can be attributed to their direct contribution to the Golgi architecture. For instance, knockdown of conserved oligomeric Golgi (COG) proteins Cog 2, 4, 6, and 8 compromises the morphological integrity of the Golgi; however, COG complex-deficient cells were not defective in Golgi re-assembly after BFA washout [93].

In many cases, depletion of individual Golgi proteins impairs intra-Golgi trafficking of cargo, followed by stalled protein export to and from the Golgi, resulting in slow ER-to-

Golgi trafficking, development of ER stress, and subsequent unfolded protein response (UPR) [94, 95]. Ultimately, sub-lethal ER stress inevitably results in Golgi disorganization because of the impaired trafficking and processing of golgins [6, 96, 97]. Alternatively, ER stress can be initiated by mutations in proteins and their subsequent misfolding and aggregation in the ER, which causes fragmentation of the Golgi and disrupts ER-to-Golgi traffic [98]. For example, depletion of MGAT1 does not impair Golgi positioning and morphology [93]; however, mutated MGAT1, which retains in the ER, results in Golgi disorganization and subsequent selective relocation of other Golgi enzymes to the ER, including Man-II and β1,4-galactosyltransferase 1 (GalT) [99]. Broadly speaking, there is no ER stress without Golgi stress, and *vice versa.*

Thus, we may postulate that only ER- or Golgi-stress related Golgi disorganization may result in mislocalization of Golgi enzymes and abnormal N- or O-glycan processing [4, 100]. Now, it is becoming clear why neither nocodazole nor cytochalasin D are able to alter glycosylation of cargo, despite destabilization of microtubule or actin network and extensive Golgi de-centralization [7, 101, 102]. Indeed, intra-Golgi transport still can occur in these cells (reviewed by Mironov and Beznoussenko [8]). However, we observed that in the cells treated with these drugs, the giantin-sensitive Golgi enzyme C2GnT-M is still situated in the Golgi [7], which implies that this type of Golgi fragmentation is likely not associated with abrogation of the ER-to-Golgi trafficking and alterations of the golgin network. Remarkably, Golgi may undergo physiological short-time de-centralization similar to that induced by microtubule-disrupting drugs. For instance, this has been observed during differentiation of myoblasts into myotubes [103, 104], or upon delivery of uroplakins to the apical plasma membrane of superficial uroepithelial cells of the urinary bladder [104]. But again, all these types of Golgi remodeling were associated with the impairment of the microtubule organization and redistribution of intermediate filaments rather than alteration of the Golgi scaffold. Quite contrary, BFA-induced Golgi collapse and subsequent ER stress [105] are accompanied by: (i) degradation of most Golgi matrix proteins, including giantin [106], (ii) giantin de-dimerization (our observation, manuscript in preparation), (iii) translocation of Golgi-resident enzymes into the ER, and (iv) abnormal glycosylation [7, 8].

GM130-GRASP65 COMPLEX: A “CRISIS MANAGER”

As we mentioned above, under stress conditions, most of the golgins are located very close to the ER cisternae [22]. Some of them can even be detected in the ER, such as GRASP55 and giantin, which also have been found to lose their dimeric structure; nevertheless, GM130–GRASP65 are detected only in these fragmented Golgi membranes [6, 46, 47]. For example, ethanol-induced Golgi disorganization does induce monomerization of giantin but has no significant impact on the cooperation between GM130 and GRASP65 [6, 61]. In addition, we have shown that giantin, but not GM130 or GRASP65, is required for post-alcohol recovery of compact and perinuclear Golgi, which, in turn, is a prerequisite for successful processing and trafficking of hepatic glycoproteins to the cell surface [107]. Recently, we detected a large fraction of AKT1 kinase in the Golgi of ethanol-treated PCa cells, which, however, was not observed in the cells depleted by GM130 (manuscript in preparation). It seems logical to hypothesize that the Golgi disorganization, the lack of giantin dimer, and the loss of cooperation between giantin and GM130 may stimulate the

opening of new GM130-specific docking sites that have been previously masked by giantin (Fig. 2b).

We were mindful of the newly emergent paradigm that GM130 is the main post-ER stress Golgi tether, and observations from other labs validate this concept. Indeed, cells infected with coxsackievirus B3 (CVB3), a causative agent of viral myocarditis, pancreatitis, and meningitis in humans, demonstrate disorganization of the Golgi, which is associated with the complex between coxsackievirus B3 (CVB3) and GM130 [108]. Additionally, Golgi undergoes significant reorganization in the cortical neurons of hibernating animals, which is associated with an increase in the GM130 expression [109]. Another clinically important example of GM130's interference with Golgi remodeling is found in cancer. The link between carcinogenesis and alterations in Golgi structure is well documented. In different cultured cells lines and tumor tissue sections, Golgi fragmentation was associated with atypical glycosylation, relocation of different Golgi enzymes to the ER, and enhanced metastatic potential of the cells [110-114]. Furthermore, in a mouse model of lung cancer, downregulation of GM130 reduces angiogenesis and cancer cell invasion, as well as induces autophagy, thus promoting cell death [115]. In androgennegative PCa cells, which demonstrate a fragmented Golgi phenotype, the activity of GM130 is directly linked to the formation of pro-metastatic glycan epitopes [20]. Remarkably, despite massive disorganization, stacking of Golgi membranes in these cells is preserved, implying that GRASPs are important for the cancer-specific Golgi remodeling. Indeed, contrary to the androgen-sensitive low-passage LNCaP cells, their high-passage counter-parts and PC-3 cells, which represent advanced androgen-refractory PCa cells, demonstrate fragmented Golgi and reduced giantin dimers [20] (Fig. 4, a and b, top panel). Surprisingly, the levels of GRASP65 tetramers were reduced in both high-passage LNCaP and PC-3 cells and, conversely, the amount of GRASP65 dimer was enhanced (Fig. 4b, lower panel), implying that GRASP65 oligomerization, but not its dimerization, is impaired (Fig. 4, b and c). The precise mechanism of these conformational changes still needs to be determined, and future studies in different cancer cells should reveal whether GRASP55 and other golgins are involved in the maintenance of this Golgi phenotype.

THE VICIOUS CIRCLE OF POST-ER STRESS TRAFFIC

The next question involves the impact of Golgi disorganization on secretion. It has been shown that knockdown of GRASPs, alone or combined, can accelerate anterograde protein trafficking through the Golgi membranes, even though it also has negative effects on protein glycosylation and sorting [102]. Similarly, cells treated with the Golgi stress inducer golgicide A demonstrate an enhancement of cargo trafficking despite Golgi fragmentation [45]. Furthermore, oversecretion of matriptase and integrins, the drivers of tumor metastasis, is documented in different types of cancer, whose cells exhibit disorganized Golgi [116, 117]. Additionally, tau protein can be released by neurons, an event linked to the propagation of tau pathology in Alzheimer's disease. Increased neuronal activity results in Golgi fragmentation, which is mediated by calmodulin-dependent protein kinase (CaMK) and positively correlates with tau release [118]. Surprisingly, upon Golgi disorganization, some Golgi matrix proteins are secreted out of the cells. In hepatocellular carcinoma (HCC) tissues, Golgi is fragmented [113], and Golgi protein 73 (GOLPH2, GP73) is detectable in

the serum of these patients. Furthermore, the content of GP73 decreased following surgical resection of HCC lesions but increased with tumor recurrence [119]. Different autoimmune diseases, especially Sjögren's syndrome, systemic lupus erythematosus, rheumatoid arthritis, and hepatitis B, are characterized by the expression of Golgi autoantigens in the serum [120]. To date, well-characterized Golgi autoantigens include giantin, p230, golgin-160, GM130, p115, golgin-97, and golgin-67 (reviewed by Hong et al. [120]). The nature of this phenomenon remains unknown and could be a subject of future studies that could also address the question whether golgins are involved in extracellular signaling.

Fragmentation of the Golgi apparatus is also observed in other different neurodegenerative diseases, which, in contrast, are characterized by the impaired axonal transport and accumulation of protein aggregates in the cell [121, 122]. This echoes other observations, demonstrating that impairment of Golgi morphology may slow down the intracellular trafficking [91]. Therefore, two alternative scenarios can be envisaged: 1) some proteins are rapidly secreted from the cells, bypassing Golgi [123], or 2) trafficking of other cargo through the fragmented Golgi stacks is accelerated by the tight contacts between ER and Golgi membranes, which otherwise seems non-realistic in cells with perinuclear and compact Golgi due to the segregation of ER and Golgi membranes. From the logical point of view, the latter seems rational, as the fusion of ER and Golgi could rescue intracellular trafficking and processing of aggregated proteins. However, prompt ER-to-Golgi trafficking does not necessarily correlate with the acceleration of subsequent transportation and secretion. Certainly, due to a lack of appropriate maturation and processing, some proteins, especially large cargo like collagen, are stacked in the fragmented Golgi membranes, thus reciprocally augmenting ER stress [6, 124, 125] (Fig. 5). This situation can be described using the chess term "zugzwang", where a player sees only moves that will damage his position, and yet does not have the option of passing.

Therefore, either elimination of the ER-to-Golgi trafficking or its acceleration, should be considered only as a transient adaptive mechanism, since persistent or severe ER stress inevitably results in the apoptotic cell death [126]. But this is not the case in cancer cells! ER stress and subsequent UPR are known to be pro-survival mechanisms in cancer [127] and we were able to detect tight ER–Golgi contact sites in advanced PCa cells (our unpublished observations). However, it remains to be determined as to how cancer cells maintain ER stress at the sub-lethal level. Perhaps, the answer will come from future studies of the anti-apoptotic mechanisms related to the changes in Golgi architecture. Similarly, despite significant progress in the understanding of the mechanisms that govern Golgi disorganization [7, 20, 82, 128-130], the dynamic localization of proteins in the fragmented Golgi, as well as the trafficking between separate ministacks, still require more attention. While we would not insist that "all roads lead to Golgi", the unlocking of Golgi paradigms and resolving the complexity of its diversified signals has the potential to open up unprecedented possibilities for new therapeutic approaches for many serious pathologies.

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Abbreviations:

BFA	brefeldin A
COPI (COPII)	coatomer protein complex I (II)
ER stress	endoplasmic reticulum stress
GRASPs	Golgi reassembly stacking proteins
Man-I	α-1,2-mannosidase I
Man-II	α-mannosidase II
MGAT1	mannosyl-(α-1,3)-glycoprotein β-1,2-N-acetylglucosaminyltransferase
PCa	prostate cancer (cells)

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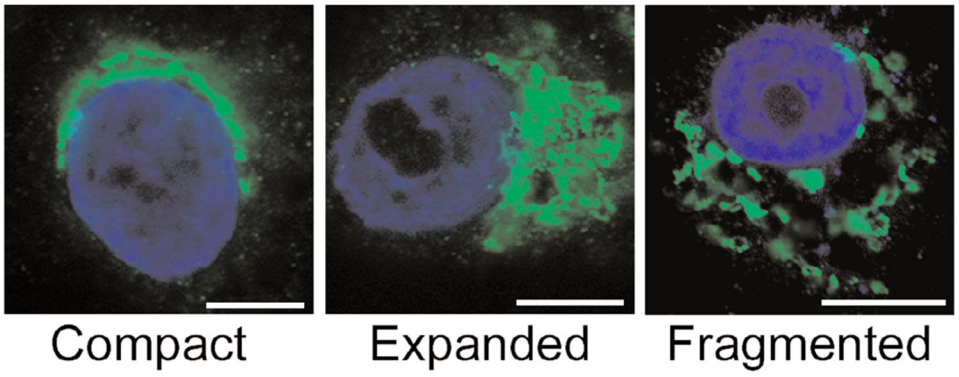

Fig. 1.

Types of Golgi morphology in VA-13 cells (staining for giantin): compact Golgi in the control cells is converted to expanded and fragmented states after 24 and 72 h of treatment with 35 mM ethanol, accordingly; bars, 10 μm. Note that the expanded Golgi, contrary to the fragmented one, still demonstrates the connectivity of its membranes.

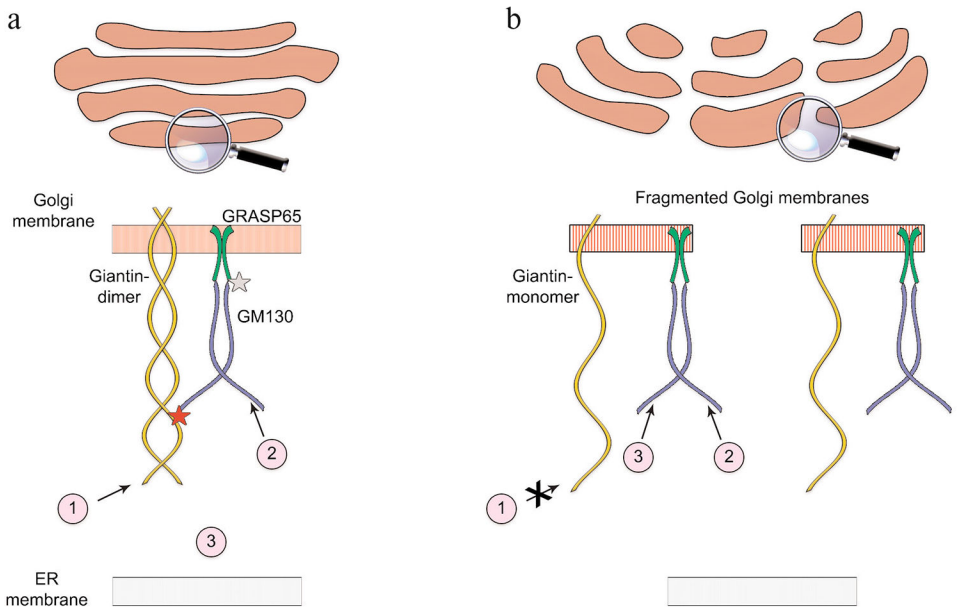

Fig. 2.

Differential Golgi targeting mechanisms. a) Under normal conditions, Golgi complex is a compact ribbon-like structure, and dimeric giantin, GM130, and GRASP65 form the tripartite tether, which determines docking of different Golgi resident enzymes: 1) giantin-dependent; 2) GM130-dependent; 3) cytoplasmic proteins, whose GM130-specific Golgi docking site is presumably masked by giantin. b) In fragmented Golgi membranes, giantin is predominantly presented as a monomer, and the interaction between giantin and GM130 is disrupted, allowing docking of cytoplasmic enzymes at the accessible GM130 site (3). Notably, the docking of giantin-sensitive enzymes is altered (1), while Golgi targeting for the GM130-sensitive enzymes remains intact (2).

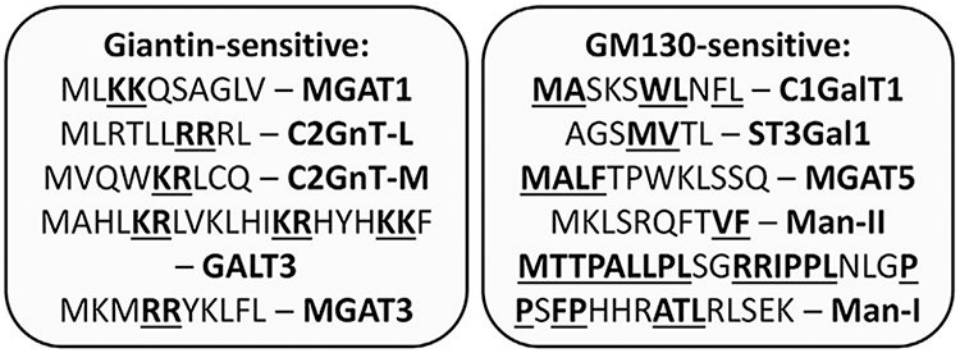

Fig. 3.

Amino acid sequences of the cytoplasmic domain of Golgi resident enzymes. Dibasic KK, KR and RR motifs in giantin-sensitive enzymes and hydrophobic regions in GM130-sensitive enzymes are bolded/underlined.

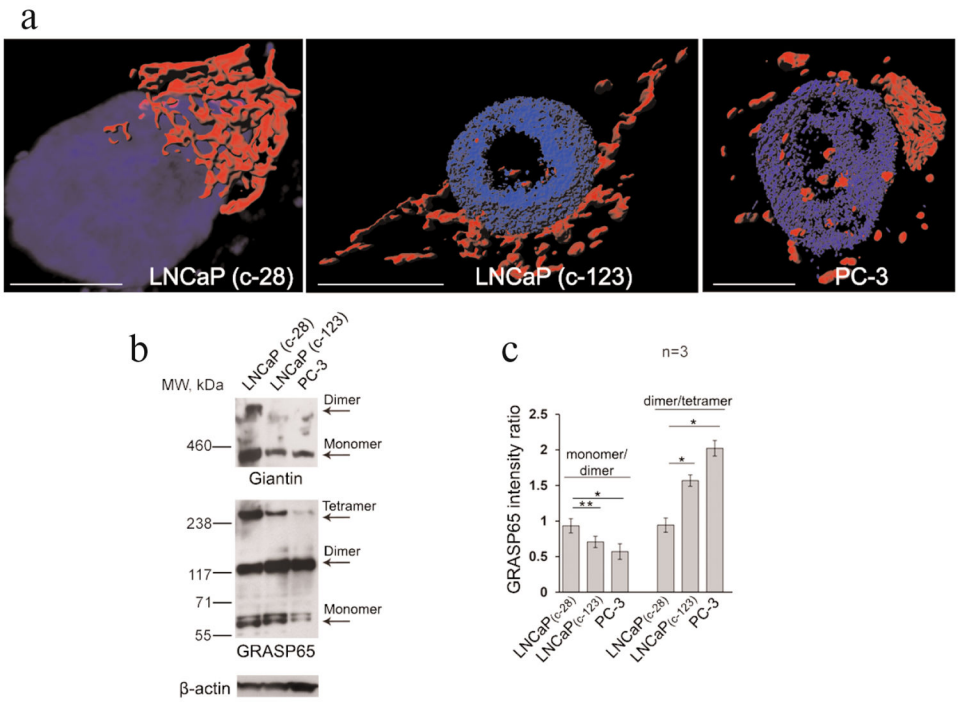

Fig. 4.

a) 3D reconstruction of structured illumination microscopy of Golgi (stained by giantin) in androgen-sensitive low-passage LNCaP (c-28), androgen-refractory high passage LNCaP (c-123), and PC-3 cells; bars, 10 μm. b) Giantin and GRASP65 Western blotting of cell lysates from panel (a); β-actin was a loading control. Oligomerization of GRASP65 and giantin was validated by the sucrose sedimentation analysis. c) Quantification of the intensity of bands corresponding to the GRASP65 monomer, dimer, and tetramer presented as a densitometric ratio to β-actin. Calculations performed within the same exposure, and data represent mean ± SD from three independent experiments; *$p < 0.01$, **$p < 0.001$.

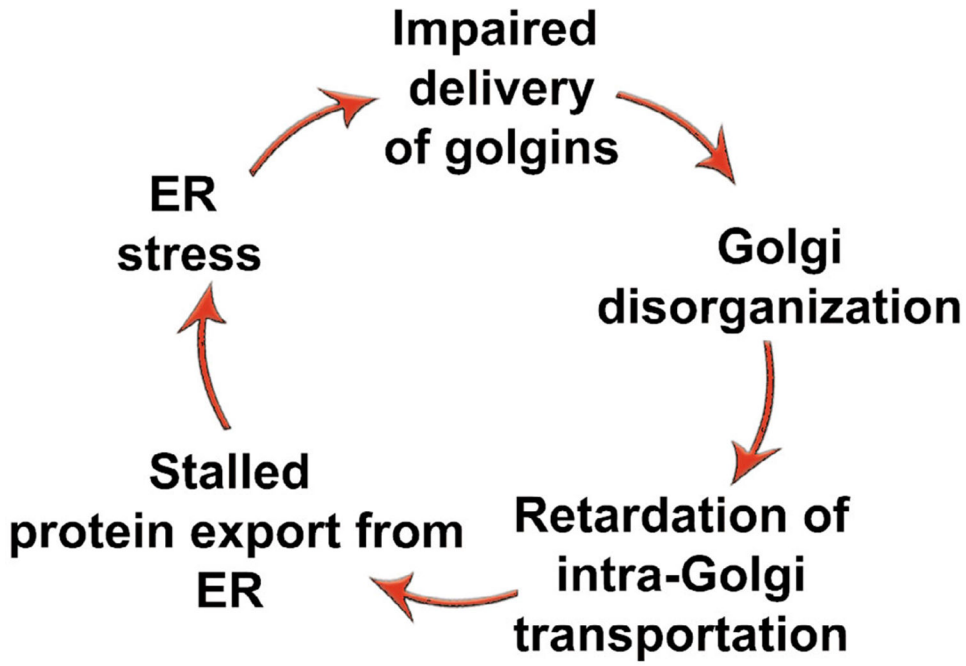

Fig. 5.
The “vicious cycle” of Golgi disorganization and ER stress.