Onco-Golgi: Is Fragmentation a Gate to Cancer Progression?

Armen Petrosyan

Department of Biochemistry and Molecular Biology, College of Medicine, University of Nebraska Medical Center, Omaha, NE, USA

Corresponding author:
Dr. Armen Petrosyan

✉ apetrosyan@unmc.edu

Department of Biochemistry and Molecular Biology, College of Medicine, University of Nebraska Medical Center, Omaha, NE, USA

Tel: 4025591794

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Abstract

The Golgi apparatus-complex is a highly dynamic organelle which is considered the "heart" of intracellular transportation. Since its discovery by Camillo Golgi in 1873, who described it as the ''black reaction,'' and despite the enormous volume of publications about Golgi, this apparatus remains one of the most enigmatic of the cytoplasmic organelles. A typical mammalian Golgi consists of a parallel series of flattened, disk-shaped cisternae which align into stacks. The tremendous volume of Golgi-related incoming and outgoing traffic is mediated by different motor proteins, including members of the dynein, kinesin, and myosin families. Yet in spite of the strenuous work it performs, Golgi contrives to maintain its monolithic morphology and orchestration of matrix and residential proteins. However, in response to stress, alcohol, and treatment with many pharmacological drugs over time, Golgi undergoes a kind of disorganization which ranges from mild enlargement to critical scattering. While fragmentation of the Golgi was confirmed in cancer by electron microscopy almost fifty years ago, it is only in recent years that we have begun to understand the significance of Golgi fragmentation in the biology of tumors. Below author would like to focus on how Golgi fragmentation opens the doors for cascades of fatal pathways which may facilitate cancer progression and metastasis. Among the issues addressed will be the most important cancer-specific hallmarks of Golgi fragmentation, including aberrant glycosylation, abnormal expression of the Ras GTPases, dysregulation of kinases, and hyperactivity of myosin motor proteins.

Keywords: Golgi; Tumor; Myosin; Apoptosis; Carcinogenesis

Golgi Disorganization and the 'Glycosylation Signature' of Cancer

Mammalian Golgi is the central station of glycosylation, composed of more than 250 glycosyltransferases that are highly organized according to the biosynthetic steps in which they participate [1]. Not surprisingly, perturbation in Golgi morphology leads to reordering of these enzymes, which in turn results in the formation of specific glycosyl epitopes. The well-recognized abnormal glycosylation in cancer occurs in the increase of sialylation, associated with a metastatic cell phenotype that has been detected both in clinical settings and experimental models [2]. It is a widely accepted view that overexpression of different sialylated antigens has not only a significant correlation with tumor progression, but that it also can protect cancer cells from apoptosis and has been suggested to confer resistance to therapy [3-6]. The major breakthrough in cancer glycobiology has come from pioneering experiments which have shown that inhibition of N- or O-glycan sialylation reduces the metastatic potential of colon cancer cells [7-9], the fragmented Golgi phenotype of which was later frequently reported on [10-13].

One of the most studied tumor-associated carbohydrate antigens is the Tn antigen, an initial O-glycan formed by linking GalNAc to the protein at Ser or Thr residue (**Figure 1a**). The Tn antigen can be further converted to the Core 1 structure (T antigen) by β1,3 galactose extension, the reaction catalyzed by Core 1 synthase (C1GalT1). Importantly, the α6-sialyltransferases (ST6GalNAc) compete with C1GalT1 for GalNAc substrate and represent an alternative short pathway which results in the formation of sialyl-Tn antigen (STn) (**Figure 1a**). Overexpression of Tn and STn antigens was described in breast, pancreas, stomach, lung, bladder, and uterus adenocarcinoma [14-17]. Due to its simple structure, Tn antigen was successfully targeted in clinics

by the use of several therapeutic vaccines [18-20]. However, enthusiasm for this treatment diminished when prostate cancer treated with Tn-based vaccines did not bear the expected fruits and led to an equivocal conclusion [21]. This result also agreed with a publication which described only 20% of prostate tumors as Tn positive [22]. Further, an anti-cancer vaccine, Theratope, designed to address the STn epitope, failed on phase III of its clinical trial [23].

In the meantime, growing evidence in the literature has indicated that the increased expression of other tumor-associated carbohydrate antigens is achieved by the extension of Core 1 structure [24,25]. We know that T antigen consists of unsialylated Core 1 structures, but Core 1 can be converted to sialyl-T antigens by α3-sialyltransferases (ST3Gal1) or by ST6GalNAc1. Notably, both T and sialyl-T antigens are overexpressed in colon, breast and prostate cancer [26-29], but they are predominantly synthesized in the absence of the active Core 2 extension enzyme, C2GnT1 [30-34]. In normal prostate and androgen-refractory prostate cancer cells, C2GnT1 was detected in the Golgi and its function seen to result in a synthesis of polylactosamine, which makes these cells susceptible to galectin-1-induced apoptosis [34,35]. In advanced androgen-refractory prostate cancer cells as well as in primary prostate tumors, Golgi was found to be fragmented. The level of Golgi disassembly was correlated with Gleason score and metastasis, but most importantly, C2GnT1, contrary to the ST3Gal1, was mislocalized to the endoplasmic reticulum (ER). Consequently, the expression level of polylactosamine was reduced, while sialyl-T antigen was enhanced, allowing cells to evade galectin-1-induced apoptosis [34] (**Figure 1b**).

Understanding the phenomenon of mislocalization of Golgi residential enzymes in the cells with fragmented Golgi phenotype was arrived at with published research that shed light on the features of the coiled-coil-rich proteins associated with the Golgi matrix, including golgins and Golgi ReAssembly Stacking Proteins (GRASPs). Central to their function are: a) the building blocks of the Golgi architecture; b) the template for Golgi reassembly; and c) the docking sites for the transport vesicles that carry various cargoes and residential proteins, including glycosidases and glycosyltransferases [36-40]. Intriguingly, knockdown of golgins by siRNAs results in a reorganization of Golgi in the majority of cases. However, most crucial Golgi disassembly was detected in cells lacking giantin [34,41,42].

Giantin is the highest molecular weight (376 kDa) Golgi matrix protein. It consists of a short C-terminal domain located in the Golgi lumen [43], where a disulfide bond connects two monomers to form an active homodimer, followed by a one-pass transmembrane domain and then a large (≥350 kDa) N-terminal region [44,45]. It has also been shown that fragmentation of Golgi in advanced prostate cancer is accompanied by impaired dimerization of giantin [34]. Given that giantin is essential for cross-bridging cisternae during Golgi biogenesis [34,44], it is becoming clear that giantin dedimerization may cause fragility of the Golgi structure. In addition to giantin, GM130 and GRASP65

are also regulating initial steps of O-glycosylation. In the cells with normal, compact Golgi, C2GnT1 is docked to this organelle by a giantin-dependent mechanism, whereas C1GalT1 and ST3Gal1 use both giantin and GM130-GRASP65 [40]. It is worth noting that GM130 is able to make a complex with giantin in the absence of GRASP65 [40,46]. This alternative docking mechanism allows C1GalT1 and ST3Gal1 (but not C2GnT-L) to be delivered to the Golgi, even though giantin is missed or presented as a monomer and Golgi is fragmented (**Figure 1b**). Finally, the shift from the Core 2 pathway to ST3Gal1-mediated glycosylation provides an excessive expression of sialyl-T antigen [34].

What remain unclear are the details of the mechanism whereby the Golgi in some cancer cells prefers to form Tn and STn instead of T and sialyl-T antigens or Core 2 elongation. Different possibilities can be envisaged here. The first and simplest explanation of overexpressed Tn and STn antigens is the decreased activity of C1GalT1, which was described in some colon cancer lines [47]. This phenomenon was further uncovered by the Cummings' lab, which showed that loss of function mutations in Cosmc, a unique chaperon for C1GalT1, causes a reduction of Core 1 extension pathway in different cancer cells, including colon, melanoma-derived, and cervical cancers [48]. However, this mechanism cannot be ascribed to many other cancers, where C1GalT1 is stably expressed and localized in the fragmented Golgi [34]. This would not have been possible in cells with mutant Cosmc because dysfunction of Cosmc results in retention of C1GalT1 in the ER [49]. The key question, then, is the mechanism that underlies the overexpression of Tn and STn despite of presence of C1GalT1.

O-glycosylation is initiated by GalNAc-transferases, GalNAc-Ts, which are present throughout the Golgi stacks and preceded function of C1GalT1 (**Figure 1a**). Because relocation of GalNAc-Ts from Golgi to the ER has been observed in colon cancer [10] and in response to growth factor stimulation [50], it seems reasonable to assume that colon cancer-specific disassembly of Golgi is accompanied by a mistargeting of GalNAc-Ts, thus partially interrupting the initial step of O-glycosylation and reducing the sensitivity of cancer cells to TRAIL-induced apoptosis [51]. On the other hand, Golgi fragmentation may result in sub-Golgi redistribution of ST6GalNAc1 as it is described in breast cancer cells [52]. This rearrangement allows ST6GalNAc1 to successfully compete with C1GalT1 for Core 1 substrate. Similarly, the overexpression of Core 3 synthase, an enzyme that in normal mucins compete with C1GalT1 for GalNAc substrate, can be a reason for down-regulation of latter during malignancy [53,54] (**Figure 1b**). The Golgi mistargeting of glycosyltransferases may also be caused by the loss of their Golgi retention partner; however, despite the significant progress in our understanding of the Golgi retention mechanism of glycosyltransferases [55,56], this possibility needs further investigation.

RAS Superfamily GTPases Promote Golgi Fragmentation and Coordinate the Function of Anti-apoptotic Kinases
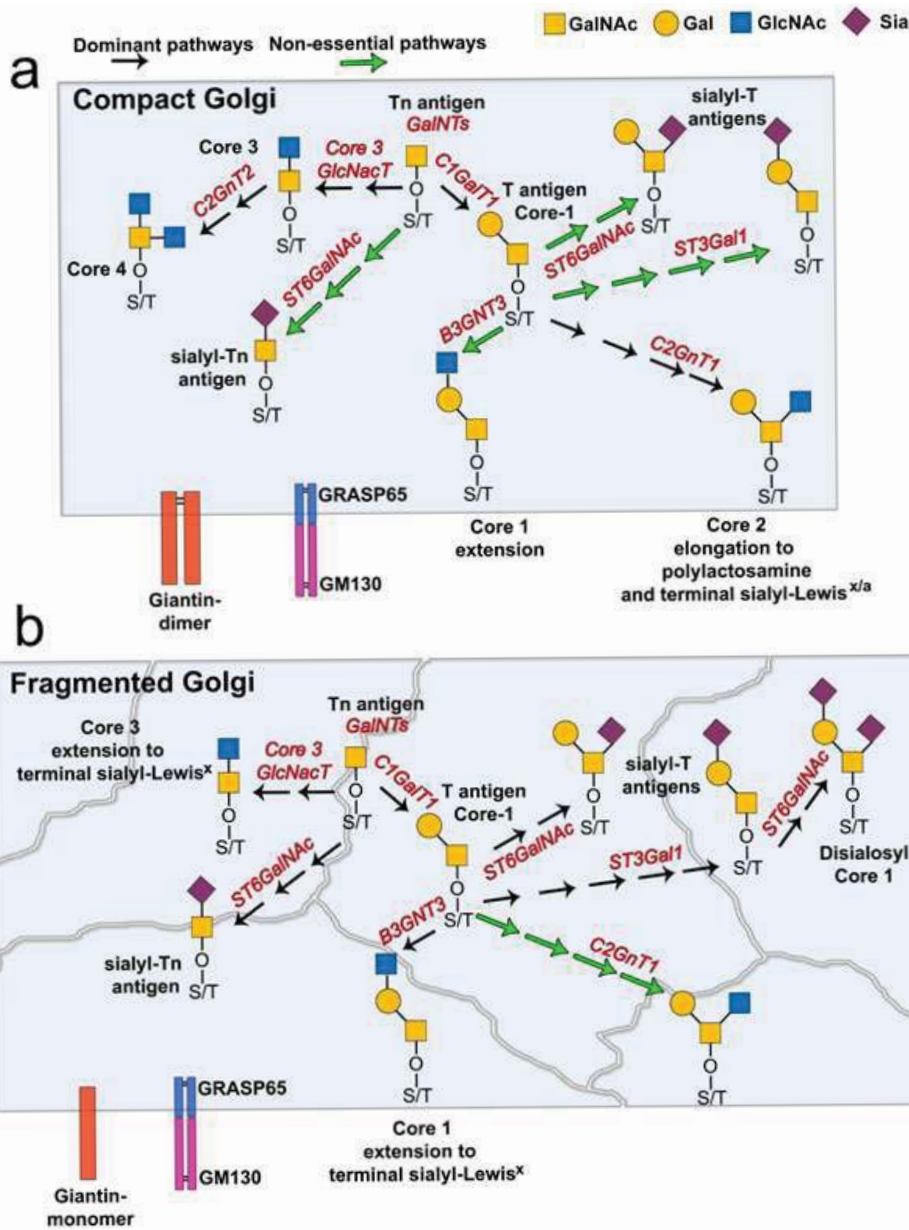
Figure 1 Biosynthesis of O-glycans under normal conditions (a) and in cancer cells (b). O-glycan synthesis is initiated by linking of GalNAc to the protein at Ser or Thr residue by the GalNTs to generate Tn antigen, which can be further converted to sialyl-Tn antigen by ST6GalNAc. Alternatively, Tn antigen is modified by the Core 3 GlcNAcT to Core 3, which in turn can generate Core 4 by C2GnT2. The Core 1 O-glycan is generated by C1GalT1. ST3Gal1 and ST6GalNAc compete with C2GnT1 for the Core 1 substrate to generate sialyl-T antigens or poly-N-acetyllactosamine structures carrying sialyl-Lewis[x], respectively. Also, Core 1 can be extended by the addition of GlcNAc by B3GNT3. This structure then galactosylated, sialylated, and fucosylated, forming sialyl-Lewis[x]. In cancer cells, of which Golgi is fragmented, the dominant O-glycosylation pathways are formation of the Tn, sialyl-Tn, T, sialyl-T, disialosyl Core 1 antigens, and Core 1 or Core 3 extension with terminal sialyl-Lewis[x]. Note that Golgi fragmentation is accompanied by dedimerization of giantin (bottom) but did not affect integrity of GM130-GRASP65.

In the past decade, substantial progress has been made in understanding the role of Rab proteins in cancer. Overexpression or activation at least dozen of Rabs has been described in different type of cancer [57]. Among them, Rab1a [58], Rab3d [59], Rab6a [34,60,61], Rab8 [62] and Rab12 [63] are localized to different compartments of the Golgi. They tightly associate with golgins and coordinate protein transport and maintenance of a Golgi organization [64,65]. It should be noted that Rab proteins, contrary to Ras, provide cancer pathways without mutation. Furthermore, while Rac proteins are mostly monomeric [66], Rabs may form a dimer, which property increases affinity of their dimer-effectors for the Golgi membrane [67]. One powerful example is a dimeric form of Rab6a, which interacts with giantin during formation of compact Golgi. In advanced prostate cancer, however, it cooperates with Myosin IIA, providing Golgi disassembly [34] (**Figure 2a**). Further, the function of Rab

proteins is closely associated with pathways mediated by kinases; Rab25 overexpression, for example, has been suggested to be a marker of ovarian [68] and breast cancer [69]. Notably, Rab25 was found abundantly expressed in the dispersed Golgi [70], and its overexpression increases signaling through the PI3K/Akt pathway and decreases expression of the proapoptotic BCL2 family members [71,72].

Recently the Bard's group has found that depletion of at least 53 signaling genes induces strong fragmentation of the Golgi [73]. Among them are a wide range of kinases whose aberrant expression has been found in different types of cancer. For instance, down-regulation of inositol-trisphosphate 3-kinase A (ITPKA) was described in oral squamous cell carcinoma [74], ketohexokinase (KHK) in renal cell carcinoma [75], protein kinase D (PKD) in prostate, breast, gastric, and colon cancer [76]. The different isoforms of protein kinase C, including α, β, δ, and η is reduced in a large number of tumors, and its decrease often correlates with tumor grade [77]. However, the down-regulation of kinases during cancer development is only one side of the coin. Indeed, several pieces of evidence strongly indicate that many other kinases are upregulated; below are only a few examples.

The elevated expression of diacylglycerol kinase, zeta, and DGKζ, contributes to increased Rho GTPase activation and the enhanced motility of metastatic colorectal cancer cells [78]. Another of the Golgi-specific kinases, MAP kinase ERK8 [73,79] and the P21-activated protein kinase (Pak1) [80] are elevated in tumor cells and positively regulate cell migration. The overexpression of Src kinases results in fragmentation of Golgi in pancreatic cancer cells [81] and secretion of angiogenic growth factors [82]. Further, the members of serine/threonine protein kinases (Ste20), YSK1 and MST4 target Golgi via the golgin GM130, and their depletion alters Golgi structure and inhibits cell migration [83]. PKCε is increased in brain, bladder, and breast cancers [77], and it is detected in the Golgi upon its activation [84]. Notably, hyperactivity of kinases in cancer is accompanied by down-regulation of phosphatases, which enzymatic action is directly opposite to that of kinases. The level of dual specificity phosphatase 6 (DUSP6) is reduced in lung cancer [85], and expression of dual-specificity phosphatase 2 (DUSP2) is low in breast, colon, lung, ovary, kidney, prostate, liver, and thyroid cancer [86]. It is important to note here that knockdown of both DUSP2 and DUSP6 significantly alters Golgi morphology [73].

Thus, the kinases play a dual role during tumor progression. Perhaps the key to understanding the nature of the Janus face of kinases lies in their different response to the Golgi structure. During malignant transformation and tumor progression, the anti-apoptotic kinases are upregulated, thus facilitating survival and proliferation [76]. Their appearance in the Golgi practically coincides with Golgi disorganization, which in turn hinders Golgi targeting of proapoptotic kinases and thereby inducing their degradation. In normal cells with unaffected Golgi, these kinases negatively regulate proliferation and activate apoptosis. Therefore, the inviolability of the Golgi is an important determinant for domination of proapoptotic kinases over their anti-apoptotic counterparts and consequently for the outcome of either programmed death or survival.

Myosin Proteins and Golgi Fission

The dynamic of Golgi membranes is triggered, among other cytoskeleton proteins, by the actin cytoskeleton and by associated unconventional myosins [87]. In many cases, the upregulation of Golgi-associated myosin motors is associated with aggressive cancer. For instance, overexpression of Myosin 1b was described in head and neck squamous cell carcinoma [88], Myosin Va in colorectal cancer [89], and Myosin VI in prostate cancer [90]. The Myosin 18a directly interacts with Golgi phosphoprotein 3 (GOLPH3) and their link triggers Golgi dispersal [91]. Given that overexpressed GOLPH3 promotes proliferation and tumorigenicity [92-94], it is becoming understandable that Myosin 18 directly coordinates with Golgi morphology. It is also intriguing that GOLPH3-Myosin 18a partnership is also necessary for Golgi fragmentation induced by DNA damage, itself a prerequisite for most mutations and cancer [95].

During the past decade, increasing attention has been given to non-muscle Myosin IIA (NMIIA). The dynamic association of NMIIA with Golgi is coordinated by Rab6a, and in tandem they control retrograde transport from Golgi to ER [96]. Recent studies have shed light on the precise mechanism of NMIIA involvement in Golgi remodeling, demonstrating that NMIIA interacts with the cytoplasmic tail of Golgi glycosyltransferases, and this link provides not only the transportation of glycosyltransferases to the Golgi, but also creates a force for Golgi disorganization after: (a) heat shock or treatment with heat shock proteins inhibitors; (b) knockdown of beta-COP; and (c) treatment with Brefeldin A [13,97-99]. The ultimate role of NMIIA in cancer progression remains controversial. Some studies indicate that cessation of NMIIA results in a decrease in contractility and an increase in cell migration [100], and the level of NMIIA is diminished in human squamous cell carcinomas with poor survival [101]. Others show that the activity of NMIIA and its phosphorylation are positively correlated with the enhanced migration and invasion of tumor cells [102-104]. Our recent observations of the role of NMIIA in Golgi fragmentation also tempt us to speculate that NMIIA is a key driver of colon and prostate cancer progression. First, NMIIA is more stably associated with Golgi of androgen-refractory prostate cancer cells than androgen-sensitive cells. Second, inhibition or siRNA knockdown of NMIIA restores compact Golgi morphology in prostate and colon cancer cells [13,34]. This process is mediated through Rab6a, which loses interaction with NMIIA, thereby facilitating giantin dimerization (**Figure 2a**). Finally, the Golgi renaissance in advanced prostate cancer is accompanied by Golgi re-targeting of C2GnT1, which, in turn, increases susceptibility to galectin-1-induced apoptosis by replacing sialyl-T antigen with polylactosamine [34] (**Figure 2b**).

The "Tug of War" in Golgi: The Choice between Death and Survival

Fragmentation of the Golgi is an essential event in all forms of apoptosis [105]. The Golgi localized caspase-2 and caspase-3 are generally accepted as the central players in the Golgi execution-phase of apoptosis, because they mediate cleavage of several golgins and GRASPs, including golgin 160 [106], giantin [107], GM130 [108], and GRASP65 [109]. The simultaneous degradation
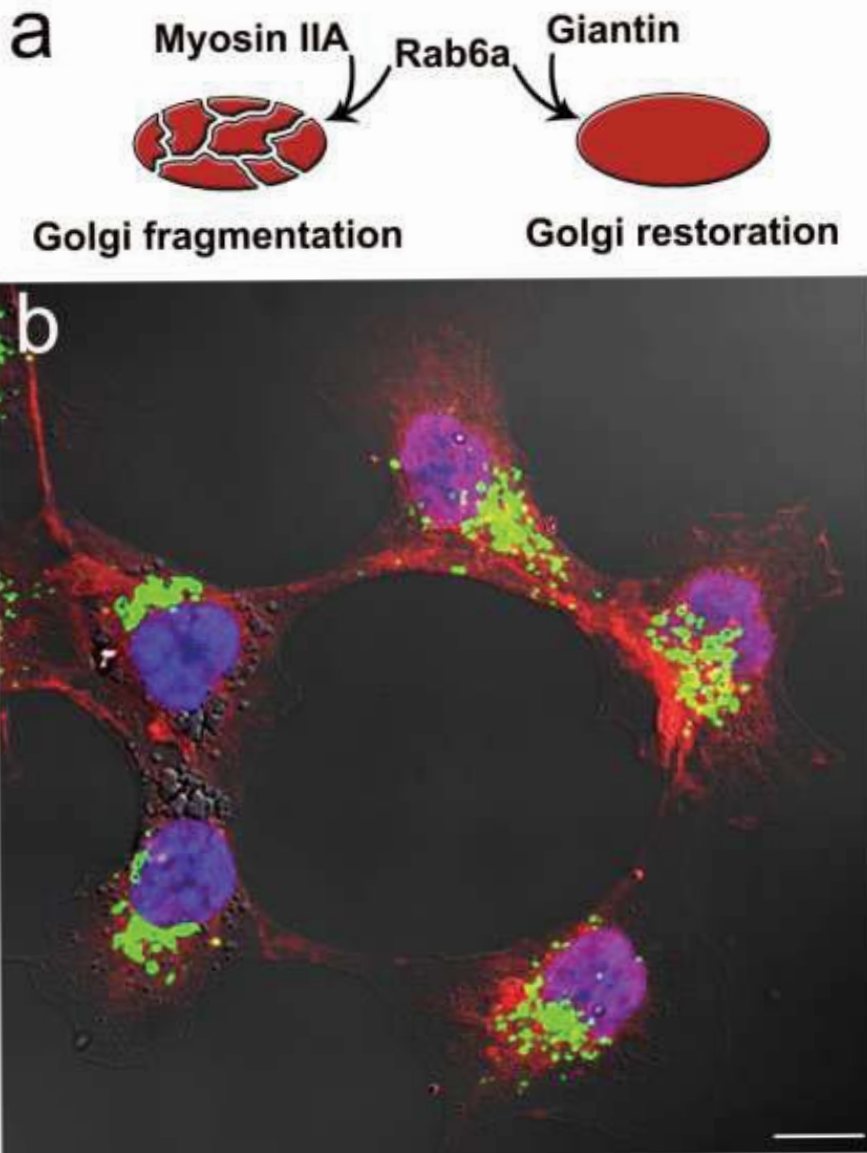
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Figure 2 The inhibition or knockdown of non-muscle Myosin IIA (NMIIA) results in restoration of compact Golgi in prostate cancer cells. (a) Giantin and NMIIA compete for Rab6a. In advanced prostate cancer, Rab6a and NMIIA associate to form fragmented Golgi phenotype. Cessation of NMIIA induces tight cooperation of Rab6a and giantin followed by dimerization of latter and formation of compact Golgi. (b) Confocal fluorescence photograph (64×; bars, 10 μm) of DU145 prostate cancer cells treated with Blebbistatin, an inhibitor of NMIIA, and stained for a Golgi marker giantin (green), polylactosamine stained with *Lycopersicon esculentum* agglutinin lectin (red), and nucleus with DAPI (blue). Restoration of compact Golgi morphology is accompanied by Golgi targeting of a Core 2 enzyme, and subsequent increased production of polylactosamine and susceptibility to galectin-1-induced apoptosis (see the Ref. 34).

of these structural proteins results in the significant fission of Golgi. However, it is important to note that giantin is more stably associated with Golgi fragments than other golgins during apoptosis [110], confirming that giantin is the cornerstone of Golgi architecture.

What is most astonishing is the high degree of fidelity with which Golgi transforms into two daughter parts during cell division. Under normal conditions, the Golgi G2 checkpoint gives the ''green light'' for entry into mitosis [111], but when DNA is damaged cells might be stopped at the G2, thus blocking the possible development of cancer [112]. At that point, cells should undergo apoptosis. This hara-kiri mechanism induced by chemical G2 checkpoint abrogators is one of the main strategies in the modern treatment of cancer [113]. Without this mechanism, the cells become malignant and permanently exhibit G2-specific fragmented Golgi [114]. The ability of tumor cells to override apoptosis is one of the hallmarks of cancer. Several anti-apoptotic mechanisms for the suppression of proapoptotic protein are employed by cancer cells for survival, including transcriptional, translational and post-translational regulation [115]. Whether these events are accompanied by dysregulation of caspases at the Golgi is uncertain, but it would seem likely, given that caspase-mediated degradation of golgins irreversibly results in apoptosis (**Figure 3**).

Targeting the Golgi as a Potential Therapeutic Intervention

Disruption of the Golgi apparatus was a promising challenge in translational research because most of these agents induce cell death. For instance, swainsonine, an inhibitor of Golgi alpha-mannosidase II, was considered as an anti-cancer drug with the potential for treating gastric carcinoma [116] and glioma [117]. However, a phase II clinical trial of GD0039 (a hydrochloride salt of swainsonine) in patients with renal carcinoma did not reveal any anti-tumor effect [118]. The other Golgi disruptive chemical, Brefeldin A, showed antiproliferative effects *in vitro* and inhibition of tumor growth *in vivo* [119,120], but the clinical implication has not progressed because of its poor solubility in water and its neurotoxicity. Moreover, as has been shown by BFA ester conjugates, the disruption of the Golgi complex is not necessary for cytotoxicity [121], indicating that the anti-tumor activity of BFA cannot be simply ascribed to its ability to induce Golgi collapse. The same Golgi disorganization approach was adopted in the series of preclinical studies which showed that silencing GM130 decreased angiogenesis and cells invasion *in vitro* and in lung cancer mice models [122]. In sum, the implication of Golgi disruptive agents looks like a dead-end, given that this strategy, in spite of its potential ability to launch apoptosis, may also accentuate Golgi fragmentation and increase the metastatic potential of cancer cells.

Over the last two decades, targeting Ras GTPAses was an attractive clinical task: at first glance, it seemed so simple to search for drugs that could interfere with GTP binding to stop mutant Ras, and in preclinical models the agents that block Ras activation through inhibition of the enzyme farnesyl transferase resulted in cell growth arrest [123]. However, in clinical studies their activity was far less promising than anticipated. Newer and more promising results came from Shokat's lab, which found a small molecule that irreversibly binds to a common oncogenic mutant, K-Ras(G12C), but does not affect the wild-type Ras [124]. However, these compounds have also not yet passed clinical tests [125]. To date, the few encouraging results we have may give us hope to develop new Rab-specific anticancer therapies. A biphosphonate derivative, 3-PEHPC [3-(3-pyridyl)-2-hydroxy-2-phosphonopropanoic acid], inhibits posttranslational modification of Rabs, thereby inducing apoptosis of human myeloma cells *in vitro* [126] and reducing skeletal tumor growth *in vivo* [127]. It will be interesting to see what potential merits these findings deliver.

The inhibitors of NMIIA may also yield novel cancer therapies. In preclinical models, Blebbistatin have shown excellent effects on Golgi restoration [34] and the blocking of invasiveness of both MCF-7 breast cancer [102] and pancreatic adenocarcinoma cells [128]. Another important consideration are the inhibitors of S100A4, a member of the S100 family of Ca^{2+}-binding proteins, which regulates carcinoma cell motility via interactions with NMIIA [129]. Also, great attention was paid to the possible treatment of cancer by the inhibitors of kinases. To date, several kinase inhibitors have received US Food and Drug Administration approval, but their implication is limited by mutation actions of kinases that abrogate drug binding and by their high toxicity [130].

Taken together, we believe that it is more important from a clinical perspective to target fragmented Golgi at the G2 phase, before cancer cells have passed the cell circle. The chemical abrogation of the Golgi fragmentation and its possible restoration could bring short-term control of malignancy, in which the fatal pathways described in this article will be avoided and apoptosis will be induced.

Concluding Remarks

Several important conclusions emerge from the phenomena described in this Review article. First, Golgi fragmentation results in the substantial rearrangement of Golgi residential glycosyltransferases, leading to the formation of cancer specific glycosyl epitopes. Second, Ras-proteins and myosin motor proteins are involved in the formation of disassembled Golgi phenotype. Third, the alteration of Golgi might ensure cancer cell survival by affecting the activity of proapoptotic kinases (**Figure 3**). It is also important to consider that downregulation of NMIIA is shown to restore compact Golgi and to increase susceptibility to galectin-1-induced apoptosis in prostate cancer cells; however, whether this phenomenon is universal and applicable to other types of cancer remains to be determined. Further studies are also needed to investigate the precise role of the GM130-GRASP65 complex and other golgins in cancer-specific remodeling of Golgi.

In sum, onco-Golgi seems the overriding condition for the survival of cancer cells. On the one hand, formation of fragmented Golgi phenotype is a cause of carcinogenesis, but on the other, it may be considered a consequence of cancer progression. Therefore, we anticipate confirmation of the existence of a vicious circle involving "Golgi fragmentation ↔ cancer progression." The most important question is whether restoration of Golgi may block the crucial downstream pathways described in this article.
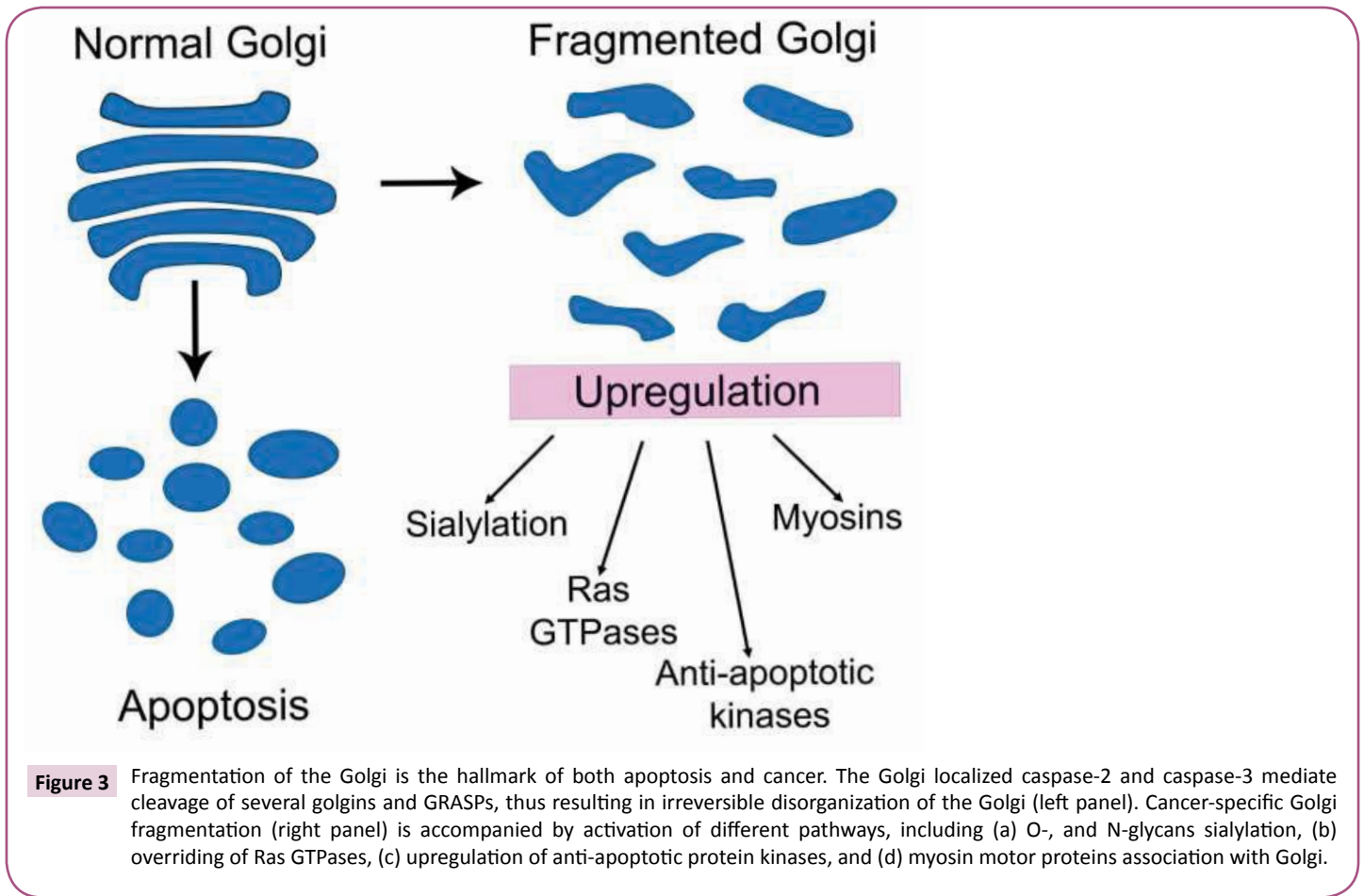
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Figure 3 Fragmentation of the Golgi is the hallmark of both apoptosis and cancer. The Golgi localized caspase-2 and caspase-3 mediate cleavage of several golgins and GRASPs, thus resulting in irreversible disorganization of the Golgi (left panel). Cancer-specific Golgi fragmentation (right panel) is accompanied by activation of different pathways, including (a) O-, and N-glycans sialylation, (b) overriding of Ras GTPases, (c) upregulation of anti-apoptotic protein kinases, and (d) myosin motor proteins association with Golgi.

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