Chapter 7
Functional Associations Between the Golgi Apparatus and the Centrosome in Mammalian Cells

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Abstract The pericentrosomal positioning of the mammalian Golgi apparatus has been observed for many years, but, until recently, its functional significance remained unclear. Several studies have now demonstrated that there are associations between the Golgi and the centrosome that are critical for the establishment of cell polarity, the organization of the centrosome, and proper cell cycle progression. In this chapter, we will review the major factors that control the positioning of the mammalian Golgi apparatus next to the centrosome. We will also discuss the functional associations between the Golgi and the centrosome during interphase, when there is physical proximity between these two organelles, and during mitosis, when the physical Golgi-centrosome proximity is temporarily lost.

7.1 Introduction

The region next to the centrosome is a major site of membrane trafficking in mammalian cells (De Matteis and Luini 2008; Wilson et al. 2011). The most prominent organelle in this area is the Golgi apparatus, which is composed of stacks of 6–8 flattened membrane cisternae. Individual Golgi stacks are laterally connected to form the so-called Golgi ribbon, in which regions with tight cisternae packing ('compact zones') are separated by connecting tubular elements ('non-compact zones'). Newly synthesized proteins are delivered via anterograde transport from the Endoplasmic Reticulum (ER) to the *cis* face of the Golgi

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apparatus, where protein sorting occurs. Proteins and lipids destined for the endosomal/lysosomal system, the cell surface, or the extracellular space transit the cisternae of the Golgi stacks in a directional manner and are glycosylated in a stepwise process. In contrast, proteins that have "escaped" from the ER are recycled back to the ER by retrograde transport. In the most *trans* cisternae, the Trans Golgi Network (TGN), cargo molecules are packaged into transport carriers for delivery to their final destinations.

In addition to the Golgi apparatus, elements of the ER-Golgi Intermediate Compartment (ERGIC) have been detected in the pericentrosomal region (Marie et al. 2009). As the name implies, the ERGIC is a dynamic organelle at the interface between ER exit sites and the *cis* Golgi, which functions as a major site of post-ER protein sorting. Interestingly, the pericentrosomal domain of the ERGIC appears to be independent of the Golgi, maintaining its close association with the centrosome under conditions when Golgi membranes are dispersed (Marie et al. 2009).

The Endocytic Recycling Compartment (ERC) is also found in the pericentrosomal region (Lin et al. 2002). This organelle, which is morphologically and functionally distinct from the early endosome, is a collection of tubular endosomes concentrated near the centrosome. It is involved in the vesicle-mediated transport of proteins and lipids that are endocytosed and then targeted either to the lysosome or recycled back to the plasma membrane. For example, some cell surface proteins, such as transferrin and low-density lipoprotein receptors, use this pathway: they are first endocytosed, then separated from their respective ligands, and finally recycled back to the cell surface via the ERC.

The placement of multiple distinct trafficking organelles next to the centrosome indicates that this particular localization may be advantageous for a mammalian cell. One obvious benefit is the convergence of trafficking compartments with the microtubule network, which facilitates efficient vesicle-mediated transport to the cell center and the cell periphery. In addition, the close proximity of the Golgi, the ERGIC, and the ERC facilitates the rapid exchange of cargo among these compartments. For example, when TGN resident proteins, such as TGN38, escape from the Golgi to the cell surface, they are recycled back to the TGN via the ERC (Ghosh et al. 1998). This trafficking route is also used by bacterial toxins (Mallard et al. 1998). For instance, Shiga toxin is taken up by endocytosis, but avoids lysosomal destruction by trafficking from the ERC to the TGN, and finally to the ER, where it is released into the cytoplasm to inhibit ribosomal activity. Interestingly, under conditions when normal recycling pathways are blocked, transferrin receptor travels from the ERC to the pericentrosomal ERGIC and then back to the plasma membrane (Marie et al. 2009). Thus, the pericentrosomal region of the cell appears to serve as a trafficking "hub" that promotes efficient cargo transfer between organelles.

While seen in some eukaryotes, including mammals, frogs, fish, and the unicellular amoeba *Dictyostelium* (Distel et al. 2010; Rehberg et al. 2005; Reilein et al. 2003; Thyberg and Moskalewski 1999), a pericentrosomal Golgi ribbon is not universal (Wilson et al. 2011). In fact, Golgi membranes of many lower eukaryotes are organized as isolated, unconnected membrane stacks, or individual cisternae distributed throughout the cytoplasm. These Golgi membranes are fully functional

for protein transport. In the yeast *Saccharomyces cerevisiae*, for example, individual Golgi cisternae are dispersed throughout the cytosol (Preuss et al. 1992; Rambourg et al. 2001). In the fission yeast *Schizosaccharomyces pombe*, Golgi mini-stacks exist, but they are distributed throughout the cytoplasm and do not form a single connected Golgi ribbon (Chappell and Warren 1989). Interestingly, studies in *Drosophila* have shown that Golgi organization can be cell type-specific (Stanley et al. 1997). In pre- and post-cellularized *Drosophila* embryos, as well as in S2 tissue culture cells, Golgi membranes appear as dispersed punctate structures that correspond to isolated Golgi mini-stacks (Kondylis and Rabouille 2009; Stanley et al. 1997). These mini-stacks localize close to the transitional ER, forming a unit for translation and transport that is also seen in *Toxoplasma*, *Plasmodium* and plants (Kondylis and Rabouille 2009). However, the *Drosophila* Golgi has also been observed as unstacked cisternae during distinct stages of development, or as a ribbon-like structure in spermatids, indicating that Golgi membranes can be organized differently within the same organism (Kondylis and Rabouille 2009).

In this chapter, we will focus on the spatial and functional relationship between the Golgi and the centrosome in mammalian cells. We will first discuss the mechanism by which Golgi membranes are positioned in the pericentrosomal region. We will then review studies on the functional connections between the Golgi and the centrosome in interphase, including the role of the pericentrosomal Golgi in directional protein secretion and cell polarization. Finally, we will discuss the link between the Golgi and the centrosome during mitosis, the stage of the cell cycle when the physical Golgi–centrosome connection is temporarily lost due to extensive Golgi fragmentation and dispersal.

7.2 Mechanisms of Golgi Positioning in Interphase Mammalian Cells

Although not essential for the typical function of the Golgi in protein and lipid transport, the positioning of the Golgi apparatus in mammalian cells next to the centrosome is actively maintained (Table 7.1). The preservation of this specific localization involves both the microtubule and actin cytoskeletal networks and their associated motor proteins and regulators (Brownhill et al. 2009). These cytoskeletal networks are linked to the Golgi by binding to either structural Golgi proteins, such as Hook3, or by directly associating with specialized phospholipids in the Golgi membranes, such as PtdIns(4,5)P_2 (Godi et al. 1998; Walenta et al. 2001). Both microtubule- and actin-associated motor proteins have been detected on the Golgi. Because microtubule motors actively contribute to the positioning of the Golgi apparatus, they will be discussed in detail. In contrast, Golgi-localized actin-associated motor proteins will not be covered because they function predominantly in the movement of vesicles to and from the Golgi, and do not seem to control Golgi localization.

Table 7.1 Factors that control the positioning of the Golgi ribbon next to the centrosome

Protein class Examples	Role in Golgi positioning	Golgi phenotype (when activity of the regulatory factor is altered)	References
Microtubules and associated proteins			
Centrosome-nucleated microtubules	Radial array with plus ends extending in all directions toward the cell periphery Critical for C-stage of Golgi reassembly	Dispersed Golgi mini-stacks	Cole et al. (1996)
Golgi-nucleated microtubules	Asymmetric array with plus ends extending toward the leading edge of the cell Critical for G-stage of Golgi reassembly	Golgi membrane clusters in periphery, no ribbon	Efimov et al. (2007), Miller et al. (2009)
Dynein	Responsible for directional movement of Golgi toward the centrosome (toward the minus ends of microtubules)	Dispersed Golgi mini-stacks	Corthesy-Theulaz et al. (1992), Harada et al. (1998)
Kinesin	Providing opposing force to dynein activity Encourages lateral spreading of Golgi membranes Minus-end directed kinesin activity has similar role as dynein	Collapsed Golgi in cell center Dispersed Golgi mini-stacks	Feiguin et al. (1994) Xu et al. (2002)

(continued)

Table 7.1 (continued)

Protein class Examples	Role in Golgi positioning	Golgi phenotype(when activity of the regulatory factor is altered)	References
Actin and associated proteins			
Actin	Similar role to kinesin in opposing dynein activity Creates tension by anchoring at the plasma membrane to encourage lateral spreading of Golgi membranes	Collapsed Golgi in cell center	di Campli et al. (1999)
Spectrin and ankyrin	Creates flexible meshwork in close association with Golgi membranes crosslinked by actin May create membrane microdomains necessary to maintain Golgi morphology	Inhibition in early anterograde transport	Godi et al. (1998)
Golgi-associated proteins			
Hook3	Links microtubules to Golgi	Fragmented Golgi	Walenta et al. (2001)
GMAP210	Not known	Dispersed Golgi mini-stacks	Yadav et al. (2009)
Golgin-160	Not known	Dispersed Golgi mini-stacks	Yadav et al. (2009)
Golgin-84	Not known	Dispersed Golgi mini-stacks	Diao et al. (2003)
Centrosome-associated proteins			
TBCCD1		Fragmented Golgi, mispositioned centrosome	Goncalves et al. (2010)

A typical mammalian cell contains two distinct populations of microtubules, which both originate in the pericentrosomal region. About half of cellular microtubules are nucleated and anchored at the centrosome, from which they extend radially toward the plasma membrane (Efimov et al. 2007). The other half are nucleated at the Golgi, from which they form an asymmetrical array, with their plus ends extending predominantly toward the leading edge of the cell (Chabin-Brion et al. 2001; Efimov et al. 2007; Vinogradova et al. 2009). Golgi-nucleated microtubules associate with CLASP proteins, which are recruited by the peripheral TGN protein GCC185 (Efimov et al. 2007). The binding of CLASP proteins to these microtubules increases their overall stability, which, together with their enhanced acetylation and tyrosination, explains why they are more difficult to depolymerize (Chabin-Brion et al. 2001; Efimov et al. 2007; Rivero et al. 2009; Thyberg and Moskalewski 1999).

Microtubules play a critical role in the organization and positioning of the Golgi apparatus (Thyberg and Moskalewski 1999). Their depolymerization by treatment with the compound nocodazole leads to the loss of the pericentrosomal Golgi ribbon, which is converted into mini-stacks at ER exit sites (Cole et al. 1996; Rogalski and Singer 1984). These mini-stacks are fully functional for protein processing and secretion, and are reminiscent of the ER-Golgi units of *Drosophila*. Upon nocodazole removal, microtubules repolymerize and promote the reassembly of the Golgi ribbon through active transport of Golgi mini-stacks toward the cell center. Interestingly, Golgi reassembly after treatment with nocodaozle occurs in two distinct steps that are each dependent on a different microtubule population (Miller et al. 2009). In the first step (Golgi- or G-phase), Golgi mini-stacks spread along microtubules and fuse into larger structures in the cell periphery. This step is dependent on Golgi-nucleated microtubules and does not occur in CLASP-depleted cells, in which this microtubule subset is absent. In the second step (centrosome- or C-phase), peripheral Golgi clusters are transferred from the cell periphery to their normal position next to the centrosome. This translocation of Golgi membranes to the cell center requires centrosome-nucleated microtubules and still takes place in CLASP-depleted cells, in which the fusion of mini-stacks in the cell periphery is prevented (Miller et al. 2009). In these cells, Golgi mini-stacks are positioned normally adjacent to the centrosome, but they are unable to form an interconnected ribbon. Thus, Golgi-nucleated microtubules are responsible for the integrity and morphology of the Golgi ribbon, whereas centrosome-nucleated microtubules determine the localization of Golgi membranes next to the centrosome (Miller et al. 2009).

Microtubules serve as tracks for the movement of Golgi membranes, but the actual locomotive force for the G- and C-stages of Golgi assembly is provided by the microtubule motor proteins dynein and kinesin (Miller et al. 2009). Microtubule motors are mechano-chemical enzymes that transport cargo along microtubule tracks, with dyneins moving toward microtubule minus ends, and kinesins generally moving toward plus ends. Dyneins associate with the Golgi apparatus and are important for Golgi organization and positioning (Allan et al. 2002; Thyberg and Moskalewski 1999). Disrupting their function by depleting dynein or ATP from the cytosol blocked the directional movement of the Golgi toward the centrosome, producing a Golgi fragmentation phenotype (Corthesy-Theulaz et al.

1992). In addition, knock-out mice for cytoplasmic dynein 1 (CD1), a TGN-associated dynein (Fath et al. 1994), developed into the blastocyst stage before embryonic death and reabsorption. Cells recovered from this CD1 knockout blastocyst had fragmented Golgi membranes in the form of peripheral mini-stacks (Harada et al. 1998). Another dynein family member, cytoplasmic dynein 2 (CD2), also localized to the Golgi apparatus, although its distribution was more ubiquitous than that of CD1 (Vaisberg et al. 1996). Blocking CD2 function by microinjection of a specific monoclonal antibody resulted in the conversion of the Golgi ribbon into peripheral mini-stacks. Similarly, interfering with the function of the minus-end directed kinesin family member KIFC3 caused Golgi fragmentation (Xu et al. 2002). These experiments provide strong support for a role of minus-end directed microtubule motors in Golgi organization and position.

The motor protein kinesin, which, in general, moves toward microtubule plus-ends, are also important for the maintenance of Golgi organization. Indeed, kinesins have been proposed to provide an opposing force to dyneins. Similar to what has been observed for dyneins, various kinesin family members localize to the Golgi (Allan et al. 2002; Gyoeva et al. 2000; Lippincott-Schwartz et al. 1995; Thyberg and Moskalewski 1999). Their RNAi-mediated knockdown resulted in the collapse of the Golgi into a circular body in the cell center, with reduction in the overall size, number, and spreading of Golgi cisternae (Feiguin et al. 1994). Thus, a balance between dynein and kinesin activity may be the critical determinant for the pericentrosomal organization of the Golgi ribbon.

In addition, there are reports implicating the actin cytoskeleton in the maintenance of a pericentrosomal Golgi apparatus. Disruption of actin filaments, specifically of branched actin structures, resulted in a collapse of Golgi morphology (di Campli et al. 1999). Under these conditions, Golgi cisternae remained in a stacked conformation, but they were swollen and condensed around the nucleus (Valderrama et al. 1998). This phenotype was reminiscent of Golgi morphology in cells with disrupted kinesin activity, suggesting that actin filaments, just like kinesins, may be antagonistic to dynein activity. It is possible that actin filaments oppose dynein activity by attaching to the plasma membrane, generating tension and encouraging lateral spreading of Golgi membranes.

Actin can also control Golgi organization through its interacting proteins spectrin and ankyrin, which have both been detected on the Golgi (Beck 2005; Beck et al. 1994, 1997; Devarajan et al. 1996; Fath et al. 1994; Stankewich et al. 1998). Spectrin is a cytoskeletal protein that is known to control membrane organization, stability, and shape by linking membranes to motor proteins or other cytoskeletal elements. Spectrin binds to membranes via the adaptor protein ankyrin, which itself associates with integral membrane proteins or membrane phospholipids. Membrane-bound spectrin-ankyrin complexes are cross-linked by short actin filaments, creating a flexible meshwork across the surface of a membrane (De Matteis and Morrow 2000; Godi et al. 1998). At the plasma membrane, the spectrin network has been found to promote the formation of specialized membrane domains by preventing the free diffusion of integral membrane proteins (Holleran and Holzbaur 1998). Spectrin and ankyrin may have an analogous role

on the Golgi and maintain the integrity of this organelle by restricting access of Golgi resident proteins to budding transport vesicles (Holleran and Holzbaur, 1998). Furthermore, Golgi-associated spectrin may serve as a scaffold for the recruitment of signaling proteins from the cytosol. The actin-related protein Arp1 is a good example for such a spectrin-binding protein (Holleran et al. 2001). Spectrin-dependent recruitment of Arp1, a central component of the dynactin complex, to the Golgi may allow this protein to control dynein activity and contribute to the regulation of Golgi positioning.

Golgi and centrosome-associated proteins also control the pericentrosomal positioning of the Golgi. Loss of either Golgin-160, GMAP210 or Golgin-84, all putative structural Golgi proteins, resulted in the dispersal of Golgi membranes into ER-associated mini-stacks, producing a phenotype that is reminiscent of nocodazole-treated cells (Diao et al. 2003; Yadav et al. 2009). Dispersal of Golgi membranes was also observed in cells depleted of the centrosomal protein TBCCD1 (Goncalves et al. 2010). Interestingly, in these cells, the centrosome was mislocalized away from the nucleus. In conclusion, diverse groups of proteins are involved in, and required for, the proper positioning of the Golgi apparatus next to the centrosome (Table 7.1), suggesting that sustaining this specific localization may be important for cell homeostasis.

7.3 A Role for the Pericentrosomal Golgi Apparatus in Cell Polarity

Cell polarity is a feature of eukaryotic cells that allows them to carry out their specialized functions. For example, neurons depend on their polarization to transmit electrical signals from one cell to the next, whereas epithelial cells use their polarized organization to protect the body from its environment. The Golgi apparatus and the centrosome both have independent roles in the establishment of cell polarity. Golgi membranes control the sorting of proteins, which is important for their delivery to the leading edge of a cell (Bergmann et al. 1983). This so-called directional transport is a prerequisite for cell polarization, and was recently shown to involve Golgi-nucleated microtubules (Bergmann et al. 1983; Rivero et al. 2009). When Rivero and colleagues selectively disrupted this subset of microtubules, there were defects in cell polarization and migration (Rivero et al. 2009). Golgi membranes also recruit the Ste20-like kinase YSK1, a protein kinase required for Golgi organization and cell polarization (Preisinger et al. 2004). A pathway that involves the interaction between STK25, the mouse homolog of YSK1, and the Golgi protein GM130 is also required for Golgi organization and polarization in cultured neurons and in vivo (Matsuki et al. 2010).

Like the Golgi, the centrosome has long been anticipated to play an important role in cell polarization. In many migrating cells, including fibroblasts and macrophages, the centrosome localizes between the nucleus and the leading edge (Kupfer et al. 1982; Nemere et al. 1985), suggesting that the position of the centrosome may

determine the direction of cell polarization. This idea is further supported by a recent study in Ptk2 cells, in which laser ablation of the centrosome caused a block in cell migration and cell polarization (Wakida et al. 2010). However, a leading role of the centrosome does not appear to be universal. In a study comparing centrosome position in migrating CHO and Ptk cells, the centrosome was localized toward the front of the nucleus in CHO, but not in Ptk cells (Yvon et al. 2002). In addition, there are conflicting results on the role of the centrosome in migrating neurons. Several studies have attributed a leading role to the centrosome in directing migration (Higginbotham and Gleeson 2007; Tsai and Gleeson 2005), but recent results from Zebrafish neurons showed that there was no correlation between centrosome positioning and cell migration (Distel et al. 2010). Indeed, it was found that the centrosome of migrating THN neurons often trailed the nucleus. Thus, additional experiments are needed to determine the exact role of the centrosome itself in cell polarization.

Interestingly, several studies support an additional role for the Golgi-centrosome relationship in the establishment of cell polarity. First, Bisel and colleagues reported that the Golgi and the centrosome move together toward the leading edge of migrating cells (Bisel et al. 2008). This coordinated movement of both organelles required the reorganization of Golgi membranes, which was mediated by ERK1-dependent phosphorylation of the peripheral Golgi protein GRASP65. In a second study, a role for the pericentrosomal Golgi ribbon in cell polarization and migration was identified (Yadav et al. 2009). By depleting the structural Golgi proteins Golgin-160 or GMAP210, Yadav and colleagues found that the Golgi ribbon was converted into dispersed mini-stacks. In these cells, normal protein transport to the cell surface occurred, but there was a specific block in directional transport toward the leading edge. As a consequence, cells did not polarize and migrate, indicating that a pericentrosomal Golgi ribbon is important for cell polarization. A third study asked directly whether it is Golgi organization or Golgi position that is important for cell polarization (Hurtado et al. 2011). Hurtado and colleagues expressed a specific domain of the Golgi scaffolding protein AKAP450, which resulted in the separation of a functional, interconnected Golgi ribbon from the centrosome. Intriguingly, these cells were unable to migrate in a wound-healing assay, indicating that the Golgi–centrosome proximity is necessary for directional protein transport and cell polarization. This study demonstrates for the first time that the physical proximity between the Golgi and the centrosome in interphase mammalian cells is important for cell polarization and is therefore of great functional significance.

7.4 Other Functional Interactions Between the Golgi and the Centrosome in Interphase

In addition to this emerging role for the Golgi–centrosome interaction in cell polarization, there are at least two other molecular associations between these two organelles during interphase. First, there are cellular functions that are performed

by the Golgi and the centrosome. The most prominent example is the nucleation of microtubules that we discussed previously. Interestingly, microtubule nucleation at the Golgi and the centrosome depends on the same protein, the large scaffolding protein AKAP450, which associates with both organelles and recruits γ-tubulin as the microtubule nucleation factor (Rivero et al. 2009). Similarly, the γ-tubulin binding protein Cdk5RAP2 has been detected on both organelles and may have a complementary role in microtubule nucleation (Wang et al. 2010). There are several other proteins, including myomegalin, Golgin-97, FTCD (58 K), and CAP350 that associate with both organelles (Hagiwara et al. 2006; Hoppeler-Lebel et al. 2007; Takatsuki et al. 2002; Verde et al. 2001), but the functional significance of their specific localizations is not known.

Another example for a common function of the Golgi and the centrosome is their role as signaling platforms. For instance, several proteins controlling cell cycle progression have been detected at the centrosome. These include the kinase complex Cdk1-Cyclin B, which is required for entry into mitosis (Jackman et al. 2003) and centriolin, which controls cytokinesis and entry into S-phase (Gromley et al. 2003). In addition, signaling molecules, such as the protein kinases PKA and NRD, proteasomal subunits, and cytoskeletal elements, such as actin and Arp2/3, associate with the centrosome (Diviani et al. 2000; Hubert et al. 2011; Wigley et al. 1999). Similarly, Golgi membranes host a large number of signaling molecules. For instance, components of the ras and src pathways have been detected on the Golgi apparatus (Bard et al. 2002; Chiu et al. 2002; Wilson et al. 2011). In addition, cell cycle regulators, such as the mitotic cyclin B2 and the cytokinesis regulator Nir2, localize to the Golgi (Jackman et al. 1995; Litvak et al. 2004). It is clear that many of these Golgi- and centrosome-associated signaling molecules fulfill functions that are unrelated to the primary roles of the Golgi or the centrosome. Therefore, similar to the enrichment of membrane trafficking organelles in the pericentrosomal region, it may be beneficial for a cell to place signaling components in close proximity in its center.

A second association between the Golgi apparatus and the centrosome concerns the regulatory crosstalk between these two organelles. For instance, there is a signaling pathway by which the Golgi apparatus influences, and even controls, the proper organization and function of the centrosome (Kodani and Sütterlin 2008). This pathway involves the *cis* Golgi protein GM130, which forms a complex with the small GTPase Cdc42 and its specific guanine nucleotide exchange factor Tuba at the Golgi (Kodani et al. 2009; Kodani and Sütterlin 2008). Interfering with GM130, Tuba or Cdc42 causes the formation of a disorganized and non-functional centrosome, suggesting that each of these three proteins is required for the maintenance of normal centrosome morphology. It is not known at this point whether additional signaling molecules are involved in this pathway, and how the signal is transduced from one organelle to the other.

The mechanism(s) that support the functional interactions between the Golgi and the centrosome are only beginning to be understood. As discussed above, cell polarity appears to depend on the physical Golgi–centrosome proximity. However, for other common functions, such as protein localization and signaling, the

importance of proximity between these organelles has not been tested. It will be interesting to address these questions in the future by expressing the AKAP450 domain that successfully disrupts Golgi–centrosome vicinity while leaving Golgi organization and functionality intact (Hurtado et al. 2011).

7.5 Functional Interactions Between the Golgi and the Centrosome in Mitosis

At the onset of mitosis, the Golgi apparatus of mammalian cells undergoes extensive reorganization. During this process, Golgi membranes lose their association with the centrosome, and are fragmented and dispersed throughout the cytoplasm. This fragmentation process is initiated in G2 with the disconnection of the non-compact zones of the Golgi ribbon and the generation of isolated, pericentrosomal mini-stacks (Colanzi et al. 2007; Feinstein and Linstedt 2007). This step depends on the recruitment of the mitotic kinase Aurora A to the centrosome, which, when blocked, prevents Golgi fragmentation and entry into mitosis (Persico et al. 2010). Next, in prophase, the isolated Golgi mini-stacks are converted into tubular vesicular elements, called Golgi "blobs". This step is mediated by the MAP kinase pathway components Raf1, MEK1, and Erk1c (Acharya et al. 1998; Colanzi et al. 2003b; Shaul and Seger 2006). Finally, Golgi "blobs" are broken down into the so-called Golgi "haze" by a mechanism that involves the protein kinases Plk1 and Cdc2 (Colanzi et al. 2003a; Lowe et al. 1998; Wei and Seemann 2009; Sütterlin et al. 2001). Upon completion of mitosis, Golgi fragments reassemble into the ribbon through the G- and C-stage steps that we have discussed previously for experimentally induced Golgi fragmentation (Miller et al. 2009). During this entire multi-step Golgi disassembly process, Golgi membranes remain separate and distinct from the ER (Jokitalo et al. 2001; Pecot and Malhotra 2004).

A number of studies support the existence of a functional link between the Golgi and the centrosome during mitosis. For example, mitotic Golgi reorganization, during which the physical Golgi–centrosome connection is lost, was found to be necessary for the regulation of cell cycle progression. When Golgi fragmentation was prevented by microinjection of GRASP65-related reagents, cells arrested in G2 and did not enter mitosis (Sütterlin et al. 2002). Preisinger and colleagues obtained similar results when they overexpressed GRASP65 (Preisinger et al. 2005). The inhibitory effect of GRASP65 on mitotic entry was only seen with wild-type GRASP65, and not with a non-phosphorylatable mutant, indicating that excess GRASP65 may titrate out the activity of a kinase important for Golgi fragmentation. Similarly, inhibiting the membrane fission protein CtBP3/BARS prevented mitotic Golgi fragmentation and blocked cells from entering mitosis (Hidalgo Carcedo et al. 2004).

There are several possible explanations for the link between Golgi fragmentation and mitotic entry. First, the conversion of the Golgi ribbon into smaller fragments may facilitate the equal partitioning of this single-copy organelle into the two

daughter cells. Second, fragmentation may promote the release of mitotic signaling components that are normally sequestered on Golgi membranes. For example, ACBD3, a critical regulator of numb signaling, is released from the Golgi during mitotic fragmentation to promote asymmetric cell division (Zhou et al. 2007). Third, an intact Golgi ribbon may cause steric hindrance during centrosome maturation and restrict centrosome movement necessary for mitotic spindle formation.

In addition, there is support for an association between mitotic Golgi membranes and the mitotic spindle. In a careful live imaging study, Shima and colleagues detected the enrichment of mitotic Golgi fragments at spindle poles, indicating that the mitotic spindle may facilitate the ordered inheritance of Golgi fragments into daughter cells (Shima et al. 1998). Spindle poles were also found to contain factors that are important for Golgi ribbon formation (Wei and Seemann 2009). In this study, cells were induced to divide asymmetrically, with both spindle poles segregating into only one of the two daughter cells. Under these conditions, the pericentrosomal Golgi ribbon reformed only in the spindle pole-containing daughter cell, and not in the daughter cell that lacked a spindle pole. This result supports the notion that Golgi ribbon determinants associate with spindle poles for their inheritance into the daughter cells; however, the nature of these ribbon determinants is not known. Finally, Golgi proteins appear to control the formation of the mitotic spindle. Three functionally diverse, Golgi-associated proteins have been identified as having a role in mitotic spindle formation. These proteins include the poly-ADP ribosylase Tankyrase (Chang et al. 2005), the peripheral Golgi protein GRASP65 (Sütterlin et al. 2005) and the phosphoinositide phosphatase Sac1 (Liu et al. 2008). RNAi-mediated depletion of each of these proteins resulted in multi-polar spindles and defects in cell cycle progression. Furthermore, GM130 was found to be required for meiotic spindle formation during mouse oocyte maturation (Zhang et al. 2011). However, the mechanisms by which these diverse proteins regulate spindle formation are not understood.

7.6 Conclusion and Perspective

While a unique physical association between the mammalian Golgi apparatus and the centrosome has been observed over many years, recent studies have found that these two organelles are also linked functionally (Table 7.2). Such interactions occur primarily during interphase, when the Golgi and the centrosome are in close vicinity. During this stage of the cell cycle, the Golgi–centrosome interaction is important for cellular processes, such as the establishment of cell polarity, the nucleation of microtubules, and the control of centrosome structure and function. Other functional Golgi–centrosome interactions are independent of organelle proximity and occur during mitosis, when the physical proximity is disrupted. These include the regulation of mitotic entry and post-mitotic reassembly of the Golgi ribbon.

It has been a challenging task to determine which characteristic of the pericentrosomal Golgi apparatus is important for the regulation of processes such as

Table 7.2 Reported functional associations between the Golgi and the centrosome in mammalian cells

Regulatory functions of Golgi-centrosome interactions	Dependent on organelle proximity?	References
Interphase: adjacent Golgi and centrosome		
Cell polarization	Yes	Hurtado et al. (2011), Yadav et al. (2009)
Signaling Platforms	Not known	Doxsey et al. (2005), Wilson et al. (2011)
Centrosome organization	Not known	Kodani et al. (2009), Kodani and Sütterlin (2008); Wilson et al. (2011)
Mitosis: separated Golgi and centrosome		
Mitotic entry	Proximity has to be disrupted	Hidalgo Carcedo et al. (2004), Preisinger et al. (2005), Sütterlin et al. (2002)
Golgi ribbon formation	Not known	Wei and Seemann (2009)
Spindle formation	Not known	Chang et al. (2005), Liu et al. (2008), Sütterlin et al. (2005), Zhang et al. (2011)

cell polarization. Either the ribbon structure, or the position, or both, could be contributing regulatory elements. To distinguish between these possibilities, one would want to separate the two organelles without losing their structural and functional integrity—i.e. to position an intact, interconnected Golgi ribbon away from the centrosome. One can think of at least three different ways to achieve this goal. First, a genetic screen could be performed, in which mutants that display a physical separation of the Golgi and the centrosome are selected. However, Golgi–centrosome proximity has predominantly been observed and studied in mammalian cells, and such a genetic approach would therefore be highly complicated. Second, small molecules could be screened for the specific phenotype of disrupting Golgi–centrosome proximity. Natural compounds, such as Brefeldin A, Norrisolide, and Ilimaquinone have been widely used to understand different aspects of Golgi regulation (Guizzunti et al. 2006; Lippincott-Schwartz et al. 1989; Takizawa et al. 1993). However, to date, there is no compound that separates the intact Golgi ribbon from the centrosome. We have recently identified a natural compound with a completely novel Golgi disrupting activity (Schnermann et al. 2010). This molecule, by the name of MacFarlandin E, converts the Golgi ribbon into small fragments, but does not disperse them. The identification of a compound with this remarkable and novel Golgi modifying activity gives hope that there may be a compound that can specifically mislocalize the Golgi ribbon without altering its overall organization and functionality. Third, interfering with Golgi-localized proteins by RNAi-mediated depletion or by overexpression of dominant negative forms could disrupt the Golgi–centrosome proximity. A recent study has successfully used this approach. By overexpressing a fragment of the Golgi-associated scaffolding protein AKAP450, Hurtado and colleagues managed to move the Golgi ribbon away from the centrosome. Under these conditions, cell polarity and cell migration was significantly reduced, demonstrating for the first time that the pericentrosomal position of the Golgi ribbon is critical for the regulation of cell

polarity (Hurtado et al. 2011). This system can now be used to test the effects of a physical separation of the Golgi and the centrosome on cellular processes that are controlled by the Golgi–centrosome interaction.

It is important to extend these observations from mammalian cells to organisms that do not have a pericentrosomal Golgi apparatus, and that may therefore lack functional Golgi–centrosome interactions. Obviously, such organisms must have developed alternative mechanisms to control important processes such as polarization. A straightforward means to achieve directional protein transport in the absence of a pericentrosomal Golgi is to deliver mRNA to specific ER-Golgi subunits for localized protein translation, sorting, and transport. This system is utilized by yeast, in which mRNAs encoding for membrane proteins are transported along the acto-myosin network to the bud tip, prior to local translation and delivery to the plasma membrane (Takizawa et al. 2000). Similarly, in *Drosophila* embryos, the mRNA of the developmental protein Gurken is positioned so that its translation and modification is restricted to a subset of ER-Golgi subunits (Herpers and Rabouille 2004). Alternatively, it is possible that the specific pericentrosomal positioning of the Golgi apparatus is a reflection of increased evolutionary complexity in higher organisms, providing an additional level of regulation required for cellular processes specific to these organisms.

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