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Form and function of the Golgi apparatus: scaffolds, cytoskeleton and signalling

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Abbreviations: TGN, *trans*-Golgi network; GOLPH3, Golgi phosphoprotein 3; PI(4)P, phosphatidylinositol-4-phosphate; GRASP, Golgi Reassembly Stacking Protein; MTOC, microtubule organizing center; GM130, *cis*-Golgi matrix protein; GMAP210, Golgi microtubule associated protein; mTOR, mechanistic target of rapamycin; ITSN-1, intersectin 1; MACF, microtubule-actin cross linking factor; AKAP450, A-kinase anchoring protein; MENA, mammalian enabled; CLASP, cytoplasmic linker associated proteins; BICD, bicaudal

Abstract:

In addition to the classical functions of the Golgi in membrane transport and glycosylation, the Golgi apparatus of mammalian cells is now recognised to contribute to the regulation of a range of cellular processes, including mitosis, DNA repair, stress responses, autophagy, apoptosis and inflammation. These processes are often mediated, either directly or indirectly, by membrane scaffold molecules, such as golgins and GRASPs, which are located on Golgi membranes. In many cases these scaffold molecules also link the actin and microtubule cytoskeleton and influence Golgi morphology. An emerging theme is a strong relationship between the morphology of the Golgi and regulation of a variety of signalling pathways. Here we review the molecular regulation of the morphology of the Golgi, especially the role of the golgins and other scaffolds in the interaction with the microtubule and actin networks. In addition, we discuss the impact of the modulation of the Golgi ribbon in various diseases, such as neurodegeneration and cancer, to the pathology of disease.

1. Introduction

The cell is a highly integrated system [1,2] and the intracellular organelles contribute an important role in the spatial regulation of signalling, cell growth, survival and homeostasis. For example it is well accepted that the endosomal system generates and modulates signalling [3], that the ER responds to intracellular and extracellular signals to modulate secretion of soluble molecules [4], and the ER, mitochondria and lysosomes function as cell sensors to monitor and respond to stress [5-7]. Given the central location of the Golgi apparatus in the cell at the cross roads of the secretory and retrograde transport pathways [8,9], it is not surprising that the Golgi apparatus can also contribute to the co-ordination of higher order cellular processes, although, the importance of the Golgi as a potential hub for regulating cellular processes has only recently been appreciated. Evidence has now emerged that the Golgi contributes to the regulation of wide range of higher order functions including cell polarisation, mitosis, directed migration, directed secretion, metabolism, autophagy and inflammation [10-16].

Given the membrane flow into and out of the Golgi, Golgi membranes are highly dynamic. Components of the trafficking machinery play an important role in regulating the dynamics of Golgi membranes. From studies over the past decade, it has become clear that components traditionally considered to be associated with Golgi membrane trafficking [17,18] also function in other processes such as cytoskeletal dynamics, receptor signalling, apoptosis and mitosis. For example, Rab6 effectors play an essential role in spindle function during mitosis [19] and, the KDEL receptor, responsible for retrograde recycling of soluble ER residents from the Golgi back to the ER, also functions as a signalling G protein coupled receptor [20]. These observations have led researchers to consider the contribution of Golgi membrane components to molecular networks which bridge different cell processes.

The Golgi stack, which consist of 4-8 flattened membrane cisternae, is polarised; the *cis* face of the stack receives cargo from the ER whereas the *trans* face represents the cargo exit site to a variety of destinations. In the majority of mammalian cells the individual Golgi stacks are linked together by a lateral fusion mechanism to form a twisted ribbon structure, and in non-polarised cells the Golgi ribbon is located close to the centrosome [21]. The

ribbon structure of the Golgi is restricted to vertebrates (see Box1). The absence of a Golgi ribbon in invertebrates infers that the ribbon morphology of the vertebrate Golgi may have roles in addition to the classical Golgi functions of membrane transport and glycosylation of proteins and lipids. Indeed, disruption of the architecture of the Golgi ribbon is associated with modulation of a variety of cell processes. The Golgi in mammalian cells can be considered a cell sensor, where there is a close relationship between Golgi morphology and regulation of higher order cell functions, including DNA repair, apoptosis, stress responses and cell polarization [22]. A key to understanding this relationship are the molecular players which influence Golgi architecture and signalling networks.

Over the past 20 years a large family of Golgi membrane associated protein called membrane tethers, such as golgins and GRASPs, have been described [23-25]. These membrane tethers extend into the cytoplasm and are found distributed throughout the Golgi stack, from the *cis* to the *trans*-side of the Golgi. Membrane tethers were initially shown to interact with components of the trafficking machinery, including Rabs and SNAREs, and to influence the efficiency of many membrane transport steps, e.g. from the ER to the Golgi, within the Golgi stack, as well as transport from endosomes to the TGN. It was also clear from these early studies that many of these membrane tethers were required for maintaining the structural integrity of the Golgi [24]. The regulation of membrane transport and membrane flux by these tethers provided one explanation for their role in maintaining Golgi integrity. Subsequent studies showed there were additional mechanisms, independent of membrane trafficking, by which these membrane tethers could influence Golgi structure.

As the interactive partners of membrane tethers (golgins/GRASP) were identified it became apparent that some of the Golgi membrane tethers could interact either directly or indirectly with the cytoskeleton. These interactions included both the microtubule and actin networks. An interaction with the cytoskeleton provides a direct mechanism for membrane tethers to modulate and regulate Golgi architecture. Given the diverse range of binding partners now known to interact with Golgi localised membrane tethers, at least some of these tethers can be considered as scaffold molecules. The term 'scaffold molecule' was coined for molecules in signalling pathways which interact with multiple components and provide efficient platforms to co-ordinate positive and negative feedback loops of signalling pathways. We use the term 'scaffold' for a subgroup of Golgi tethering proteins to indicate

their capacity to interact with multiple components and to co-ordinate multiple cellular pathways.

TEXT BOX

Golgi architecture and location in Eukaryotes

There are differences in the organization of the Golgi apparatus across eukaryotes. In plants, invertebrates and many protists, Golgi stacks exist as independent units and are scattered as individual stacks throughout the cytoplasm. These Golgi mini-stacks are functional in glycosylation and in membrane transport. In vertebrates, the organization of the Golgi is dramatically different. In vertebrates, the predominant architecture of the Golgi arises from the lateral fusion of individual mini-stacks into a twisted continuous ribbon structure. This was probably the organisation of the Golgi that Camillo Golgi was able to detect with his silver stain in 1901[26]. The Golgi ribbon is found in a central or juxtanuclear location in most cell types, a location supported by the radial centrosomal microtubule array in non-polarized cells. A Golgi ribbon is a typical feature of cells during interphase which is then disassembled during mitosis into a collection of vesicles and tubules to allow partitioning of Golgi membranes between the two daughter cells [27]. The view of a Golgi ribbon as a static structure is likely to be overly simplistic and it has been proposed that the Golgi may be in a dynamic balance between mini-stacks and the ribbon [28]. Indeed, there are examples associated with differentiation programs where the Golgi ribbon is fragmented to individual Golgi stacks without loss of function. For example, differentiated myoblasts have Golgi ministacks [29]. The terminal differential of uroepithelial cells is associated with dispersal of Golgi fragments (mini-stacks) to deliver uroplakins to form plaques at the apical membrane surface of these cells in the urinary bladder [30]. Also, the differentiation of gastric parietal cells results in the loss of the ribbon and scattered Golgi mini-stacks in the very membrane dense cytoplasm of these acid producing cells [31]. Neurons have both a Golgi ribbon in the soma (cell body) and individual mini-stacks along dendrites, known as Golgi outposts [32], and the later example indicates a highly regulated mechanism to balance two distinct Golgi morphologies.

Understanding the roles of the Golgi ribbon structure is an important basic biological question that is also is relevant to various diseases and disorders, including neurodegeneration and dementia, which are associated with the loss of the Golgi ribbon and the appearance of a dispersed fragmented Golgi. In addition, a number of intracellular pathogens are able to remodel the Golgi structure resulting in the fragmentation of the Golgi ribbon [33]. An important unresolved issue is the contribution of the loss of the Golgi ribbon to the pathology of these diseases. Here we will review the role of golgins/GRASPs and other scaffold molecules in regulating and modulating the Golgi structure and highlight the cellular networks that are influenced by the changes in Golgi morphology.

2. Characterisation of Golgi structure

The architecture of the Golgi is dramatically influenced by a wide range of cell processes [24,27,34], implying that the machinery responsible for promoting these cellular processes either regulate or are influenced by the morphological status of the Golgi. The importance of the relationship between signalling pathways and Golgi morphology was demonstrated by genome wide analyses where 20% of the total kinase and phosphates in the genome influenced Golgi structure- either via fragmentation of the Golgi ribbon or by compaction of the Golgi within the juxtanuclear region [35].

The Golgi ribbon can undergo rapid remodelling events, such as in mitosis or the repositioning of the Golgi for directed migration [24,27]. Golgi dynamics are regulated by membrane flux from the ER [18,36], and by interactions between the cytoskeleton and molecular scaffolds on Golgi membranes. Both microtubules and actin are essential to maintain the structure of the Golgi [37,38] and respond dynamically to signalling events [28]. Microtubules can be considered to provide a pivotal role in generating and positioning the Golgi ribbon whereas actin fine tunes the Golgi architecture, for example in regulating the balance of Golgi stacks and the ribbon [22]. The centrosome, and also the Golgi organelle itself, function as microtubule organizing centres (MTOC) [39,40]. Microtubules are nucleated on the *cis*-Golgi and are stabilised by interactions with the plus ends of

microtubules at the *trans*-Golgi. The Golgi MTOC promotes clustering of Golgi stacks following mitosis followed by the transport of these Golgi elements to the centrosome to promote ribbon formation [38]. Loss of microtubules disperses the Golgi whereas loss of actin collapses the Golgi into a more compact structure at the centrosome [22,41,42], a finding which indicates a role for actin in defining the precise Golgi architecture.

A number of Golgi proteins interact with the cytoskeleton. These can be classified into three groups, the golgins, Golgi stacking proteins, and a third group representing additional membrane protein complexes (Fig. 1 and Table 1). These groups are discussed in detail as follows.

3. Membrane Scaffolds of the Golgi

i. Golgins

Golgins are a family of membrane proteins defined by their selective location at the Golgi apparatus and a high percentage of coiled-coil regions. They were initially identified as autoantigens recognised by autoantibodies from serum of patients with systemic autoimmune diseases [43-45]. The majority of golgins are recruited from the cytoplasm to the cytoplasmic face of Golgi membrane proteins by small G proteins of the Arf family, whereas the remaining golgins are embedded as integral membrane proteins [23]. As a consequence of their extensive coiled-coil structure over most of the length of the polypeptide (75-85% of golgin sequences), golgins extend considerable distances (up to ~300 nm) from the membrane into the cytosol. The coiled-coil regions of the golgins, defined by heptad repeats, are discontinuous with short breaks of unstructured sequences which allows for considerable flexibility in their extended 'rope-like' structure [46]. More than 11 mammalian golgins have been identified localised throughout the Golgi stack [23]. Collectively, golgins interact with a wide range of binding partners including small G proteins, Rabs and Arfs, SNAREs, and microtubule and actin linker proteins and molecular motors [47].

From a variety of *in vivo* experiments involving knockdowns, golgins were shown to be required for membrane trafficking and also to bridge between Golgi cisternae [8,48]; *in vitro* studies provided further evidence for a role in the docking or attachment of transport vesicles to their target membrane [49]. More recent studies, using an elegant approach involving redirection of golgins to mitochondria membranes, has provided direct evidence *in vivo* that

golgins capture transport vesicles loaded with cargo [50]. In addition to capturing transport carriers, a number of golgins interact with cytoskeletal components, including GCC88, golgin-245/p230, GCC185, GMAP210, golgin-160, giantin, GM130 and optineurin (Table 1). These golgins are located on both *trans* and *cis* side of the Golgi stack and the rims of the stack cisterna, hence they have the potential to organise the cytoskeleton around the Golgi (see Fig. 1). The nature of the interactions of the golgins with the cytoskeleton, and functions associated with these interactions, are summarised as follows.

GCC88

The role of golgins in regulating the structure of the Golgi is highlighted by recent studies on GCC88. GCC88 is one of four golgins localised at the TGN which contain highly conserved C-terminal GRIP domains. The GRIP domain is responsible for the recruitment of GCC88 to the TGN membranes by the interaction with membrane bound Arl1-GTP [51]. As for other golgins, GCC88 is a parallel homo-dimer with ~80 % of the sequence predicted to be coiled coil structures [52]. In addition to a role in regulating endosome-to-TGN retrograde transport [53], GCC88 has recently been shown by our laboratory to be coupled to the actin cytoskeleton [42]. A modest overexpression of GCC88 results in disruption of the Golgi ribbon and dispersal of intact Golgi mini-stacks throughout the cytoplasm, a finding which provided a strategy to explore the function of the Golgi ribbon. HeLa cell clones expressing twice the level of endogenous GCC88 showed an absence of the typical Golgi ribbon, rather Golgi mini-stacks were scattered throughout the cytoplasm, as defined by super-resolution SIM light microscopy and EM tomography [54]. Depletion of GCC88 by siRNA in these clones restored the Golgi ribbon, with the length of the Golgi cisternae even longer than those of the parental cells [54]. Treatment with actin depolymerizing drugs resulted in a reversal of the phenotype mediated by the overexpression of GCC88 [42]. Thus, GCC88 regulates the balance between Golgi mini-stacks and Golgi ribbon by an actin dependent process. Using the proximity-based biotinylation method, BioID and MS analysis, intersectin-1 (ITSN-1), a guanine nucleotide exchange factor for cdc42 [55], was identified as candidate interactor of GCC88 [42]. Interestingly, the long isoform of ITSN-1, containing the GEF for cdc42 was shown to be located on the TGN of HeLa cells. Pull down and immunoblotting experiments confirmed the interaction of ITSN-1 with GCC88 and that the interaction of GCC88 with the long isoform of ITSN-1 was responsible for the loss of the Golgi ribbon. Based on these studies we have proposed that GCC88 promotes actin assembly at the TGN via an interaction

with ITSN-1 which mediates an outward force towards the cell membrane resulting in disassembly of the continuous Golgi ribbon into discrete mini-stacks [42] (Fig. 2).

The manipulation of the Golgi ribbon by increasing the level of GCC88 studies has revealed a novel mechanism for the Golgi ribbon to regulate the autophagy pathway [54]. The lack of a Golgi ribbon in GCC88 stably transfected HeLa cell resulted in a dramatic increase in the number of LC3-II positive autophagosomes. The increase in the number of autophagosomes was shown to be due to increased autophagosome synthesis rather than a block in autophagic flux. The induction of autophagy in cells without a Golgi ribbon was due to compromised mTOR signalling. There was a dramatic reduction in Golgi associated total mTOR and phosphorylated mTOR in cells lacking a Golgi ribbon compared with parental cells. Increased autophagy was not due to either ER stress or nutrient deprivation. Notably, fragmentation of the Golgi ribbon by a variety of other treatments also results in an autophagic response [54,56].

Golgin-245 (p230)

Golgin-245/p230 is also a TGN golgin with a GRIP domain. Golgin-245 interacts with microtubule-actin cross linking factor (MACF) 1, a >600 kDa protein that connects microtubules to the actin filaments [57]. Depletion of golgin-245 resulted in the loss of the ribbon and formation of mini-stacks located at ER exit sites, indicating golgin-245 is involved in Golgi positioning, possibly by connection with microtubules [58]. Knock down of golgin-245, or the interactive partner MACF1, has also been shown to inhibit phagophore biogenesis following starvation, due to a block in transport of mAtg9-containing membranes from the TGN [59]. Thus, the interaction of golgin-245 with MACF1 plays a key role Golgi structure and also the regulation of autophagy [59].

GCC185

GCC185 is another member of the TGN golgin family with a GRIP domain. However, unlike the other GRIP domain family members, the GRIP domain of GCC185 binds Arl1 very weakly and the mechanism for membrane binding remains unclear [51,60]. GCC185 is one of the important components in the organisation of the Golgi MTOC and knockdown of GCC185 results in perturbation of the Golgi MTOC and extensive Golgi fragmentation [39,61]. Microtubules are nucleated on the *cis*-Golgi (see GM130 below) and then stabilized

by GCC185 on the *trans*-Golgi. The association of microtubules with GCC185 is mediated by the interaction with cytoplasmic linker associated proteins (CLASPs), which are microtubule stabilizing proteins which bind to the plus end of microtubules [39,62]. Arl4a also interacts with GCC185 and has been shown to be required for the GCC185-CLASP interaction [63]. Deletion of the Arl4a interacting region of GCC185 results in loss of binding to CLASP1 and CLASP2 and Golgi fragmentation [63]. In contrast to these knockdown studies, CRISPR/Cas9 knockout of GCC185 in the human retinal pigment epithelium (RPE1) cell line resulted in only a mild phenotype [40], raising the issue of whether the interaction between GCC185 and CLASP can be compensated in a chronic knockout condition.

The Golgi anchored microtubules, mediated via GCC185, promote the assembly and lateral fusion of dispersed Golgi stacks after mitosis [39]. Unlike the centrosomal microtubules, which form symmetrical arrays, Golgi microtubules are polarised and drive asymmetrical vesicle transport [62]. In addition, Golgi-derived microtubules are considered fundamental in cell migration and polarisation [38,64]. Hence GCC185 is required for the maintaining the integrity of the Golgi structure.

Giantin

Giantin is the largest of the golgin proteins which is anchored to *cis*-Golgi cisternae by a C-terminal transmembrane domain. Giantin can interact with other golgins, such as p115, interactions that are considered relevant to tether COPI vesicles to Golgi cisternae and also to tether adjacent cisternae [65-67]. Giantin is also implicated in lateral Golgi tethering [68] and ciliogenesis [69,70], as depletion of giantin reduces ciliogenesis by >50%. The dynein light chain of the microtubule motor is essential for cilogenesis and giantin is required for the localisation of the dynein-2 intermediate chain WD-repeat protein 34 (WDR34) at the base of the cilium [70]. However, whether this is due to a direct interaction between giantin and WDR34 or an indirect interaction is not known at this stage. Abnormal ciliogenesis in the neural tube was also observed in either giantin knockdown or giantin knockout in zebrafish [69]. Notably, the phenotype was less severe in mutant knockout Zebrafish compared with knockdowns which could be due to compensatory mechanisms from the chronic absence of the giantin protein in the knockout, and which could also explain the differences in phenotype with rodent giantin mutant null models [71].

GM130

GM130 is one of the most extensively investigated golgins and is located on the *cis*-Golgi [72]. In addition to roles associated with tethering of COPI vesicles [67], GM130 regulates both the actin and microtubule networks via interactions with a number of factors during interphase and mitosis.

GM130 is central to the ability of Golgi membranes to establish an MTOC on this organelle. GM130 promotes nucleation of microtubules on the *cis*-Golgi via the interaction with AKAP450 [38]. AKAP450 is a large coiled-coil protein localised mainly at the Golgi via the interaction with the N-terminus of GM130. AKAP450 recruits γ-tubulin directly to the *cis*-Golgi membrane and also indirectly by the recruitment of γ-tubulin ring complex (γ -TuRC), to promote the nucleation of microtubules and to cap the microtubules minus ends [40,73]. Hence, AKAP450 is essential for Golgi microtubules nucleation. These Golgi microtubules are further stabilised by the interaction of GCC185/CLASP complexes on the TGN (see GCC185 above). Loss of the Golgi MTOC by knockout of GM130 results in fragmentation of the Golgi [74,75]. Recently, GM130 has also been shown to be responsible for the recruitment of the new scaffold, septin 1 (SEPT1), to the *cis*-Golgi; SEPT1 also promotes microtubule nucleation and perinuclear positioning of the Golgi [76].

GM130 has also been reported to regulate centrosome organisation by a putative actin dependent process [77]. A number of Golgi membrane components are required for centrosome organisation and function, including GM130. Cdc42, a Rho small GTPase which promotes actin polymerisation, and Tuba, the specific GEF for Cdc42, have both been identified as GM130 interacting proteins to form a large multi-component complex. Knock down and/or expression of dominant-interfering mutants demonstrated that GM130, Cdc42 and Tuba are all required for normal centrosome organisation [77]. However, the detailed mechanism by which actin regulates centrosome organisation is not clear. Nonetheless, GM130 provides a bridge for the Golgi to regulate centrosomal organisation via interactions with cytoskeletal components.

GM130 also plays a role during mitosis in the organisation of the mitotic spindle. Upon mitotic entry, Cdk1 phosphorylates GM130 resulting in the dissociation of p115 from GM130 and disassembly of the Golgi stack into clusters of tubules and vesicles [78]. In addition, phosphorylated GM130 can bind importin α to these mitotic Golgi membranes [79]. The spindle assembly factor, TPX2, a component of the importin α complex, is released from Golgi membranes as a consequence of the interaction of the complex with GM130 and the released activated TPX2 then promotes microtubule nucleation. These microtubules then capture GM130 associated Golgi membranes to link the Golgi membranes to the spindle and ensure Golgi inheritance to both daughter cells [79].

Given the diverse set of GM130 interaction partners, not surprisingly knockout of GM130 results in major perturbations to the Golgi ribbon structure [80]. Mice lacking GM130 die soon after birth. Conditional knock out of GM130 in the central nervous system results in Golgi fragmentation, atrophy of dendrites and neuronal degeneration in mice [80]. EM analysis of the GM130 knockout neuronal cells showed a reduction in Golgi cisternal length and cisternal stacking [80].

GMAP210

GMAP210 is recruited to the *cis*-Golgi via interactions with membrane associated Arf1 [81,82]. In addition to tethering tubulovesicles to the *cis*-Golgi, GMAP210 has also been proposed to link the Golgi to microtubules by an interaction with the microtubule minus ends and the nucleating protein γ-tubulin [83]. GMAP210 may also play a role in stabilising or anchoring the centrosome to the Golgi. Depletion of GMAP210 results in dispersal of the Golgi stacks and, furthermore, redirection of GMAP210 to the mitochondria results in an association of mitochondria with centrosomes [82]. Analysis of various tissues of mice deficient in GMAP210 by EM also revealed a major disruption in the normal Golgi architecture [84]. It remains unclear how GMAP210 can be recruited to the Golgi and also bind γ-tubulin through the same C-terminal GRAB domains [81,85].

Golgin-160

Golgin160 is localised to the *cis*-Golgi and has been identified as a dynein cargo [86]. Golgin 160 knock-down results in dissociation of dynein from Golgi membranes, fragmentation and dispersion of the Golgi ribbon, and impaired ER to Golgi trafficking of temperature sensitive viral cargo protein, VSVG-GFP. Golgin160 interacts with dynein via its coiled-coil cc7 domain. Dynein recruited by golgin 160 has been reported to mediate movement of Golgi elements from the cell periphery to the cell centre [34].

Optineurin

Optineurin has multiple coiled-coil domains and, therefore, can be considered a golgin [87]. Notably optineurin has been reported to bind the actin motor protein, myosin VI. Knock down of optineurin reduced the level of mysosin VI at the Golgi and resulted in Golgi fragmentation and a reduction in anterograde transport of membrane cargo to the cell surface [87]. Based on these findings, optineurin has been proposed to play a role in maintaining the structure of the Golgi and also in the regulation of exocytosis [87,88]

Lava Lamp (Drosophila protein)

Lava lamp is a *Drosophila* golgin which binds to the microtubule motor, dynein, and the dynein co-factor dynactin as well as the cytoskeletal protein, spectrin [89]. Lava lamp is essential for an early stage of *Drosophila* embryogenesis which requires dynein-dependent movement of the Golgi along microtubules [89]. Lava lamp has also been reported to play a role in transport of Golgi outposts in the dendrites of Drosophila neurons [90].

Bicaudal-D

Bicaudal D1 (BICD1) and Bicaudal D2 (BICD2) are coiled-coil golgins recruited to the TGN by Rab6 [91]. The Bicaudal D proteins bind to dynactin and recruit the dynein-dynactin complex to the *trans*-Golgi where the dynein motor may be required for retrograde movement of transport vesicles from the TGN to the ER or for organisation of the Golgi membranes at the MTOC. Overexpression of BICD2 or mutations of BICD2 in congenital spinal muscular atrophy (SMA) are associated with Golgi fragmentation [92].

ii. GRASPs

Golgi Reassembly and Stacking Proteins (GRASPs) play important roles in the formation of the Golgi stack by functioning as a molecular 'glue' to adhere cisternae tightly together [93]. They are peripheral membrane proteins and can be observed as molecular bridges between cisternae by EM. There are two GRASPs, GRASP55 and GRASP65, and both can dimerize. GRASP65 has been shown to connect to the cytoskeleton.

GRASP65

GRASP65 was identified as a peripheral protein associated with *cis*-Golgi membranes in a cell-free assay established for studying Golgi stack reassembly when exposed to the alkylating reagent N-ethylmaleimide (NEM) [94]. Structurally, GRASP65 comprises an evolutionary conserved N-terminal GRASP domain followed by a short region containing a GM130-binding site and a C-terminal Ser/Pro rich (SPR) domain [95]. GRASP65 forms dimers and oligomers which in turn tether the cisternal membranes together into Golgi stacks [95]. GRASP65 is targeted to the Golgi membrane through a N-terminal myristoylated glycine residue and its interaction with GM130 [96]. The SPR domain is phosphorylated by mitotic kinases and phosphorylated GRASP65 is implicated in Golgi disassembly and reassembly process during the cell cycle [97,98].

Numerous studies have indicated a role of GRASP65 in Golgi cisternae stacking and linking the stacks to form a Golgi ribbon [93]. For example, overexpression of a non-phosphorylated mutant form of GRASP65 in interphase HeLa cells resulted in enhanced stack formation and inhibited mitotic Golgi fragmentation. On the other hand, depletion of GRASP65 by RNA interference led to reduced number of cisternae in the Golgi stacks [99] or Golgi ribbon fragmentation [75,100]. CRISPR/Cas9 knockout of GRASP65 resulted in defects in Golgi structure, including increased occurrence of disorganized membranes, appearance of short unaligned cisternae and reduced number of cisternae in a stack [101,102]. GRASP65 facilitates linking of the Golgi ribbon by recruiting an actin elongation factor, MENA (mammalian enabled) onto the Golgi. MENA then enhances actin polymerization at the Golgi stacks tugging them toward each other to form a ribbon [103]. Although changes in GRASP65 expression levels are not yet associated with any disease or disorders, phosphorylation of GRASP65 is mechanistically linked to Golgi fragmentation in Alzheimer's disease [104,105].

iii. Other Golgi structural proteins

In addition to the golgins and GRASPS, there are other Golgi structural proteins which interact with the cytoskeleton, namely GOLPH3 and formin.

GOLPH3

Golgi phosphoprotein 3 (GOLPH3; also known as GPP34/GMx33/MIDAS) [106,107] a peripheral membrane protein localized to the *trans*-Golgi [107,108] was originally identified through characterization of Golgi membrane proteins by proteomics [106,107].

GOLPH3 has been proposed to bind small actin filaments through phosphatidylinositol-4-phosphate (PI4P) enriched TGN membranes [109] and the unconventional motor MYO18A to generate an acto-myosin tensile force required for Golgi vesiculation and ribbon extension [110]. However, the absence of motor activity for MYO18A fails to explain the mechanism behind inducing such a pulling force [111]. Nevertheless, perturbations in the GOLPH3 pathway affect Golgi morphology as well as multiple cellular processes such as vesicular trafficking, secretion, mTOR signalling and cell survival [110,112,113]. Inhibition of GOLPH3 pathway either by siRNA mediated knockdown of GOLPH3 or MYO18A leads to enhanced Golgi compaction and, in addition, to altered Golgi-to-plasma membrane trafficking, increased apoptosis and reduced cell survival after DNA damage [112]; while overexpression of GOLPH3 results in extension of the Golgi ribbon leading to fragmentation [110] and increased cell survival when treated with DNA damaging agents [112]. GOLPH3 has also been proposed to play a role in localisation of Golgi glycosyltransferases [114].

Formin

The formin homology 2 (FH2) domain protein 1 (FHDC1), enriched on the *cis*-Golgi, binds microtubules via a unique C-terminal domain and actin via its FH2 domain [115,116]. Either depletion or overexpression of FHDC1 results in dispersal of the Golgi ribbon into functional mini-stacks, revealing the potential role of both actin and microtubule Golgi networks in maintaining the ribbon structure. It has been proposed that FHDC1 acts in an actin-dependent manner to stabilise the new microtubules as they are transferred from the

GM130/AKAP450 complex on the *cis*-Golgi to the GCC185/CLASP complex on the TGN [115].

4. Changes in Golgi structure in disease

The Golgi undergoes morphological changes during normal physiological conditions, for example during differentiation, mitosis and cell polarisation. Recently the regulation of the inflammasome response was also shown is be associated with changes in Golgi architecture, notably dispersal of TGN membranes to facilitate the assembly of the NACHT, LRR and PYD domains-containing protein 3 (NLRP3) scaffold [16]; therefore, new roles continue to be discovered for the Golgi to promote and regulate cell pathways.

Over the past 10-15 years there have been an increasing number of studies reporting perturbations in the structure of the Golgi ribbon associated with diseases, disorders and infections. These include stress responses [117], metabolic perturbations [56], cancer [118], neurodegeneration [119,120], and various infections such Chlamydia which remodel the Golgi membranes [33]. Many of the alterations in Golgi structure involve the scaffolds discussed in this review which influence the microtubule and actin networks. For a detailed review of the reported changes in Golgi morphology associated with disease the reader is referred to a number of recent reviews [4,11,28,42,121,122] . Here we will briefly summarise the involvement of Golgi scaffolds in these conditions.

Stress responses arising from oxidative or pharmacological intracellular damage are associated with fragmentation of the Golgi ribbon and modulation of the golgin scaffolds are associated with these responses [123]. Caspase 2, which is located on Golgi membranes, has non-apoptotic roles in response to oxidative stress, tumour progression and aging [124,125]. Several golgins, including golgin-160 have been reported to be caspase 2 substrates [124,126]. Golgin-160 is degraded and the fragments from golgin 160 can be imported into the nucleus and may induce gene expression and contribute to the stress response pathway [127]. Another example of intracellular damage is liver injury from alcohol, which is

associated with Golgi fragmentation associated with reduced levels of the dimeric form of the golgin, giantin [128,129].

Fragmentation of the Golgi ribbon is commonly associated with tumour cells [118]. The alterations of Golgi structure are associated with changes in glycosylation which impact on metabolism and tumourigenesis [130] [118], and also DNA repair pathways [112]. The molecular basis for the fragmentation has only been defined in a few cases. Interesting, overexpression of different Golgi Rabs have been reported for a variety of cancers, for example Rab1A, Rab6A and Rab8 [131-133]. Some of these Rabs interact with golgins and molecular motors these interactions are likely to affect their function. For example, Rab6A interacts with giantin and non-muscle myosin IIA to promote either a compact Golgi or fragmented Golgi. In prostate cancer, the latter pathway dominates, resulting in Golgi ribbon dispersal [130]. The upregulation of Golgi-associated myosin motors has also been reported in tumours, for example, myosin Va in metastatic colorectal cancer [134]. It is possible that the upregulation of these motors results in increased actinomyosin forces which disperse the Golgi ribbon.

A characteristic of tumour cells is the avoidance of apoptosis following DNA damage. A relationship has also been reported between the architecture of the Golgi and the cell response to DNA damage response. GOLPH3 was identified as the first Golgi localised onco-protein in a screen for amplified genes in solid tumours [113]. GOLPH3 gene is amplified in a number of carcinomas including lung, breast, prostate, pancreatic and ovarian cancers, moreover elevated expression levels of GOLPH3 correlated with poor patient prognosis [135,136]. Multiple studies have demonstrated that overexpression of GOLPH3 drives oncogenesis in cell culture and xenograft models; conversely, inhibition of its expression reverses *in vitro* and *in vivo* carcinogenic properties [112,137-139]. Overexpression of GOLPH3 results in Golgi fragmentation and enhanced cell survival following DNA damage, whereas depletion of GOLPH3 restores a compact Golgi and increases apoptosis after DNA damage. GOLPH3 is regulated by phosphorylation by the DNA damage response kinase, DNA-PK, and has also been reported to regulate mTOR signalling [112,113]. Hence the GOLPH3 scaffold connects the cytoskeleton of the Golgi and signalling pathways.

Golgi fragmentation and loss of the Golgi ribbon is associated with a diverse range of neurodegenerative diseases [119,120,140,141]. Although the molecular mechanisms associated with the loss of the ribbon in these diseases remain unknown, it is very likely that the loss of the Golgi ribbon contributes to the pathology of disease. For example, in model systems, involving tau-mediated cytotoxicity of neuroblastoma cells, dispersal of the Golgi ribbon is an early event dependent on the GCC88- and actin- mediated pathway [54] [42]. Golgi fragmentation in tau-overexpressing cells is accompanied by compromised mTOR activity [54]. Amyloid-β in Alzheimer's disease has been reported to activate cyclin dependent cdk5, which phosphorylates GRASP65 and GM130 resulting in Golgi fragmentation [105]. Also relevant is the finding that the induction of Golgi fragmentation *in vivo*, by knock-out of the golgin GM130, results in neurodegeneration [80]. Clearly there will be multiple pathways leading to loss of the Golgi ribbon and, given the above findings, it is likely that Golgi scaffolds will play a major role in the reported changes in Golgi architecture. Different pathways of Golgi fragmentation are also likely to result in a range of different consequences.

5. Golgi as a signalling hub

A very diverse cohort of signalling molecules are located on Golgi membranes, including kinases, phosphatases, trimeric G proteins, and phosphoinositides [4,142,143]. Moreover, a variety of signalling pathways have been reported to influence Golgi structure and function, including mTOR, MAPK, PTEN, Src, Hck, PKA/cAMP, ERK signalling (see [4,143]). The evolution of the Golgi ribbon in higher eukaryotes has been proposed to provide a platform for additional regulation of complex signalling networks compared with lower eukaryotes [28]. As mentioned previously, a relationship between signalling pathways and Golgi morphology was revealed by a genome wide kinome and phosphatome screen which identify 150 signalling genes which dramatically influenced the morphology of the Golgi, either inducing fragmentation or compaction [35]. The link between kinases/phosphatase and Golgi morphology strongly suggests that signalling networks regulate cytoskeletal re-modelling of the Golgi morphology. A number of the Golgi scaffolds discussed in this review have been shown to influence signalling pathways, for example GM130, GCC88, as well as GOLPH3 and golgin-160 which were discussed in the previous section.

The GM130 scaffold mediates a number of signalling pathways via the interaction with AKAP450. AKAP450 recruits PKN, PP2a or PP1 to the Golgi [144] and may influences a number of cellular events, including cell cycle progression and intracellular traffic. mTOR activity has been reported to be modulated by GOLPH3, as discussed above, and by Golgi fragmentation mediated by the golgin, GCC88 [54]. In the case of GCC88, increased expression of GCC88 converts the Golgi ribbon into Golgi mini-stacks and results in a reduction in mTOR activity [54]. Reduced mTOR activity is associated with reduced levels of mTOR and activated p-mTOR on scattered Golgi mini-stacks. It has been proposed that the machinery to recruit mTOR to the Golgi does not function after ribbon fragmentation [54].

An important consideration that could influence Golgi signalling is the impact of membrane-membrane contact sites between the Golgi and other organelles. The Golgi has been shown to make contacts with the ER [145] and the late endosomes/lysosomes [146,147], and membrane-membrane contacts between organelles are known to regulate a number of cellular processes. An important issue that needs to be addressed is whether the loss of the Golgi ribbon, mediated by the Golgi scaffolds, influences these membrane-membrane contact sites and thereby indirectly modulates a variety of signalling pathways.

6. Conclusions and Perspectives

The formation of the higher-order Golgi ribbon structure in vertebrates has long suggested a role for the Golgi beyond the traditional functions of membrane transport and glycosylation. An emerging theme from work from numerous laboratories is the Golgi as a cell sensor, where this organelle is integrated into a complex molecular wiring system to regulate a network of pathways. Key molecular players in this network are the membrane tethers, or scaffolds, including golgins and GRASPs. These Golgi scaffolds are very versatile molecules due to the coiled-coil regions which act as interactive platforms. Scaffolds interact with a diverse range of partners including components of the actin and microtubule cytoskeletal system. In many cases the scaffold molecules link interactions with the

cytoskeletal to maintain the structure of the Golgi as well as influencing various signalling pathways involved in regulating of a range of cellular processes.

The ribbon morphology of the Golgi is regulated by scaffold molecules which interact with microtubules and also with actin. Whereas the dynamics of the Golgi microtubules are now well understand, the mechanism(s) by which F-actin regulates the structural integrity and architecture of the Golgi complex remains poorly understood. One impediment to understanding the role of actin in regulating Golgi architecture is that actin is technically very difficult to visualize at the Golgi, probably due to the highly dynamic nature of the short actin filaments within the Golgi [37]. Improved fluorescent probes and imaging approaches are required to be able to monitor actin dynamics in live cells. In addition, the inhibition of selective myosin motors provides an avenue to explore the relationship between Golgi dynamics and function.

More details are required on understanding the assembly and regulation of the scaffold complexes on Golgi membranes. Many experiments so far have analysed the effect of knock-down, knock-out or overexpression of the scaffolds on Golgi structure and function. This is a fairly crude approach as multiple interactions will be affected by changes in levels of the scaffolds. In addition, discrepancies in phenotype between knockdowns and knockouts may be compounded by the capacity of cells to adjust or compensate over long term loss of a Golgi scaffold molecule [69,148]. Dissection of the interaction networks mediated by the Golgi scaffolds requires the introduction of mutations which selectively eliminate individual interactions. A systems approach is also required to define the relationship between scaffold binding partners, cytoskeletal interactions and cellular pathways that are modulated by these interactive platforms.

Many of the studies analysing the functions of Golgi scaffolds have been performed using cultured cell lines. Examination of the roles of the golgins and GRASPs in tissues and specialized cells in model organisms and the identification of mutations in Golgi membrane tethers in human disease has revealed phenotypes associated with a wide range of physiological processes [149], which may reflect their potential roles in co-ordinating cellular networks. The use of inducible knock-out systems and introduction of defined mutations that eliminate interactions with specific binding partners will be useful to identify the function of

scaffold interactions in different tissues and organs. Key roles for Golgi scaffolds have also been implicated in cancer and neurodegenerative diseases. Defining the scaffold interactions which contribute to these diseases will provide a deeper understanding of the underlying molecular mechanisms of these conditions and may also identify targets for treatment of these pathological conditions.

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Conflict of Interest Statement

The authors have no conflict of interest to declare.

TABLE 1

Scaffold molecules of the Golgi and their interactors with actin and microtubule cytoskeletal networks[1]

A. Both actin and microtubule interactors

Golgi Components	Interactors	Function	References
Golgin-245 (p230)	MACF1, microtubule motor?	Role in maintenance of Golgi structure, regulation of autophagy and minus end directed transport of Golgi membranes along microtubules	[57,58] [59]
GM130	AKAP450, importin α, Cdc42, Tuba	Regulates Golgi as a microtubule organizing centre and centrosome organisation; a role in organisation of mitotic spindle	[38] [77,79]
Lava lamp	dynein, spectrin	Required for dynein-dependent movement of Golgi along microtubules during embryogenesis	[89]

B. Microtubule interactors

Golgi Components	Interactors	Function	References

GCC185	CLASP1, CLASP2, Arl4a	Required for the organization of Golgi MTOC by stabilizing microtubules on the *trans*-Golgi	[39,62,63]
GMAP210	microtubules, γ-tubulin	Links microtubules to the *cis*-Golgi	[82,83]
Formin	microtubules	Stabilizes new microtubules during transfer of microtubules from the cis-Golgi to the GCC185/CLASP complex on *trans*-Golgi	[115,116]
Golgin-160	dynein	Mediates movement of Golgi elements from cell periphery to the cell centre	[86]
Bicaudal D	dynein-dynactin complex	Functions in movement of transport vesicles from the TGN and organization of the Golgi as a MTOC.	[91]

C. Actin interactors

Golgi Components	Interactors	Function	References
GCC88	ITSN-1	Promotes actin assembly at the TGN to regulate the balance of the Golgi ribbon and mini-stacks	[42]
Optineurin	myosin VI	Regulates Golgi structure and exocytosis	[87]
GOLPH3	actin filaments, MYO18A	Binds actin filaments to promote Golgi ribbon extension	[109,110]
GRASP65	MENA	Role in linking the stacks into the Golgi ribbon by enhancing actin polymerization, via MENA	[103]

[1]Abbreviations: MACF, microtubule-actin cross linking factor: ITSN1, intersectin-1; MENA, mammalian enabled; CLASP, Cytoplasmic linker associated proteins; AKAP450, A-kinase anchoring protein; MENA, mammalian enabled; CLASP, cytoplasmic linker associated proteins

Legends to Figures

Figure 1. Golgi proteins which interact with microtubule and actin cytoskeletal networks

Shown are the golgins (diamond), GRASPs (hexagon) and other scaffold proteins (quadrilateral) of the Golgi, their location on the Golgi stack and whether they interact with actin filaments (green), myosin motors (light green), microtubules (red) or microtubule motor dynein (orange).

Figure 2. Model of the regulation of the Golgi actin cytoskeleton by the GCC88-ITSN-1 pathway

Shown is the model proposed by Makhoul et al [42] for coupling the interaction between GCC88 and ITSN-1 with actin polymerisation at the TGN. GCC88 binds and recruits the long form ITSN-1 to the TGN. The long form of ITSN has GEF activity for Cdc42. Activated Cdc42 at the TGN promotes actin nucleation possibly via the interaction of Cdc42 with WASP and the Arp2/3 complex. The ability of GCC88 to disperse the Golgi ribbon is also dependent on the myosin motor, non-muscle myosin IIA [42]. The balance of the outward actinomyosin forces the inward dynein-microtubule forwards result in a "tug-of-war" which define the status of the Golgi architecture. An increase in the levels of GCC88 results in the loss of the Golgi ribbon, whereas a decrease in the level of GCC88 results in an enhanced Golgi ribbon. The figure is a modification from [42].

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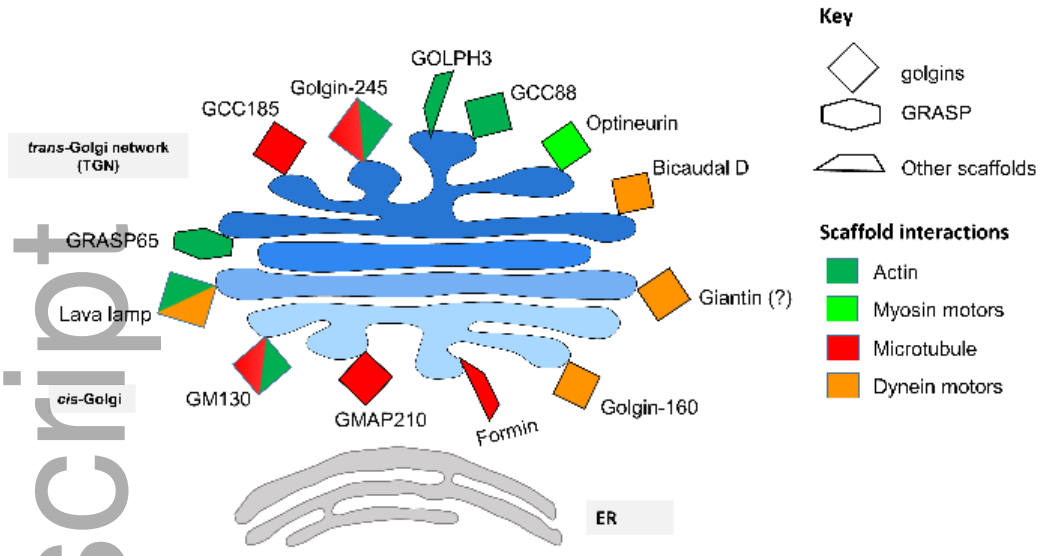

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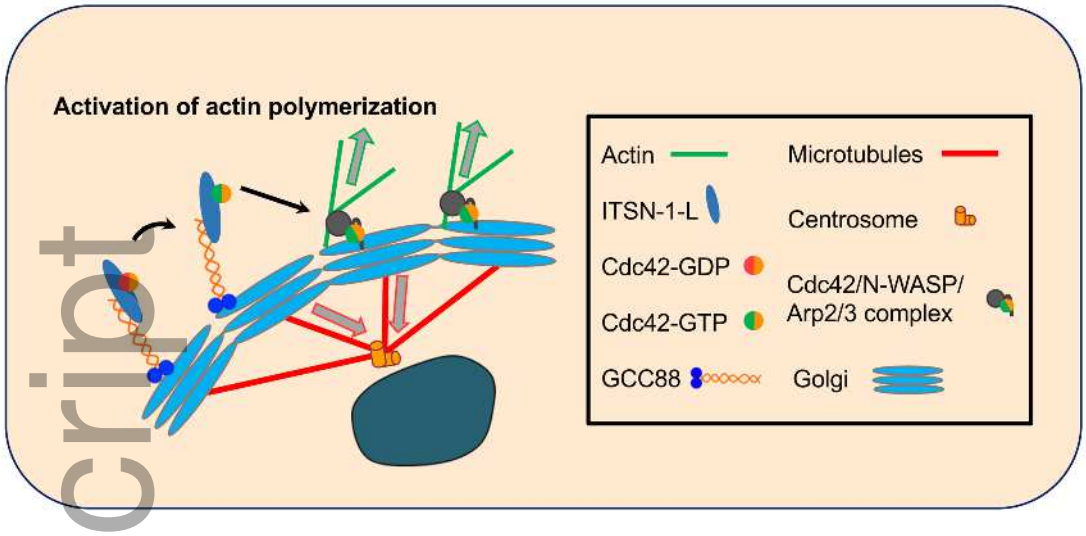

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