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Handb Exp Pharmacol. Author manuscript; available in PMC 2018 August 14.

Published in final edited form as:
Handb Exp Pharmacol. 2018 ; 245: 227–247. doi:10.1007/164_2017_65.

Conserved Oligomeric Golgi and Neuronal Vesicular Trafficking

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Abstract

The conserved oligomeric Golgi (COG) complex is an evolutionary conserved multi-subunit vesicle tethering complex essential for the majority of Golgi apparatus functions: protein and lipid glycosylation and protein sorting. COG is present in neuronal cells, but the repertoire of COG function in different Golgi-like compartments is an enigma. Defects in COG subunits cause alteration of Golgi morphology, protein trafficking, and glycosylation resulting in human congenital disorders of glycosylation (CDG) type II. In this review we summa rize and critically analyze recent advances in the function of Golgi and Golgi-like compartments in neuronal cells and functions and dysfunctions of the COG complex and its partner proteins.

Keywords

COG; Conserved oligomeric Golgi; Glycosylation; Golgi outpost; Golgi satellite

1 Golgi Apparatus in Neurons

The history of the Golgi apparatus and understanding of neuronal function have been intertwined since the first studies by Camillo Golgi (Golgi 1989). All eukaryotic cells constantly synthetize and uptake proteins, lipids, and other macromolecules moving them anterograde (endoplasmic reticulum [ER] to plasma membrane [PM]) and retrograde (PM to ER) between various intracellular compartments. The mammalian Golgi is a stack of flattened double-membrane compartments called cisternae and is the central station along these pathways. The major functions of the Golgi include, but are not limited to, protein and lipid glycosylation, sphingomyelin and glycolipid biosynthesis, macromolecule sorting, and formation of secretory granules. Though the Golgi can be compartmentalized and defined by multiple regions (*cis, medial, trans, trans*-Golgi Network [TGN], Fig. 1), the organelle as a whole is a dynamic functional unit. The contents of each cisterna vary depending on the state of the cell (Goldfischer 1982). Stress-dependent differences allow functional flexibility and adaptation to challenges to homeostasis. This is the likely reason for variations in Golgi morphology in different species and cell types (Mironov et al. 2017; Mollenhauer and Morre 1978). The flattened, stacked Golgi structure described above is conserved in many species.

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However, others, including yeast S. *cerevisiae*, have Golgi compartments that are spatially separated and disbursed throughout the cell (Mogelsvang et al. 2003; Rossanese et al. 1999). Neurons contain the standard mammalian structure in the perinuclear region of the soma with smaller Golgi-like organelles throughout dendrites (Fig. 1).

The Golgi apparatus has long been studied in the perinuclear region of neurons, historically through thiamine pyrophosphatase (TTPase) which has a distinct activ ity rate within different neuronal cell types (Castellano et al. 1989). TTPase activity suggests that Golgi machinery is present in axons and presynaptic axon terminals (Griffith and Bondareff 1973). Further, peptide hormones and neuropeptides released by axons require Golgi enzymes for processing. However, extensive analyses have not detected Golgi membranes within axonal regions (Bunge 1973; Horton and Ehlers 2003; Merianda et al. 2009; Tennyson 1970). Axons demonstrate de novo protein synthesis (Koenig 1967), contain mRNA (Giuditta et al. 1986), and have markers for protein translation and glycosylation positing the likelihood of functional equivalents to standard secretory organelles within axons (Merianda et al. 2009).

Though Golgi-like structures are not present in axons, these structures are functionally important in dendrites. Hippocampal neuron survival depends upon maintaining dendritic arborization through functional synaptic connections associated with satellite secretory regions found at dendritic branch points known as Golgi outposts (GO) (Ye et al. 2007). Smaller Golgi-like membranes, Golgi satellites (GS), exist in dendritic regions distal to GO and shape dendrite morphol ogy via a poorly understood mechanism (Fig. 1). These smaller membranes lack detectable levels of some standard Golgi markers (Table 1), like Golgi tether GM130 which is required for mature dendritic arborization (Liu et al. 2017; Zhou et al. 2014). This suggests that both GO and GS are equally important to dendritic function in a spatiotemporally dependent fashion. GO and GS contain glycosylation enzymes and glycosylated proteins indicating that a portion of Golgi function takes place within these smaller organelles. Quassollo et al. (2015) showed that GO are generated from somatic Golgi-derived tubules that migrate into major dendrites (Quassollo et al. 2015). Larger GO (>1 um), localized to first- or second-order segments of major dendrites; smaller GO (0.3–1 um) preferentially localized to second-order and greater segments of major dendrites and in minor dendrites (Quassollo et al. 2015). Mikhaylova et al. (2016) showed that GS have a separate function from GO, have a somatic Golgi origin, contain glycosylation machinery, and are in close association with dendritic ER-Golgi intermediate compartments (ERGIC) (Mikhaylova et al. 2016). Further biogenic analysis of GO and GS is necessary to determine if these are indeed separate organelles. Electron microscopy (EM) may be able to overcome some limitations to endogenous protein expression. EM analysis of Golgi-like membranes in dendrites reveals that the TGN and *trans*-Golgi markers TGN38 and Rab6 are present in smaller structures (Pierce et al. 2001). The dendritic spine apparatus, which could be generated from dendritic ER, is a source of local protein synthesis with similar trafficking components (Cajigas et al. 2012). Similarly to the formation of dendritic spine apparatus during long-term potentiation, GO and GS could form and function during neuronal development where protein translation and trafficking must be rapid, abundant, and precise (Hanus and Ehlers 2016).

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2 Golgi Trafficking and Glycosylation in Neurons

Depending on the cell type, 30–50% of proteins are synthesized in the ER and then transported to the Golgi inside double-membrane COPII-coated vesicles. Once in the lumen, proteins are posttranslationally modified by various resident enzymes as they move through the Golgi. Within the TGN, modified proteins are sorted and repackaged into vesicles for redistribution elsewhere.

There are several hypothetical Golgi transport models to describe this process stemming from the two primary models: vesicular transport and cisternal maturation. The vesicular transport model depicts a static Golgi where cargo traverse the stack transported within vesicle carriers. Vesicles bud off the cisternae and traffic in both the anterograde and retrograde directions (Rothman 2002). The cisternal maturation model is more dynamic whereby unstable compartments are initially created by the homotypic fusion of ER-derived vesicles. Cargo proteins are held within a cisternal lumen that "matures" in a cis-to-trans direction. Resident Golgi proteins move through the stack as they modify cargo and require recycling to earlier Golgi compartments (Glick et al. 1997; Glick and Nakano 2009; Mironov et al. 1997; Pelham 2001). Additional models describe transient corridors that open and close between cisternae which could allow a diffusion-like transport process (Beznoussenko et al. 2014; Pfeffer 2010). Building upon cisternal maturation, the cisternal progenitor model describes Golgi cisternae that mature by continual fission and fusion with adjacent cisternae (Pfeffer 2010). There is evidence to support all of these models (Glick and Luini 2011; Pelham and Rothman 2000), and the transport process is likely dependent upon cargo and cell type. For example, larger cargo that could not fit within the 60–80 nm Golgi vesicle could move within the cisternae or through a transient corridor between cisternae. Neurons have an additional, unique transport processes that could bypass the Golgi completely. For example, both NMDA and AMPA receptors collaborate during synaptic excitation at the postsynapse yet reach the PM via two different trafficking pathways. AMPA receptors utilize the standard pathway for delivery to the PM, and NMDA receptors traffic in a SAP97-/CASK-dependent pathway from the somatic ER to the dendritic ER and then to dendritic GO (Jeyifous et al. 2009).

All intra-Golgi trafficking models rely heavily on transport vesicles to move cargo between cisternae. The arsenal of core trafficking components required to maintain these processes include small GTPases of the Rab and Arf subfamilies, soluble N-ethylmaleimide-sensitive factor [NSF] attachment protein receptors (SNAREs), Sec1/Munc18-like (SM) proteins, tethers, and coat proteins (Bonifacino and Glick 2004). Multi-subunit tethering complexes (MTCs) are an important class of proteins that regulate these components (Cottam and Ungar 2012; Willett et al. 2013b). The MTC that regulates retrograde trafficking at the Golgi is the conserved oligomeric Golgi (COG) complex (Ungar et al. 2002; Whyte and Munro 2001) which maintains the correct distribution of glycosylation enzymes throughout the Golgi (Pokrovskaya et al. 2011).

Glycosylation is the sequential trimming and extension of an oligosaccharide chain and is an essential ER/Golgi process. An estimated 2% of the genome is dedicated to the glycosylation machinery (Freeze et al. 2014). N-glycosylation is the covalent attachment of

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a carbohydrate chain to an asparagine residue in the consensus sequence Asn-X-Ser/Thr (Marshall 1974; Stanley et al. 2009). Initially, a nascent protein receives a dolichol-linked precursor structure within the ER, and then further modifications are introduced as the protein passes through the Golgi. Although N-glycans can exist as extensively branched structures, they may be grouped into three simplified models: high mannose (core/ immature), hybrid, and complex (Fig. 2). Unlike N-glycosylation which is initiated by linkage of a core sugar structure, O-glycosylation is initiated by the covalent linkage of a single carbohydrate, most commonly to a serine or threonine residue. O-glycosylation takes place at a site with no apparent consensus sequence and is generally a single or binary chain initiated by one of many single sugars (Moremen et al. 2012). O-glycosylation of secretory and transmembrane proteins occurs mainly within the Golgi. Mucin-type glycans are the most abundant and are initiated by a single GalNAc sugar (Brockhausen et al. 2009).

Neurons have more immature/core N-glycan structures on the cell surface, suggesting that N-glycosylation does not follow the intricate process that results in the complex sugar structures observed in other cell types (Hanus et al. 2016) (Fig. 2). Hanus et al. (2016) speculate that proteins with immature N-glycans bypass the Golgi as Golgi disassembly had no effect on PM distribution of these proteins (Hanus et al. 2016). Via an unidentified sorting process, proteins could exit the ER/cis-Golgi, without completely traversing the Golgi, and produce fully functional receptors (Hanus et al. 2016; Jeyifous et al. 2009). Although GO and GS contain glycosylation enzymes and polysialylated proteins (Mikhaylova et al. 2016), it is not yet known if proteins that avoid traditional Golgi trafficking pathways are modified in GO and GS.

Glycolipids are carbohydrates linked by glycosyl linkage to a lipid moiety. In mammals, the lipid backbone is ceramide resulting in a subclass of glycolipids termed glycosphingolipids. Glycosphingolipids are essential for neural development and function (Simpson et al. 2004). Though galactosylceramide (GalCer) is the major glycolipid of the mammalian brain, glucosylceramide (GlcCer) plays an essential role as a precursor to most oligoglycosylceramides such as gangliosides, sialic acid-containing glycosphingolipids. Ganglioside synthesis begins when glucose is added to the ceramide on the cytosolic face of the *cis*-Golgi. The resulting GlcCer is flipped into the lumen for extension similarly to N-glycans. In the developing brain, there is a shift in the balance of simple versus complex gangliosides (Yu et al. 1988). GM3 ganglioside is more abundant in mid-embryonic mouse brains, while GM1 ganglioside is predominant afterward and into adulthood (Ngamukote et al. 2007) (Fig. 2). This means that abundance of specific gangliosides relies heavily on Golgi trafficking regulators and receipt of a signal to alter processing.

3 COG Complex in Golgi Trafficking and Glycosylation

Because trimming and extension of an oligosaccharide chain is non-template driven, regulatory steps must ensure that proteins traversing the Golgi stack interact with glycosyltransferases in the proper order. During processing, enzymes move through the Golgi with their target proteins and then recycle back to *cis/medial* cisternae. The COG complex is a multi-subunit tethering complex that regulates retrograde recycling by tethering intra-Golgi vesicles carrying resident Golgi proteins, like glycosylation enzymes (Ha et al.

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2016; Shestakova et al. 2006; Suvorova et al. 2002; Ungar et al. 2002; Willett et al. 2014; Witkos and Lowe 2017). This eight-part complex composed of unique subunits (COG1–8) is localized to the cytosolic face of the Golgi. The most compelling evidence for COG function comes from human patients with mutations in COG subunits resulting in congenital disorders of glycosylation (CDG) (Table 2) (Climer et al. 2015). The COG complex is evolutionally conserved and is found in the majority of eukaryotic cells (Klinger et al. 2016; Koumandou et al. 2007). In humans, COG is constitutively expressed in all cell types throughout development. It is highly expressed in the nervous system as active COG complexes were first purified from the bovine brain (Ungar et al. 2002; Walter et al. 1998).

COG structure has been difficult to determine. Currently, only fragments have been solved by crystallography including a C-terminal portion of human COG4 and partial structures for yeast COG2 and the COG5/COG7 dimer (Cavanaugh et al. 2007; Ha et al. 2014; Richardson et al. 2009). The major difficulty is attributed to misfolding of bacterially expressed COG subunits. Physiologically, COG subunits likely require stabilization during folding by an interaction with other COG proteins. Nonetheless, each subunit likely has N-terminal coiled-coil regions that are utilized for complex assembly, and C-terminal extended α-helical domains. COG shares these structural characteristics with other protein complexes in the complexes associated with tethering containing helical rods (CATCHR) family: DSL1, GARP, EARP, and exocyst (Chou et al. 2016; Whyte and Munro 2001, 2002; Yu and Hughson 2010). EM provided the first structural details of purified, soluble COG complex, and concomitant biochemical analysis demonstrated the bilobed organization of the subunits (Ungar et al. 2002). Subsequent analyses have also confirmed the COG complex is functionally and structurally divided into two sub-complexes (lobe A, COG1–4, and lobe B, COG5–8) with long flexible extensions (Fig. 3) (Cavanaugh et al. 2007; Fotso et al. 2005; Ha et al. 2014, 2016; Lees et al. 2010; Richardson et al. 2009; Ungar et al. 2002). Recent experiments by Willett et al. (2016) suggest that the COG sub-complexes temporarily interact with each other during vesicle tethering/fusion. Mutations that prevent the lobe A–B interaction are also inhibitory to COG function. A cleavable fusion construct that leashes COG1 (lobe A) and COG8 (lobe B) together is inhibitory, demonstrating that functional COG alternates between separate sub-complexes and the complete complex. According to this model, the lobe A sub-complex is mostly located on Golgi membranes with lobe B on vesicle membranes (Willett et al. 2016). COG is functionally and structurally destabilized when any of the COG subunits are depleted. Recent evidence from COG subunit KO cell lines demonstrated that each COG subunit is essential to the overall function of the complete complex (Bailey Blackburn et al. 2016; Blackburn and Lupashin 2016). Indeed, while each cell line could cope with the removal of one COG subunit, the overall function of the COG complex was greatly diminished due to destabilization of the other COG subunits.

4 COG Interactions with Core Trafficking Components

The COG complex dynamically interacts with the core components of intra-Golgi trafficking and is an interaction hub of the Golgi (Willett et al. 2013b) making it possible for COG influence to ripple out in many directions. The COG complex organizes the core trafficking machinery, through events not fully delineated, toward the goal of aligning a vesicle with the

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target membrane to enable membrane fusion and cargo release. The major COG protein interactors are Rabs, COPI coat, vesicular tethers, SNAREs, and SM proteins (Fig. 3).

Rab-GTPases are molecular switches that are active and inactive in the GTP- and GDP-bound states, respectively (Hutagalung and Novick 2011). Regulatory and effector proteins link all Rabs together in a network via the sequential activation of downstream Rabs and inactivation of upstream Rabs (Ortiz et al. 2002). Active Golgi Rabs were proposed as recruiters of the COG complex to Golgi and vesicle membranes (Suvorova et al. 2002). Later it was shown that COG can directly interact with roughly a dozen of mammalian Golgi-localized Rabs (Rab1a/b, Rab2a, Rab4a, Rab6a/a'/b, Rab10, Rab14, Rab30, Rab39, Rab43) (Fukuda et al. 2008; Miller et al. 2013) creating the potential for COG to exhibit some control of multiple phases of the Rab cascade.

Coat proteins recruit cargo and enable budding of vesicles from donor membranes (Rout and Field 2017). There are three main types of coat proteins. COPII coats mediate formation of ER-to-Golgi vesicles which fuse together to form the ERGIC and possibly the cis-Golgi cisternae (D'Arcangelo et al. 2013). COPI coats mediate intra-Golgi and Golgi-to-ER retrograde vesicular trafficking (Dodonova et al. 2015; Papanikou et al. 2015). Endocytic clathrin coats bud from TGN membranes and form endocytic vesicles (Robinson 2015). COG interacts with the COPI coat and regulators/adaptors of COPI and clathrin coats (Willett et al. 2014). Additionally, coat subunits might contain some additional targeting information directing vesicles to the target membrane where they are caught by tethering factors (Cheung and Pfeffer 2016; Miller et al. 2013; Tripathi et al. 2009).

There are two groups of vesicular tethers: coiled-coil proteins and multi-subunit tethers (Witkos and Lowe 2017). Coiled-coil tethers are proteins approximately 100–200 nm in length that catch incoming vesicles trafficking be1tween compartments and stabilize Golgi structure (Cheung and Pfeffer 2016; Gillingham and Munro 2016). COG interacts with P115, CASP, GM130, Golgin-84, TMF, and Giantin (Miller et al. 2013; Sohda et al. 2007, 2010) to potentially help reel in the vesicle after it is caught (Miller et al. 2013).

The COG complex also physically and/or functionally interacts with several proteins belonging to other CATCHR tethers including exocyst components Sec6 and Exo70 (Arabidopsis Interactome Mapping 2011; Giot et al. 2003), GARP subunit Vps51 and Vps52 (Tarassov et al. 2008), as well as with DSL1 subunit Tip20 (Uetz et al. 2000). These interactions may indicate either transient formation of super-CATCHR assemblies or the existence of new hybrid CATCHR complexes with enigmatic function.

Membrane fusion is driven by the formation of SNARE complex consisting of three to four SNARE proteins contributing four SNARE domains (Weber et al. 1998). COG has the potential to interact with the intra-Golgi SNARE complex STX5/GS28/YKT6/GS15 and the endosome-to-Golgi SNARE complex STX16/STX6/Vti1a/Vamp4 (Laufman et al. 2009, 2013; Shestakova et al. 2007; Willett et al. 2016), thereby giving COG regulatory access to routes into and out of the Golgi. Comparative analysis of COG8-STX16 and COG4-STX5 interactions by a COG-based mitochondrial relocalization assay revealed that COG8 and COG4 initiate the formation of different tethering platforms that can redirect two

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populations of Golgi transport intermediates to the mitochondrial. This result uncovered a role for COG sub-complexes in defining the specificity of vesicular sorting within the Golgi (Willett et al. 2013a). SNARE complexes require regulation by SM family proteins that assist relevant SNARE complex formation and prevent unintended fusion events (Baker et al. 2015; Rizo and Sudhof 2012). COG was shown to interact with two SM proteins, specifically, intra-Golgi Sly1 and endosome-to-Golgi VPS45, that regulate the STX5 and STX16 SNARE complexes, respectively (Laufman et al. 2009; Willett et al. 2013a).

Additionally, COG interacts with BLOC-1, an eight-subunit complex involved in vesicle trafficking through the endocytic pathway (Mullin et al. 2011). In the SH-SY5Y neuroblastoma cell line, BLOC-1 interacts with the COG subunits 2–8, and BLOC-1-deficient mice (Dtnbp1$^{sdy/sdy}$) show a moderate reduction in COG7 expression in hippocampal extracts (Gokhale et al. 2012). Furthermore, COG-KO HEK293T cells have enlarged endosomal-like inclusions that have not been observed in wild-type cells (Bailey Blackburn et al. 2016). All together, these studies highlight the impact of COG across the endocytic pathways in addition to the well-defined role in Golgi trafficking.

5 Defects in COG-Deficient Cells and Organisms: Potential Neuronal Connections

The first COG mutants were identified in screens for defects in the LDL receptor in Chinese hamster ovary (CHO) cells (Kingsley and Krieger 1984). Mutants *ldlb* and *ldlc* demonstrated dramatic alterations to glycosylation of the LDL receptor (Kozarsky et al. 1986) and were later described as part of a large collaborative complex now known as the COG complex (Chatterton et al. 1999; Ungar et al. 2002). Further, siRNA knockdown (KD) and CRISPR/Cas9 KO of COG subunits demonstrated that defects in one COG subunit cause structural and functional defects for the entire COG complex as well as to Golgi structure and function. KD of one COG subunit decreases the membrane association of the other COG subunits (Willett et al. 2014) and causes Golgi fragmentation and the accumulation of non-tethered COG-dependent (CCD) vesicles (Pokrovskaya et al. 2011; Zolov and Lupashin 2005). Additionally, the CCD vesicles carry Golgi v-SNAREs GS15/BET1L and GS28/GOSR1, enzymes MAN2A1 and MGAT1, and recycling protein GPP130, confirming CCD Golgi origin. Mislocalization of glycosylation enzymes MAN2A1, MGAT1, B4GALT1, GalNT2, and ST6GAL1 alters their expression (Pokrovskaya et al. 2011; Shestakova et al. 2006). COG KD also resulted in destabilization of both intra-Golgi STX5/GS28/Gs15/Ykt6 (Shestakova et al. 2007) and endosome-to-Golgi STX16/STX6/Vt1a/Vamp4 (Kudlyk et al. 2013; Laufman et al. 2011, 2013) SNARE complexes. Moreover, transient depletion of COG subunits delays retrograde delivery of Shiga (Zolov and Lupashin 2005) and SubAB toxins to cis-Golgi and delays Sub-AB-mediated cleavage of GRP78 in the ER lumen (Smith et al. 2009).

On the cellular level, destabilization of the COG complex has no effect on proliferation or viability of HEK293T cells (Bailey Blackburn et al. 2016); however, decreased COG function leads to lethality in yeast (Kim et al. 1999; Ram et al. 2002; Suvorova et al. 2002; Van Rheenen et al. 1998, 1999) and humans (Climer et al. 2015). Human congenital

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disorders of glycosylation (CDG) are a result of malfunctioning glycosylation in the ER (type I), or in the Golgi (type II). CDG patients with COG mutations present with neurological disorders (Climer et al. 2015) highlighting the essential need for glycosylation and/or other aspects of COG function in neurons during fetal and early childhood development (Table 2). Glycan changes in patients are measured by mass spectrometry, binding of PNA lectin (unsialylated T- antigen, Core 1 O-glycan), isoelectric focusing pattern of serum ApoCIII (Core 1 O-glycan), and transferrin (N-glycan). Using these tools on CDG patient samples and COG-deficient cell lines, it has been demonstrated that deficient COG results in an overall reduction in sialylation, fucosylation, galactosylation, and increased amounts of high mannose and hybrid N-glycans (Abdul Rahman et al. 2014; Bailey Blackburn et al. 2016; Palmigiano et al. 2017). Additionally, COG deficiency reduces binding of cholera toxin (Ctx) in cellular models indicating decreased availability of the Ctx receptor (Bailey Blackburn et al. 2016), GM1-like glycolipids (Lencer et al. 1992). This demonstrates that ganglioside processing, in addition to N- and O-linked glycans, is also affected by COG deficiency.

6 Neuropathology and Defects in COG-Associated Proteins

Golgi morphology and function is maintained by the combined effort of all of the core components of Golgi trafficking. Modification of any of these proteins can result in subtle or dramatic Golgi phenotypes including, but not limited to, Golgi fragmentation, shortened or elongated cisternae, and increased Golgi-associated vesicles. Golgi fragmentation is a common phenotype of neurological disorders (Gonatas et al. 2006) indicating that protein trafficking is malfunctioning in diseased neurons. Indeed, COG trafficking partners have been extensively analyzed in disease models for influence on Golgi morphology and disease progression (Table 3).

Recently, human neuroblastoma cell line SH-SY5Y, human kidney HEK293T cells, and D. *melanogaster* dopaminergic neurons were used to investigate the interactions between COG and the copper transporter, ATP7A (Comstra et al. 2017). These studies revealed that the COG complex interacts with ATP7A and functions in a similar pathway to direct copper transport in neurons. ATP7A contributes to three human diseases: Menkes disease, occipital horn syndrome, and X-linked distal spinal muscular atrophy type 3.

7 Discussion and Perspective

The Golgi is critically important to the life and function of neurons. Both dendrites and axons rely on Golgi components for growth and signaling. Nonstandard protein synthesis, trafficking, and modification processes are also essential. Further investigation is required to identify the alternative trafficking pathways and machinery that result in bypass of the somatic Golgi as well as synthesis and modification to proteins in axons and distal dendrites. The paucity of research into the role of the COG complex in neuronal trafficking is a major hindrance toward understanding COG-CDG. Several unanswered questions remain with regard to the Golgi aspects of neuronal protein trafficking: How much Golgi function is retained in GO and GS? Are these indeed separate organelles with different repertoire of glycosylation machinery? What is the COG complex interactome in neuronal cells? Does it

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have any specific function (via potential expression of neuron-specific isoforms) in neuronal tissue during development? Does COG complex or its sub-complexes localize to GO or GS and play a role in tethering dendritic vesicles to GO/GS?

Metal transporters that deliver of ions essential for enzymatic reactions have mutations that lead to neurodegenerative disorders. The congenital disorders of glycosylation disease family include COG, a Golgi vesicle tethering complex, and TMEM165, a putative Mn ion transporter in the Golgi. Recently, COG has been associated with the Golgi copper transporter, ATP7A (Comstra et al. 2017), whose dysfunction also has neurodegenerative impacts in three separate diseases. It is very likely that COG regulates the trafficking of these ion transporters to maintain the critical ion balance required for Golgi enzymatic reactions and overall neuronal homeostasis.

Potential therapies for the glycosylation defects of COG-CDG patients could include mannose supplementation which has been effective in mice for CDG-I (Rush et al. 2000). Mn supplementation in cultured cells and galactose supplementation in human patients can rescue phenotypes associated with defects in TMEM165 (Morelle et al. 2017; Potelle et al. 2017). COG, as an interaction hub for Golgi and endosomal trafficking machinery, may require compound therapies to correct multiple defects. COG5 and COG7 are binding partners of the COG lobe B sub-complex, and COG-CDG mutations were shown to destabilize this interaction (Ha et al. 2014). Small molecule targeted therapy is a potential complement that could stabilize the COG subunit folding and COG5/COG7 interaction.

Viral delivery of exogenous COG subunits could compensate for the defective COG subunit in COG-CDG patients. Analysis in tissue culture cells has not yet detected a detrimental phenotype associated with overexpressed COG proteins. With the advent of CRISPR/Cas9 targeted gene manipulations, it may be possible for gene therapy to replace existing mutant genes with wild type.

Acknowledgments

We are very grateful to Tanner E. Brackett for the creation and design of Fig. 1. This work was supported by the NIH grants GM083144 and U54 GM105814 and by the Pilot grant from the Arkansas Biosciences Institute.

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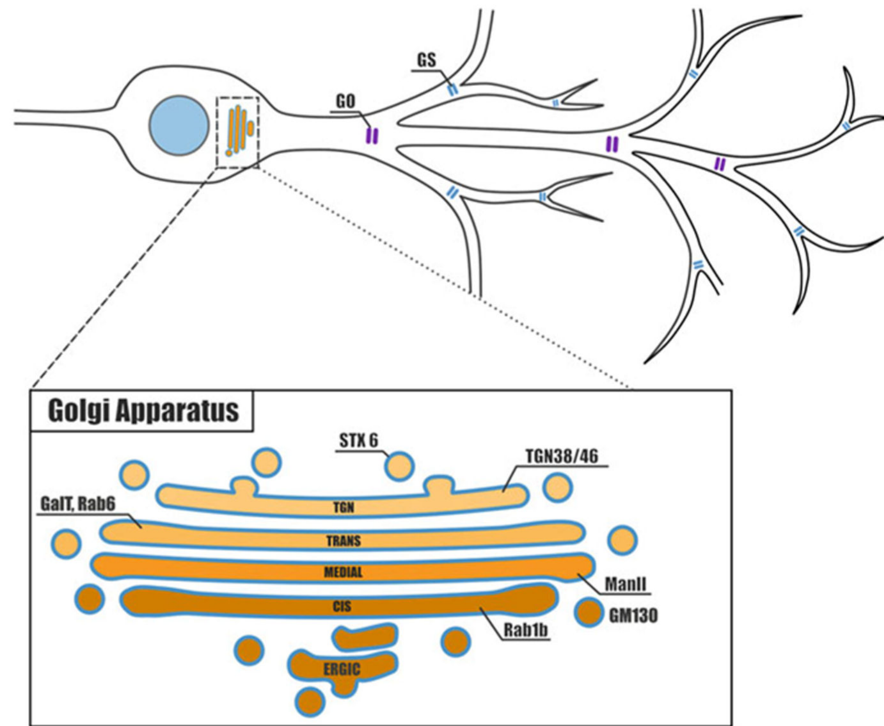

Fig. 1.
Neuronal Golgi and Golgi-like compartments. Neuronal Golgi includes the perinuclear Golgi of the soma, and dendritic mini-stacked Golgi outposts (GO, purple) and smaller Golgi satellites (GS, blue). Insert depicts major Golgi sub-compartments and protein markers

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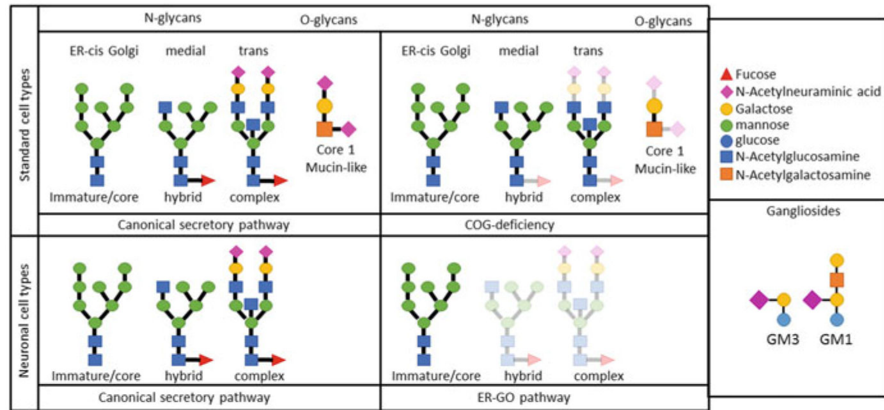

Fig. 2.

Glycosylation in neurons. N-glycosylation begins in the ER by the addition of a core glycan structure to a nascent protein. Trimming and extension take place throughout the Golgi. In COG-KO cells, N- and O-glycans are undergalactosylated and undersialylated. Neurons have an additional trafficking route that bypasses the Golgi resulting in underglycosylated structures

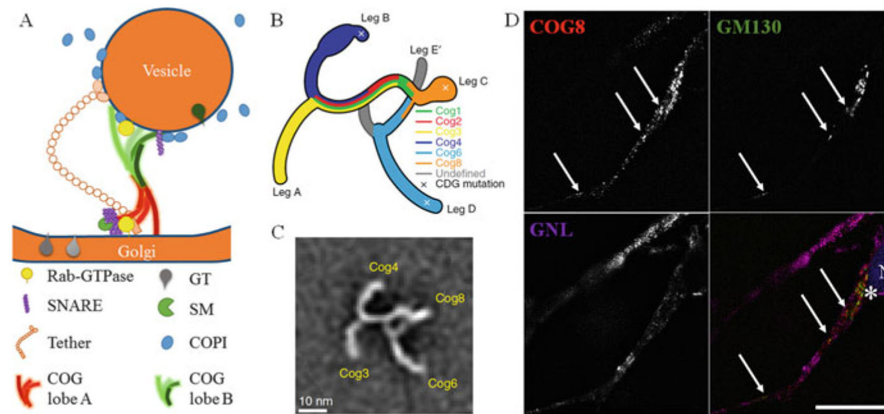

Fig. 3.

COG structure and localization. (a) Vesicular trafficking components. (b, c) Reprinted by permission from Macmillan Publishers Ltd: [Nat Struct Mol Biol] (Ha et al. 2016), copyright (2016). (b) COG complex structure determined by class averaging of (c) EM images of purified yeast COG. (d) Endogenous COG8 in differentiated H9 human stem cell line. Co-stained for endogenous GM130 and lectin GNL-647 (high mannose-binding lectin). Arrows indicate COG8 in smaller GM130-positive compartments outside perinuclear (N) Golgi (*). Scale bar = 10 μm

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Table 1

Golgi markers in neurons

Marker	Localization	Endogenous	Exogenous	citation
Arf1-HA	GA, GO		x	Jeyifous et al. (2009)
GalT2-YFP	GA, GO		x	Quassollo et al. (2015)
GalT-GFP	GA, GO		x	Jeyifous et al. (2009) and Mikhaylova et al. (2016)
GalT-YFP	GA, GO		x	Ye et al. (2007)
GM130 (Golga2)	GA, GO, GS	x		Jeyifous et al. (2009), Mikhaylova et al. (2016), and Quassollo et al. (2015)
ManII (Man2a1)	GA, GO, SA	x		Pierce et al. (2001) and Quassollo et al. (2015)
ManII (Man2a1)-GFP	GA, GO		x	Mikhaylova et al. (2016) and Ye et al. (2007)
Rab1b	GA, GS, SA	x		Mikhaylova et al. (2016) and Pierce et al. (2001)
Rab6-GFP	GA, GS		x	Mikhaylova et al. (2016)
Rab6	GO/SA	x		Pierce et al. (2001)
St3gal5-GFP	GA, GS		x	Mikhaylova et al. (2016)
SialT2	GA		x	Quassollo et al. (2015)
STX6	GA, GS	x		Mikhaylova et al. (2016)
TGN38	GA, GS, SA	x		Mikhaylova et al. (2016) and Pierce et al. (2001), Quassollo et al. (2015)

GA Golgi apparatus, *GO* Golgi outpost, *GS* Golgi satellite, *SA* dendritic spine apparatus

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Table 2

Neuropathology and defects in COG complex subunits

COG proteins			
Protein	Disorder	Neurological phenotypes	References
COG1	CDG-IIg (COG1-CDG)	Cerebral atrophy, developmental delay, hypotonia	Foulquier et al. (2006)
COG2	CDG-II (COG2-CDG)	Developmental delay, epilepsy	Kodera et al. (2015)
COG4	CDG-IIj (COG4-CDG)	Developmental delay, epilepsy, hypotonia, lack of speech, nystagmus	Reynders et al. (2009) and Ng et al. (2011)
COG5	CDG-IIi (COG5-CDG)	Ataxia, cerebral atrophy, developmental delay, epilepsy, hypotonia	Paesold-Burda et al. (2009), Fung et al. (2012), and Rymen et al. (2012)
COG6	CDG-IIl (COG6-CDG)	Ataxia, cerebral atrophy, developmental delay, epilepsy, hypotonia, optic nerve atrophy, sensorineural hearing loss	Huybrechts et al. (2012), Lubbehusen et al. (2010), Rymen et al. (2015), and Shaheen et al. (2013)
	Shaheen syndrome (SHNS)	Intellectual disability	
COG7	CDG-IIe (COG7-CDG)	Cerebral atrophy, developmental delay, epilepsy, hypotonia	Wu et al. (2004), Ng et al. (2007), Morava et al. (2007), and Zeevaert et al. (2009)
COG8	CDG-IIh (COG8-CDG)	Cerebral atrophy, developmental delay, hypotonia	Foulquier et al. (2007), Kranz et al. (2007), and Yang et al. (2017)

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Table 3

Neuropathology and defects in COG-associated proteins

COG partners			
ATP7A	Menkes disease	Early childhood neurodegeneration, severe neurologic impairment	Zlatic et al. (2015)
GM130	Neurodegeneration	Developmental delay, ataxia, decreased size of dendritic arbors	Liu et al. (2017) and Zhou et al. (2014)
GS27	Myoclonus epilepsy/early ataxia Parkinson's disease	Lack muscle coordination, gait abnormality. Trafficking deficient cytotoxicity in NRK and PC12 cells	Corbett et al. (2011) and Thayanidhi et al. (2010)
GS28	Neurodegeneration	Retinal degeneration in *D. melanogaster* photoreceptors	Rosenbaum et al. (2014)
Rab1a	Parkinson's disease sporadic ALS	Neuroprotective in *C. elegans, D. melanogaster*, and rat neurons, rescue from the neurotoxic effects of α-Syn. Rab1 is misfolded and dysfunctional resulting in defective ER-Golgi trafficking	Cooper et al. (2006), Gitler et al. (2008), and Soo et al. (2015)
Rab1b	Alzheimer's disease	Dominant negative Rab1b blocks trafficking of APP and decreased the secretion of Ab	Dugan et al. (1995)
Rab2	Parkinson's disease	Reduced expression of Rab2 rescues Golgi fragmentation in PD models	Rendon et al. (2013)
Rab4a	Neumann-Pick disease, Alzheimer's disease, Down syndrome	Developmental delays and dementia. Postmortem samples: Increased Rab4 in patients with AD and mild cognitive disorder. Aβ partially co-localizes with Rab4 in a mouse model of Down Syndrome	Arriagada et al. (2010), Cataldo et al. (2000), Choudhury et al. (2004), and Ginsberg et al. (2010)
Rab6a	Alzheimer's disease	Dominant negative mutant of Rab6 increased the secretion of sAPP and decreased Aβ secretion	McConlogue et al. (1996)
Sec22b	Parkinson's disease	Trafficking-deficient cytotoxicity in NRK and PC12 cells	Hasegawa et al. (2003, 2004)
SNAP29	CEDNIK syndrome	Cerebral dysgenesis, neuropathy, ichthyosis, and keratoderma	Sprecher et al. (2005) and Fuchs-Telem et al. (2011)
STX5	Parkinson's disease, neurodegeneration, Alzheimer's disease	Trafficking-deficient cytotoxicity in NRK and PC12 cells. Decreased STX5 causes accumulation and degradation of rhodopsin in *D. melanogaster* photoreceptors. Regulates processing of APP in PC12, HeLa, COS-7, and NG108–15 cell lines and hippocampal neurons, overexpressed STX5 coincides with accumulation of Aβ	Rendon et al. (2013), Thayanidhi et al. (2010), Satoh et al. (2016), and Suga et al. (2005, 2015)
Vti1a/b	Neurodegeneration	Perinatal lethality in double knockouts mouse model. Neurodegenerative phenotypes: Major axon tracks are missing, reduced in size, or misrouted	Kunwar et al. (2011) and Walter et al. (2014)
Ykt6	Parkinson's disease	Trafficking deficient cytotoxicity in NRK and PC12 cells	Hasegawa et al. (2003, 2004)