

The role of the Golgi apparatus in disease (Review)

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Received August 12, 2020; Accepted January 15, 2021

DOI: 10.3892/ijmm.2021.4871

Abstract. The Golgi apparatus is known to underpin many important cellular homeostatic functions, including trafficking, sorting and modifications of proteins or lipids. These functions are dysregulated in neurodegenerative diseases, cancer, infectious diseases and cardiovascular diseases, and the number of disease-related genes associated with Golgi apparatus is on the increase. Recently, many studies have suggested that the mutations in the genes encoding Golgi resident proteins can trigger the occurrence of diseases. By summarizing the pathogenesis of these genetic diseases, it was found that most of these diseases have defects in membrane trafficking. Such defects typically result in mislocalization of proteins, impaired glycosylation of proteins, and the accumulation of undegraded proteins. In the present review, we aim to understand the patterns of mutations in the genes encoding Golgi resident proteins and decipher the interplay between Golgi resident proteins and membrane trafficking pathway in cells. Furthermore, the detection of Golgi resident protein in human serum samples has the potential to be used as a diagnostic tool for diseases, and its central role in membrane trafficking pathways provides possible targets for disease therapy. Thus, we also introduced the clinical value of Golgi apparatus in the present review.

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Key words: Golgi apparatus, Golgi dysfunction, Golgi resident protein, disease, diagnosis, therapy

1. Introduction

The Golgi apparatus is a processing and sorting hub in the transport and targeting of soluble cargo proteins and lipids to different destinations in the cell (1). Considering its central role in the secretory pathway, alterations in the structure and function of the Golgi apparatus are expected to affect the homeostasis of cellular proteins and lipids. Increasing evidence suggests that structural changes and functional disorder of the Golgi apparatus are involved in many human diseases such as neurodegenerative diseases (2-4), ischemic stroke (5,6), cardiovascular diseases (7,8), pulmonary arterial hypertension (9,10), infectious diseases (11-13), and cancer (14). However, much work is still needed to elucidate how the Golgi apparatus affects the progression of these diseases.

In this review, we describe the central roles of the Golgi apparatus in cells, and discuss diseases associated with structural changes and functional disorder of the Golgi apparatus. We highlight some of the studies that explore links between mutation in genes encoding Golgi resident proteins and human diseases. By analyzing their pathophysiology, we found that the majority of genes leading to human diseases are involved in membrane trafficking. Considering the mechanistic links between Golgi resident proteins, membrane trafficking, and the development of genetic diseases, we suggest a term for these disorders based on their similar pathophysiology: Golgi apparatus membrane trafficking disorders.

2. Golgi apparatus structure and function

In 1898, the Italian anatomist Camillo Golgi initially described the cell organelle that bears his name, the Golgi apparatus (15). The Golgi apparatus is characterized by a series of flattened, cisternal membrane structures forming the so-called Golgi stack, which is surrounded by vesicles. Based on the distribution of resident proteins, the Golgi stack can be divided into three regions: The cis-, medial-, and trans-Golgi cisternae (16). The Golgi stacks in vertebrate cells are laterally interconnected by tubular membranes and exhibit a twisted ribbon-like network known as the Golgi ribbon (17). The structure of the Golgi ribbon is supported by the Golgi matrix (18). The Golgi matrix is believed to comprise highly dynamic structural proteins, which is important for structural integrity and vesicular trafficking.

The Golgi apparatus has two main functions. The first is the post-translational protein modification. Similar to glycosylation, it is a common post-translational modification

occurring in the endoplasmic reticulum (ER) and Golgi and the glycan processing occurs throughout the Golgi stacks. The second is the sorting, packing, routing and recycling of these modified cargos to the appropriate cellular destinations (1). The main secretory pathway can be divided into the following steps (19): First, newly synthesized proteins or lipids enter the exit sites of the ER and are sorted into budding vesicles that are dependent on the COPII. Second, vesicles move to the ER-Golgi intermediate compartment (ERGIC) and forward to the cis-Golgi networks (CGN). Third, proteins or lipids enter cis-Golgi cisternae and move towards the trans-Golgi cisternae. Vesicular transport and cisternal maturation are the two classical models of intra-Golgi transport (20). The vesicular transport model proposes that Golgi cisternae are static, and the cargos are transported through them by COPI vesicles. The cisternal maturation model suggests that cisternae are dynamic structures, while Golgi enzymes are recycled via retrograde transport of COPI vesicles. Fourth, vesicles reach the trans-Golgi networks (TGN), which are involved in the sorting of products to their final destinations such as lysosomes, endosomes, or the plasma membrane.

3. Structural and functional changes of the Golgi apparatus in diseases

The structural integrity of the Golgi apparatus is vital for its normal function, and Golgi fragmentation could result in a wide range of diseases and disorders. Functional changes of the Golgi Apparatus include perturbations in Golgi pH, aberrant Golgi glycosylation, and membrane trafficking. Golgi fragmentation has been found to often be an early causative event in the process of cell apoptosis (21,22). With pharmacological or oxidative stress, a series of changes occur in the Golgi apparatus, such as cargo overloading, ionic imbalance, and abnormal luminal acidity. These changes can lead to defects in membrane trafficking. We previously presented 'Golgi stress' as a new concept to explain the Golgi-specific stress response (23). The Golgi stress response constitutes autoregulation to repair the Golgi apparatus and may initiate signaling pathways to alleviate stress. The nucleus signaling pathways of the Golgi stress response was identified in a previous study: The procaspase-2/golgin-160, TFE3, HSP47, and the CREB3-ARF4 pathways (24). If these pathways fail to repair overstimulation, the Golgi is completely disassembled, inducing cell apoptosis.

Apoptosis triggered by structural changes and functional disorder of the Golgi contributes to the pathogenesis of many diseases, such as neurodegenerative diseases (25), ischemic stroke (5,6), cardiovascular diseases (26), pulmonary arterial hypertension (9,10), infectious diseases (12,13), and cancer (27). A summary of diseases relating to the Golgi apparatus, classified on the basis of the main organ affected is shown in Fig. 1.

Neurodegenerative disease. Structural and functional changes of the Golgi apparatus are associated with several neurodegenerative diseases, such as Amyotrophic lateral sclerosis (28), Alzheimer's disease (29), Parkinson's disease (3), Huntington's disease (30), Creutzfeldt-Jacob disease (31) and multiple system atrophy (32). Golgi fragmentation is not a consequence

of apoptosis, but a very early event in the pathological cascade in neurodegenerative disorders and precedes other pathological changes in the neuron (33). Golgi fragmentation may alter neuronal physiology, and induce failures in transport to axons, dendrites, and synapses (34). Finally, Golgi alteration may trigger a stress response and, as consequence, result in neuronal death. Furthermore, Golgi fragmentation in neurodegenerative disease alters protein trafficking and production, such as amyloid precursor protein in Alzheimer's disease (35), and sodium-dependent vitamin C transporter 2 in Huntington's disease (36). The causes of Golgi fragmentation in neurodegenerative diseases may be diverse. First, alteration of the microtubule and microfilament stabilization may also be the cause (37). In Alzheimer's disease and other tauopathies, tau-induced microtubule-bundling may result in Golgi fragmentation (38). Furthermore, perturbations in Golgi pH are also responsible for Golgi fragmentation. The Purkinje cells from the Golgi pH regulator conditional knockout mice exhibited Golgi fragmentation, followed by axonal degeneration and neuronal loss (39).

Infectious disease. Golgi fragmentation has been identified in diseases such as infection by Orf virus (12), *Chlamydia trachomatis* (40,41), Hepatitis C virus (HCV) (42), Human Rhinovirus (HRV) (13), and *Rickettsia rickettsii* (43). Golgi fragmentation in these infectious diseases is mainly reflected in two aspects: i) Escaping from the immune response. In infected cells, Golgi fragmentation reduces MHC class I complex surface expression by defective membrane trafficking (43,44), which may aid in escaping host cellular immune recognition (12); ii) Enhancing viral replication. In human rhinovirus-1A infection, the Golgi in host cells is fragmented and rearranged into vesicles that appear to be used as the membrane source for the assembly of viruses (45). Similarly, in Oropouche virus replication, proteins in the endosomal sorting complex required for transport in the host cell are hijacked in Golgi cisternae to mediate remodeling of Golgi membranes, resulting in enlargement of the Golgi stacks, where the endosomal sorting complex required for transport participates in the assembly of viral factories (46). Thus, structural changes in the Golgi apparatus may enhance viral replication in infectious diseases by providing membranes.

Cancer. Aberrant Golgi glycosylation is reported to regulate invasion of cancer cells, such as in prostate (47), breast (48), and gastric cancer (49). Golgi glycosylation is involved in basic molecular and cellular biology processes occurring in cancer, such as cell signaling transduction and communication, cancer cell dissociation and invasion, cell-matrix adhesion, cancer angiogenesis, immune regulation and metastasis (50). Similar to epithelial cadherin, a transmembrane glycoprotein, is involved in epithelial cell-cell adhesion in tumors (51). The Golgi glycosylation of N-linked glycans on epithelial cadherin can affect the epithelial-mesenchymal transition, which is related to the formation of metastatic lesions (49). This process is suggested to help cancer cells leave their original position during wound healing and other normal physiological processes, which is an essential mechanism for metastasis and diffusion of cancer cells (52,53). The GOLPH3 complex is an important molecular component in the process of Golgi-driven

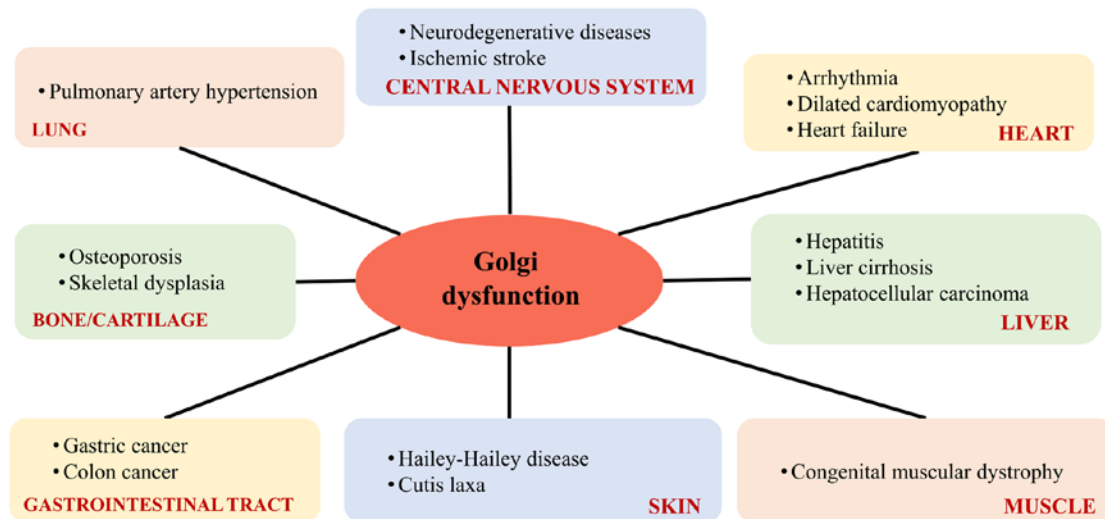


Figure 1. Disorders relating to Golgi dysfunction. Disorders relating to Golgi apparatus dysfunction are grouped according to the main tissues/organs affected.

tumor progression. The role of the GOLPH3 complex in cancer includes: i) Regulating Golgi glycosylation, which is important in driving the cancer phenotype (54); ii) promoting the cellular DNA damage response that enhances cellular survival under DNA damage (55); iii) interacting with components of the retromer complex that enhances growth-factor-induced mTOR signaling (56); and iv) regulating cell migration by promoting reorientation of the Golgi apparatus towards the leading edge (57). In addition to GOLPH3, the Golgi protein GM130 is important in Golgi glycosylation and protein membrane trafficking in cancer cells. Downregulation of GM130 induces autophagy, inhibits glycosylation, decreases angiogenesis, and suppresses tumorigenesis (58). In general, aberrant Golgi glycosylation causes carcinogenesis, but may also be a consequence of cancer progression.

Other diseases. Golgi dysfunction was also observed in pulmonary arterial hypertension, and cardiovascular diseases. In an *in vivo* model of pulmonary arterial hypertension, Golgi dysfunction and intracellular trafficking with trapping of diverse vesicle tethers, giantin, p115, and soluble N-ethylmaleimide-sensitive factor attachment protein receptors (SNAREs) were observed in the Golgi membranes of enlarged pulmonary arterial endothelial cells and smooth muscle cells (9,10,59). Golgi-mediated membrane trafficking dysfunctions play important roles in the pathogenesis of pulmonary arterial hypertension (60).

Structural changes and functional disorder of the Golgi apparatus have been identified in many cardiovascular diseases, such as heart failure, dilated cardiomyopathy, arrhythmia, and chronic atrial fibrillation (61-64). A previous review clarified the relationship between the Golgi apparatus and various cardiovascular diseases (26). For example, in dilated cardiomyopathy patients, morphological changes in Golgi vesicle are consistent with the secretion of natriuretic peptide as the rate of protein secretion affects the morphology and size of Golgi vesicles (7). In addition, the Golgi vesicle area is inversely proportional to the left ventricular end-diastolic diameter and the end-systolic diameter, and is proportional to the left ventricular ejection fraction (65).

4. Mutant Golgi resident proteins involved in disease

In addition to being an intermediate site in pathogenic cascades in diseases, the Golgi apparatus can be the primary target for diseases caused by genetic mutations in Golgi resident proteins. Mutations in proteins localized to the Golgi apparatus can be deleterious for the structure and function of this organelle, impeding membrane trafficking pathways through it (Fig. 2) and resulting in disease. We highlight some of the studies that explore links between Golgi resident proteins and disease.

Golgi matrix protein and diseases. Adjacent Golgi stacks are linked by tubules forming a membrane network termed the Golgi ribbon (66). This structure is a highly ordered and continuous structure that is adjacent to the nucleus. The Golgi ribbon comprises proteins that mediate cisternal stacking and the material supporting the Golgi ribbon is the Golgi matrix (67). The concept of the Golgi matrix was introduced by Slusarewicz and colleagues, who isolated a detergent-insoluble, salt-resistant Golgi fraction in 1994 (18). The main function of the Golgi matrix is maintaining normal structure and mediating protein trafficking through the Golgi cisternae. During cisternal progression, the Golgi matrix must be dynamic to adapt to Golgi structural changes.

Golgi matrix proteins include golgins and Golgi reassembly stacking proteins (GRASPs) (67), both of which are important for maintaining Golgi structure and regulating protein and lipid trafficking through the stacks. Golgins are a family of conserved coiled-coil proteins that were originally identified as a group of Golgi-localized antigens (68,69). The golgins not only capture incoming vesicles, but also clearly distinguish vesicles from different origins (70). GRASPs include GRASP65 (71) and GRASP55 (72). The former localizes to the cis-Golgi cisternae while the latter localizes to the medial/trans-Golgi cisternae. The functions of GRASPs include Golgi structure formation, specific cargo transport, apoptosis, and cell migration (73).

Given the important multiple functions of Golgi matrix proteins, mutation of Golgi matrix proteins has serious consequences on health. Increasing studies support that

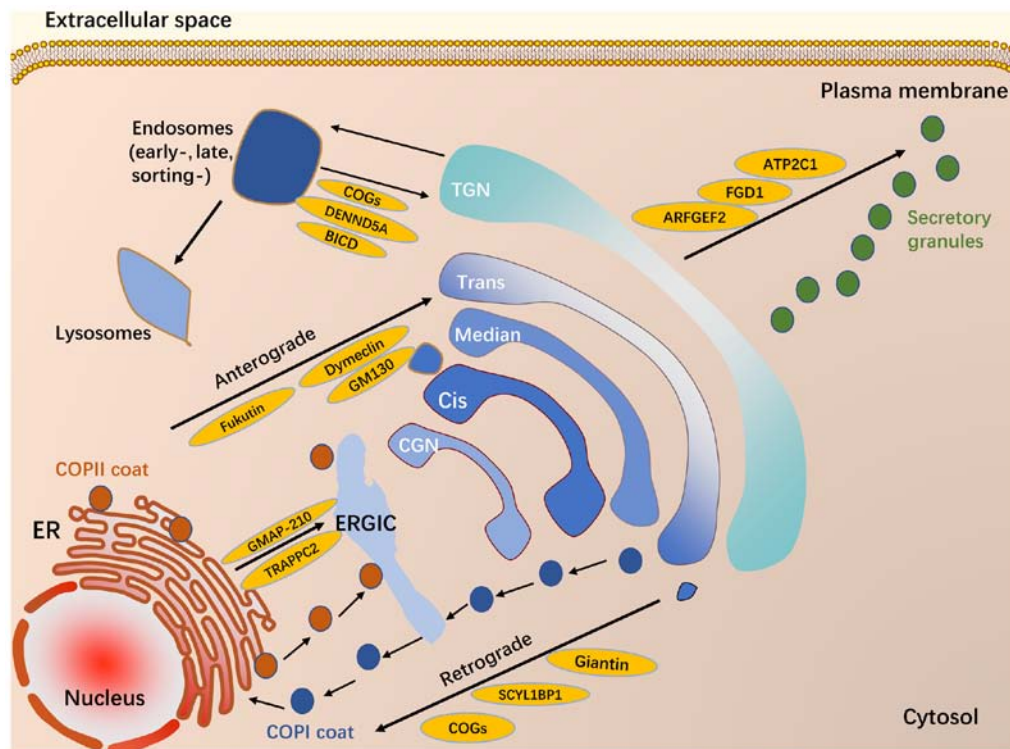


Figure 2. Golgi resident proteins and membrane trafficking pathway. The main membrane trafficking pathways are included. Newly synthesized proteins enter the ER and are sorted into budding vesicles that are dependent on the COPII. Vesicles move to the ERGIC and forward to the CGN and the trans-Golgi cisternae. Finally, vesicles reach the TGN and cargos sort to their final destinations such as lysosomes, endosomes or the plasma membrane. Different mutation in Golgi resident proteins affect different membrane trafficking pathway: i) GM130, Giantin, Fukutin, Dymeclin and SCYL1BP1 (involving anterograde trafficking); ii) COGs (involving retrograde trafficking); iii) TRAPPC2 and GMAP-210 (involving ER to ERGIC); iv) FGD1, ATP2C1 and ARFGEF2 (involving TGN to plasma membrane); and v) COGs, DENND5A and BICD (involving endosome to TGN).

the mutation of Golgi matrix proteins including GM130, Bicaudal-D (BICD), GMAP-210, giantin (74), and SCYL1BP1 (also known as GORAB) (75), leads to diseases. The present review included some proteins as examples to elaborate on the pathogenic mechanism of Golgi matrix proteins.

The first example is GM130 (also known as GOLGA2), the first identified Golgi matrix protein (76). GM130 is a peripheral membrane protein attached to the Golgi membrane that is important in maintaining the adaxial Golgi reticular structure (77). In neurodegenerative diseases, *GM130* knockout in hippocampal neurons is reported to cause damage to dendritic structures (78). In mouse neuron experiments, specific knockout of *GM130* resulted in disruption of the Golgi architecture and positioning in cerebellar Purkinje cells and to deficient secretory cargo trafficking. As a consequence, progressive cerebellar atrophy of Purkinje cells resulted in delayed movement and ataxia in mice (79). This animal experimental study indicates that *GM130* mutations are causative in neurodegenerative disease.

A second example is BICD, a golgin that interacts with Rab6 on the TGN (80). Of two homologous sequences, BICD1 and BICD2, the latter binds to a subgroup of motility protein activator proteins and is a connecting molecule between the motility protein and cargo (81). High expression of BICD in normal nervous systems is important for maintaining the normal lamellar structure of the cerebral cortex, hippocampus, and cerebellar cortex (82). The brain cortex, hippocampus and cerebellar cortex neurons of *BICD2*-knockout mice have impaired migration function (82,83) and eventually, damage the brain and cerebellar cortex layer structure. Previous

findings showed that, missense mutations in *BICD* resulted in spinal muscular atrophy (84,85) and hereditary spastic paraplegia (86) by changing the normal morphological structure of the golgi. The core pathogenic mechanism may be a *BICD2* mutation resulting in abnormal cargo trafficking in motor neurons. This trafficking results in neuronal growth disorders and eventually neuronal dysfunction.

The third example is giantin, encoded by the *Golgb1* gene. Giantin is a member of the golgin family and is a tethering factor for COPI vesicles and functions in the CGN (87). Mutations in the *Golgb1* gene lead to lack of expression of giantin protein and a pleiotropic phenotype including osteochondrodysplasia in a rat model (88) and a ciliopathy-like phenotype in a zebrafish model (74). Both pathogenic mechanisms involve disturbance of extracellular matrix components, which are transported by intracellular membrane trafficking systems. Giantin knockout leads to changes in expression of Golgi-resident glycosyltransferases, which could affect extracellular matrix deposition (89).

The fourth example is GORAB (also known as SCYL1BP1). GORAB, localized to the trans-side of the Golgi, is a member of the golgin family and interacts with Rab6. Mutation in *GORAB* results in geroderma osteodysplastica (GO) characterized by wrinkly skin and osteoporosis (75). GORAB functions in COPI trafficking, and acts as a scaffolding factor for COPI assembly at the TGN by interacting with Scyl1. *GORAB* mutations perturb COPI assembly at the TGN, and result in reduced recycling of COPI-mediated retrieval of trans-Golgi enzymes and improper glycosylation (90).

A final example of the effects of loss of expression of a Golgi matrix protein is GMAP-210 (also known as TRIP11). This CGN golgin acts in asymmetric membrane tethering (91). In animal experiments, a nonsense mutation in *Trip11* led to a loss of GMAP-210, which led to abnormal Golgi-mediated glycosylation and cellular transport of proteins in chondrocytes and osteoblasts of mice (92). Similarly, *GMAP-210* mutations were found in patients with human chondrodysplasia achondrogenesis 1A (92), and odontochondrodysplasia (93).

Other Golgi resident proteins and diseases. In addition to matrix proteins, several proteins that localize to Golgi membranes are also important for normal Golgi structure and function such as the tethering factors Rab GTPases and SNAREs, which regulate the specific targeting and fusion of transport carriers with Golgi membranes. The maintenance of Golgi luminal ion concentrations depends on the secretory pathway $\text{Ca}^{2+}/\text{Mn}^{2+}$ ATPases and vacuolar H^{+} ATPase (V-ATPase). Therefore, the impaired performance of mutated Golgi resident proteins creates serious and highly diverse pathologies in the Golgi. Emerging studies on patient genetics have identified mutations in Golgi resident protein-coding genes that are related to diseases. We focus on some of these proteins, and discuss the activities of mutated Golgi resident proteins that result in disease.

Golgi ion pump. The release and uptake of Ca^{2+} by Golgi membranes is mainly mediated by secretory pathway $\text{Ca}^{2+}/\text{Mn}^{2+}$ ATPases (SPCA1 and SPCA2), which are encoded by the *ATP2C1/ATP2C2* genes. The proteins transfer Ca^{2+} from the cytoplasm to the Golgi and maintain the stability of intracellular free Ca^{2+} (94). The maintenance of Golgi luminal Ca^{2+} and Mn^{2+} directly affects the optimal activity of Golgi glycosyltransferase and the trafficking of cell adhesion proteins to the cell plasma membrane (95). Knockdown of *SPCA1* affects the morphology and structure of the Golgi and causes mis-localization of proteins. Clinically, mutations in the *ATP2C1* gene on chromosome 3q21 can lead to Hailey-Hailey disease, an autosomal dominant skin disorder in humans (96,97). The possible pathogenetic mechanism may be dysfunction in Ca^{2+} signaling at the Golgi membrane and dysfunction of processing, modification and trafficking of desmosomal proteins (98).

Golgi acidity is an important role for maintaining the morphological integrity of the Golgi and transporting various kinds of cargo (99,100). Under normal conditions, the Golgi cavity is weakly acidic and the pH of the Golgi reticular structure decreases gradually from the CGN to the TGN (101). The Golgi luminal pH is regulated by V-ATPase (102), AE2a $\text{HCO}_3^-/\text{Cl}^-$ exchanger, and Golgi pH regulator (103). Luminal pH is closely tied to Golgi function. Partial V-ATPase dysfunction is related to multiple disease states (104). *ATP6V1E1*, *ATP6V1A*, and *ATP6V0A2* encode different subunits of the V-ATPase pump. A study showed that Golgi subunit-isoform of the V-ATPase (*ATP6V0A2*) mutations lead to structural changes in the extracellular matrix that is responsible for skin elasticity (105). Clinically, the dysfunction of the Golgi-localized V-ATPase caused by mutations in the *ATP6V0A2* gene is directly related to cutis laxa. Mutations in *ATP6V1E1* or *ATP6V1A* also cause autosomal-recessive

cutis laxa (106). Autosomal recessive cutis laxa type II is a heterogeneous condition characterized by sagging, inelastic, and wrinkled skin (107,108). The mechanism may involve impaired intracellular acidification of the Golgi and damaged retrograde trafficking from the Golgi to the ER (100,108).

ATP7A and *ATP7B* are the key regulators of cellular Cu^{2+} metabolism. Under basal conditions (normal copper levels), *ATP7A* is located in the TGN and travels to the plasma membrane at high copper levels. Mutations in the *ATP7A* result in mislocalization of *ATP7A* protein and impaired copper-responsive trafficking between the TGN and plasma membrane, which contributes to the development of Menkes disease (109). Menkes disease is a lethal multisystemic disorder characterized by neurodegeneration and connective tissue abnormalities as well as typical sparse and steely hair. Similarly, mutations in the *ATP7B* contributes to the development of Wilson's disease (110). Wilson's disease, also known as hepatolenticular degeneration, results in hepatic and/or neurological deficits, including dystonia and parkinsonism.

Golgi resident glycosyltransferase. The Golgi apparatus is an important organelle for the post-translational modification of cargos. The post-translational modification of secreted and membrane proteins is mediated by the Golgi resident enzymes such as glycosyltransferases, glycosidases, and kinases. Glycosylation is an enzymatic reaction that chemically links monosaccharides or polysaccharides (glycans) to other saccharides, proteins, or lipids (111). Golgi glycosylation is a modification by Golgi-resident glycosylation enzymes including glycosidases and glycosyltransferases (112). The normal function of Golgi glycosylation depends on the precise Golgi localization and normal activities of Golgi resident enzymes. The proper localization of Golgi resident enzymes is controlled by finely regulated vesicular trafficking in the Golgi. If the balance between anterograde and retrograde trafficking is defective, Golgi glycosylation is affected, resulting in Golgi glycosylation abnormalities (113). Mutations in Golgi resident putative glycosyltransferases are directly linked to human congenital muscular dystrophies: Like-acetylglucosaminyl-transferase (LARGE) in congenital muscular dystrophy syndrome (114), fukutin in Fukuyama-type congenital muscular dystrophy (115), and fukutin-related protein in band muscular dystrophy syndrome (116). These mutations appear to affect cell migration in the developing brain, resulting in combined clinical manifestations in muscle and brain development. In an animal model, mutations in Golgi resident glycosyltransferases are also associated with the neurodegenerative disease, such as ST3GAL5, β 1,4-galactosyltransferase 4 (B4GalT4) (117), and glycosyltransferase 8 domain containing 1 (GLT8D1). GLT8D1 is a glycosyltransferase enzyme located in the Golgi apparatus. A recent study reported that mutated GLT8D1 induces motor deficits in zebrafish embryos consistent with amyotrophic lateral sclerosis (118). However, another study suggested that GLT8D1 is not likely the causative gene for ALS in mainland China (119).

Rab GTPase. Rab proteins are members of the small Ras-like GTPase family that regulate the four steps of membrane transport by recruiting effector molecules. Golgi-associated Rab proteins including Rab1, Rab2, Rab6, Rab18, Rab33B, and

Rab43 have a central role in Golgi organization and membrane trafficking (120). Rab33B is localized to medial-Golgi cisternae and is important in Golgi-to-ER retrograde trafficking. Rab39B, a neuronal-specific protein, is a novel Rab GTPase that localizes to the Golgi and is related to synapse formation. Mutations in the *Rab33B* coding gene cause Smith-McCort dysplasia (121) and mutations in the *Rab39B* gene cause X-linked mental retardation (122).

SNAREs. SNAREs are proteins involved in docking and fusion of transport to intermediate membranes. Golgi SNAP receptor complex member 2 (*GOSR2*) is a member of the SNAREs family that localizes to the CGN and is involved in ER-to-Golgi trafficking (123). Homozygous mutations in *GOSR2* lead to progressive myoclonus epilepsy (124). Clinical manifestations include early ataxia, myoclonus, and convulsive seizures. A possible mechanism involves *GOSR2* mutations leading to *GOSR2* protein that cannot be localized to the CGN and blocks SNAREs complex formation. SNAREs complex dysfunction could lead to the impaired fusion of vesicles with cis-Golgi cisternae, hindering ER-to-Golgi membrane trafficking. The perturbation of early ER-to-Golgi transport may result in changes in the regulated release of neurotransmitters and proper sorting of neurotransmitter receptors at synapses in neurons, potentially leading to epilepsy (125,126).

5. Golgi apparatus membrane trafficking disorders

In the above section, we introduced the pathophysiology of some diseases related to Golgi resident proteins. A summary of genetic diseases caused by mutations in genes encoding Golgi resident proteins is presented in Table I. By analyzing the pathophysiology of these diseases, we found that the majority of genes leading to human diseases are involved in defects in membrane trafficking (Fig. 2). For example, *TRAPPC2* mutation, involving the membrane trafficking pathway between ER-to-Golgi in bone cells and chondrocytes, results in X-linked spondyloepiphyseal dysplasia tarda (127). The conserved oligomeric Golgi (COG) complex is a conserved, hetero-octameric protein complex localized in the Golgi cis/medial cisternae (128). In addition to the COG3 subunit, mutations in seven other COG subunits result in human congenital disorders of glycosylation (CDG) type II, which is mainly marked by misregulation of protein glycosylation, and defects in retrograde trafficking through the Golgi (129,130). The mutation in *FGD1* resulting in Aarskog-Scott syndrome may lead to the obstruction of post-Golgi trafficking, such as the Golgi-to-plasma membrane trafficking pathway (131). Mutation in *TRIP11* mainly involves ER to ERGIC and anterograde trafficking (132). Therefore, membrane trafficking defects play a major role in the pathogenic process of mutation in genes encoding Golgi resident protein. Intracellular membrane trafficking is a fundamental process responsible for compartmentalization of the biosynthesis pathway and secretion cargos, including hormones, growth factors, antibodies, matrix and serum proteins, digestive enzymes, and many more. Defective membrane trafficking results in protein sorting defects, undegraded proteins due to defective Golgi-to-lysosome trafficking, downregulation of protein secretion, and mislocalization of proteins.

Considering the mechanistic links between Golgi resident proteins, membrane trafficking, and the development of genetic diseases, we suggest a term for these disorders based on their similar pathophysiology: Golgi apparatus membrane trafficking disorders. It is a group of genetic diseases in which the mutation of the gene encoding Golgi resident protein results in membrane trafficking defects within the cells. Golgi apparatus membrane trafficking defects typically result in the accumulation of undegraded proteins, mislocalization of proteins, and impaired glycosylation of proteins. However, the cascade events following the Golgi apparatus and defective membrane trafficking, ultimately leading to human diseases, remain to be clarified in further research.

Although the Golgi apparatus-mediated membrane trafficking pathway exists in all kinds of tissues and organs in human, the trafficking defects on tissues is often selective. The most sensitive to membrane trafficking defects is the nervous system, skin, bone, cartilage, and skeletal muscle and the reasons for mutations occurring in these genes mostly affecting these tissues remain to be elucidated. Firstly, neurons are extraordinarily polarized cells, the extension of dendrites and axons requires a significant expansion of the cell surface area, and new plasma membrane proteins must be delivered through the membrane trafficking. For the nervous system, intracellular trafficking functionally impacts neuronal development, homeostasis, as well as neurodegeneration (133). Secondly, it is generally known that skin, bone, cartilage, and skeletal muscle fiber comprise large amounts of the extracellular matrix which define the structure and physical properties. Almost all extracellular matrix components are transported by intracellular trafficking systems. Alterations in Golgi apparatus membrane trafficking can lead to glycosylation abnormalities. The assembly and maintenance of the extracellular matrix are susceptible to impairment of matrix protein glycosylation. Thus, the skin, bone, cartilage, and skeletal muscle are most sensitive to impaired glycosylation of cargo proteins, and membrane trafficking defects. Therefore, the loss of some Golgi resident proteins, such as ATP6V1A, ATP6V1E1 (106), ATP6VOA2 (108), TMEM165 (134), GOLGB1 (88), SCYL1BP1 (75), TRAPPC11 (135), TRAPPC2 (136), and TRIP11 (92), manifest primarily in these matrix-rich tissues.

6. Clinical value of Golgi apparatus

The Golgi apparatus participates in the occurrence and development of disease and could be the key to finding new targets for disease diagnosis and therapy.

Biomarker discovery. Golgi glycoprotein 73 (GP73, also referred to as GOLPH2), a resident Golgi membrane protein, is predominantly expressed in biliary epithelial cells in the normal human liver (137). GP73 expression is upregulated in chronic Hepatitis B virus (HBV) infection (138), chronic HCV infection (139), non-alcoholic fatty liver disease (140), and hepatocellular carcinoma (HCC) (141,142). Serum GP73, a new marker for HCC, is reported to appear earlier than serum α -fetoprotein. The combined detection of serum α -fetoprotein and GP73 can improve sensitivity and specificity for HCC diagnosis (143,144). However, several studies showed GP73 levels were not higher in HCC patients than in patients with

Table I. Human diseases caused by mutations in genes encoding Golgi resident proteins.

Gene	Function	Disease	Main clinical manifestation	Cellular effect	(Refs.)
<i>AP1S2</i>	Coat adapter	X-linked mental retardation syndrome	Mental retardation	Brain-specific defect of AP-1-dependent intracellular protein trafficking	(165)
<i>AP3D1</i>	Coat adapter	Hermansky-Pudlak syndrome	Immunodeficiency; Neurodevelopmental delay; Seizure	Impaired lysosomal trafficking	(166)
<i>ARFGEF2</i>	GTPase activator	Periventricular nodular heterotopia	Malformation of cortical development	Defective TGN-cell membrane trafficking	(167)
<i>ATP2C1</i>	Ion pump	Hailey-Hailey disease	Skin disorder	Defective trafficking of desmosomal proteins to cell membrane	(96)
<i>ATP6V1A</i>	Ion pump	Cutis laxa type II	Wrinkled skin	Defective retrograde transport; Abnormal glycosylation	(106,168)
<i>ATP6V1E1</i>	Ion pump	Cutis laxa type II	Wrinkled skin	Defective retrograde transport; Abnormal glycosylation	(106)
<i>ATP6VOA2</i>	Ion pump	Cutis laxa type II	Wrinkled skin	Defective Golgi trafficking; Abnormal glycosylation of CDG-II	(108)
<i>ATP7A</i>	Ion pump	Menkes disease; Occipital horn disease	Neurodegeneration; Connective tissue disorder	Defective Golgi trafficking of copper;	(109)
<i>ATP7B</i>	Ion pump	Wilson's disease	Hepatic and/or neurological disorder	Defective Golgi trafficking of copper	(110)
<i>ATXN2</i>	Signaling	Spinocerebellar ataxia type 2	Progressive ataxia; slow saccades	Disrupted calcium homeostasis	(169)
<i>Bicaudal-D</i>	Golgin	SMA; HSP	Neurodegeneration	defective targeting and transport of Golgi resident proteins.	(84,86)
<i>COG</i>	Tethering	CDG-type II	Neurodegenerative disorder	Defective retrograde and endosome-to-TGN trafficking; Abnormal glycosylation	(170)
<i>COPA</i>	Coat	COPA syndrome	Interstitial lung, joint and kidney disorder	Defective membrane trafficking	(171)
<i>DENND5A</i>	GTPase activator	Epileptic Encephalopathy	Refractory seizures and cognitive arrest	Defective endosome-TGN trafficking	(172)
<i>DYM</i>	Unknown	Dygge-Melchior-Clausen syndrome	Spondyloepimetaphyseal dysplasia; intellectual disability	Defective ER-Golgi trafficking	(173)
<i>FGD1</i>	GTPase activator	Aarskog-Scott syndrome	Facio-genital dysplasia	Reduction in FGD1 trafficking from Golgi	(131)
<i>FKRP</i>	Glycosyltransferases	Limb girdle muscular dystrophy	Muscular dystrophy	Abnormal glycosylation	(116)
<i>Fukutin</i>	Glycosyltransferases	FCMD	Muscular dystrophy	Abnormal glycosylation; Impaired ER-to-Golgi trafficking of mutant protein	(115)
<i>GOSR2</i>	SNARE	Progressive myoclonus epilepsy	Seizure	Mislocalization of mutant protein to cis-Golgi;	(124)
<i>HERC1</i>	GTPase activator	Idiopathic intellectual disability	Intellectual disability	Defective cis to trans Golgi compartment trafficking	(174)

Table I. Continued.

Gene	Function	Disease	Main clinical manifestation	Cellular effect	(Refs.)
<i>LARGE</i>	Glycosyltransferases	Congenital muscular dystrophy Type 1D	Muscular dystrophy	Abnormal glycosylation	(114)
<i>OSBPL2</i>	Lipid transport	Autosomal dominant nonsyndromic hearing loss	Hearing loss	Abnormal lipid metabolism	(175)
<i>RAB33B</i>	Rab GTPase	Smith-McCort dysplasia	Skeletal dysplasia	Golgi fragmentation; Defective Golgi membrane trafficking	(176)
<i>RAB39B</i>	Rab GTPase	X-linked Mental retardation	Mental Retardation; Autism; Epilepsy; Macrocephaly	Defective Golgi membrane trafficking	(122)
<i>SIP</i>	Serine protease	Spondyloepiphyseal dysplasia	Skeletal dysplasia	Defective Golgi-to-lysosome transport	(177,178)
<i>SCYL1BP1</i>	Golgin	Geroderma osteodysplastica	Osteoporosis; Wrinkly skin	Reduced recycling of trans-Golgi enzymes; Defective COPI traffic and glycosylation	(75,90)
<i>SLC35A1</i>	CMP Synal Transporter	CDG-II	Neurodegenerative disorder	Abnormal glycosylation	(179)
<i>SLC35A2</i>	UDP Gal Transporter	CDG	Developmental delay; Seizures; Ataxia	Abnormal glycosylation	(180)
<i>TMEM165</i>	Ion pump	CDG-II	Neurodegenerative disorder	Mislocalization of mutant protein resulting in abnormal Golgi glycosylation	(134)
<i>TRAPPC11</i>	Tethering	Congenital muscular dystrophy	Muscular dystrophy	Defective trafficking and Hypoglycosylation of mutant protein	(135)
<i>TRAPPC2</i>	Tethering	Spondyloepiphyseal dysplasia tarda	Skeletal dysplasia	Abnormal trafficking between ER and Golgi	(136)
<i>TRIP11</i>	Golgin	Achondrogenesis type 1A; Odontochondrodysplasia	Skeletal dysplasia	Golgi fragmentation; Abnormal Golgi-mediated glycosylation	(92,93)
<i>VPS53</i>	Unknown	Progressive cerebello-cerebral atrophy type 2	Mental retardation; Microcephaly; Epilepsy	Impaired NPC2 protein sorting to lysosome and cholesterol accumulation	(181)

other liver diseases such as cirrhosis (145,146). In addition to being a marker, the expression of GP73 is critical for chemotherapeutic resistance in HCC cell lines (147).

Transmembrane protein 165 (TMEM165) functions in ion homeostasis, membrane trafficking, and glycosylation in the Golgi apparatus (148). Findings of a study showed that mutations in TMEM165 cause CDG type II in humans (134). Other research has found that expression of TMEM165 mRNA and protein is apparently increased in HCC patient tissues and contributes to the invasive activity of cancer cells (149). This result indicates that TMEM165 is a possible biomarker for HCC. GS28 is a member of the SNAREs protein family. GS28 protein immunoreactivity was observed in both nuclear and cytoplasmic compartments of cancer cells. High nuclear expression of GS28 is associated with poor prognosis for colorectal (150) and cervical cancer patients (151).

Anti-Golgi antibodies (AGAs) were first found in 1982 in the serum of patients with Sjogren's syndrome complicated with lymphoma (152). AGAs have also been found in other immunological diseases (153-155). Currently, at least 20 Golgi autoantigens are known, including golgin-97, golgin-67, golgin-245, golgin-95, golgin-160, and giantin. AGA positivity is commonly found in connective tissue diseases such as Sjogren's syndrome, rheumatoid arthritis, and systemic lupus erythematosus (154,156); cerebellar malignant disease such as idiopathic late-onset cerebellar ataxia (157); infectious diseases such as HBV/HCV infection, Epstein-Barr virus infection and HIV infection (155,158,159); and tumors, such as HCC and lung cancer (160). Although AGAs are not specific to any disease, their clinical detection may be helpful for classifying and following the progress of some connective tissue diseases. For example, compared to anti-BICD2-negative patients, single specificity anti-BICD2 patients may be more associated with inflammatory myopathy and interstitial lung disease (161).

Biomarkers are crucial for early diagnosis, assessing response to treatment, and classifying diseases into subtypes. Biomarker discovery involves many critical steps such as clinical study design, sample collection, data integration, and protein/peptide identification and preservation. These steps should be carefully controlled before confirmation and verification. Therefore, in clinical applications, these biomarkers are potential diagnostic markers. Large-scale investigations are needed and more sensitive and specific detection methods need to be researched.

Golgi-based therapeutics. In addition to biomarker discovery, the functions of the Golgi apparatus and its associated molecules in maintaining cell structural integrity and its central role in membrane trafficking pathways provide possible targets for disease therapy. These targets may be direct, due to genetic disease (Table I), or indirect, as in cancer. Compared to non-transformed and normal cells, cancer cells have morphological and functional changes in the Golgi apparatus that drive invasion and migration in a unique microenvironment. These changes provide therapeutic targets for interventions. A research team developed a bovine serum albumin pH-responsive photothermal ablation agent that preferentially accumulates in the Golgi of cancer cells compared to normal cells due to morphological changes in the Golgi apparatus (162). The agent is activated by the weakly acidic microenvironment of the Golgi in cancer cells for

photothermal therapy. In this method, a photothermal ablation agent converts light energy into heat and kills cancer cells with high specificity and minimal invasiveness by hyperpyrexia (162). Another research team developed a prodrug nanoparticle system, which appeared to target the Golgi apparatus and realized retinoic acid release under an acidic environment. The retinoic acid-conjugated chondroitin sulfate could reduce the expression of metastasis-associated proteins by inducing Golgi fragmentation (163). Those findings suggest that the Golgi apparatus is a promising target for the development of novel drugs. A review summarized small molecules as drugs targeting the Golgi apparatus for the treatment of diseases (164), such as LTX-401, inhibitors of Golgi-associated lipid transfer proteins, glucosylceramide synthase inhibitors, O-glycosylation inhibitors, PI4KIIIb inhibitors and inhibitors of ARF activation. Whether these drugs that target the Golgi apparatus can be applied in clinical practice needs to be determined.

7. Conclusion

The central role of the Golgi apparatus in critical cell processes such as the transport, processing, and sorting of proteins and lipids has placed it at the forefront of cell science. Several previous studies have suggested that the Golgi apparatus plays a critical role in diseases, particularly in neurodegenerative diseases. However, few studies focus on human diseases caused by mutations in genes encoding Golgi resident proteins and summarize the common features of these genetic diseases. In the present review, we summed up the genetic diseases caused by mutations in genes encoding Golgi resident proteins. By analyzing their pathophysiology, we identified that the majority of genes are involved in membrane trafficking. The nervous system, skin, bone, cartilage, and skeletal muscle are the most sensitive tissues to defective membrane trafficking. It is reasonable to hope that our basic knowledge of Golgi-mediated membrane trafficking will continue to provide insights into the pathogenesis of genetic diseases and that studies of these diseases will continue to enhance our understanding of the critical role of the Golgi apparatus in diseases. In addition, the finding of Golgi-related biomarker and Golgi-based therapeutics further emphasize the importance of Golgi apparatus in human pathology. Taken together, advances in Golgi apparatus biology provide opportunities to translate discoveries into clinical medicine. Thus, we highlighted the importance of underlying clinical insights and provided a new direction for future research.

Acknowledgements

Not applicable.

Funding

The present study was supported by grants from the National Natural Science Foundation of China (grant no. 81974213).

Availability of data and materials

Not applicable.

Authors' contributions

JL and YH were mainly responsible for collecting relevant information and completing this review. ZJ, LZ and TL were mainly responsible for consulting literature materials and revising the manuscript. ZH was responsible for the conception of this review and the assignment of tasks. There was no additional assistance with manuscript preparation. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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