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The Golgi apparatus in neurorestoration

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ABSTRACT

The central role of the Golgi apparatus in critical cellular processes such as the transport, processing, and sorting of proteins and lipids has placed it at the forefront of cell science. Golgi apparatus dysfunction caused by primary defects within the Golgi or pharmacological and oxidative stress has been implicated in a wide range of neurodegenerative diseases. In addition to participating in disease progression, the Golgi apparatus plays pivotal roles in angiogenesis, neurogenesis, and synaptogenesis, thereby promoting neurological recovery. In this review, we focus on the functions of the Golgi apparatus and its mediated events during neurorestoration.

1 Introduction

The Golgi apparatus—a highly dynamic cellular organelle—functions in the processing and sorting of proteins and lipids during trafficking from the endoplasmic reticulum (ER) 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 anticipated to affect the homeostasis of cellular proteins and lipids. Increasing evidence suggests that structural changes and functional disorders of the Golgi apparatus are involved in many neurodegenerative diseases [2–4]. However, whether the Golgi apparatus also participates in neurorestoration in such diseases remains unclear. In this review, we describe the central

roles of the Golgi apparatus in cells and discuss neurodegenerative diseases associated with structural changes and functional disorders of the Golgi apparatus. Finally, we highlight the role of the Golgi apparatus in neurorestoration.

2 Structure and function of the Golgi apparatus

In 1898, the Italian anatomist Camillio Golgi discovered this cell organelle that now bears his name—the Golgi complex or apparatus [5]. In mammalian cells, the Golgi apparatus comprises dozens of flattened, parallel, interconnected cisternae. The pile of Golgi cisternae is referred to as the Golgi stack. Based on the distribution of resident proteins, the Golgi stacks can be

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divided into three functional compartments: cis-, medial-, and trans-Golgi cisternae [1]. The Golgi stacks are connected to the cis- and trans-Golgi networks (CGN and TGN, respectively). CGN is connected to the first cis-Golgi cisterna [6] and is involved in ER–Golgi trafficking. TGN is involved in the sorting of cargos to their final destination.

The Golgi apparatus is the central hub of the secretory pathway [7]. The main secretory pathway can be divided into the following steps. First, newly synthesized proteins or lipids enter the exit sites of ER and are sorted into budding vesicles that depending on the membrane-bending properties of coat protein complex II. Second, vesicles move to the ER–Golgi intermediate compartment and forward to CGN. Third, proteins or lipids enter the cis-Golgi cisternae and move toward the trans-Golgi cisternae. Finally, vesicles reach TGN, which is involved in protein glycosylation and sorting of cargos to their final destination, such as lysosomes, endosomes, or the plasma membrane.

Vesicular transport and cisternal maturation are the two classical models of intra-Golgi transport. In this review, we focus on the cisternal maturation model. This model proposes that the Golgi cisternae are dynamic structures that shift from the cis-toward the trans-Golgi side. This shift can be divided into three stages [8]. At the cisternal assembly stage (which involves ERGIC and cis-Golgi cisternae), ER-derived COPII vesicles deliver cargo to a cisterna and are balanced by a retrograde-directed pathway that recycles machinery proteins to ER in COPI vesicles. Next, at the carbohydrate synthesis stage (which involves medial and trans-cisternae), cisternae exchange cargo with other cisternae via COPI vesicles. Finally, at the carrier formation stage (which involves TGN), cisternae produce clathrin-coated vesicles while receiving incoming material from endosomes.

3 Structural and functional changes of the Golgi apparatus in neurodegenerative disease

The Golgi apparatus is a highly organized sub-cellular organelle that acts as a cellular sensor, adapting and changing its structure depending on the physiological state of the cell. Structural changes of the Golgi apparatus result in the dispersal or complete disassembly of the Golgi stacks, forming a fragmented Golgi apparatus in a process termed Golgi fragmentation. Cell apoptosis can result in Golgi fragmentation, as demonstrated in an *in vitro* model of mechanical cell injury [9]. However, Golgi fragmentation often represents an early causative event rather than a secondary step before cell apoptosis [10, 11]. Under pharmacological or oxidative stress, several changes occur in the Golgi apparatus, such as cargo overloading, ionic imbalance, and perturbation of glycosylation and luminal pH [12–14]. These changes can lead to insufficient Golgi glycosylation and Golgi-mediated membrane trafficking (Golgi stress). The Golgi stress response represents autoregulation to repair the Golgi apparatus and may initiate signaling pathways to alleviate stress. Nuclear signaling pathways of the Golgi stress response have been demonstrated [15–17]. In the procaspase-2/golgin-160 pathway, procaspase-2 interacts with upstream apoptotic regulators and mediates the cleavage of Golgi matrix proteins such as golgin-160 and giantin, which generally exhibit nuclear localization signals. Nuclear fragments of Golgi matrix proteins enter the nucleus and participate in the stress repair pathway. Moreover, in the TFE3 pathway, dephosphorylation and nuclear translocation of TFE3 result in the transcription of Golgi apparatus stress element-containing genes, which increase the levels of Golgi glycosylation enzymes and trafficking components. Furthermore,

in the HSP47 pathway, HSP47 downregulation leads to Golgi fragmentation and Golgi stress-induced apoptosis. In the CREB3/ARF4 pathway, ARF4 is localized to the Golgi membranes and regulates Golgi-to-ER trafficking; when ARF4 is downregulated under Golgi stress, CREB3 is activated and translocated to the nucleus, upregulating ARF4 transcription. If these pathways fail to repair overstimulation, the Golgi is completely disassembled, inducing cell apoptosis.

Structural changes of the Golgi apparatus are typical of many neurodegenerative diseases, such as amyotrophic lateral sclerosis [2, 18, 19], Alzheimer's disease [3], Parkinson's disease [4], Huntington's disease [20], Creutzfeldt–Jacob disease [21], and multiple system atrophy [22]. Golgi fragmentation has been proposed to be a late event in cellular apoptosis. Meanwhile, Golgi fragmentation has been reported to occur before microtubule degeneration and may be a trigger for neuronal loss [23]. In the pathology of neurodegenerative diseases, the Golgi apparatus initially appears to exhibit an adaptive response, such as compensatory expansion. However, when neurons are overstimulated by excitotoxins and oxidative insults, the Golgi apparatus gradually appears to disperse and undergo atrophy [24]. Mechanisms of neuronal Golgi fragmentation involved in the pathogenesis of neurodegenerative diseases include the (1) impairment of endosome-to-Golgi retrieval of membrane proteins [25]; (2) disruption of ER-to-Golgi trafficking by mutant growth hormones [26]; and (3) interruption of the ER–lysosome–Golgi network, which is important for protein glycosylation [27]. Normal Golgi glycosylation assists in protein folding, making intermediates more hydrophilic, which may prevent mutant protein aggregation—a crucial cascade event for neurodegeneration. The inhibition of neuronal Golgi fragmentation decreases or delays cell apoptosis [28], indicating that fragmentation of the neuronal Golgi apparatus

is a key contributor to neuronal cell apoptosis and neurodegeneration. The association between the Golgi apparatus and neurodegenerative diseases is presented in Fig. 1. Oxidative stress signals result in Golgi stress and initially elicit a protective effect. However, overstimulation shows damaging effects and results in Golgi fragmentation, which is a positive feedback module that enhances Golgi stress signaling and accelerates neuronal dysfunction, ultimately leading to neurodegeneration.

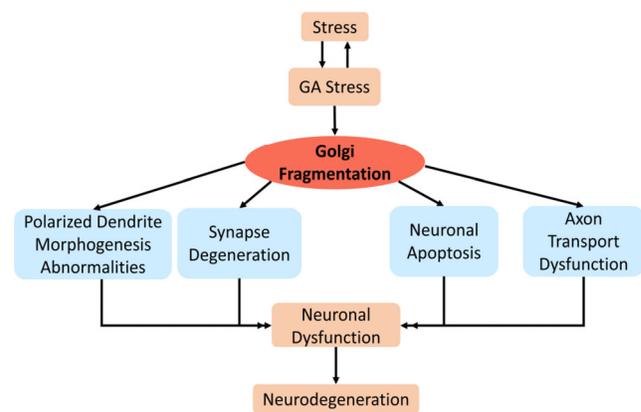


Fig. 1 Possible links between Golgi stress, Golgi fragmentation, and neurodegeneration. Stress signal enables the sensing of Golgi stress, which acts as a positive feedback module that enhances stress signaling. If the stress is very severe, it contributes to Golgi fragmentation and subsequently apoptosis, polarized dendrite morphogenesis abnormalities, axon transport dysfunction, and synapse degeneration, eventually resulting in neurodegeneration.

4 Roles of the Golgi apparatus in neurorestoration

4.1 Golgi apparatus and neurogenesis

In the adult mammalian brain, neurogenesis occurs in two neurogenic niches throughout life: the subventricular zone (SVZ) [29] and the subgranular zone (SGZ) [30]. Adult-born granule cells are continuously generated in the SGZ of the hippocampus dentate gyrus [31]. These new neurons contribute to memory formation and

mood regulation [32, 33]. During development, granule cells bear a single primary dendrite with branches extending toward the molecular layer and a long axon projecting through the hilar area into the CA3 region [34]; the mature adult-born granule cells are devoid of basal dendrites. Polarized dendritic establishment is important for proper formation of neural circuits and signal integration [35]. Accumulating evidence suggests that the development of polarized dendrites in adult-born granule cells is related to the Golgi apparatus. By analyzing the Golgi-related genes of adult-born granule cells, a study found that *STK25* and *STRAD* regulate neuronal development. Knockdown of these two proteins could result in aberrant dendrite establishment [36]. In the dentate gyrus of 8-week-old mice, the Golgi apparatus is predominantly located in the initial segment of the primary dendrite. Downregulation of the Golgi matrix protein GM130 or overexpression of GRASP65 in the dentate gyrus could disrupt Golgi deployment, potentially affecting the initiation and extension of dendrites [37]. Thus, the polarized distribution of the Golgi apparatus is essential for dendrite polarity in adult-born hippocampal granule cells. The Golgi apparatus associates with adult-born dentate granule cells in SGZ and also contributes to the identity and cytoarchitecture of neural stem and progenitor cells in SVZ and ventricular zone [38]. Moreover, the polarized architecture of neural stem cells is related to asymmetric Golgi subcellular localization [39]. In bipolar epithelial neural stem cells, the Golgi apparatus shows very specific and noncanonical features [40].

Reelin [41–43], liver kinase B1 (LKB1) [36, 37], PIPNA/PITPNB [44], STK25 [36], and Brefeldin A-inhibited guanine exchange factor 2 (BIG2) [45] regulate Golgi subcellular localization. Figure 2 illustrates the related signaling pathways contributing to polarized dendrite morphogenesis in

adult-born neurons. The mechanism of polarized Golgi distribution contributing to dendrite polarity may be related to the polarized post-Golgi membrane trafficking. The Golgi-mediated membrane trafficking pathways deliver proteins from the soma to dendrites, and the blockade of ER-to-Golgi trafficking could suppress dendritic growth [46]. Protein kinase D (PKD)1 and PKD2, which are required for the post-Golgi trafficking, regulate the directionality of Golgi-derived vesicles [47, 48]. The loss of function of PKD1 and PKD2 in the hippocampal neurons results in the mislocalization of axon-specific vesicles sorted by TGN, thus converting pre-existing dendrites into axons [49]. In normal hippocampal neurons, the post-Golgi membrane trafficking is preferentially directed toward a single principal dendrite, indicating an association between asymmetric Golgi apparatus distribution and dendritic outgrowth [50]. Therefore, malformation

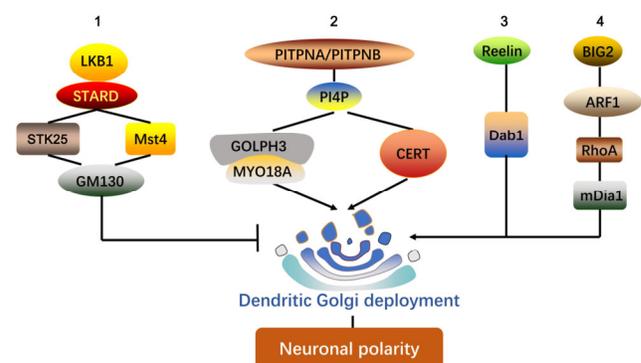


Fig. 2 Signaling pathways regulating Golgi distribution and neuronal polarity during neurogenesis. (1) STK25 and Mst4, downstream effectors of LKB1, co-immunoprecipitate with STRAD and bind to the Golgi matrix protein GM130. These two effectors are enriched in the Golgi apparatus and essential for Golgi organization. (2) The lipid transfer proteins (PITPNA/PITPNB) potentiate the PI4P-dependent recruitment of GOLPH3 to the Golgi apparatus, which promotes MYO18A-directed localization of the Golgi to the apical compartment. (3) Reelin and Dab1 regulate Golgi extension into the apical process of pyramidal neurons. (4) BIG2–ARF1–RhoA–mDia1 signaling regulates dendritic Golgi deployment and dendrite growth in adult newborn hippocampal neurons.

of Golgi structure and localization during neurogenesis could inflict structural and functional damage to nascent neurons.

4.2 Golgi apparatus and synaptogenesis

The formation and stabilization of synapses in the central nervous system involve a complex process including several precise steps. The initial stage of synaptogenesis involves the delivery of some proteins and lipids to the site of contact between the axons and dendrites. This process is mediated by vesicular carriers that fuse with the synaptic plasma membrane to deliver synaptic receptors. The Golgi apparatus, the main station for the modification, maturation, and sorting of proteins, plays an important role in the delivery of synaptic proteins. When a vesicle exiting the Golgi apparatus is impaired, the transport of prototypic active zone cytomatrix molecules out of the soma is inhibited [51]. TGN-derived carriers are important vehicles for the transport and release of synaptic proteins to the synaptic contact sites [52]. In addition to being a single-copy perinuclear organelle in the soma in most mammalian cells, the neuronal Golgi apparatus includes satellite Golgi outposts (GOPs) in dendrites as an extension of the somatic Golgi apparatus. In cultured hippocampal neurons, GOPs localize predominantly to the dendritic branchpoints and are typically present in the first-order segment of the apical dendrite [50]. Evidence suggests that GOPs are essential for the membrane trafficking of receptors to synapses [53]. Through live-cell imaging, the involvement of GOPs in the trafficking of membrane proteins and secreted neuronal growth factors was demonstrated [54]. A recent review has illustrated the proteins associated with GOPs, such as the kainate receptor GluK2, synapse-associated protein 97, and N-methyl-D-aspartate receptor [55]. Impaired GOPs contribute to decreased GOP synthesis and plasma membrane protein

supply [56].

In cultured neurons, piccolo and bassoon co-localize with markers of TGN. Impairing the Golgi-binding region and blocking Golgi-derived vesicle formation can reduce bassoon levels at synapses [51]. In the cerebellum of GM130-KO mice, the soma-to-dendritic trafficking of post-synaptic density protein 95 was reduced, which can cause reduced neurotransmitter receptor abundance [57]. Thus, maintaining the normal structure and function of the Golgi apparatus is essential for synaptic proteins membrane trafficking.

4.3 Golgi apparatus and angiogenesis

Angiogenesis—the formation and maintenance of blood vessel architecture—plays critical roles in the recovery of cerebrovascular disease. Vascular endothelial growth factor (VEGF) is a primary driver of angiogenesis. During vascular tube formation, VEGF regulates endothelial cell proliferation and migration. Vascular endothelial growth factor receptor 2 (VEGFR2), the primary cognate receptor of VEGF, is expressed in endothelial cells and mediates signaling pathways to promote angiogenesis [58]. Given the importance of VEGFR2 in blood vessel formation, regulating VEGFR2 expression is a primary means of controlling angiogenesis. Brefeldin (a fungal metabolite that disrupts ER-to-Golgi membrane trafficking) can evidently reduce the levels of endothelial cell surface VEGFR2. Thus, the delivery of newly synthesized VEGFR2 from the Golgi apparatus to the endothelial plasma membrane is an important limiting mechanism in VEGFR2 expression [59].

Before VEGF stimulation, VEGFR2 in endothelial cells is localized in the Golgi apparatus. Several studies have investigated the molecular machinery required for VEGFR2 trafficking from the Golgi apparatus to the plasma membrane (Table 1). Syntaxin 6, a member of the soluble

Table 1 Golgi apparatus-related molecular machinery regulating VEGFR2 expression in angiogenesis.

Molecules	<i>In vivo</i> model	<i>In vitro</i> model	Association with the Golgi apparatus	Function in angiogenesis	Reference
Syntaxin 6	Syntaxin 6-cyto-treated mouse ear	Syntaxin 6-deficient HUVEC	Inhibiting syntaxin 6 increase VEGFR2 trafficking from Golgi to the lysosomes for degradation, without the inhibition of VEGFR2 synthesis	Syntaxin 6 deletion reduces plasma membrane and total cellular VEGFR2 expression and blocks angiogenesis	[59]
Syntaxin 16	NA	LDL-exposed HUVEC	Regulates endosome–trans-Golgi network trafficking of VEGFR2	Syntaxin 16 deletion increases total cellular VEGFR2 expression and may promote angiogenesis	[61]
Myosin 1c	NA	Myosin 1c-deficient HUVEC	Myosin 1c depletion results in increased VEGFR2 trafficking from the Golgi to lysosomes for degradation	Myosin 1c deletion reduces plasma membrane and total cellular VEGFR2 expression and blocks angiogenesis	[62]
KIF13B	Mice injected with KIF13B-shRNA-treated Matrigel	KIF13B-knockdown HUVEC	KIF13B interacting with VEGFR2 cargo and microtubules in the Golgi initiates VEGFR2 trafficking	KIF13B deletion reduces VEGFR2 plasma membrane expression and blocks angiogenesis	[64]
Src family kinases	Diabetic mice	High-glucose-exposed HUVEC	Src family kinases mediate ROS-induced VEGFR2 phosphorylation, which reduces VEGFR2 abundance in the Golgi	Src family kinases reduce cell surface VEGFR2 abundance and block angiogenesis	[84]
YAP/TAZ	YAP/TAZ-ECKO mice	YAP/TAZ-knockdown HBMEC	YAP/TAZ deletion impairs VEGFR2 exit from TGN	YAP/TAZ deletion reduces VEGFR2 plasma membrane expression and blocks angiogenesis	[63]
SENP1	SENP1-ECKO mice	SENP1-deficient HUVEC	SENP1 deletion induces VEGFR2 hyper-SUMOylation and accumulation of VEGFR2 in the Golgi	SENP1 deletion reduces VEGFR2 plasma membrane expression and blocks angiogenesis	[85]

VEGFR2: vascular endothelial growth factor receptor 2; HUVEC: human umbilical vein endothelial cell; LDL: low-density lipoprotein; ROS: reactive oxygen species; TGN: trans-Golgi network

N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) protein family, is localized primarily in the Golgi apparatus and involved in the post-Golgi trafficking of VEGFR2. Functional inhibition of syntaxin 6 can reroute VEGFR2 from the plasma membrane to lysosomes and block VEGF-induced angiogenesis [59]. Syntaxin 16, another member of the SNARE protein family, is associated with endosome-to-TGN retrograde trafficking [60]. In low-density-lipoprotein-exposed endothelial cells, VEGFR2 abundance is markedly reduced, depending on syntaxin-16-mediated endosome-TGN trafficking [61]. In addition to syntaxins, myosin 1c (Myo1c)

plays a role in the delivery of a VEGF-induced secretory VEGFR2 pool from TGN to the plasma membrane [62]. Myo1c expression can be regulated by YAP/TAZ activity in postnatal brain endothelial cells. Meanwhile, lack of YAP/TAZ results in impaired Golgi-to-plasma membrane trafficking of VEGFR2 [63]. The kinesin-3 protein KIF13B can bind to VEGFR2 at the Golgi apparatus and initiate its trafficking to the endothelial cell surface [64]. Although previous studies confirmed that the above molecules contribute to VEGFR2 trafficking from the Golgi apparatus, the associations among syntaxin 6, Myo1c, YAP/TAZ, and KIF13B warrant further exploration.

5 Role of the Golgi apparatus in neurorestorative therapies

Neurorestoration is supported by a complex interplay of multiple molecular pathways. Structural and functional changes of the Golgi apparatus interrupt the processing, modification, sorting, and trafficking of proteins and lipids to their final destination, resulting in a series of pathological changes during the pathogenesis of neurodegenerative diseases. A number of molecules target the Golgi apparatus through different mechanisms. Uncovering the regulatory networks that target the Golgi apparatus can provide new therapeutic strategies of neurorestoration. However, whether these molecules can be applied in the clinical practice requires further research.

5.1 Therapies aimed at protecting the Golgi structure

Loss of synapse integrity and function has been considered a starting point for neuronal loss and an important early feature in many neurodegenerative diseases. Golgi fragmentation, a common feature in many neurodegenerative diseases [65], interrupts the processing and trafficking of secretory proteins and subsequently synaptogenesis. Restoration of the Golgi structure may serve as a therapeutic strategy of neurorestoration.

Under physiological conditions, Cdk5 plays critical roles in synaptic functions and dendritic spine formation [66, 67]. In Alzheimer's disease models, overactivated Cdk5 alone enhanced Golgi fragmentation by promoting GM130 and GRASP65 phosphorylation [68, 69]. The use of Cdk5 inhibitor peptide rescued A β -induced Golgi disassembly. In addition to Alzheimer's disease, Golgi fragmentation plays a role in isoflurane-related neurotoxicity. Isoflurane is a widely used anesthetic, which increases the risk of postoperative cognitive decline in the elderly.

In cultured primary hippocampal neurons, the proportion of fragmented Golgi increased following isoflurane treatment, resulting in significantly decreased neuronal viability [70]. Roscovitine, a Cdk5 inhibitor, shows protective effects against Golgi fragmentation and isoflurane-related neurotoxicity.

5.2 Therapies aimed at regulating the Golgi deployment

Dysfunctional Golgi localization during neurogenesis could induce functional damage to nascent neurons. The regulation of Golgi deployment in nascent neurons is a potential therapeutic target for the treatment of neurodegenerative diseases neurogenesis. The Rho family of small GTPases (Rho GTPases) plays key regulatory roles in correct dendrite development, which is essential for establishing neural circuitry. Accumulating studies have implicated critical roles of Rho GTPase-dependent signaling in the regulation of Golgi polarization and deployment as well as of neuronal morphogenesis [71, 72]. Cell division cycle 42 (Cdc42), a small Rho GTPase localized to the Golgi apparatus, plays a crucial role in neuronal polarization [73] and vesicle trafficking [74]. In polarized nascent neurons, Cdc42 is distributed asymmetrically, and this distribution depends on the presence of active Cdc42 in the Golgi apparatus. The active Golgi-localized Cdc42 is transported to specific regions of the plasma membrane to regulate cellular polarity [75]. The absence of Cdc42 abrogates the reorientation of the Golgi apparatus and alters cell polarity. Following reelin treatment, Cdc42 is activated, leading to the translocation of the dendritic Golgi apparatus and promotion of neuronal development [72, 76].

5.3 Therapies aimed at rescuing Golgi-mediated membrane trafficking

Defects in Golgi-mediated membrane trafficking

are a hallmark of many neurodegenerative disorders [77]. In an *in vitro* model of early-stage epilepsy, the collapse of the ER–lysosome–Golgi network resulted in decreased reelin processing, which may contribute to the initiation and propagation of seizures [27]. Thus, restoring this network could be a novel therapeutic strategy for attenuating epilepsy. In animal models of Parkinson’s disease, blockage of ER-to-Golgi membrane trafficking via alpha-synuclein (α Syn) is a critical cellular lesion contributing to dopaminergic neuronal degeneration [78]. Elevated expression of Rab1, a protein mediating ER-to-Golgi membrane trafficking, can protect against α Syn-induced dopaminergic neuronal loss [79] and improve their survival to control motor function [80]. A disintegrin and metalloproteinase 10 (ADAM10) is the major α -secretase that controls amyloid precursor protein shedding in the brain and restricts β -amyloid peptide formation in Alzheimer’s disease [81]. ADAM10 trafficking from the dendritic Golgi outposts to the synaptic membranes is a key modulator of its activity. Increasing ADAM10 activity via regulating synaptic trafficking may be efficacious for treating Alzheimer’s disease [82, 83].

6 Summary

Accumulating evidence has identified the Golgi apparatus as a central signaling hub between the exocytic and endocytic routes of membrane trafficking. Collectively, the reported findings assert that the Golgi apparatus exerts potent neurorestorative effects by contributing to neurogenesis, synaptogenesis, and angiogenesis. Multiple functions of the Golgi apparatus in neurorestoration provide multiple therapeutic targets for neurodegenerative diseases. However, additional research investigating the complex association between the Golgi apparatus and neurorestoration is still warranted given that its

involvement in neurorestoration remained to be investigated systematically.

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Conflict of interests

All contributing authors report no conflict of interests in this work.

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