Molecules and Cells

Minireview

Golgi Stress Response: New Insights into the Pathogenesis and Therapeutic Targets of Human Diseases

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The Golgi apparatus modifies and transports secretory and membrane proteins. In some instances, the production of secretory and membrane proteins exceeds the capacity of the Golgi apparatus, including vesicle trafficking and the post-translational modification of macromolecules. These proteins are not modified or delivered appropriately due to the insufficiency in the Golgi function. These conditions disturb Golgi homeostasis and induce a cellular condition known as Golgi stress, causing cells to activate the 'Golgi stress response,' which is a homeostatic process to increase the capacity of the Golgi based on cellular requirements. Since the Golgi functions are diverse, several response pathways involving TFE3, HSP47, CREB3, proteoglycan, mucin, MAPK/ETS, and PERK regulate the capacity of each Golgi function separately. Understanding the Golgi stress response is crucial for revealing the mechanisms underlying Golgi dynamics and its effect on human health because many signaling molecules are related to diseases, ranging from viral infections to fatal neurodegenerative diseases. Therefore, it is valuable to summarize and investigate the mechanisms underlying Golgi stress response in disease pathogenesis, as they may contribute to developing novel therapeutic strategies. In this review, we investigate the perturbations and stress signaling of the Golgi, as well as the therapeutic potentials of new strategies for treating Golgi stress-associated diseases.

Keywords: Golgi stress, Golgi stress response, human disease, pathogenesis, therapeutic target

INTRODUCTION

The Golgi apparatus is involved in the intracellular transport and maturation of proteins and lipids (Rohn et al., 2000; Viotti, 2016). More than a third of all human genes are known to encode proteins that travel through the Golgi (Yuen et al., 1997). The Golgi has a distinctive structure with several layers of flat, semicircular vesicles known as cisternae. Most research has concentrated on the molecular and physiological mechanisms behind the Golgi apparatus's structural characteristics and material transport (Duden, 2003; Klumperman, 2000; Lee et al., 2004; Tamaki and Yamashina, 2002; Watson and Stephens, 2005). Recent studies indicate that the Golgi functions as a signaling hub in intracellular signal transduction pathways involved in the development and progression of many diseases (Cancino and Luini, 2013; Makhoul et al.,

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2019; Spano and Colanzi, 2022). The pathophysiological involvement of the Golgi is attracting interest because protein quality control, which is known to have a significant association with the pathogenesis of numerous diseases, is associated with the Golgi (Schwabl and Teis, 2022).

Pathophysiological cellular stress stimuli affect Golgi homeostasis directly (Li et al., 2019; Liu et al., 2021), resulting in Golgi stress. In response to Golgi stress, cells activate adaptive mechanisms to overcome the stress and restore Golgi homeostasis. Although Golgi stress is not as well established as endoplasmic reticulum (ER) stress, increasing evidence indicates that distinct signaling cascades are involved in the Golgi stress response. This review highlights the potential triggers of Golgi stress, related signaling mechanisms, and therapeutic strategies that target Golgi stress signaling.

FACTORS DISRUPTING FUNCTIONAL AND MORPHOLOGICAL INTEGRITY/HOMEOSTASIS OF THE GOLGI APPARATUS

The Golgi apparatus is a highly reactive organelle that exhibits functional and morphological perturbations in response to molecular-level and contextual factors.

Molecular-level factors

Several small compounds that trigger Golgi stress via various mechanisms have been discovered. Stressors include monensin (Boss et al., 1984; Ellinger and Pavelka, 1984) and nigericin (Suga et al., 2015), which are ionophores that neutralize luminal pH and block intra-Golgi trafficking, and lithocholylglycine, which inhibits α-2,3-sialyltransferase activity (Chang et al., 2006). Targeting the ADP ribosylation factor (ARF) proteins with compounds, such as Brefeldin A (Robineau et al., 2000) and Golgicide A (Saenz et al., 2009), induces Golgi stress by increasing redistribution of the Golgi in the ER. Exo2 prevents the anterograde movement of the viral glycoprotein VSVG (vesicular stomatitis virus G) from the ER to the Golgi, resulting in a selective disruption of the Golgi without affecting the *trans*-Golgi network (TGN) (Feng et al., 2004). Also, DNA damage induced by chemotherapeutic agents, such as camptothecin and doxorubicin, triggers Golgi fragmentation and inhibits vesicular transport via DNA-PK-mediated GOLPH3 phosphorylation (Farber-Katz et al., 2014).

Contextual factors

Numerous cancer cell lines, including breast (Sewell et al., 2006), colon (Kellokumpu et al., 2002), and prostate cancer cells (Nolfi et al., 2020), exhibit fragmented Golgi. The structural and functional changes in the Golgi contribute to the survival, proliferation, and metastasis of cancer cells (Bui et al., 2021; Petrosyan, 2015). The uncontrolled proliferation of cancer cells requires massive protein synthesis, which impacts the Golgi's regulation of the cancer cell secretome (Bajaj et al., 2022). Cancer-induced perturbations of the Golgi can evoke intrinsic signals to alter Golgi architecture and trafficking kinetics (Howley and Howe, 2018).

In addition, cancer cells and microenvironments conducive to tumor growth are essential components of both primary and secondary tumors (Baghban et al., 2020). Golgi perturbation is induced by microenvironmental stressors, including acidification, hypoxia, and nutritional deprivation (Bui et al., 2021). Interrupting glycosylation, nutrient deficiency, and especially glucose deficiency contribute to Golgi stress. The functional alterations of Golgi have also been associated with neurodegenerative diseases such as Huntington's disease (Sbodio et al., 2018), amyotrophic lateral sclerosis (Park et al., 2020) and Alzheimer's disease (Suga et al., 2022), and metabolic diseases such as diabetes (Bone et al., 2020) and lipotoxicity (Bascil Tutuncu et al., 2022).

CELLULAR RESPONSE TO GOLGI STRESS

In response to Golgi stress, cells activate an adaptive signaling pathway known as the Golgi stress response, which assists cells in coping with the stress by enhancing the capacity of the Golgi for maturation and secretion of proteins and clearing the accumulation of proteins within the Golgi.

Recent research has shed light on a critical component of the regulatory mechanism underlying the Golgi stress response. This component includes transcription factor binding to IGHM enhancer 3 (TFE3), CAMP Responsive Element Binding Protein 3 (CREB3), mitogen-activated protein kinases/erythroblast transformation specific (MAPK/ETS), the protein kinase R (PKR)-like ER kinase (PERK), proteoglycan, mucin, and heat shock protein 47 (HSP47) pathways (Fig. 1). TFE3 is a transcription factor that acts as a master regulator of lysosomal biogenesis and immune response (Beckmann et al., 1990; Lawrence et al., 2019; Mathieu et al., 2019; Willett et al., 2017). It has been reported that Golgi stress-mediated dephosphorylated TFE3 binds a Golgi apparatus stress response element (GASE) to activate the transcription of Golgi-associated genes, including glycosylation enzymes (fucosyltransferase 1, sialyltransferase 4A, sialyltransferase 10, and UDP-N-acetylhexosamine pyrophosphorylase-like 1), Golgi structural proteins (GM130, Giantin, and GCP60), and vesicular transport components (RAB20, STX 3A, and WIPI49) (Oku et al., 2011; Taniguchi et al., 2015). Treating cells with Brefeldin A activates the CREB3-ARF4 pathway and inhibits the function of ARF proteins. Consequently, the cytoplasmic domains of CREB3 are released from the ER membrane and translocated into the nucleus to upregulate the Golgi-associated genes, including *ARF4*, resulting in Golgi stress-induced apoptosis (Howley et al., 2018; Reiling et al., 2013).

MAPK and PERK pathways involve the enzyme-mediated cascade in response to Golgi stress. The MAPK cascade and ETS family transcription factor induce apoptosis under Golgi stress (Baumann et al., 2018). PERK, a protein kinase that belongs to the eIF2α kinase subfamily, activated upon ER stress, has been identified as a pathway activated by the Golgi stressor monensin (Sbodio et al., 2018). Interestingly, PERK-mediated Golgi stress response acts via the eIF2α/ATF4/AARE (amino acid response elements) but is independent of the ER-resident chaperone BiP/GRP78, suggesting that this pathway is a distinct type of stress response. In addition, although transcription factors have not been identified, certain signaling pathways are known to contribute to the Golgi stress response. For example, the proteoglycan pathway is activated in case of insufficient proteoglycan glycosylation in

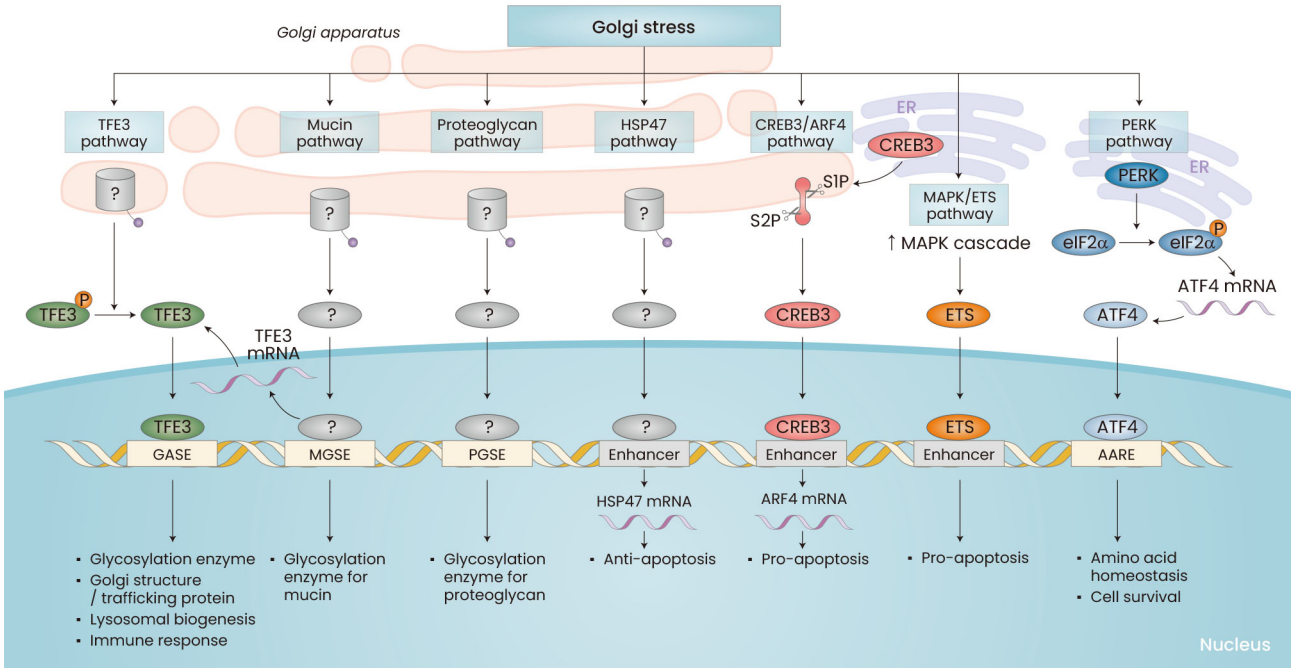

Fig. 1. Golgi stress response pathway. Golgi stress-induced dephosphorylation of TFE3 promotes the transcription of target genes via GASE. Insufficient glycosylation of mucin and proteoglycans activate Golgi stress response through MGSE-mediated activation of TFE3 and PGSE, respectively. Golgi stress-induced HSP47 mediates anti-apoptosis. CREB is cleaved by Golgi proteases (S1P and S2P) in response to Golgi stress and increases ARF4 expression. As kinase-mediated Golgi stress responses, MAPK and PERK pathway induces the phosphorylation of ETS and eIF2α, respectively. Phosphorylation of eIF2α increases the expression of ATF4, which activates target genes via AARE. See the text for details. TFE3, transcription factor binding to IGHM enhancer 3; HSP47, heat shock protein 47; CREB3, CAMP Responsive Element Binding Protein 3; ER, endoplasmic reticulum; MAPK/ETS, mitogen-activated protein kinases/erythroblast transformation specific; PERK, protein kinase RNA-like endoplasmic reticulum kinase; GASE, Golgi apparatus stress response element; MGSE, mucin-type Golgi stress response element; PGSE, proteoglycan-type Golgi stress response element; ATF4, Activating transcription factor 4; AARE, amino acid response elements.

the Golgi. It upregulates the transcription of genes encoding glycosyltransferase and sulfotransferase through an enhancer known as proteoglycan-type Golgi stress response element (PGSE) (Sasaki et al., 2019). Mucins are highly glycosylated, viscous proteins, and inadequate glycosylation of mucins induces a mucin-type Golgi stress response accompanied by TFE3 activation via mucin-type Golgi stress response element (MGSE) (Jamaludin et al., 2019). HSP47 is an ER chaperone, and its upregulation in response to Golgi stress protects cells against apoptosis (Miyata et al., 2013).

Notably, it has been recently reported that the Golgi stress response participates in protein homeostasis through three Golgi-associated degradation signaling pathways: Golgi apparatus-related degradation (GARD), endosome and Golgi-related stress-responsive associated degradation (EGAD), and Golgi membrane-associated degradation (GOMED).

Golgi stress changes Golgi morphology via proteasome-mediated degradation of the Golgi tethering factor GM130 bound to the cytosolic side of the Golgi membrane (Eisenberg-Lerner et al., 2020). This process, known as GARD, enables the Golgi to rapidly adjust its structure via localized proteasomal degradation in response to stress. In addition, GARD may be associated with the pathogenesis of virus infection. For example, herpes simplex virus has been reported to downregulate GM130 and induce Golgi fragmentation (He et al., 2020). It remains to be determined whether GARD-dependent regulation of Golgi stress is a feature of viral infection accompanied by Golgi fragmentation.

In EGAD, Golgi membrane proteins are degraded by Golgi and cytosolic proteasomes without returning to the ER (Schmidt et al., 2019). An example of EGAD is Orm2, the Golgi membrane protein in budding yeast. Orm2 is a conserved subunit of the serine:palmitoyl-coenzyme. It is a transferase complex that negatively regulates the production of sphingolipids (Hannun and Obeid, 2018). Orm2 is polyubiquitinated by the Golgi-localized Dsc E3 ligase complex, separated from the membrane by the ATPase VCP/CDC48, and subsequently degraded by cytosolic proteasomes, in contrast to most Golgi-polyubiquitinated proteins, which are sorted by the endosomal sorting complex required for transport (ESCRT) components for vacuolar/lysosomal degradation (Schmidt et al., 2019). It is possible that EGAD-dependent proteasomal degradation of Orm2 functions as the post-ER checkpoint to regulate lipid metabolism in budding yeast.

While GARD and EGAD contribute to proteostasis by using the proteasome system, GOMED is a distinct mechanism that degrades Golgi trafficking proteins via *trans*-Golgi membranes (Noguchi and Shimizu, 2022). When Golgi traf-

ficking is disrupted, the *trans*-Golgi membrane invaginates and engulfs proteins that could not be secreted or delivered to the plasma membranes, causing them to be accumulated in the TGN as degrading cargos; this process is also known as ATG5/ATG7-independent alternative autophagy (Nishida et al., 2009). WIPI3, a polyphosphoinositide-binding protein, has been recently reported as a key regulator of GOMED that binds to the Golgi membrane to form autophagosome-like structures (Yamaguchi et al., 2020). WIPI3-mediated alternative autophagy is required to maintain neuronal cells via a mechanism different from ATG-dependent canonical autophagy.

In Golgi stress response research, an unsettled but essential question is: what are the properties of molecules that sense Golgi stress and initiate signaling? Sensors for each pathway of Golgi stress response have not been elucidated. However, several candidates have recently been suggested. For example, it has been reported that GOLPH3, a peripheral membrane protein localized to the Golgi, is not only a Golgi stress sensor but also an initiator that transmits Golgi stress signals to the downstream pathway (Li et al., 2016). ATG9A/MARCH9/GRASP55 has been suggested as a direct sensor of heat-induced Golgi stress (Luo et al., 2022). Identifying common or individual sensors for these seven pathways would be essential for characterizing the Golgi stress response.

GOLGI STRESS IN DISEASES

Recent findings of Golgi stress signaling in human diseases

Recent research has uncovered new Golgi stress-mediated regulators and mechanisms involved in the infections and immune responses caused by pathogens such as viruses, bacteria, and parasites. For example, Influenza A virus infection leads to TGN dispersion, which depends on the NLR family pyrin domain containing 3 (NLRP3) inflammasome activation (Pandey and Zhou, 2022). TGN serves as a platform for the recruitment of NLRP3 and its downstream adaptor proteins, resulting in the formation of an active inflammasome. Interestingly, it has been reported that the Golgi stressor nigericin induces NLRP3 aggregation on dispersed TGN (Chen and Chen, 2018). This implies that Golgi fragmentation-induced Golgi stress constitutes an antiviral host defense by facilitating aggregation of NLRP3 inflammasome. Like the Influenza A virus, host cells infected by *Shigella* bacteria upregulate SIRT2, a potent lysine defatty-acylase, which is upregulated via the CREB3-mediated Golgi stress response (Wang et al., 2022). SIRT2 then removes the lysine fatty acylation that was introduced by *Shigella* virulence factor IcsB to boost the innate immunity of the host, suggesting the importance of SIRT2 in counteracting *Shigella* infection. In contrast to *Shigella*, a genome-wide CRISPR-Cas9 screen revealed that *Plasmodium* parasites, surprisingly, utilized Golgi stress during host infection (Vijayan et al., 2022). Knock-out of centromere protein J (CENPJ), a centrosomal MT organizing complex (MTOC) protein, enhances the efficiency of *Plasmodium* infection. This suggests that the parasite relies on non-centrosomal MT (Vijayan et al., 2022). Considering that the host Golgi acts as a non-centrosomal MTOC (ncMTOC) at the parasite periphery and Golgi-mediated MTOC repositioning regulates host vesicular trafficking to the parasite (De Niz et al., 2021; Romano et al., 2013; Zhu and Kaverina, 2013), the investigation of the involvement of ncMTOCs in the Golgi stress response would provide new insights into not only Golgi stress signaling but also novel mechanisms of parasite-host interactions.

In non-small cell lung cancer (NSCLC), cellular retinoic acid binding protein 2 (CRABP2) is involved in PERK/ATF4-mediated Golgi stress (Meng and Luo, 2021). CRABP2 was initially identified as a regulator of retinoic acid signal transduction (Zhang et al., 2019). However, high CRABP2 levels correlate with poor prognoses, such as poor overall survival, increased recurrence, and advanced lymph node metastasis, in NSCLC patients (Wu et al., 2019). This implies that CRABP2-associated Golgi stress is involved in metastatic lung cancer via the PERK pathway.

Notably, it has been linked to the neurotoxic effects of Golgi stress (Suga et al., 2022). Golgi stress induced by several compounds such as monensin, nigericin, Exo2, and golgicide A increases the expression of ER-Golgi SNARE Syntaxin5 isoforms, decreases βAPP processing, and consequently, increases the accumulation of β-amyloid. However, when Golgi stress continues, caspase-3 is activated, leading to neuronal cell death. The Golgi stress-induced PERK pathway also contributes to Huntington's disease (Sbodio et al., 2018). However, mild-Golgi stress may have a cytoprotective role via the PERK pathway in Huntington's disease. These results suggest that the Golgi stress response, like other stress responses, acts as a defense mechanism that allows cells to adapt or overcome stress under short and moderate stress conditions but acts as an aggravating factor that causes disease under strong and continuous stress conditions.

Potential therapeutic targets of the Golgi stress in human diseases

To improve the therapeutic index of a drug, it is most desirable to deliver the therapeutic molecule in its active form to the intracellular therapeutic active site of the targeted organelle (Sakhrani and Padh, 2013). Strategies are being actively developed to improve efficacy and minimize the toxicity of drug treatment for targeting organelles, especially for the Golgi. For example, chondroitin sulfate-based prodrug nanoparticles have been recently developed to target the Golgi in tumor cells. They reduce photodynamic immunotherapy-mediated immunosuppression by blocking the production of immunosuppressive cytokines (Li et al., 2022a).

The development of Golgi stress response-targeting therapeutics is a promising research area (Table 1). Results from previous studies have provided novel mechanistic insights to modulate Golgi stress response in diseases. For example, a low concentration of monensin prevents the toxicity associated with cysteine deprivation in Huntington's disease by upregulating the reverse transsulfuration pathway by PERK-mediated Golgi stress response and its targets, including cystathionine γ-lyase (Sbodio et al., 2018). This reveals that low-grade Golgi stress, which does not result in toxicity, can upregulate cytoprotective defensive systems and may prime or precondition cells to survive subsequent stresses. Therefore, rather than completely suppressing the Golgi stress response, balancing it at an appropriate level would be

Table 1. Potential therapeutic strategy targeting the Golgi stress in human diseases

Potential therapeutic target gene/pathway	Roles related to Golgi stress response in disease	Function in disease model		Reference
		Related disease	Results by modulation of target gene/pathway	
Targeting the Golgi stress response				
PERK/ATF4 pathway	Inhibitor of protein translation/cell survival	HD	Upregulation of CSE and restoration of cysteine metabolism by activation of the PERK/ATF4 pathway induced by low levels of monensin treatment	(Sbodio et al., 2018)
Klotho, CREB34L/TFE3 pathway	Cell proliferation, stress response and apoptosis	Immunosenescence	Activation of CREB34L/TFE3 Golgi stress pathway and production of pro-inflammatory cytokines; Inhibition by klotho overexpression in monocyte	(Mytych et al., 2020)
GM130/CASP3	Target of TFE3 pathway; Maintenance of Golgi structure/apoptosis	HSE caused by HSV-1 infection	GM130-mediated Golgi stress and down-regulation of GM130, occludin and claudin in HSV-1 infection; Reverse effects by overexpression of GM130	(He et al., 2020)
GM130	Control of protein glycosylation and vesicle transport	ICH	Modification of Golgi morphology, GM130 decrease and autophagy by ICH; Reverse effects and neuroprotective effects by overexpression of GM130	(Deng et al., 2022)
HIF-1α/HO-1 pathway	Regulation of oxidative stress	ALI	Increase of GM130, MAN2A1, Golgin 97 and decrease of GOLPH3 by activation of HIF-1α/HO-1 pathway; Reverse effects by knockdown of HO-1	(Li et al., 2021)
CASP2	Apoptosis	HDL 17	Recovery of differentiation by knockdown of CASP2 in myelin cell accompanying AIMP2 Y35X mutation	(Ochiai et al., 2022)
Ferroptotic cell death cascade	non-apoptotic cell death characterized by iron-dependent oxidative degradation of lipids	Potential diseases related to ferroptosis; PVL, AKI, cancer, neurodegeration	Golgi stress induced by Golgi disruptors induces ferroptosis and apoptosis; Protective effect to Golgi and cell by ferroptosis inhibitor and low levels of ferroptosis inducers	(Alborzinia et al., 2018)
Targeting the Golgi-associated degradation pathways				
GARD/GM130	GM130 degradation by ubiquitin-proteasome	Multiple myeloma (MM)	Activation of GM130-dependent Golgi stress response and apoptosis by monensin treatment in MM cells	(Eisenberg-Lerner et al., 2020)
EGAD	Selective protein degradation by ubiquitin-proteasome	Potential diseases by defects in proteostasis	Proteasomal degradation of Orm2 by Dsc ubiquitin ligase complex; Maintenance of sphingolipid homeostasis	(Schmidt et al., 2019)
GOMED/Wipi3	Alternative autophagy and degradation of secretory/cell membrane proteins	Diabetes	Digestion of (pro)insulin granules in Atg7 knockout β-cells	(Yamaguchi et al., 2016)
		Neurodegenerative disease	Behavioral defects, cerebellar neuronal loss and iron accumulation caused by failure of alternative autophagy in Wipi3 knockout mice	(Yamaguchi et al., 2020)

PERK, protein kinase RNA-like endoplasmic reticulum kinase; ATF4, activating transcription factor 4; HD, Huntington's disease; CSE, cystathionine γ-lyase; CREB34L, cyclic AMP response element binding 34L; TFE3, transcription factor binding to IGHM enhancer 3; GM130, Golgi matrix protein of 130 kDa; CASP3, caspase-3; HSE, herpes simplex encephalitis; HSV-1, herpes simplex virus 1; ICH, intracerebral hemorrhage; HIF-1α, hypoxia-inducible factor 1-alpha; HO-1, heme oxygenase-1; ALI, acute lung injury; MAN2A1, mannosidase alpha class 2A member 1; GOLPH3, Golgi phosphoprotein 3; CASP2, caspase-2; HDL, hypomyelinating leukodystrophies; AIMP2, aminoacyl-tRNA synthase complex-interacting multifunctional protein 2; PVL, periventricular leukomalacia; AKI, acute kidney injury; GARD, Golgi apparatus-related degradation; EGAD, endosome and Golgi-associated degradation; GOMED, Golgi membrane-associated degradation.

beneficial for treating Huntington's disease.

It is also possible that Golgi-associated degradation pathways such as GARD, EGAD, and GOMED are involved in proteinopathies, which have an archetypal feature of protein misfolding and accumulated structures (Bayer, 2015). The clearance of the proteins is essential for maintaining cell integrity (Bae et al., 2012; Deleidi and Maetzler, 2012). For example, the brain could be damaged by the dysfunction of protein clearance including unfolded protein response, autophagy, and phagocytosis (Alvarez-Erviti et al., 2010; Chiti and Dobson, 2017; Hartl, 2017; Kumar et al., 2016). Theoretically, enhancing the clearance capacity of the proteins via the Golgi stress-induced degradation pathway would provide a novel approach to treating proteinopathies including neurodegenerative diseases.

CONCLUSION AND PERSPECTIVES

The Golgi research area has focused on the structure and function of the Golgi or Golgi proteins. However, only a few studies exist on Golgi stress-associated pathogenesis. The extent and significance of the Golgi stress response are not entirely known. This is primarily due to a lack of reliable and precise experimental approaches specific to the Golgi. However, Golgi-specific experimental methods, particularly imaging techniques, are being actively developed. GoI_{ROS} has been developed as a fluorescence probe for O_2^- and H_2O_2 in the Golgi (Wang et al., 2019). It could quantitatively measure the Golgi reactive oxygen species and the pharmacological effect of antihypertensive drugs. In addition to GoI_{ROS}, several other Golgi-targeted probes have been developed. Golgi-NO has been developed as the Golgi-targeted fluorescent probe for visualizing nitric oxide (NO) in the Golgi (He et al., 2022). NO is a crucial neurotransmitter involved in various diseases, including Alzheimer's disease. This novel Golgi-targeted probe would be used as a tool for investigating the dysfunctional role of nitrosylation. Gol-NCS, an isothiocyanate-based Golgi-targeting fluorescent probe for cysteine (Cys), has been developed to detect the fluctuation of Cys content of Golgi and monitor the production of endogenous Cys during Golgi stress (Zhu et al., 2022). Golgi-Nap-CORM-3 is a Golgi-targetable fluorescent probe that detects carbon monoxide (CO)-releasing molecule-3 (CORM-3). It consists mainly of metal carbonyl compounds and is used as an experimental tool to deliver CO (Li et al., 2022b). Many different fluorescent probes have been developed that specifically target the Golgi, and they may prove helpful in advancing our understanding of the diseases associated with Golgi stress.

Insights from the above aspects will facilitate the understanding of why Golgi stress is induced via different pathways and how distinct Golgi stress signaling pathways are implicated in human diseases. To modulate the Golgi stress response with a therapeutic potential for various diseases, the characterization of the signaling pathways induced by the Golgi stress, the various substrates, and their regulatory processes is paramount. Golgi stress response is an active research area with many challenging questions. A comprehensive understating of the Golgi stress response will provide a complete view of the role of Golgi-associated pathogenesis in diseases, including diabetes, infectious diseases, inflammatory diseases, cancer, and neurodegenerative diseases

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AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST

The authors have no potential conflicts of interest to disclose.

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