Clinical and Experimental Health Sciences

The Roles of the Golgi in Various Diseases

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ABSTRACT

The primary function of the Golgi is to perform post-translational modifications on proteins, allow them to be transported within the cell. The Golgi has more functions in the cell, according to research into its unknown structure and functions. It has been discovered that, in addition to substance process and transport, it plays a role in autophagy, lipid formation, calcium homeostasis, and apoptosis regulation. The fact that the Golgi has so many tasks has caused question marks about what kind of illnesses or diseases it can cause in case of a problem with Golgi. A mutation at Golgi can disrupt its function by cause of the Golgi fragmentation. It can be seized by living organisms or molecules, called infectious agents, outside the mutation. Disintegration and disorders in the Golgi structure and function are examples of neurodegenerative diseases and cancer. In addition, studies prove that the SARS-CoV-2 virus, which causes pandemic in the world, is also linked to the Golgi. The diseases that can be caused by the Golgi are highlighted in this review, as are treatment studies. Treatment strategies for the Golgi that causes many diseases are still developing and studies are ongoing.

Keywords: Golgi, cancer, neurodegenerative diseases, SARS-CoV-2, treatment

1. INTRODUCTION

The Golgi is a central organelle of the secretory pathway, located at the junction of the exocytic and endocytic intracellular substance transport pathways. The Golgi has an important role in carrying the post-translational modification of proteins, classification of lipids, and proteins to their final targets. In addition to these duties, it also has an important effect on cellular responses such as apoptosis and stress (1). The Golgi was one of the first organelles to be discovered and studied in depth due to its enormous size. It was discovered in 1897 as part of Camillo Golgi's study of the nervous system and was defined as "apparato reticolare interno," "a thin and elegant network in the cell body completely within the nerve cells" (2). The Golgi in the cytoplasm is located near the endoplasmic reticulum (ER) and somewhere near the cell nucleus. While animal cells have one or more Golgi, there may be hundreds of the Golgi in plant cells. Its main function has been preserved throughout evolution and its structural organization varies among species. The Golgi is surrounded by a single-layer membrane and is found in eukaryotic cells. Immature mammalian red blood cells and sperms do not contain the Golgi. The Golgi is in charge of cell organization and defense, including cell division and apoptosis. The Golgi can give reactions that affect the future of the cell under the stress conditions seen in cells. Mutations in the relevant genes can cause the Golgi to become dysfunctional or seized by infectious agents, and it can be misregulated in multifactorial diseases like neurodegeneration and cancer, as well as COVID-19.

2. THE GOLGI' FUNCTIONS

The Golgi is a central node in intracellular membrane traffic at the intersection of exocytic and endocytic pathways, and thus plays an important role in separate to the newly synthesized and recovered proteins and lipids from the ER and transport them to their final destinations (3). The Golgi performs post-translational modification of proteins and also produces enzymes of the lysosome, an important organelle. Enzymes in cisterna perform glycolysis and phosphorylation processes of proteins as post-translational modification. Proteins are processed along with the Trans-Golgi network (2).

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In addition to protein modification and transport, the Golgi actively regulates mitotic entry, cytoskeletal organization, and apoptosis. The Golgi serves as a signaling platform for several cellular functions, including signaling initiated by receptors in this plasma membrane (1). It also mediates autophagy and protects the ER and axonal homeostasis (4). The Golgi promotes axon development and is thought to play a role in dendrite development (6).

3. STRUCTURE OF GOLGI

The Golgi consists of cisterna stacks arranged in a polarized manner, connected by membrane tubules to form the Golgi ribbon located near the centrosome. The cisterna cluster is functionally divided into three regions: cis Golgi network, medial Golgi network and trans Golgi network (TGN) (1). Each section contains different enzymes that selectively modify proteins based on their location. Cisterns also carry the structural proteins needed for their repair.

Several glycosidases and glycosyltransferases are found in the lower portions of the Golgi and are in charge of produce glycoproteins and glycolipids. During proteolysis, lumenal proteinases cleave many secretory proteins in TGN. Microtubule organization and Golgi matrix proteins are required for the development of the Golgi ribbon. The centrosome-derived microtubules are moved along by cytosolic dynein to the (-) end of the microtubules. The Golgi stacks are then held nearby by Golgi-oriented microtubules, which facilitate tubular connections between them (5).

The centrosome dissolves and becomes dispersible during neuronal differentiation, allowthem for the formation of microtubules and the formation of appropriate axonal and neuronal morphology. The formation of microtubules involves folding, dimerization, and polymerization of alpha and beta-tubulins. Tubulin-binding cofactors are supplemented with five tubule-specific chaperones known as TBCA-TBCE in the final stages of this complex process (6).

COP I coated vesicles bud in the ER-Golgi interstices or Golgi. COP II coated vesicles are vesicles budding from the ER and responsible for carry towards the Golgi.

4. PROTEINS OF GOLGI

The Golgi proteins can be divided into various protein classes such as structural proteins, cytoskeletal proteins, and molecular motor proteins. Golgi structural proteins are helical-coil proteins that have been expanded to form a proteinaceous matrix around the Golgi. Their dismantlement causes a structural change in the Golgi. Golgi Reassembly Stacking Proteins (GRASPs), golgins, kinases, phosphatases, ubiquitin E3 ligases, and deubiquitinases have all been identified as proteins with different functions in preserve the Golgi structure and regulate the Golgi function (5). Golgins are proteins found in the Golgi that form a matrix that aids in the maintenance of the organelle's structure. Golgins are also involved in vesicle transport regulation.

4.1. Structural Proteins of the Golgi

Golgi Reassembly Stacking Proteins (GRASP65 and GARSP55) have been shown to form tubular connections between Golgi stacks and contribute to trafficking order (6). GRASP65 belongs to the cis-Golgi region, whereas GRASP55 belongs to the medial / trans-Golgi (TGN) region. These two proteins form homodimers in their areas. Dimers act as an adhesive between cisterns, oligomerized, allowing them to stay together (5).

4.2. Metabolic Proteins of the Golgi

One of the Brain Imaging and Cognitive Disorders (BICD) genes, BICD2 gene, encodes the Bicaudal D2 protein, which is classified as a golgin due to its interaction with the Golgi small GTPase RAB6A. BICD2 activates the protein by binding to the dynein complex and ensures that it binds to the substances to be transported.

Sterol regulatory element-binding proteins (SREBPs) are lipid biosynthesis regulators. SREBPs are an example of a protein whose function is dependent on ER-regulated transport but does not directly affect ER or Golgi function. When cholesterol levels are low, COPII vesicles transport SREBP from the ER to the Golgi. SREBP can then be cleaved by Golgi-specific proteases. As a result, an N-terminal portion is released, which enters the nucleus and activates transcription of genes involved in cholesterol uptake and synthesis. Therefore, the Golgi is critical for the SREBP pathway (7).

4.3. Trafficking Proteins of the Golgi

Sacsin Molecular Chaperone (SAC), SAC1 is also in charge of ER and the Golgi trafficking. SAC1, unlike SREBPs, has a significant impact on the regulation of ER-Golgi localization and Golgi trafficking. Phosphatidylinositol-4-phosphate (PtdIns / 4 P) is essential for trafficking between the Golgi and the plasma membrane. On the cytosolic surface of the trans-Golgi, PtdIns / 4 P is excessive. The PtdIns / 4P binding protein functions in non-vesicular lipid transport (7). Therefore, SAC1 phosphorylates PtdIns / 4P to produce phosphatidylinositol. In cells without growth factors, SAC1 oligomerizes and provides trafficking from ER to the Golgi through the PtdIns / 4P. It activates the p38 / MAPK pathway in the presence of growth factors, allow the separation of SAC1 oligomers and SAC1 to transport the substance to the ER via COPI. This increases PtdIns / 4 P in the Golgi, causes substances to be transported from the Golgi to the plasma membrane (7).

Golgi Phosphoprotein 3 (GOLPH3L), which is found only in vertebrate salivary glands, small intestines, and skin tissues, is a phosphoprotein with multiple alternative phosphorylation sites. GOLPH3 is a peripheral membrane protein that regulates vesicle budding and membrane traffic from the TGN to the plasma. GOLPH3 binds to phosphatidylinositol 4-phosphate (PI4P), which causes it to be localized to the TGN. GOLPH3 dissociates from TGN when PI4P is depleted. GOLPH3 also binds to Myosin XVIIIA (MYO18A), an actin-based motor

protein, to connect the Golgi membranes to the actin cytoskeleton. This bridging effect generates the necessary tension for vesicle budding, trafficking, and the Golgi ribbon maintenance. Tensile force is lost when GOLPH3 or MYO18A levels are low, that leads to the Golgi strip to shrink and the number of vesicles formed in the TGN to decrease. The GOLPH3 complex is thought to be a hub for the regulation of the Golgi. It is known that GOLPH3 and MYO18A can cause cancer which is involved in the transport of substances between the Golgi and the plasma membrane. GOLPH3 degradation results in impaired phosphorylation of Protein kinase B (AKT). Similarly, over-expression of GOLPH3 stimulates enhanced protein phosphorylation. In breast cancer, overexpression of AKT and GOLPH3 decreases transcriptional activity and boosts cell proliferation through increase phosphorylation of AKT's substrate Forkhead box O (FOXO1) (7). The GOLPH3 complex is crucial for cellular responsiveness.

5. THE GOLGI AND STRESS

The Golgi is a crucial organelle for cellular homeostasis. Unstable membrane flow, altered microtubule dynamics, and incorrect modifications of proteins, which are the mechanisms that cause the Golgi fragmentation and dysfunction, can also cause stress in the Golgi (8). The Golgi stress response is an autoregulation system. The Golgi has been associated with numerous signaling molecules. Because of this, it has been proposed that the Golgi can recognize and send stress signals, act as a hub in the cellular signaling network (9). When the synthesis of the secretory and membrane proteins is more than the Golgi capacity, it cannot be modified or transported due to the insufficiency of the Golgi function (10). This situation causes stress in the Golgi. To cope with this stress, cells also activate some homeostatic mechanisms to increase the capacity of the Golgi in response to cellular needs (11). The most common response of the Golgi to stress is the Golgi fragmentation. The Golgi fragmentation occurs by various mechanisms.

One of the response mechanisms that cause stress breakdown is apoptosis. The morphology changes seen in the Golgi in cells exposed to stress may be the result of ongoing apoptosis or cause apoptosis. Examples are death receptor endocytosis and the Golgi disruption in the organellar response to apoptotic initiation. Some Golgi proteins have also been shown to regulate apoptosis (12).

5.1. Stress Responses of the Golgi

The Golgi stress response's mechanism is still being fully described. However, the Golgi responds to the stress that occurs in the cell through some mechanisms. These include apoptosis and overexpression or underproduction of certain proteins. Some studies have shown that some Golgi proteins have a role as stress agents.

When the GOLPH3 protein is phosphorylated, it is localized to TGN. Through its interactions with the retromer complex and activation of the mTOR inhibitor rapamycin, which boosts cell proliferation and size, GOLPH3 has been demonstrated to regulate cell proliferation. This DNA damage can abnormally increase the tensile strength for the Golgi fragmentation (12). It is well known that many cancers have excessive GOLPH3 expression. Cancer cells become more susceptible to substances that cause DNA damage when GOLPH3 levels are reduced, indicates that the Golgi fragmentation caused by GOLPH3 phosphorylation may act as a protective mechanism (13). In reaction to the stress brought on by oxygen-glucose deprivation, GOLPH3 encourages cell autophagy (14).

Stress responses caused by oxidative or intracellular damage can cause the Golgi fragmentation. Golgin-160 is the substrate for Caspase 2 found in Golgi membranes. Under stress conditions, Golgin-160 is impaired and may contribute to the stress response pathway by inducing gene expression (15).

In one study, the finding of decreased cell adhesion and migration with GRASP depletion from the Golgi adhesion proteins reinforces the essential role of the Golgi agglomeration in protein traffic, modification, and signaling. Under stress conditions, GRASP proteins also function as membrane bonds outside of the Golgi. GRASP proteins increase during substance exchange and under autophagy stress conditions. It suggests that GRASP55 may function as a stress sensor and an effector in the stress response due to its emerging roles as an energy sensor in the Golgi and a membrane thread in autophagy (16).

During apoptosis, caspase-3 and caspase-8 break the p115 protein. When p115 develops caspase resistance, it slows down the process of the Golgi fragmentation, which results from apoptosis, especially in cancer cells (12).

The Sun et al. study claims that, Soluble NSF Attachment Protein Receptor (SNARE) GS28, one of the other proteins of the Golgi causes apoptosis induced by cisplatin depending on p53 (17) According to this mechanism, overexpression of GS28 causes pro-apoptotic phosphorylation of p53. The cell stimulated by phosphorylation also becomes sensitive to cisplatin, which is an apoptosis inducer. Thus, GS28 controls apoptosis by regulate to the pro-apoptotic phosphorylation of p53.

It has been suggested that the ubiquitin-proteasome system also contributes to the Golgi autoregulation in addition to proteins. According to the study, Eisenberg-Lerner A and co-workers showed that the proteasome-mediated the Golgi cleavage is actively regulated and this degradation can be reversed. They showed that the Golgi can provide a signal to initiate apoptosis through C/EBP-homologous protein (CHOP) activation as an alternative response to stress (18).

When we consider the signal pathways mentioned earlier, some mechanisms attract attention. When we look at the molecular process, to identify the stress factor that happens in the Golgi, a sensor molecule, a transcription factor, and target genes produce Golgi-related proteins such as glycosylation enzymes are required (11). When the sensors are activated, down-regulation transcription factors cause transcriptional induction of the Golgi-related genes. This situation causes transcription factors such as Transcription

factor E3 (TFE3), cAMP response element-binding protein (CREB), and the genes related to Heat shock protein 47 (HSP47), and the Golgi that they affect to be directed towards the Golgi expansion and eventually apoptosis (19). Signal pathways and their responses are shown in Figure 1.

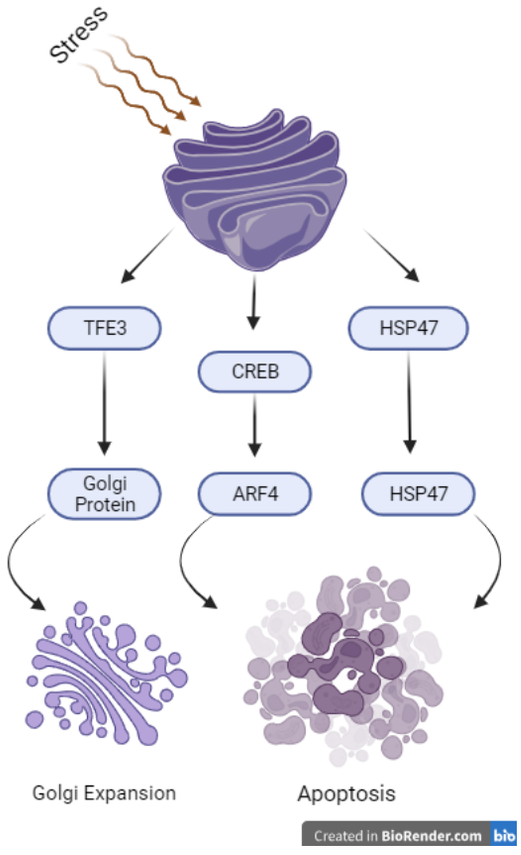

Figure 1. *Golgi-related signal pathways and their stres response. Transcription factor E3 (TFE3), cAMP response element – binding protein (CREB), Heat shock protein 47 (HSP47), ADP-ribosylation factor 4 (ARF4).*

There are studies examine TFE3, proteoglycan, CREB3, and HSP47 signaling pathways in terms of shadow.

5.1.1. TFE3 Signal Pathway

The TFE3 pathway improves the overall function of the Golgi. The TFE3 pathway has the Golgi structural proteins as target genes. TFE3 is phosphorylated at Ser108 and captured in the cytoplasm in properly expanding cells. TFE3 is dephosphorylated at Ser108 in response to the Golgi stress, which displaces the nucleus and stimulates transcription from Golgi stress response element (GASE) (11). TFE3 expression increases in the Golgi stress. Subsequently, in its promoters, the Golgi activates GASE expression, one of the stress response elements (20). According to one study, the Golgi expansion was noted along with the TFE3 pathway's impact on teh Golgi proteins as a second stress response after receive the signal (19).

5.1.2. CREB3 Signal Pathway

In a study examining Brefeldin A (BFA) and Granacalsin (GCA), which cause the Golgi to become stressed and lose its function, CREB was determined as another signal pathway (21). BFA causes the Golgi stress-induced apoptosis. BFA is used to enable the CREB3 path. BFA has been referred to as an anti-virus agent that prevents tiny G proteins like ADP-ribosylation factors **(**ARFs) from functioning (19). They identified these proteins in a study they conducted using Chronic Myeloid Leukemia Cells. They discovered that ARF4 is the gene impacted by Brefeldin A (BFA) on the CREB pathway (22). It has been noted that the Golgi-induced apoptosis is also decreased when ARF4 expression is inhibited by RNA interference. Death receptor 4 (DR4) and Trafficking Protein Particle Complex Subunit 13 (TRAPPC13) are two of the CREB3 pathway's target genes. While TRAPPC13 is a part of a TRAPP III complex that regulates autophagy flux under specific stress conditions, DR4 encodes a death receptor that governs cell death brought on by the Golgi stress (21).

5.1.3. HSP47 Signal Pathway

The target gene for the HSP47 pathway is HSP47, which is responsible for collagen folding in the ER. According to studies, collagen dynamics contribute to the Golgi stress-induced cell death. Treatment with BG (BenzylGalNAc), a glycosylation inhibitor, activates the HSP47 pathway (23). This pathway regulates the Golgi-induced apoptosis. In a study with BG in 2013, HSP47 was inhibited by RNA interference. As a result, the Golgi was fragmented and this caused apoptosis activation (23). In a study conducted on this study in 2017, they reported that BG-induced apoptosis decreased when the HSP47 pathway was overexpressed (19). Despite studies, the sensors, transcription factors, and enhancers that regulate the HSP47 pathways have not been clarified.

5.1.4. Proteoglycan Signal Pathway

Glycoproteins called proteoglycans are present in a variety of tissues, including cartilage (21). Glycosyltransferases are among the proteoglycan pathway's target genes, and they are all necessary for proteoglycan-type glycosylation. Syndecan 2 (SDC2) is the core protein of a proteoglycan. Overexpression of this protein can induce a deficiency in glycosylation enzymes that cause the Golgi stress due to proteoglycans (11).

Despite all of these research findings, the basic processes controll the Golgi morphology in stress response remain unknown. More research is required, particularly on signaling pathways. Even though the Golgi structure is changeable, it is carefully regulated. Mammalian cells rapidly deconstruct the Golgi's composition and function during the cell cycle and recombined (12) and may be impaired under stress conditions and pathological conditions such as DNA damage, energy/nutrient deprivation, and pro-apoptotic conditions.

6. DISEASES CAUSE BY THE GOLGI

The unbalanced membrane flow observed in the Golgi, altered microtubule dynamics, the modification of the Golgi structural proteins, and the proteolytic cleavage are the fragmentation mechanisms of the Golgi. Dysfunctions resulting from the breakdown of the Golgi structure have been observed in neurodegenerative diseases, some pathogen-borne diseases, and cancer. The fragmentation of the Golgi was first described in Amyotrofik lateral skleroz **(**ALS) patients' motor neurons (4). The loss of the Golgi organization is a common feature of many neurodegenerative diseases. Mutations in the appropriate code genes may cause the Golgi to become dysfunctional (1).

Unlike Somatic Golgi, the Golgi in Neurons creates "Golgi exit points" that allow local trafficking in neurites localized in axons and dendrites. Axonal transport is a type of neuronal transport that allows a substance to be transported between cellular proteins and vesicles in the axon, either towards or away from the cell (4).

There are also studies on the Golgi' effects on SARS-CoV-2 virus infection and COVID-19 disease.

6.1. Cancer

The Golgi, mitochondria, lysosomes, and ER organelles have many roles in cancer onset or progression. The Golgi is associated with protein/lipid synthesis and transfer. Additionally, it is crucial for tumor development, medication resistance, cancer metastasis, and immune evasion (25). Irregularities in the Golgi such as abnormal glycosylation, irregularity of kinases, and hyperactivation of myosin motor proteins may be related to cancer metastasis. Overactivation of the Rabs, work with golgins in protein transport and the Golgi building care, has been observed in a variety of cancer. Tumor cells were discovered to have elevated levels of kinases connected with the Golgi disorganization (5).

In some cancer genome studies, the GOLPH3, MYO18A and phosphatidylinositol transfer protein cytoplasmic 1 **(**PITPNC1) genes found in the Golgi have been commonly described as cancer-leading factors. GOLPH3, which is in charge of vesicle transport, creates a pull force for trafficking in cells (26). Any situation that affects the GOLPH3 function may cause disruption or even cessation of trafficking. This situation may cause even cancer formation.

High levels of GOLPH3, the first of the genes, are linked to a poor prognosis in numerous malignancies. GOLPH3 causes oncogenic transformation as a result of an increased expression, according to research on genes that frequently reproduce in cancer. GOLPH3 degradation affects transformation in the reverse direction, according to cell culture studies. The number of replicas of the GOLPH3 gene was found to be increased in 56% of lung carcinomas, 37% of prostate carcinomas, 32% of breast carcinomas, 33% of pancreatic carcinomas, 24% of colon carcinomas, and 37% of ovarian carcinomas (26). Another gene related to the Golgi MYO18A was shown to be one of the cancer-cause genes in a research of somatic copy alterations and gene expressions in the exploration of the causes of breast cancer. 11% of metastatic breast tumors and 21% of prostate cancers were discovered to have highly expressed MYO18A genes. The high expression of the PITPNC1 gene in breast cancer causes cancer cell migration and metastasis (26). It was observed that tumor formation increased as a result of PTEN destruction, which is responsible for the trafficking. PTEN-regulated alternative splicing (AS) irregularity is thought to be linked to cancer (27).

In another study, over-expression of GOLPH3, which is involved in the trafficking, leads to increased phosphorylation of AKT. GOLPH3 often replicates in various types of solid tumors such as melanoma, lung cancer, breast cancer, glioma, and colorectal cancer. GOLPH3 overexpression is linked to prognosis in a variety of tumor types, including 52% of breast tumors and 53% of glioblastomas (28). GOLPH3 roles in tumor formation may correlate with a variety of cellular activities including:

Contributing to malignant secretory phenotypes by regulating the Golgi-plasma membrane traffic.

Increasing glycosylation of cancer-related glycoproteins or controlling the recycling of key signal molecules.

It affects the genomic stability and responsiveness to DNA damage.

It demonstrates that GOLPH3 overexpression in these cancer types can be used as a positive biomarker for tumor progression and poor survival (25).

The Golgi fragmentation is thought to promote cell proliferation in breast cancer by decreasing transcription activity (6).

One of the most significant causes of cancer cell formation and spread is DNA damage. Excess GOLPH3 expression increases cancer cell survival in the presence of DNA damage (26).

6.2. Alzheimer's Disease (AD)

Alzheimer's Disease is a central nervous system disease, characterized by progressive memory loss. Structural changes, such as fragmentation of the Golgi, represent an early preclinical feature of various neurodegenerative diseases, including Amyotrophic Lateral Sclerosis, Alzheimer's and Creutzfeld-Jacob diseases, spinocerebellar ataxia type 2. Since the earliest stages of the development of the disease, fragmentation, and distribution of the Golgi have been observed in the neurons of those with Alzheimer's disease. Phosphorylation of GRASP65, one of the Golgi proteins, is known to cause Alzheimer's (2).

One of the effect hypotheses of the Golgi cleavage on AD is the accumulation of neurofibrillary tangles (NFT) in the neuron cells when the corrective protein Tau is phosphorylated. A small proportion of early Alzheimer's cases bind to mutations of Amyloid Precursor Protein (APP) or Presenilin proteins. Besides, more than 20 genes involved in lipid metabolism, inflammatory response, and endocytosis are risk factors for late AD (1).

Although there are still uncertainties about Alzheimer's causes, there are some hypotheses when looking at the causes at the cell level. One of them is the accumulation of neurofibrillary tangle (NFT) in the cell as a result of hyperphosphorylation of Tau, which is involved in the regulation of microtubules.

In many pathological studies, it is argued that the biggest reason for Alzheimer's is the accumulation of Ab peptides. The amyloid cascade hypothesis has also been studied in recent years for its effect on Alzheimer's disease. This theory is characterized by the accumulation of extracellular b – amyloid peptides (Ab) outside the cell caused by abnormal APP folding. Various studies based on this hypothesis prove its accuracy. The type I membrane protein APP, which is synthesized in the ER, is cleaved to produce the Ab peptide. This formed peptide is localized with in trans-Golgi network (TGN) after passing via the exocytic and endocytic processes. It has been demonstrated that peptide increased production is directly involved in a neurodegenerative cascade that results in synaptic dysfunction and neuronal death.

Ab can induce activation of the cyclin-dependent kinase 5 (CDK5), a serine/threonine kinase that is vital for neuronal function and causes the Golgi degradation as a result of its excess phosphorylation. In this case, it causes many neurodegenerative diseases, especially Alzheimer's (1). Ab effects are shown in Figure 2.

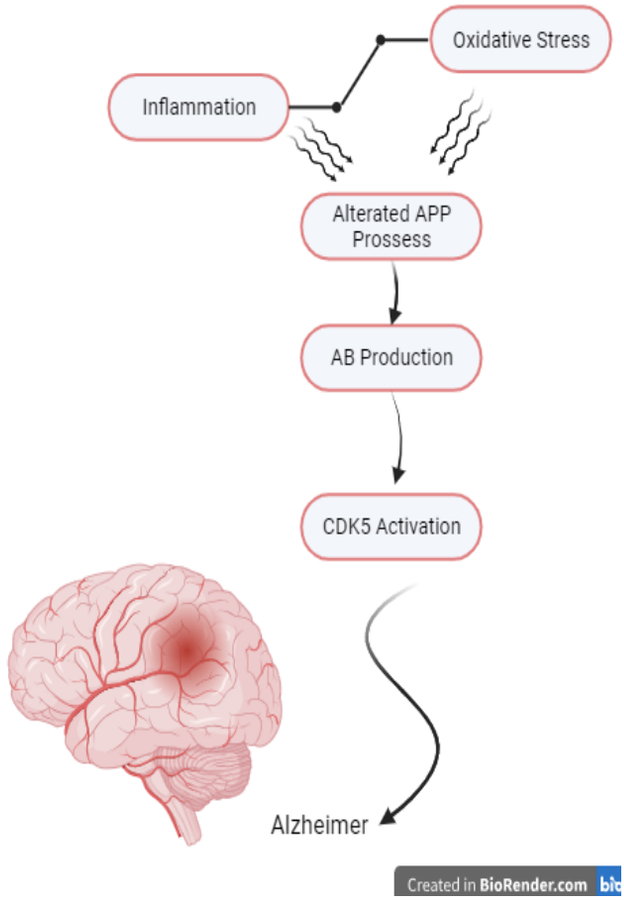

Figure 2. *Ab effects in Alzheimer's. Amyloid Precursor Protein (APP), b-amyloid peptides (Ab), cyclin-dependent kinase 5 (CDK5).*

6.3. Amyotrophic Lateral Sclerosis (ALS)

Motor neurons in the spinal cord, brainstem, and cerebral cortex gradually degenerate in Amyotrophic Lateral Sclerosis (ALS), a fatal neurological condition. Degradation of motor axons and loss of neuromuscular synapses leads to progressive muscle weakness and denervation of skeletal muscle fibers that cause paralysis and usually become fatal when reaching critical muscle groups 2-5 years after disease onset. Although the cause of ALS is uncertain, the disintegration of the Golgi has been detected in ALS patients' motor neurons and cellular disease models. More than 20 gene mutations, including superoxide dismutase (SOD1), and chromosome 9 open reading frame 72 (C9ORF72), may be related to ALS (6). The Golgi fragmentation and SOD1 or optineurin mutations have been defined in ALS patients (4). Mutations in the SOD1 gene form part of ALS forms. These forms are among the most frequently used ALS animal and disease models. As a result of the SOD1 mutation, unstable microtubules are observed (6).

Another known mutation is at the tubulin gene Tubulin Alpha 4a (TUBA4A), which encodes the adult spinal cord and the major alpha-tubulin isoform of the brain in rare forms of ALS. In vitro overexpression of various ALS-induced TUBA4A mutations causes serious changes in the somatic microtubule network. Varioustypes of human ALS and SMA result from mutations in a protein called Dynein, its regulator BICD2 or Optineurin, and mediate vesicle transport in the secretion pathway (6).

6.4. Spinal Muscle Atrophy (SMA)

SMA is a disease characterized by muscle weakness and degeneration of spinal motor neurons. This autosomal recessively inherited disease is caused by a mutation caused by the deletion of the Survival Motor Neuron (SMN) gene. It was observed that BICD2 mutation was inherited as an autosomal dominant form. The BICD2 gene synthesizes the Bicadual D2 protein found in the Golgi. 70% of the factors that cause autosomal dominant SMA are still unknown (2).

The typical SMA caused by the loss of the SMN (Survival Motor Neuron) gene may potentially be caused by a disruption of the communication between microtubules and COP I vesicles. Elevated Stathmin-1 levels are linked to microtubule degradation, axon degradation, and loss of neuromuscular connections In SMA cellular models. Besides, SMN has been shown to connect the COP I subunit to the a-COP and cooperate with the second trafficking on the motor axons. Interruption of SMN / a-COP interaction causes SMN to accumulate in the Golgi and decreased neurite enlargement. Therefore, the Golgi is assumed to be cleaved in SMA mice and patients with SMA / COPI / microtubule dysfunction (6).

6.5. COVID-19

The SARS-CoV-2 virus shows the single-stranded, positive-sense RNA genome; with four structural protein-coding

genes at the 3' end: spike (S), membrane (M), envelope (E), and nucleocapsid (N). Unlike S, the E protein of SARS-CoV-2 has not yet been extensively studied (29). Envelope (E) protein of SARS-CoV-2 is the least-studied protein type. The E protein is a key factor in ER-Golgi localization by affecting the intracellular activities of the host via the C-terminal end area, which is predicted to have a b-coil-b structure leading to its localization in the endoplasmic reticulum, the Golgi, and ER-Golgi space. has been proven. The outcome of a research, a significant difference was observed in the amino acid sequence at the C-terminal end of the E protein. The study's findings revealed that mutations in the region where the Golgi originated and played a crucial function during infection at the C-terminal end of the E protein. These results require more studies on the protein (30). One of the most prominent changes in cells infected with SARS-CoV-2 was the proliferation of the Golgi and related vesicles, as well as the expansion of Golgi sacs. In the study, they observed that particles filled with virions derived from the Golgi in virus-infected cells budded in the cytoplasm (31). It was shown that the majority of genes taken from the SARS-CoV-infected 2B4 cell line caused hyperactivation of the immune system, stimulation of signaling pathways, and subsequently cytokine storm. Phosphatase and tensin homolog (PTEN), which also strongly affects the Golgi, essential function in the activation of dendritic cells, B and T cells that cooperate with genes in cytokine storm in COVID-19 patients, and in the secretion of pro-inflammatory cytokines (32). Considering the studies carried out, we can think that SARS-CoV-2 affects the Golgi in the host cells they infect, it may also cause a change in morphology, and the organelle may undergo stress and cause different cellular responses. More recently, organelle-oriented treatments suggest that detailed studies will apply to COVID-19 disease.

7. TREATMENT APPROACHES IN THE GOLGI FRAGMENTATION

The Golgi, which plays an important role in the formation and maintenance of cellular integrity, is also crucial in disease treatment. As a treatment method, it is an important strategy to target the fragmentation of the Golgi in damaged cells. Small molecules act as inhibitors are known to target the components of the Golgi with different mechanisms of action. Some of these molecules affect the main regulators of the Golgi (such as GTPase, ARF, and PI4KIIIb); others inhibit the Golgi enzymes related to glycosylation or lipid transfer proteins (3). Brefeldin A (BFA), an inhibitor of ARF activation, is a fungal toxin that disrupts the structure of the Golgi. Glycosylation is the most common posttranslational modification. It is thought that inhibition of O-glycan synthesis, which provides the addition of oligosaccharides, may be useful for cancer treatment (3).

The first glycosyltransferase that changes ceramide into the universal precursor of all glycolipid species is glucosyl ceramide (GlcCer) synthase, which is in charge of create glycolipids. Clinically, GlcCer synthase inhibitors are used for substrate reduction therapy (SRT) in the treatment of hepatosplenomegaly, anemia, and thrombocytopenia brought on by the buildup of GlcCer. Currently, substrate reduction therapy (SRT) and enzyme replacement therapy (ERT) are being employed as treatments. In conjunction with ERT, the enzyme is ingested by macrophages and aids in the disintegration of accumulated GlcCer. SRT decreases the quantity of GlcCer by preventing GlcCer Synthase from synthesize it (3).

Inhibitory treatments planned to be used in Alzheimer's disease are still under investigation. GRASP65 is a caspase-3 substrate, which plays a role in the formation of Golgide protein cisterna stacks and the bonding of these stacks invertebrate organisms, and damage to this protein causes the Golgi fragmentation. Concerning this, it is thought that the Golgi integrity can be achieved with GRASP65 in model cell lines and that the modulation of GRASP65 will be therapeutically useful in prevent the expression of non-phosphorylated mutants (33).

Depletion of the Golgi structural proteins GRASP65 and GRASP55 reduces the level of a5b1 integrin. As a result of decreasing this integrin level, adhesion, migration, and invasion of HeLa cells and breast cancer decrease (34). According to this information, molecular treatment methods that can provide the formation or destruction of GRASP65 and GRASP55 proteins in cancer cells should be considered.

Many studies have shown that specific degradation of GOLPH3 returns cancer phenotypes and overexpression of GOLPH3 leads cancer to metastasis in cell culture. It is advised to consider the possibilities of GOLPH3 complex inhibition as a cancer treatment strategy. PITPNC1 is localized in the Golgi and its collapse results in the Golgi's compression, which disrupts the function of the GOLPH3 complex. Besides, knockout of PITPNC1 has previously led to impaired migration, invasion, and metastasis of aggressive breast and colorectal cancer cell lines. The Golgi PtdIns (4) Drugs target the P / GOLPH3 complex will represent a new therapeutic approach based on all available treatment approaches for cancer (26).

The tumor suppressor PTEN acts as a lipid and protein phosphatase. For the treatment of malignancies caused by PTEN loss, it is believed that the Golgi secretion inhibitors, either alone or in conjunction with PI3K/Akt kinase inhibitors, may be therapeutically beneficial (27).

In a study for the treatment of stomach cancer, M-COPA (2-methylcopropilinamide), which causes the Golgi breakdown in cancer cells, was used. M-COPA downregulates cell surface expression, inhibiting the development of gastric tumors that overexpress RTKs such the MET receptor for hepatocyte growth factor (35).

The majority of cancer-related deaths occur from lung cancer, and the five-year survival rate is also relatively low. Non-small cell lung cancer (NSCLC) develops resistance to platinum-based conventional chemotherapy, which is among the causes of this poor prognosis. In one of the studies,

Epidermal growth factor receptor (EGFR) – tyrosine kinase inhibitors (EGFR-TKI) were used to increase survival. These inhibitors have been shown to improve survival in people with non-small cell lung cancer (NSCLC) who have EGFR activate mutations. On the other side, it has been discovered that the disease gives resistance to chemotherapy. As an advanced study, M-COPA, previously used in the treatment of stomach cancer, was used in this study for this resistance. The M-COPA EGFR targeting the Golgi prevented the transport of the protein to the cell surface and proved to show an antitumor effect in resistant cells (35). This study also provides pre-clinical evidence for the treatment of resistant cells.

Because of the adhering studies, we can say that many treatment methods can be done by affecting the Golgi. For the treatment of a variety of diseases, medications that target the Golgi resident proteins are now in the clinical trial phase. Studies targeting the Golgi have been reported to continue the development of novel methods for delivering drugs, such as cell-penetrating peptides or nanoparticles, by minimizing side effects.

8. CONCLUSION

This article discusses the significance of the Golgi in the cell, its function, its responses to stress, and the diseases it causes are examined. Consequently, the Golgi is a central organelle and a key point in cell organization for the modification of proteins. The Golgi reacts to stress, which can cause fragmentation and even cell apoptosis or rescue the cell. Due to mutations that occur in the Golgi, they can also cause cancer, especially neurodegenerative diseases. Since the mutations that occur in the Golgi fragmentation, there are treatment studies on this subject. However, some difficulties observed in the treatment development are increasing the target's specificity and overcoming the cell membrane barrier.

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