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# Golgi ribbon disassembly during mitosis, differentiation and disease progression

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## Abstract

The Golgi apparatus is tightly integrated into the cellular system where it plays essential roles required for a variety of cellular processes. Its vital functions include not only processing and sorting of proteins and lipids, but also serving as a signaling hub and a microtubule-organizing center. Golgi stacks in mammalian cells are interconnected into a compact ribbon in the perinuclear region. However, the ribbon can undergo distinct disassembly processes that reflect the cellular state or environmental demands and stress. For instance, its most dramatic change takes place in mitosis when the ribbon is efficiently disassembled into vesicles through a combination of ribbon unlinking, cisternal unstacking and vesiculation. Furthermore, the ribbon can also be detached and positioned at specific cellular locations to gain additional functionalities during differentiation, or fragmented to different degrees along disease progression or upon cell death. Here, we describe the major morphological alterations of Golgi ribbon disassembly under physiological and pathological conditions and discuss the underlying mechanisms that drive these changes.

## Structure and function of the Golgi apparatus

The Golgi apparatus is a key membrane-bound organelle in the secretory pathway that is essential for all eukaryotic cells. The morphology of the Golgi is highly conserved and is featured by the densely packed cisternae that are layered on top of each other to form stacks [1]. Despite similar appearance, each individual cisterna houses a specific set of enzymes and represents a functionally distinct reaction chamber for processing incoming substrates [2]. Upon export from the endoplasmic reticulum, the newly synthesized proteins arrive at the *cis*-Golgi network (CGN) and take on their journey through individual cisternae of the stacks [3]. On their way from *cis* to *medial* to *trans* cisternae, the cargo proteins undergo various types of post-translational modifications including glycosylation, phosphorylation,

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sulfation, acetylation, methylation and proteolytic cleavage [4]. The molecules then exit the stacked cisternae at the *trans*-Golgi network (TGN), where they are sorted into specific vesicles and delivered to their final destinations such as the endosomal-lysosomal compartments, the cell surface, or the extracellular space. In this sense, the Golgi serves as a processing and sorting station for proteins and lipids in the biosynthetic pathway. This role is shared among all eukaryotes and is carried out in most cases by stacked cisternae [5].

Although a single stack or even unstacked cisternae are sufficient to sustain secretion in simple protozoa and budding yeast, most organisms contain multiple stacks that are distributed throughout the cell [6,7]. Uniquely to mammals, the stacks are further connected by tubular membranes into an elongated, twisted, but continuous structure named the Golgi ribbon. The interconnection of stacks is not strictly required for the secretory function of the Golgi, since disrupting the ribbon into discrete mini-stacks by microtubule depolymerization does not prevent cargo trafficking to the cell surface. However, transport kinetics is reduced in the initial phase but resumed to normal level at later stages [8], indicating that mini-stacks need to be fully dispersed and matured to become transport-competent [9].

Though dispensable for secretion, the ribbon organization greatly expands the functional repertoire of the Golgi in mammalian cells. The homotypic connections between adjacent cisternae of the stacks enlarge the membrane compartment such that large cargos as collagen can be readily accommodated [10,11*]. Similarly, a continuous ribbon allows proper packing of the von Willebrand factor into larger Weibel-Palade bodies, which impacts platelet aggregation [12**,13]. Furthermore, by laterally linking stacks, the Golgi apparatus is consolidated into one single entity that in most cases is asymmetrically positioned in the juxtanuclear region and in close proximity to centrosomes, the primary microtubule-organizing center (MTOC) in proliferating cells [6]. This confined pericentriolar localization of the ribbon plays an important role in establishing and maintaining cell polarity. The orientation of the ribbon guides membrane traffic towards a particular area of the plasma membrane, which lays the cornerstones for many polarization events in mammalian cells, such as neurite outgrowth [14], epithelial polarization [15] and directional cell migration [16–18]. In addition to these secretory and polarity functions, the Golgi has emerged as a versatile platform that supports a broad range of cellular processes. The Golgi can actively modulate the microtubule network [19,20], forms a hub for a variety of signaling pathways [21–24] and participates in the regulation of calcium and pH homeostasis [25], stress response [26,27], apoptosis [28] and autophagy [29,30**].

## Golgi ribbon and the microtubule network

In proliferating cells, the structural integrity and the perinuclear positioning of the Golgi ribbon are tightly coordinated with the microtubule cytoskeleton and depend on the minus end-directed motor dynein. Disruption of the microtubule network with nocodazole or inhibition of dynein function at the Golgi disperses the ribbon into mini-stacks that are scattered throughout the cytoplasm [31–33]. Upon removal of nocodazole, microtubules regrow from Golgi membranes in addition to the centrosomes, exemplifying the function of the Golgi as an MTOC [34–36]. Two distinct microtubule networks originating from the centrosomes and the Golgi contribute to build a pericentriolar ribbon in cycling interphase

cells [37]. In support of microtubule growth from the Golgi, the core component and modulators of the microtubule-nucleating y-tubulin ring complexes (γ-TuRCs), including γ-tubulin, AKAP450, Cdk5Rap2 and myomegalin, have been found localized to Golgi membranes where they collaborate to initiate microtubule nucleation [38–40,20]. Moreover, microtubule-associated proteins (MAPs), such as the minus-end binding protein CAMSAP2 and the plus-end tracking proteins CLASPs that recruits the microtubule-crosslinking protein MTCL1 to the Golgi, also help anchor and stabilize Golgi-derived microtubules and thus contribute to Golgi organization and function [36,41,42*].

The unique architecture and organization of the Golgi ribbon best exemplifies the hierarchical assembly of the cellular organelles [5]. Interestingly, this also implies that distinct mechanisms must be in place to disintegrate a larger structure such as the Golgi ribbon into its simpler units (stacks, cisternae, vesicles). These steps can occur simultaneously or independently, thus giving rise to different degrees of disassembly or fragmentation phenotypes. In many cases, disintegration of the Golgi ribbon also accompanies the rearrangement of the microtubule network. Below we describe the major morphological transformations during physiological processes including ribbon disassembly in mitosis and structural variations upon differentiation, as well as fragmentation under pathological conditions.

## Mitotic disassembly of the Golgi ribbon

Best characterized among the fragmentation processes are the mechanisms that drive the disassembly of the Golgi during mitosis when it is most extensive and complete [43–45]. Interestingly, mitotic Golgi disassembly is not common to all organisms [6]. In plants and yeast, the stacked cisternae stay intact and are fully functional in secretion throughout the entire cell cycle [46,47]. The reason why the Golgi is disassembled in animal mitosis has long been an open question [48]. The fact that Golgi stacks are interconnected into a continuous ribbon poses a challenge for mammalian cells to equally partition the organelle. Disassembly of the ribbon into vesicles thus helps to segregate the Golgi membranes into the daughter cells. Furthermore, the disassembly of the ribbon also controls mitotic progression and spindle dynamics [49,50*,51*]. This mutual regulation of Golgi inheritance and cell division ensures the propagation of a functional Golgi ribbon through successive generations [52].

Once committed to mitotic entry, mammalian cells rapidly remodel their cellular structures to prepare for division [53]. To this end, the continuous Golgi ribbon swiftly disassembles into a collection of tubular-vesicular membranes, which are then partitioned with the help of the spindle into the daughter cells where they reassemble into a Golgi ribbon [54–56] (Figure 1a). The morphological changes of the Golgi in early mitosis are referred to as mitotic Golgi disassembly or mitotic Golgi fragmentation and both terms are often used interchangeably. Here we use the term mitotic Golgi disassembly because Golgi fragmentation is also used for irreversible processes such as apoptosis or necrosis [57,26]. Mitotic Golgi disassembly constitutes a series of highly orchestrated actions that are coordinated with the reorganization of other cellular contents (Figure 1a). More specifically, it is a multi-step process achieved through a combination of ribbon unlinking, cisternal

unstacking, as well as tubulation and vesiculation of the Golgi membranes (Figure 1b) [43]. All these distinct mechanisms contribute to the rapid and drastic remodeling of mitotic Golgi membranes, though the extent of their interdependency and redundancy are not completely defined yet.

## Lateral unlinking: from the ribbon to stacks

Ribbon unlinking initiates Golgi disassembly in late G2 phase before cells commit to mitosis. At this step, the lateral connections between cisternae are severed and individual stacks are released [58]. Scission of the interconnecting tubules requires the membrane fission protein CtBP/BARS. Blocking its activity by microinjection of inhibitory antibodies or dominant negative mutant proteins interferes with G2/M transition, indicating that ribbon unlinking is an important first step in mitotic Golgi disassembly [59,60]. In parallel, mitotic entry is delayed when blocking the Golgi proteins GRASP65 and GRASP55 [61–64], which function as lateral tethers of adjacent stacks during ribbon formation [65]. Ribbon unlinking further depends on JNK2 to phosphorylate GRASP65 at Ser277 [66], the same site that is also phosphorylated by ERK in interphase and by Cdk1 during mitosis [62,64,16]. These results have led to a proposed Golgi-based G2/M checkpoint [61,60], although the precise surveillance cascade that halts mitotic entry remains to be determined. Recent studies have begun to shed light on the key players in this pathway. Failure in ribbon unlinking in G2 prevents activation of the Src kinase at the TGN. Consequently, the Aurora-A kinase fails to be recruited to the centrosomes and remains inactive. As active Aurora A is a prerequisite of centrosome maturation and spindle formation, mitotic entry is thus forfeited [67,68*].

Surprisingly, severing of the stacks in late G2 is also monitored in *Drosophila* S2 cells where the Golgi stacks are present in pairs but not interconnected into a centralized ribbon. Analogous to ribbon unlinking in mammalian cells, pairs of fly Golgi become separated in late G2, which is also required for the transition into mitosis [69]. Despite their resemblance, the two processes are driven by very distinct mechanisms. While stack separation in flies is caused by actin depolymerization, ribbon unlinking in mammals is mediated through GRASP65/55 and/or BARS [70].

In late G2 phase, the unlinked stacks remain concentrated in the perinuclear region of the mammalian cells [60]. Upon mitotic entry, when the interphase microtubules are rapidly dismantled and remodeled to form a bipolar spindle, the stacks begin to scatter. Proper dispersal of the Golgi requires the dissociation of the microtubule motor cytoplasmic dynein from its Golgi receptor golgin160 [33]. Concomitant with the dispersal, the cisternae further unstack and vesiculate, leading to the complete disassembly of the Golgi apparatus.

## Unstacking: from stacks to cisternae

Unstacking of cisternae in early mitosis is mediated through phosphorylation of GRASP65 and GRASP55, which were first identified as stacking factors that align cisternae into stacks [71,72]. Both GRASPs are homodimers that are attached via lipid modifications to the cytoplasmic face of the Golgi cisternae. During interphase, GRASP proteins assemble into antiparallel homo-tetramers *in trans*, which link apposing cisternae into stacks as well as laterally tether stacks within the ribbon [73,74]. Upon phosphorylation in early mitosis,

*trans*-oligomerization of GRASP proteins is reversed, causing cisternal unstacking [74,75]. GRASP65 is phosphorylated by Cdk1/cyclin B and Plk1 at multiple sites [76], while GRASP55 is a mitotic target of the MAP kinase ERK2 [74,77].

## Vesiculation: from cisternae to vesicles and tubules

Coinciding with unstacking, the membranes further disassemble into vesicles. Unstacking not only physically releases the cisternae, but also significantly speeds up vesiculation. The unstacked cisternae expose a larger surface area that becomes more accessible to recruit the components required for vesicle budding [78]. During interphase, budding and fusion of COPI transport vesicles at the Golgi are delicately balanced to maintain its function and morphology [79]. Upon entry into mitosis, phosphorylation of GM130 by Cdk1 prevents the vesicle tethering factor p115 from binding and thus blocks vesicle docking [80].

Furthermore, membrane fusion is also suppressed in mitosis [81]. Heterotypic fusion of vesicles with Golgi cisternae is inhibited via the ubiquitin E3 ligase HACE1 that monoubiquitinates the SNARE protein syntaxin 5 and thus prevents SNARE complex formation [82**]. In addition, homotypic fusion of Golgi membranes mediated by the AAA-ATPase p97 is also blocked upon mitotic phosphorylation of its adaptor proteins p47/VCIP135 and p37 [83–85]. In sum, vesicles continue to bud but fail to dock and fuse with cisternae, which quickly drives the equilibrium towards vesiculation [86].

Together, Golgi disassembly upon mitotic entry is facilitated through several processes that are driven by mechanistically distinct pathways to disassemble different parts of the Golgi [5]. Employing multiple mechanisms to drive disassembly makes this process extremely robust and efficient. In support of this notion, cells can still progress through mitosis when each individual process is blocked. These have been demonstrated by manipulating GRASP65 [62,74], p47 [85], BARS [60], syntaxin 5 ubiquitination [82**] or COPI vesicle budding [87].

The consequence of challenging such robustness in mitotic disassembly has been recently revealed. By filling the Golgi lumen with a unbreakable polymer that physically prevents its remodeling before progression into mitosis, cells could progress into M-phase with an intact Golgi, but strikingly centrosome separation is blocked [51*]. Accordingly, the cells fail to set up a bipolar spindle and become arrested with monoasters by an active spindle assembly checkpoint (SAC). This demonstrates that mitotic Golgi disassembly, just like spindle formation, is closely monitored by a signaling pathway that cross-talks with the SAC. Furthermore, upon disassembly the vesiculated Golgi membranes further participate in spindle formation. This is achieved by GM130 that binds and recruits importin α to the Golgi membranes [50*]. Sequestration of importin α relieves its inhibition on the spindle assembly factor TPX2, which in turn triggers microtubule nucleation in the vicinity of Golgi membranes. GM130 then captures the nascent microtubules and thus couples the Golgi membranes to the forming spindle. Collectively, mitotic Golgi disassembly not only passively serves a means to divide the organelle *per se* but also proactively mediates mitotic progression and spindle assembly.

## Morphological variations of the Golgi ribbon during differentiation

In contrast to extensive disassembly during cell division, the ribbon possesses relatively minor morphological variations upon differentiation. These structural alterations enable the Golgi to fulfill specialized functions in post-mitotic differentiated cells (Figure 2). In neurons, for example, Golgi stacks can be detached from the somatic ribbon and are frequently found in dendrites [88]. These dendritic Golgi outposts function as local secretion units for synaptic receptors as well as sites for microtubule nucleation, thus regulating dendritic outgrowth and branching (Figure 2b) [14,89,90]. Golgi outposts are not locally established by *de novo* formation within major dendrites. Instead, they are generated through deployment and fission of tubules that originate from the somatic Golgi ribbon. This process is regulated by a RhoA-ROCK signaling pathway that activates two Golgi-localized kinases, protein kinase D1 (PKD1) and LIM domain kinase 1 (LIMK1), to promote tubule fission [91*]. In addition to outposts, dendrites further contain Golgi satellites, which represent simplified secretory micro-compartments that, in contrast to Golgi outposts, are seemingly deprived of essential Golgi proteins functioning in sorting and structural organization [92]. Whether these secretory units are indeed Golgi elements derived from the somatic ribbon, their exact ultrastructure and how they relate to Golgi outposts await further clarification.

## Golgi ribbon fragmentation under pathological conditions

A fragmented Golgi ribbon is commonly associated with many stress and pathological conditions, including apoptosis [26,93], pathogen infection [94], amyotrophic lateral sclerosis (ALS) [95,96], Alzheimer's disease [97,98], Parkinson's disease [99,100] and various forms of cancer [101–103]. Despite similar phenotypic characteristics among these diseases, the mechanisms that cause Golgi fragmentation and dysfunction can range from imbalanced membrane flux, altered microtubule dynamics, to post-translational modifications or irreversible proteolytic cleavage of Golgi structural proteins. It is not clear whether the mechanisms that drive Golgi ribbon disassembly in mitosis or differentiation are also underpinning Golgi fragmentation during disease progression. In fact, the correlation between the observed morphological alterations and dysfunction of the Golgi is often unclear, as the fragmentation may directly cause, partially contribute to, or merely be the outcome of pathology.

In an effort to determine the contributions of Golgi fragmentation to neurodegenerative diseases, a recent study showed that gene deletion of the golgin GM130 in mice causes severe trafficking defects, concomitant with disruption and aberrant positioning of the Golgi, resulting in the death of Purkinje neurons and ataxia [104**]. Likewise, down-regulation of GM130 in zebrafish leads to microcephaly and muscle defects, which were also observed in a human patient with GM130 mutations who developed microcephaly and neuromuscular disorders [105]. Furthermore, GM130 knock out mice showed reduced body size and male infertility due to abnormal spermatogenesis caused by defects in sorting Golgi-derived vesicles [106]. These findings suggest that Golgi disruption and secretion dysfunction might be sufficient to cause severe phenotypes associated with neurodegenerative and other diseases.

On the other hand, the microtubule network also plays an important part in Golgi fragmentation during pathogenesis that share some morphological similarities with those during cell division and differentiation [107]. During differentiation of many cell types, including keratinocytes, hippocampal neurons, skeletal muscle and pancreatic cells [108–111], the microtubule nucleation activity of centrosomes is attenuated, leaving the Golgi as the key organelle to nucleate microtubules [112,88]. In pancreatic beta cells, for instance, microtubules predominantly grow from Golgi membranes instead of centrosomes [113*]. Furthermore, Golgi outposts in neurons can promote dendrite branching by generating non-centrosomal microtubules [90,114], although additional nucleation sites persist after experimentally removing Golgi outposts from dendrites [115]. Intriguingly, suppression of microtubule dynamics at Golgi outposts reduces terminal but not initial branching of dendrites in flies. This was observed upon deletion of the fly homologue of AKAP450, a γ-TuRC binding protein that is targeted to the Golgi by GM130 [116] and is indispensable for microtubule nucleation [42*]. A comparable phenotype is seen in Purkinje neurons of GM130 knockout mice where only terminal branching and arborization but not initial formation of dendrites is affected. Deletion of GM130 coincides with the loss of AKAP450 from the Golgi [104**], suggesting that defective dendrite branching may be partially attributable to the impaired microtubule nucleation from the Golgi. However, since the extensive dendrite branching of Purkinje cells depends on a functional secretory pathway, it is likely that the severe secretory perturbation further aggravates the phenotype [104**].

Reduced microtubule nucleation in combination with defective Golgi transport has also been linked to ALS, where loss of the Golgi-localized tubulin-binding cofactor E (TBCE) disrupts Golgi-derived microtubules and fragments the ribbon in motor neurons [95,117]. Similarly, a mouse model with impaired dynein/dynactin function exhibited a fragmented Golgi and developed ALS-like phenotypes [118,119], corroborating that Golgi ribbon disruption induced by cytoskeletal alterations are associated with various neurodegenerative disorders [120].

During differentiation and fusion of myoblasts (Figure 2c), the Golgi ribbon becomes dispersed and the microtubule network is reorganized while centrosomes lose their microtubule nucleation activity [121,111]. In skeletal muscle, microtubules are nucleated from the Golgi and nuclear membranes [112]. Dysregulation of these membrane-associated microtubules may lead to defective organization and thus alter the muscle function as found in Duchenne muscular dystrophy [111].

## Concluding remarks

The Golgi ribbon represents a higher level of structural organization that correlates with more complex and advanced functions. Building on this new module, mammalian cells can expand its functionality by refining or disabling it at specific time and place. Recent progresses in studying differentiated cell types have suggested that ribbon disassembly could benefit the organism as a whole by meeting the needs for local secretion in specialized cells. On the other hand, accumulating evidence revealed that ribbon disassembly could also be the backstage driving force and/or the outcome of several notorious diseases. Stemming from our current understanding of Golgi disassembly in normal conditions, we have just

begun to decipher the complexity of these processes, which may or may not share unifying mechanisms that underlie these morphological changes. More importantly, it is especially challenging but definitely important to dissect whether the structure-function relationship is actually causal or merely correlative, as this could completely change the strategy for diagnosis, drug development and treatment of the related diseases.

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## Highlights

- Golgi disassembles in mitosis via ribbon unlinking, unstacking and vesiculation
- Golgi ribbon disassembly is required for mitotic progression and spindle assembly
- Golgi ribbon disassembly often accompanies with microtubule remodeling
- During differentiation the Golgi ribbon disassembles to gain additional functions
- Fragmentation and dysfunction of the Golgi ribbon are linked to several diseases

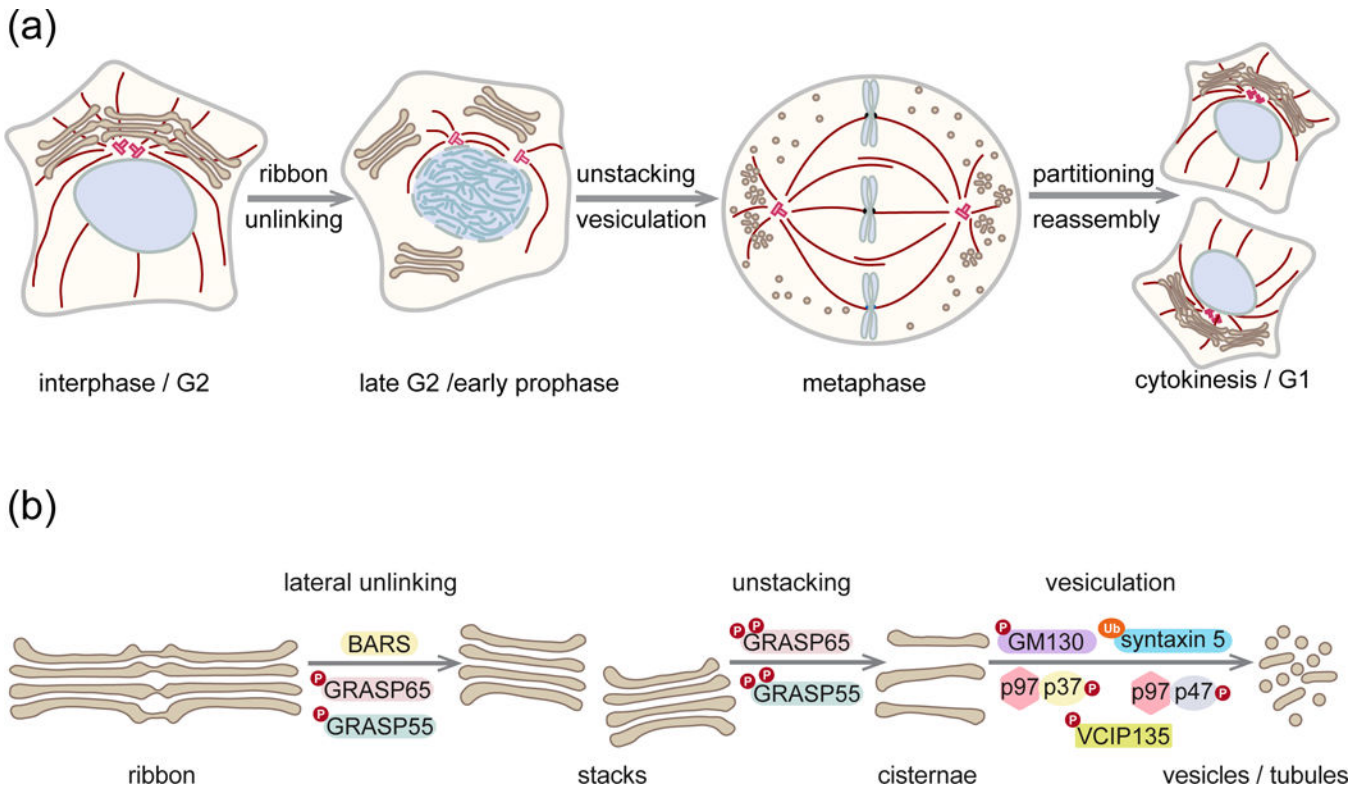


**Figure 1.**

Golgi ribbon disassembly in mitosis. (a) During interphase, the Golgi stacks are interconnected into a ribbon that is localized close to the centrosomes. In late G2, the lateral connections between stacks are severed, which unlinks the ribbon and allows progression into mitosis. The cisternae then further unstack and vesiculate. Upon partitioning with the aid of the spindle, the mitotic Golgi membranes reassemble a ribbon in both daughter cells. (b) Stages and main players in mitotic Golgi disassembly. Ribbon unlinking in late G2 requires the membrane fission protein BARS and the phosphorylation of GRASP65 and GRASP55. Once the cells entered mitosis, further phosphorylation of GRASP 65 and GRASP55 induces cisternal unstacking. Simultaneously the cisternae vesiculate due to inhibition of both vesicle tethering (mediated by phosphorylation of GM130) and heterotypic fusion (mediated by ubiquitination of the t-SNARE syntaxin 5). Meanwhile, homotypic fusion of Golgi membranes is also blocked by phosphorylation of the p97 adaptors p37 and p47 and the co-factor VCIP135.

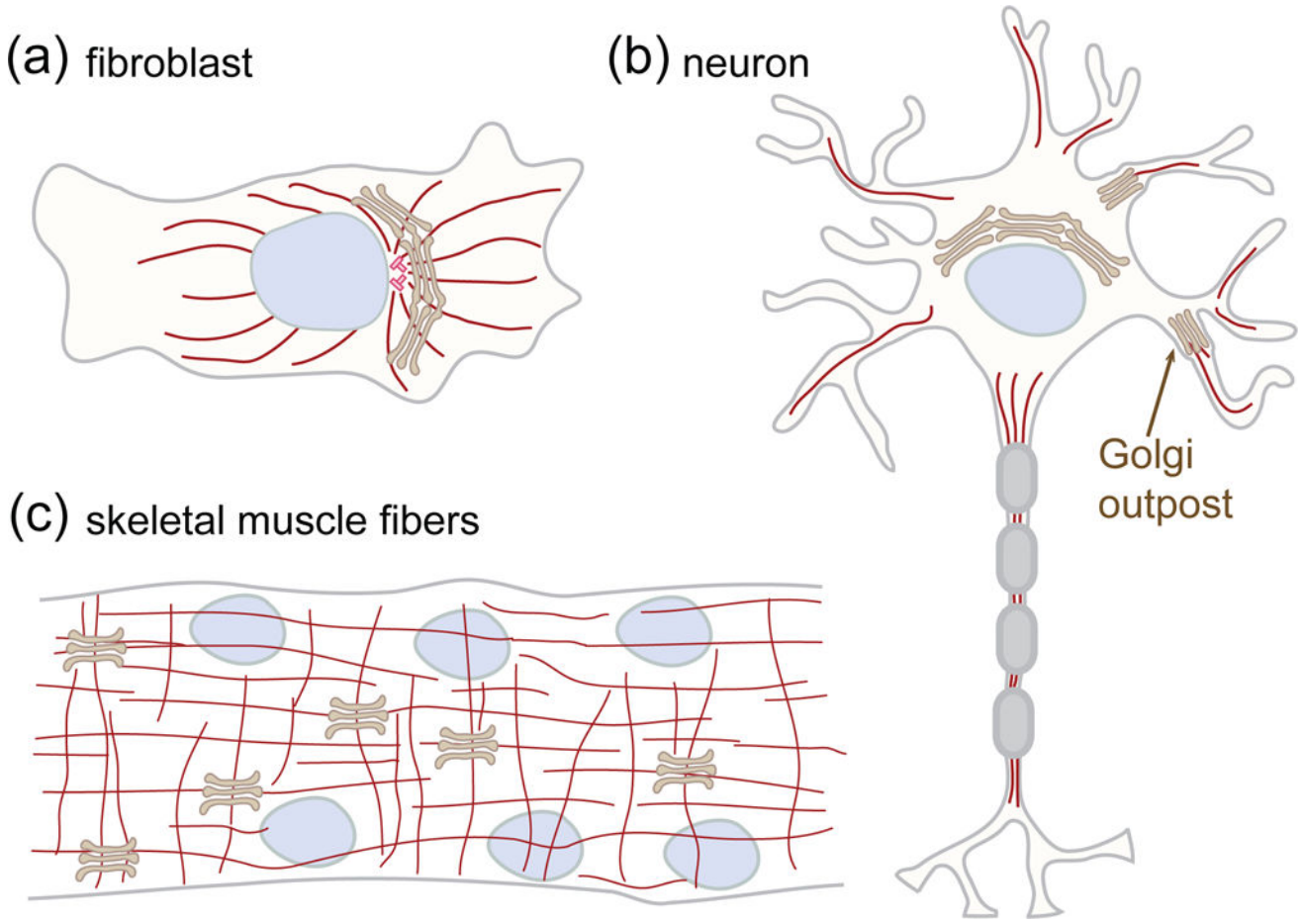


**Figure 2.**

Golgi stacks in proliferating and differentiated mammalian cells. (a) Golgi ribbon in fibroblasts. The stacks are laterally linked together into a continuous ribbon that localizes in the perinuclear and pericentriolar region of the cell. (b) Golgi outposts in neurons. During neuronal differentiation, some stacks detach from the somatic ribbon and relocated to dendrites. These Golgi outpost function as sites for local secretion and microtubule nucleation to regulate dendrite outgrowth. (c) Golgi stacks in muscle fibers. In skeletal muscle fibers, the ribbon is broken up into stacks. Microtubules originating from the nuclear membrane and from Golgi stacks form a grid-like network.