Organelle Positioning in Neurons and Skeletal Muscle Cells

Nöron ve İskelet Kası Hücrelerinde Organel Konumlanması

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ABSTRACT

Organelles are dynamic compartments, whose spatial positions are tightly regulated for cellular functions. An increasing number of studies have shown dysregulations in organelle positions, especially in muscular and neurological diseases, therefore understanding the basic mechanisms of organelle positioning could help to develop new therapeutic strategies. In this review, we focused on the mechanisms of organelle positioning in two specialized cells, muscle and nerve, as well as the contribution of mispositioning to disease pathomechanisms.

Keywords: Organelle positioning, Cytoskeleton, Myopathies, Neurodegenerative diseases

Received: 03.05.2021 **Accepted:** 04.05.2021

ÖZET

Organeller dinamik kompartımanlar olup konumları hücresel işlevler için sıkı bir şekilde düzenlenmektedir. Artan sayıda çalışma, özellikle kas hastalıkları ve nörolojik hastalıklarda organel konumlarında düzensizlikler olduğunu göstermiştir. Bu nedenle organel konumlanmasında görevli temel mekanizmaları anlamak, yeni tedavi stratejilerinin geliştirilmesine yardımcı olabilecektir. Bu derlemede, özelleşmiş hücre tipleri olan kas ve sinir hücrelerine odaklanılmış, organel konumlanma mekanizmaları ve hatalı organel konumlanmasının hastalık patomekanizmalarına olan katkısı özetlenmiştir.

Anahtar Sözcükler: Organel konumlanması, Hücre iskeleti, Miyopatiler, Nörodejeneratif hastalıklar

Geliş Tarihi: 05.03.2021 **Kabul Tarihi:** 05.04.2021

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doi:http://dx.doi.org/10.12996/gmj.2021.79

INTRODUCTION

Organelles are intracellular compartments where molecules come together to perform specific functions. Organelles are mobile structures, and recent studies have served to highlight the importance of their spatial organization on their function (Figure 1). The spatial distribution of organelles is differentially regulated by changes in the cytoskeletal arrangement, membrane contact sites, and environmental stimuli, such as nutrient availability (1). Nevertheless, organelle movements are primarily orchestrated by the cytoskeletal network. Microtubules are the key decorators of organelle movement, and two types of mechanisms (class I and II) are involved in organelle positioning. In class I, microtubule polymerization/depolymerization creates a pushing or pulling force, thereby defining the position of the organelle. Pushing is regulated by polymerization, while pulling is controlled by depolymerization and/or motor proteins. In contrast, in class II, the organelle can slide in either direction along the microtubules. Plus-end and minus-end movements on the microtubules are governed by kinesin and dynein motor proteins, respectively. Cell type, geometer, and stage (dividing/nondividing), together with the distance covered, are the important determinants of organelle position (2). However, the role(s) of the actin filaments in organelle movement are less well defined. Actin-mediated organelle transport occurs via the (i) myosin motor proteins, such as myosin Va during endoplasmic reticulum (ER) transport, (ii) actin flow, as in nuclear transport, and (iii) actin polymerization (3). Intermediate filaments (IFs) are the sole members of the cytoskeleton which do not interact with specific motor proteins. IFs not only stabilize the positions of the organelles, but also contribute to their positioning by providing anchoring sites (4). Given the complexity of their morphology, intracellular organization of the organelles is quite sophisticated in both neural and muscle cells. Organelle mispositioning can cause several myopathies, neuromuscular and neurodegenerative/neurologic diseases, or contribute to pathophysiology of other types of disease (Tables 1–4). Therefore, this review was designed to summarize the molecular mechanisms underlying organelle positioning in two neighboring cells, neurons and skeletal muscle, as well as document the contribution of organelle mispositioning to various pathologies.

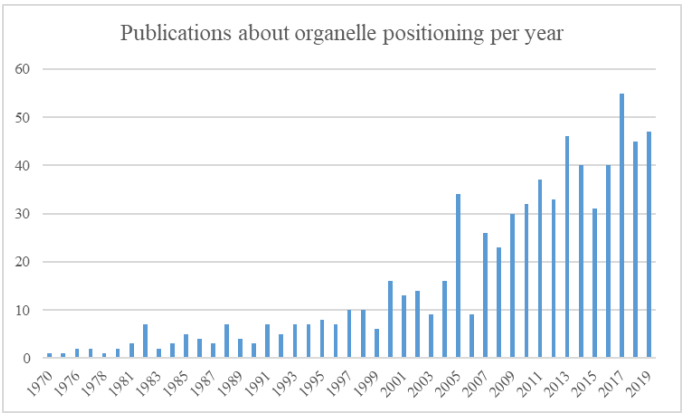

Figure 1. Number of PubMed records showing the increase in the number of publications about organelle positioning over the years.

Nuclear Positioning

Proper positioning of the nucleus is vital for the coordination of all cellular processes. Nuclei are usually positioned in the center of cells; however, there are exceptions like muscle and neuron cells; in striated muscle, nuclei are located at the cell periphery, while in neurons, they are located within the central portion of the soma, not the whole cell. Regardless of cell type, localization of the nucleus varies according to the stages of the cell cycle, differentiation, and migration status of the cells (5).

Neuron

Two types of nuclear movement, interkinetic nuclear migration (INM) and nucleokinesis, occur during nervous system development. INM is a cell cycle-synchronized oscillatory movement restricted to the neural epithelial stem cells and radial glial progenitor cells (6). During mitosis, the nucleus is in the apex of the cells, then migrates and remains in the basal position during the S phase. Afterwards, it migrates back to the apex in G2 and apically enters the division (7) (Figure 2A).

The exact mechanism underlying INM is not well understood; however, it has been reported that rat brain nuclei migrate along the microtubules and knockdown of dynein inhibits basal-apical movement, while Kif1a, kinesin family member 1A, is required for basally directed nuclear movement (8). The role of the actomyosin complex has also been reported. Studies have shown that myosin II is needed for apical to basal INM in mouse embryonic telencephalon cells (9). Nucleokinesis is the other nuclear movement known to occur during neuronal migration. Although it is not well defined, this term is used to describe the movement of both the nucleus and the cell body after the extension of a leading neurite (Figure 2B). It has been shown in mouse medial ganglionic eminence cells, a large swelling containing the Golgi apparatus and centrosome separates and then moves into the leading neurite and then the nuclei translocate to the displaced Golgi apparatus and centrosome (10). Nucleokinesis is regulated by microtubule-motor proteins, cell polarity (*Par*) genes, actomyosin, and LINC complexes (10, 11). Alterations in both INM and nucleokinesis have been linked to the pathogenesis of several diseases (Table 1).

Skeletal muscle

Muscle cells -myofibers- are multinucleated cells whose nuclei are predominantly found in the cell periphery. Multinucleation of myofibers is caused by the fusion of mononucleated myoblasts during development. Mispositioning of the nucleus, especially internalization, is common in several muscle disorders. It has been suggested that centrally positioned nuclei are a consequence of myofiber repair and that mutations in the genes encoding nuclear or cytoskeleton-related proteins cause muscle disease (Table 1).

Table 1. Diseases with impaired nuclear positioning

Diseases	***System***	***References***
Spastic paraplegia-30	*KIF1A1* mutation analysis of patients	(12)
Lissencephaly	LIS1 knock-down; COS7 cell line and rat	(13)
CNM	Mouse primary myoblasts, patient muscle biopsies	(14)
EMD	$Lmna^{-/-}$ mouse embryonic fibroblasts, NIH 3T3 fibroblasts, patient fibroblasts Nesprin-1 mutant mouse	(15) (16)
Schizophrenia	Entorhinal cortex of patients	(17)
Epilepsy	Surgical examination of patients	(18)

EMD; Emery-Dreifuss muscular dystrophy, CNM; Centronuclear myopathy

Nuclear centration

After myoblast-myotube fusion, nuclei of myoblasts move to the center of the myotube. This movement is directed by microtubules and the dynein/dynactin complex (Figure 2C). When microtubules are emanating, nuclei pull the microtubules anchored on other nuclei with the help of the dynein/dynactin complex move it into the nuclear envelope. Nuclear centration requires Cdc42, a Rho family GTPase, as well as Par3 and Par6, which play roles in the accumulation of motor proteins in the nuclear envelope (19, 20).

Nuclear spreading

Nuclei spread evenly along the myotube by microtubule motor proteins during myotube formation (20) (Figure 2C). Three mechanisms have been proposed; first, anti-parallel microtubules, which are anchored to the nuclear envelope, slides and adjacent nuclei can be positioned by microtubule-associated protein 7 (MAP7) and kinesin family member 5b (Kif5b) (21). The second mechanism involves the nuclear envelope protein, nesprins. It has been shown that recruitment of nesprin-dependent kinesin-1 to the nuclear envelope is necessary to allow for the distribution of the nuclei within the myotubes (22). Mice with mutant nesprin proteins exhibit more centrally localized nuclei and smaller fiber size, which is consistent with Emery-Dreifuss muscular dystrophy disease (16). The final mechanism described in Drosophila melanogaster, which involves dynein anchorage at myotube poles via Raps/Pins protein and can pull on microtubules by a +TIP protein, Clip190 (23).

Nuclear dispersion

Nuclear dispersion is a movement of the nuclei to the periphery of the muscle cells (Figure 2C). It is a two-step process: first, the nuclei are spread along the myofiber via the microtubule/Map7/Kif5b complex (21) and then they are localized to the periphery by Amph2, N-WASP, actin, and nesprin-dependent mechanisms. Mutations in Amph2 causes disruption of N-WASP-Amph2 interactions as well as N-WASP distribution in CNM patients (14).

Nuclear clustering

A single myofiber consists of three regions: the myotendinous junction, the body (costameres), and the neuromuscular junction (NMJ). A cluster of three to eight nuclei, which are larger and rounder than the others, have been found at NMJs where acetylcholine receptors cluster (24). It has been suggested that clustering of the nuclei could be relevant synapse formation, as these nuclei express NMJ-specific mRNAs. This distribution might also be nesprin-1dependent, since nesprin knock-out mice showed nuclear anchoring defects (25).

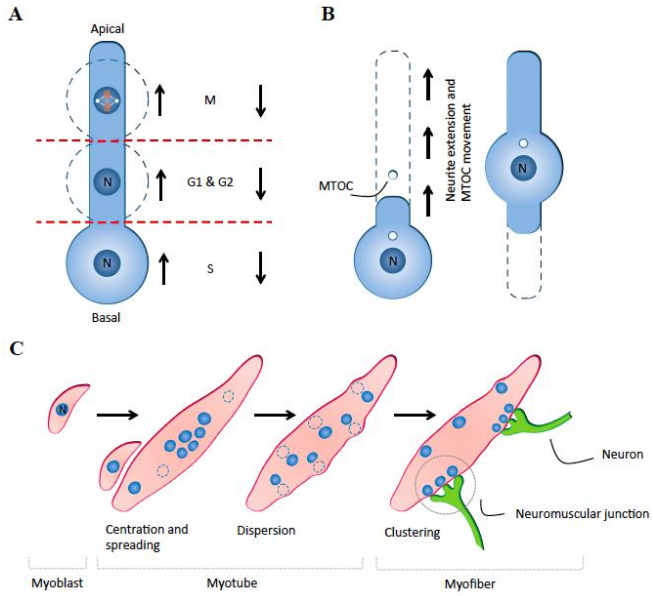

Figure 2. Mechanisms of nuclear positioning. A: Interkinetic nuclear migration and B: nucleokinesis in neuronal cells, C: movement of nucleus in muscle differentiation.

Mitochondrial Positioning

Mitochondria are dynamic organelles known to localize to the perinuclear and peripheral regions of the cell, depending on cellular requirements. Intracellular mitochondrial transport and distribution are associated with organelle-level quality control mechanisms, such as mitochondrial fusion, fission, and mitophagy. Mitochondrial fusion and fission proteins (Mitofusin2 and Drp1) have been linked to dynein and Miro-Milton proteins, respectively. Overexpression of Drp1, a key protein in mitochondrial fission, in mouse skeletal muscle causes changes in mitochondrial transport, disrupting the desmin network and activating the kinesin-1 complex (26). Similarly, downregulation of the mitochondrial fusion protein Marf/MFN in *Drosophila* induces an abnormal distribution of the axonal mitochondria decreasing the proportion of mobile mitochondria (27). Mitophagy and mitochondrial motility have also been interrelated, since defective mitochondria are known to travel to the cell body from the axons. The association between mitophagy proteins, Pink1 and Parkin, and various mitochondrial transport proteins, such as Miro, has also been well established in the literature (28)

Neuron

Neurons have a high number of mitochondria, as they are high-energy-demanding cells (Figure 3). Mitochondria move long distances in neurons and are primarily transported on microtubules by motor proteins, mitochondrial Rho GTPases (MIROs) and various adaptor proteins (29). Retrograde movement is regulated by dynein, while anterograde movement is mediated by kinesin motor proteins, trafficking kinesin-binding proteins (TRAK1 and TRAK2) and syntabulin (30, 31). Actin filaments also play a role in mitochondrial transport over short distances, especially in microtubule-poor, actin–rich sites such as axonal branch points and growth cones (32, 33). MIRO proteins also play a role in linking myosin 19, an actin motor protein, and the mitochondria (34, 35).

Intracellular calcium and extracellular glucose levels are two important parameters affecting the distribution of the mitochondria. Intracellular calcium levels are sensed by the mitochondrial outer membrane protein, MIRO1 (36). Mitochondria become less motile in Ca^{2+}-rich sites due to dissociation of MIRO1 from microtubules; however, the exact mechanism has not been elucidated.In contrast, milton is O-GlcNAcylated in the presence of glucose which leads to a decrease in mitochondrial motility. Although the exact mechanism is not clear, mitochondria concentrate close to the extracellular high-glucose microdomains where ATP is produced (37). Mitochondrial membrane potential is another parameter that affects the mitochondrial distribution in neuronal cells. A high membrane potential drives anterograde transport, while a low membrane potential induces retrograde movement (38).

The majority of mitochondria are found to be in a stationary within the synapses by anchoring on microtubules, actin filaments, plasma membrane and ER, whereas one-third of the mitochondria found in the axons are known to be motile (39). The motility of the mitochondria in the axons decrease as cortical neurons mature. This is likely a result of the increased expression of mitochondrial docking protein, syntaphilin (40). Impaired mitochondrial movement/distribution due to genetic alterations or dysregulation of their post-translational modifications have all been linked to several neurodegenerative diseases (Table 2).

Skeletal muscle

Skeletal muscle has two different mitochondrial pools: subsarcolemmal and intermyofibrillar (Figure 3). Subsarcolemmal mitochondria are longer, tubular-shaped, and have higher energy production capacity than intermyofibrillar mitochondria, which are smaller and rounder in shape (41). They are both highly motile during early postnatal development; however, as the skeletal muscle matures, the mitochondria start to tether the sarcoplasmic reticulum and become less motile (42). Intermyofibrillar mitochondria are arranged in “crystal-like patterns” in both slow- and fast-twitch muscle fibers; however, mitochondria are more tightly packed in slow-twitch muscles due to their mitochondria-rich nature (43). As in the neurons, intracellular Ca^{2+}-rich domains also affect mitochondrial distribution. In order to exchange calcium, most of the mitochondria connect with the sarcoplasmic reticulum (44) and many of the mitochondria in the skeletal muscle cells interact with IFs, such as desmin, which are critical to the stacking of mitochondria into Z-discs (45). Aberrant mitochondrial distribution has been implicated in some muscular dystrophies (Table 2). In Megaconial congenital muscular dystrophy (CMD), megaconial mitochondria accumulate underneath the sarcolemma, while the center of the muscle fiber is devoid of mitochondria (46). Moreover, in primary myoblast cells of Megaconial CMD patents, large mitochondria are concentrated around the nucleus (Aksu-Menges et al., unpublished data).

Table 2. Diseases with impaired mitochondrial positioning

Diseases	*System*	*References*
Alzheimer's disease	Hippocampal neurons of $Tau^{+/+}$, $Tau^{+/-}$, and $Tau^{-/-}$ mouse	(47)
Parkinson's disease	COS-7 and HEK-293FT cells	(48)
Huntington's disease	Postmortem brain samples and primary neurons of transgenic BACHD mice	(49)
ALS	NSC34 cell line expressing mutant SOD1	(50)
SMA	Type I patient iPSC-derived motor neurons NSC34 cell line	(51, 52)
Megaconial CMD	Skeletal muscle tissue of patients	(53)
DMD	mdx model	(54)

ALS; Amyotrophic lateral sclerosis, SMA; Spinal muscular atrophy, CMD; congenital muscular dystrophy, DMD; Duchenne muscular dystrophy

Lysosome Positioning

Lysosomes are found throughout the cell, but they are primarily found in two locations, both of which are linked to their function and cellular conditions. These include the perinuclear pool near the microtubule-organizing center (MTOC) and the cell periphery. Under physiological conditions, in non-polarized cells, lysosomes are located in the central region surrounding the MTOC (perinuclear cloud), while in polarized cells such as neurons, lysosomes are found in the cell body as well as axons and dendrites. However, lysosomal distribution and movement may change in response to specific environmental conditions. For instance, cytosolic acidification causes perinuclear positioning. Starvation, aggresome formation, and drug-induced apoptosis may also trigger perinuclear positioning.

Under nutrient-rich conditions, mTORC1 is activated, and lysosomes are generally located near the plasma membrane. Whereas in starvation, intracellular pH increases, mTORC1 is inhibited, promoting autophagy and perinuclear positioning (55). Lysosomes can move in anterograde and retrograde directions. Anterograde transport depends on kinesin motor proteins such as KIF1A, KIF1B, KIF2, KIF3, KIF5A, KIF5B, and KIF5C while retrograde transport is regulated by dynein; however, in neurons, dynein contributes to lysosome transport in both directions. The proteins, which are responsible from its positioning associates with lysosome via GTPases. Arl8b, a lysosomal GTPase, engages kinesin-1 via its adapter, SKIP, which fosters displacement toward the plus ends of microtubules. Rab7, a small GTPase, can promote centrifugal movement, which occurs from the center of the cell to the periphery, by association of kinesin and its adaptor, FYCO1. Rab7 is also involved in centripetal lysosome movement, which occurs towards the minus-end and is facilitated by the interactions between the Rab-interacting lysosomal protein, RILP, and the dynein complex. However, the net effect of Rab7 is centripetal, and Rab-depleted lysosomes are located more peripherally (56). In addition, lysosomes are attached to both dynein and kinesin when they are tubulated in response to bacterial infection in the macrophages and dendritic cells allowing the production of the phagosomes and the delivery of the histocompatibility complex (MHC) class II (MHC-II) molecules to the dendritic cell surface.

Neuron

Lysosomes are abundant throughout the neuronal cell body; however, they are also found in axons and dendrites (Figure 3). Lysosome positioning is controlled by neuronal demands (57). During autophagy, autophagosomes fuse with endosomes in the distal axon and are transported to the cell body via dynein and adaptor proteins Rab7, JIP1, JIP3, and Snapin. They gradually acidify acquiring their full degradative activity and turn into true lysosomes. A recent study revealed that lysosomes move from the cell body into the axons of mouse cortical neurons and target autophagosomes for local degradation in distal axons (58). Additionally, lysosomal positioning has been shown to be a key determinant in postsynaptic remodeling facilitated by the lysosomal degradation of various synaptic proteins. Lysosomes localize to the primary and secondary dendrites of rat hippocampal neurons and are known to move bidirectionally. Microtubule destabilization increases the number of stationary lysosomes, while actin filament destabilization increases lysosomal trafficking in dendrites, suggesting that microtubules and actin act in some coordinated way within the synapse (59).

Mutations in the components of the lysosome-positioning machinery may result in psychiatric and neuromuscular disease. In addition, lysosome mispositioning may be a contributor to or a consequence of neurodegenerative disease (Table 3). Lastly, lysosome mispositioning is one of the major symptoms in lysosome storage diseases.

Skeletal muscle

Lysosome-autophagy degradation in the skeletal muscles is an active mechanism in both physiological and pathological conditions, such as myopathies. Autophagic vacuole accumulation in skeletal muscle fibers is common in several neuromuscular diseases (60, 61). However, it is not known whether alterations in lysosome positions contribute to the pathology of these diseases. In wild-type rat myofibers, late endosome/lysosomes are predominantly found in the perinuclear area underneath the sarcolemma, but there are some in the interior parts of the fibers (62). An *in vitro* study using mouse C2C12 cells showed that rapsyn is required for the clustering of lysosomes within the juxtanuclear region of myoblasts, and rapsyn deficiency leads to scattered lysosomes throughout the cytoplasm (63).

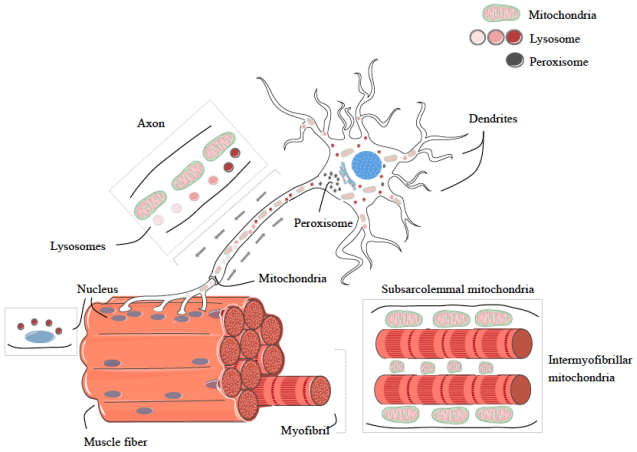

Figure 3. Positions of mitochondria, lysosome and peroxisome in muscle and nerve cell.

Golgi Positioning

The Golgi apparatus is usually situated in the center of the cell, akin to the nucleus, near the juxtanuclear centrosome (Figure 4). The centrosomal localization of the Golgi necessitates minus-end-directed dynein-mediated motility along the microtubules, which is regulated by Cdc42 and dynein binding proteins such as LIS1, NDE1, and NDEL1 (64). This means that cells lacking dynein cannot concentrate the Golgi in the perinuclear region, but the Golgi can still associate with the microtubules (65). Dynein 1 is the primary motor protein mediating Golgi positioning, while kinesin plays a minor role (65, 66). Golgi ribbons may also be directed towards the MTOC (67). The Golgi is the second major mammalian MTOC (68). Both Golgi and microtubule assembly help to form Golgi ribbons after mitosis. In addition, even in the absence of the microtubules the Golgi will remain functional, but the Golgi ribbon will become fragmented (69). Moreover, as opposed to the centrosome, which composes a symmetric array, MTOC-directed Golgi is polarized, which drives asymmetrical vesicular transport and promotes cellular polarity (70).

Neuron

Golgi positioning can define the polar morphology of the neurons. During development, the Golgi first localizes to the axon emergence site and then moves to the apical side of the pyramidal neurons (71). The Golgi sends outposts into the longest and more complex dendrites to allow for the nucleation of the microtubules, thereby increasing dendritic arbor elaboration (72). After the identification of Golgi's role in cellular polarity, a patient with a *GOLGA2* mutation was reported (73). *GOLGA2* encodes the Golgi assembly protein, GM130, which creates a molecular link between the Golgi and the cytoskeleton.

Table 3. Diseases with impaired lysosome and Golgi positioning

Lysosome	*System*	*References*
Schizophrenia	Post-mortem brain tissues	(78)
ALS	Molecular genetic analysis of patients	(79)
CMT2	Molecular genetic analysis of families	(80)
Hereditary spastic paraplegia type 10	Molecular genetic analysis of a family	(81)
CDCBM2	Molecular genetic analysis of patients, in vitro and in vivo models	(82)
SPOAN	Molecular genetic analysis of patients, patient fibroblasts and IPSC-derived motor neurons, phenotypic analysis of zebrafish model	(83)
Huntington's disease	HD knock-in mice and primary fibroblasts from a HD patient	(84)
Alzheimer disease	Postmortem brain tissue from individuals with Alzheimer disease	(85)
Golgi apparatus		
A neuromuscular disease with microsephaly	Molecular genetic analysis of a patient, patient lymphoblastoid cell line , zebrafish and mouse	(73)
DMD	*mdx* mouse	(77)

ALS; Amyotrophic lateral sclerosis, CMT2; Charcot–Marie–Tooth disease type 2B, CDCBM2; Cortical dysplasia with other brain malformations type 2SPOAN; Spastic paraplegia, optic atrophy and neuropathy, DMD; Duchenne muscular dystrophy

However, many Mendelian diseases caused by mutations in Golgi-related genes generally result in Golgi fragmentation or glycosylation disorders (74). This phenomenon may be related to Golgi positioning, which is crucial and may be an "all or nothing" determinant in neuron polarity.

Skeletal muscle

The Golgi adopts various positions in myoblasts and myotubes. *In vitro* studies have shown that Golgi ribbons assume a pericentrosomal location in mouse myoblasts, whereas during differentiation, the Golgi ribbons are dispersed as small stacks of cisternae, called Golgi elements, and are positioned close to the ER exit sites. In the myotubes the Golgi elements surround the nuclei (75). In addition, Golgi elements are static and their distribution is different in slow and fast-twitch muscle fibers (76). A recent study showed that the position of the Golgi elements is altered in muscle fibers from a DMD *mdx* model, which may indicate the possible indirect role of dystrophin on Golgi positioning (77). Several other neurodegenerative diseases linked to the mislocalization of the Golgi apparatus are described in Table 3.

ER and Peroxisome Positioning

The ER has two main domains: the nuclear envelope and the peripheral domain, which also has interconnected subdomains, namely, rough (RER) and smooth ER (SER) (Figure 4). RER primarily localizes to the perinuclear zone as membrane sheets while SER localizes to the peripheral zones as a network of interconnected tubules (86). The ER is a dynamic network of tubules and flattened cisternal sheets. ER-shaping proteins alter the shape and distribution of this network according to cell type and cellular demand (87). The ER is primarily made up of tubular networks in non-secretory cells (88) and is redistributed during ER stress, changes in Ca^{2+} concentrations, cell division, and motility (89-91). ER tubules co-localize with microtubules, and there are two mechanisms for microtubule-assisted ER movement (92). ER sliding by kinesin-1 and dyneins, is the faster of the two mechanisms. Inhibition of kinesin or dynein leads to a decrease in the ER tubular network and an increase in ER sheets (93). The second mechanism, which is the slower of the two, relies of the "tip attachment complex" which involves the interaction of End-binding protein 1 (EB1) and Stromal interacting molecule 1 (STIM1) proteins.

Since ER tubules associate with the plus ends of microtubules its movement depends on microtubule growth and shrinkage, which is most commonly observed in the peripheral part of the cell (94). In neuronal cells, the ER localizes to the soma, axon, and dendrites; however, its distribution within each compartment is different. Axonal ER forms an interconnected network of thin tubules and is nearly free of ribosomes (95). On the other hand, in both the soma and dendrites, the ER is composed of stacked membrane sheets with ribosomes (96). Although the morphology of the ER in the soma and dendrites is similar, the ER in the dendritic spines has a more complex structure, often referred to as the spine apparatus (97, 98). Decreased ER movement has been reported in ataxin-2 deficient *Drosophila* neurons *in vitro* (99) and although it has been known that ataxin-2, a tubular ER protein, is related to spinocerebellar ataxia type-2 (SCA2), the detailed mechanism underlying this relationship remains unclear (100). In skeletal muscle, the ER has a complex morphology. In addition to subsarcolemmal RER, a specialized form of ER, sarcoplasmic reticulum (SR), is composed of a tubular network and terminal cisternae (101). However, it is mostly unknown how an organelle with such a complex structure is positioned correctly in the myofibers.

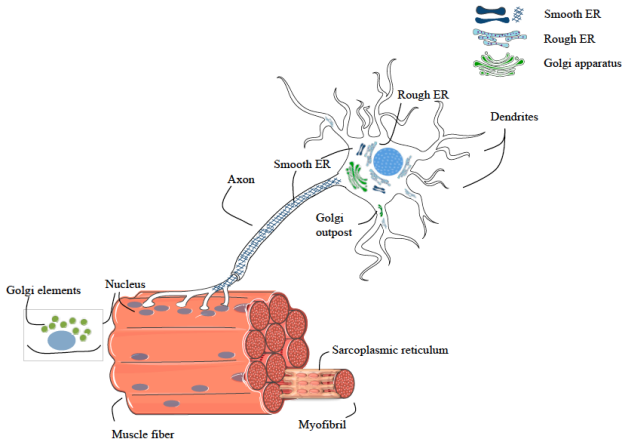

Figure 4. Positions of endoplasmic reticulum and golgi apparatus in muscle and nerve cells.

Peroxisomes are evenly distributed in most cells; however, they are largely unknown for muscle cells. On the other hand, peroxisomes are critical for the nervous system as peroxisome dysfunction is associated with several neurological diseases (102). In mouse neurons, peroxisomes are mostly localized within the perinuclear region, but are rarely described in the axons and dendrites (Figure 3) (103).

Peroxisome positions are determined by both the microtubules and the ER contact sites in neuronal cells (104). In addition, microtubule-associated protein TAU is involved in peroxisome distribution, and overexpression of TAU leads to the accumulation of peroxisomes in the cell body, while localization in the neurites disappeared *in vitro*. This suggests that TAU may inhibit peroxisome trafficking (105). Microtubule-dependent peroxisome mispositioning has also been observed in patients with Alzheimer's disease and hereditary spastic paraplegia (Table 4). The ER contact sites also determine peroxisome positioning and a recent study revealed that overexpression of a peroxisomal membrane protein, ACBD5, in mice hippocampal neurons reduced long range peroxisome movement in neurites and altered the intracellular distribution of these organelles (104).

Table 4. Diseases with impaired ER and peroxisome positioning

Endoplasmic reticulum		
SCA2	Ataxin-2 deficient cultured *Drosophila* neurons	(99)
Peroxisome		
Alzheimer's disease	N2a neuroblastoma cells and rat primary hippocampal neurons; patient post-mortem brain tissues	(105); (106)
Hereditary Spastic Paraplegia with SPAST mutations	Patient neuronal cells differentiated from olfactory neurosphere-derived stem cells	(107)

SCA2; Spinocerebellar ataxia type-2

CONCLUSION

Organelle mispositioning is associated with several diseases. However, it remains unclear whether this is a primary cause or a consequence of these pathologies. The list of diseases discussed here is far from complete and it will continue to grow as we develop our understanding of organelle function. Detailed studies, together with advances in technologies, especially in optogenetics and 3D culture systems, will help to elucidate the molecular mechanisms regulating organelle movement and the functional consequences of their mispositioning in various diseases.

Conflict of interest
No conflict of interest was declared by the authors.

Acknowledgement
We would like to thank to Nazlı Tunalı for drawings of Figure 2. For drawings of Figure 3 and 4, Smart Servier Medical Art (https://smart.servier.com/) images were modified as presented.

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