Chapter 7
Mitochondrial Dynamics and Neurodegeneration

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Abstract In vivo, mitochondria display a high degree of connectivity and mobility. Within the cell, mitochondrial fusion and fission machineries tightly control the dynamics and distribution of the mitochondrial network. Due to their key energetic role, the localization of mitochondria at intracellular sites of high-energy demand is crucial to maintain cell energy metabolism. Neurons are metabolically active cells with high-energy demands at locations distant from the cell body (see Chaps. 8 and 9). Consequently, they are particularly dependent on mitochondrial distribution and function. Accordingly, new evidence identifies defective mitochondrial dynamics as a central pathological event underpinning a number of early and late-onset neurodegenerative disorders. Mutations in genes encoding proteins playing central roles in mitochondrial dynamics and functions have been identified in patients with peripheral neuropathies such as Charcot-Marie-Tooth (CMT) and dominant inherited optic atrophy. Moreover, defects of mitochondrial dynamics have recently been associated with common neurodegenerative diseases such as Parkinson's, Alzheimer's, and Huntington's diseases. Understanding the regulation of mitochondrial dynamics in neurons may open new avenues for the development of therapies in neurodegenerative diseases.

Keywords Neurodegenerative diseases • Mitochondria • Mitochondrial dynamics Bioenergetics

7.1 Introduction

Mitochondria are organelles originally observed in spermatocytes more than a century ago [1]. The name *mitochondrion* is based on their microscopic appearance and is derived from the Greek language for the words thread (*mitos*) and granules (*chondros*). Mitochondria are double membrane bound: the inner membrane delimits the

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matrix and intermembrane space (IMS), whereas the outer membrane separates the IMS from the cytosol. The inner mitochondrial membrane has the highest density of protein in the cell and can be dissociated in two domains: the boundary region, which constitutes flattened membranes that are in close proximity to the outer membrane, and the cristae membranes, which are lamellar invaginations with highly curved edges. The cristae invaginations house the oxidative phosphorylation system (OXPHOS) [2–4]. This system is composed of two functional entities, i.e., the respiratory/electron transport chain (RC) and the phosphorylation system, which includes the ATP synthase and membrane carriers, such as the ATP/ADP carrier (ANT) and the phosphate carrier (PiC). The RC is historically defined as consisting of mobile electron carriers: coenzyme Q and cytochrome *c* and four complexes, denoted complex I–IV, which perform substrate oxidation to drive proton extrusion from the mitochondrial matrix to the IMS. The proton electrochemical potential difference across the inner membrane (ΔP) is then used by the ATP synthase to drive ATP synthesis thus coupling proton transport to ATP production [5] (see Chap. 1 for details).

Interestingly, complexes I, III, and IV of the RC and ATP synthase are under dual genetic control. The mitochondrial genome (mtDNA) only encodes 13 proteins that are all components of the OXPHOS system, and nuclear genes encode the remaining mitochondrial proteins. The nuclear genome encodes the mitochondrial proteome required for the maintenance and expression of mtDNA [6], protein synthesis [7], import and degradation [8, 9], iron-sulfur cluster synthesis [10], citric acid and urea cycles, fatty acid oxidation, and additional metabolic pathways.

Mitochondria form a dynamic network inside the cell, and specialized transport machineries ensure their mobility and proper subcellular localizations. Due to their key energetic role, mitochondria are often positioned at intracellular sites of high-energy demand. In the muscle, mitochondria are embedded between myofibrils that consume ATP during contraction. Likewise, in neurons mitochondria are transported to and accumulate in synapses to provide the energy required to maintain and regulate neurotransmission. Thus, proper control of mitochondrial subcellular localization and network morphology is an absolute requisite to maintain energy homeostasis and cell functions. This chapter will review recent findings on the energetic relevance of mitochondrial dynamics and its implication in neurodegenerative disorders.

7.2 Mitochondrial Dynamics

"Mitochondrial dynamics" describes the continuous changes in the position, size, and shape of mitochondria within cells. In eukaryotic cells, mitochondria are arranged in a wide variety of shapes, ranging from long interconnected tubules to individual spheres [11–13]. Mitochondrial morphology is highly plastic and dynamic, and mitochondria can travel long distances on the cytoskeletal track. Depending on the cell type, mitochondrial mobility can be mediated through either

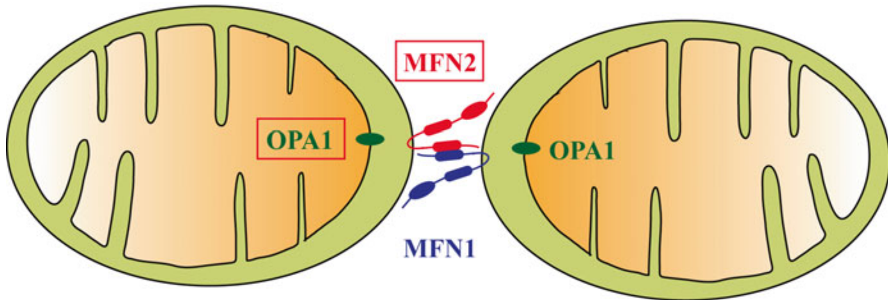

Fig. 7.1 The mammalian machineries involved in mitochondrial fusion. Heterotypic interaction between the mitochondrial outer membrane proteins MFN1 and MFN2 is depicted. OPA1 is located in the intermembrane space and associated with the inner mitochondrial membrane. A *red square* highlights protein implicated in diseases

the microtubules or the actin cytoskeleton [14, 15]. In neurons, mitochondrial transport occupies a key role in the delivery and renewal of axonal and synaptic mitochondria [16]. Interestingly, while the cytoskeleton is important to ensure proper mitochondrial intracellular distribution and transport, it is not required to maintain mitochondrial network morphology [17–20]. Mitochondrial network morphology is in fact the result of balanced fusion and fission controlled by protein members of the dynamin-related protein (DRP) family. Recent microscopic, structural, and biochemical studies have led to the characterization of the core machinery of mitochondrial fusion and fission.

7.2.1 Mitochondrial Fusion

The identification of fuzzy onion (FZO) as an essential protein mediating mitochondrial fusion events occurring during spermatogenesis in *drosophila* drove rapid advances in our knowledge of the mitochondrial dynamic machinery [21]. The characterization of this evolutionary conserved GTPase protein in budding yeast (FZO1) showed that this outer mitochondrial membrane protein functions in mitochondrial fusion [22, 23]. Genetic screens, performed in yeast, led to the identification of the protein machineries involved in mitochondrial fusion and fission [24]. This approach revealed that the core of the yeast mitochondrial fusion machinery is composed of three proteins. FZO1 and MGM1 (Mitochondrial Genome Maintenance 1) [25–27], respectively, control fusion of the outer and inner mitochondrial membrane, whereas UGO1 (UGO is Japanese for fusion) is proposed to be a two membrane-spanning protein mediating the interaction between FZO1 and MGM1 [28–30]. In contrast to UGO1, both FZO1 and MGM1 present mammalian homologues known as mitofusin 1 and mitofusin 2 (MFN1 and MFN2) [31] and OPA1

(optic atrophy 1) [32, 33], respectively (Fig. 7.1). MFN1 and MFN2 show 81 % similarity to each other and are 52 % similar to *drosophila* FZO [19]. Both MFNs are ubiquitously expressed in mammals, although their mRNA and protein levels strongly differ according to the tissues [17, 31, 34, 35]. The posttranscriptional and posttranslational mechanisms regulating MFNs tissue-specific expression remain largely unknown. Like FZO1, MFNs are anchored to the outer mitochondrial membrane by two transmembrane segments and contain one GTPase and multiple predicted coiled-coil-forming domains which are exposed and face toward the cytosol [17, 36]. The C terminal coiled-coil domain has been shown to mediate MFN1 and MFN2 antiparallel homotypic and heterotypic complexes [19, 37]. Even though both MFN1 and MFN2 are expressed in mouse embryonic fibroblasts, each protein is essential to maintain mitochondrial network morphology [19]. However, despite their high similarity, MFN1 and MFN2 exhibit different GTPase and membrane-tethering capacities [38]. These functional disparities could explain why the mitochondrial network morphology aberration in *Mfn2* knockout MEFs can be efficiently rescued by MFN1 overexpression, whereas, overexpression of MFN2 only mildly rescues the diffracted mitochondrial network of *Mfn1* knockout MEFs [19]. Interestingly, activity or degradation of FZO1/MFNs proteins is highly regulated by phosphorylation and ubiquitination at distinct lysine residues [39–42].

In mammals, OPA1 is the main actor controlling the fusion of the mitochondrial inner membrane. MGM1/OPA1 presents multiple isoforms that are located in the IMS or associated with the inner membrane [25–27, 43]. The proteolytic processing of OPA1 generates so-called non-cleaved or long OPA1 (L-OPA1) and cleaved or short OPA1 (S-OPA1) isoforms. The regulated cleavage of OPA1 isoforms by OMA1 (metallopeptidase that exerts activities overlapping with the m-AAA protease) [44, 45] or YME1L (mammalian orthologue of the yeast *Yme1*) [46–48] results in the loss of the transmembrane domain of the protein and controls the role of OPA1 in mitochondrial fusion. Furthermore, the alternative splicing of OPA1 pre-mRNA introduces additional complexity and yields a total of eight isoforms presenting one or two processing sites and expressed in a tissue-specific manner [49]. However, in contrast with the proteolytic processing, which is common to both orthologues OPA1 and MGM1, the alternative splicing is uniquely involved in the generation of mammalian OPA1 isoforms.

7.2.2 *Mitochondrial Fission*

Yeast genetic screens for an extragenic suppressor of fusion mutants led to the identification of key regulators of mitochondrial fission. The key component of the fission machinery DNM1 (dynamin-1) is a cytosolic protein which can be recruited into punctuate structures on the outer mitochondrial membrane [50, 51]. According to the most recent model, this DNM1p recruitment to the outer mitochondrial membrane is mediated by FIS1 (mitochondrial fission protein 1) [52] and causes membrane constriction through its interaction with adaptor proteins MDV1 (mitochondrial

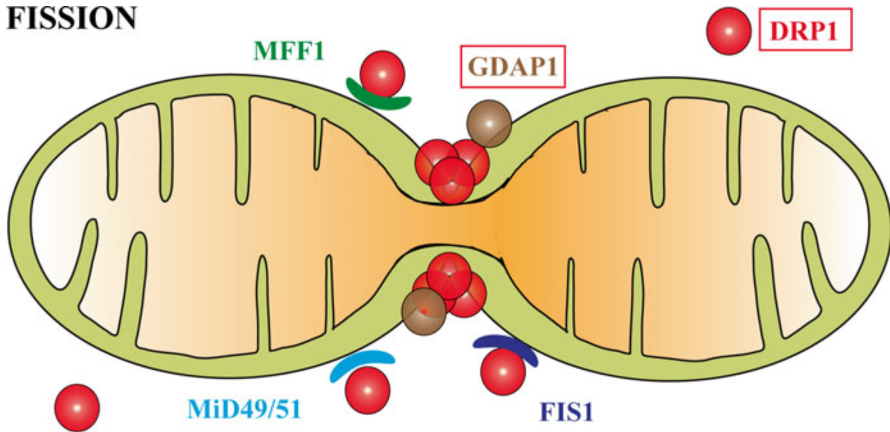

Fig. 7.2 Mammalian mitochondrion under fission. The scheme illustrates DRP1 recruitment to the outer membrane constriction sites by adaptor proteins: FIS1, MFF1, MiD49/51. GDAP1 is located at the mitochondrial outer membrane to mediate mitochondrial fission. A *red square* highlights protein implicated in diseases

division 1) [53–58] and CAF4 (CCR4-associated factor 4) [59, 60]. After its recruitment, DNM1 forms extended spirals [61], which undergo conformational change upon GTP hydrolysis leading to the constriction and division of mitochondria [62].

Extension of these studies to mammalian cells led to the identification of dynamin-related protein 1 (DRP1), also called DLP1 (dynamin-like protein 1) in humans, and FIS1 as components of the mammalian fission machinery [63–65] (Fig. 7.2). However, no orthologues of MDV1 and CAF4 were found in mammals; instead, a growing body of evidence indicates that the mitochondrial fission factor, MFF [66], and the mitochondrial elongation factors, MID49 and MID51 (mitochondrial dynamic proteins of 49 and 51 kDa) [67–71], are further components of the fission machinery. In addition, GDAP1 (ganglioside-induced differentiation-associated protein 1) is a tail-anchored protein of the mitochondrial outer membrane that regulates mitochondrial fission [72, 73]. Whereas GDAP1 recessive mutations are associated with decreased mitochondrial fission activity, dominant mutations result in impairment of mitochondrial fusion [74]. Phylogenetic and structural analyses suggest that GDAP1 belongs to a subfamily of glutathione-S-transferases (GSTs). However, no functional GST activity associated to this protein has been found so far [75]. Unlike other proteins involved in mitochondrial fusion and fission containing GTPase and dynamin domains, GDAP1 sequence analysis does not suggest any involvement in mitochondrial dynamics.

Mitochondrial fission is highly regulated and controlled. For instance, DRP1 undergoes several posttranslational modifications such as phosphorylation [76–79], S-nitrosylation [80, 81], ubiquitination [82–84], and sumoylation [85–87]. These modifications control the activity and subcellular localization of DRP1 [19]. Furthermore, in contrast to mitochondrial fusion, the core of the mitochondrial fission machinery plays a similar role in peroxisomes [65, 88, 89].

7.3 What Are the Physiological and Bioenergetic Roles of Mitochondrial Dynamics?

Mitochondrial fusion plays a critical role in controlling mitochondrial OXPHOS activity through maintenance of the mitochondrial genome. The complete loss of mitochondrial fusion is associated with a loss of the mitochondrial genome in yeast and with a partial loss of mtDNA in mammals [22, 23, 90–92]. Moreover, the mtDNA maintenance defect observed in mitochondrial fusion deficient skeletal muscle is associated with an accumulation of mitochondrial point mutations and deletions [92]. Remarkably, where emerging data indicate that the majority of mitochondrial fission sites are located in close proximity to mtDNA molecules [93, 94] and endoplasmic reticulum contact sites [95, 96], the loss of mitochondrial fission has no deleterious effect on mtDNA levels [51, 97, 98]. Understanding the role of mitochondrial dynamics in the maintenance and protection of mtDNA continues to attract great scientific interest. Intriguingly, partial impairment of mitochondrial fusion caused by the loss of MFN2 in different mammalian tissues or cultured cells affects mitochondrial bioenergetics without drastically affecting OXPHOS subunits or mtDNA levels [99–101].

Despite their high similarity and their common role in mitochondrial fusion through their physical interaction, MFN1 and MFN2 seem to functionally differ. Ubiquitous knockout of the *Mfn1* or *Mfn2* genes results in embryo lethality in mid-gestation [19], due to placental dysfunction [19, 102]. Remarkably, by using a conditional knockout allele in conjunction with cre-recombinase expression only in the embryo, *Mfn1* or *Mfn2* knockout mice are born alive [102]. Mice ubiquitously lacking MFN1 are apparently healthy, whereas loss of MFN2 causes mouse lethality in the early postnatal period and triggers cerebellar atrophy causing severe defects in movement and balance [102]. Despite its well-established role in mitochondrial fusion, a growing body of evidence suggests that MFN2 has additional functions, such as tethering mitochondria with the endoplasmic reticulum (ER) [103], lipid droplets [104], and with the Miro/kinesin system [105, 106]. However, the role of MFN2 in mediating ER-mitochondrial tethering has been recently revised [107, 108]. The different functions of MFN2 are supported by in vivo studies in mice, showing that MFN2 is required for normal glucose homeostasis [99], steroidogenesis [104, 109], is essential for cerebellum development and function [102], and for the axonal projections of dopaminergic neurons [110, 111]. Interestingly, the loss of MFN2 in Purkinje or dopaminergic neurons is associated with a loss of complex IV activity [102, 110]. In contrast, loss of MFN2 in the liver, skeletal muscle, and heart is associated with mild OXPHOS dysfunctions, which are not due to the loss of OXPHOS protein complex levels or activities [99, 112]. Similarly, loss of function of MFN2 in mouse and human fibroblasts cultivated with glucose and high serum shows no gross bioenergetic defects [19, 108, 113]. Interestingly, respiratory chain deficiency observed in MEFs cultivated under low-serum conditions and in mouse heart lacking MFN2 is caused by a deficiency of the terpenoid synthesis pathway affecting the levels of coenzyme Q [101]. This interesting observation demonstrates

that bioenergetic defects associated with loss of mitochondrial fusion are not only related to mitochondrial genetic impairments but could originate from anabolic pathway dysfunctions.

Mitochondrial bioenergetics and mitochondrial fusion are heavily interdependent since mitochondrial fusion requires the membrane potential generated across the inner mitochondrial membrane by the respiratory chain [18, 114–116]. Moreover, bioenergetic defects impair mitochondrial dynamics [117] through the proteolytic processing of OPA1 [118]. The strong connection between mitochondrial fusion and bioenergetics could explain the mitochondrial network remodeling observed when cells are metabolizing non-fermentable [119, 120] or high-energy demanding carbon sources [121, 122]. In addition, downregulation of DRP1 activity under starvation has been shown to increase mitochondrial fusion to prevent the degradation of mitochondria through autophagy [123, 124]. In contrast, DRP1 upregulation [77, 85] and MFN2 downregulation [39] under apoptotic conditions promote mitochondrial fragmentation and the following release of proapoptotic factors from mitochondria mediated by BAK [BCL2-antagonist/killer] and BAX [BCL2-associated protein X] [125].

7.4 Mitochondrial Dynamics and Neurodegeneration

Mitochondrial dynamics hold a central role in maintaining proper mitochondrial distribution and function. Therefore, it is not surprising that alterations in mitochondrial fusion and fission significantly impair neuronal functions. The importance of mitochondrial fusion and fission proteins in the biology of neurons is underscored by the occurrence of several neurodegenerative diseases that result from mutation of these genes. For example, mutations in *Mfn2* are associated with Charcot-Marie-Tooth disease type 2A, and *Opa*1 mutations cause autosomal dominant atrophy characterized by progressive degeneration of the optic nerve.

7.4.1 Charcot-Marie-Tooth Neuropathy

Charcot-Marie-Tooth [CMT] diseases represent a group of clinically and genetically heterogeneous inherited neuropathies affecting motor and/or sensory neurons. With a prevalence between 1 and 8 cases per 10,000 people, CMT is the most prevalent inherited neuropathy [126–128]. CMT type 2A accounts for 22 % of autosomal dominant neuropathies. Typical clinical symptoms of CMT2A are progressive distal limb muscle weakness and/or atrophy, stepping gait, distal sensory loss, and mobility impairment, which can lead to wheelchair dependency. In addition, optic atrophy can be associated with CMT2A presenting an unusually severe phenotype with an early age of onset [129]. However, while affecting a highly specific set of neurons, i.e., neurons with the longest axons [peripheral sensory and motor neurons], the

clinical and electrophysiological phenotypes of CMT2A are very diverse. A major step in the comprehension of the disease was made when several studies identified pathogenic mutations in the *Mfn2* gene [129–131], and to date about 60 different *Mfn*2 mutations have been identified in CMT2A patients [132]. Remarkably, homozygous expression of mutated MFN2^{T105M} in mouse motor neurons recapitulates the key clinical signs of CMT2A. As previously observed in CMT2A neurons [133, 134], affected motor neurons exhibit improper mitochondrial distribution [135]. However, since MFN2 is important for the maintenance of mitochondrial bioenergetics and mitochondrial transport in different types of neuron [102, 110], the molecular role of MFN2 in axonal integrity maintenance remains to be elucidated.

MFN2 is not the only protein involved in mitochondrial dynamics to be associated with the Charcot-Marie-Tooth disease. Unlike other Charcot-Marie-Tooth disease-linked genes, the various GDAP1-associated mutations are associated with demyelinating [136], axonal, or mixed forms of CMT disease with recessive or dominant modes of inheritance, showing a wide range of severity and onset of disease [137–139]. CMT diseases caused by autosomal recessive GDAP1 mutations are generally severe and lead to aggressive disorders appearing during early childhood. The rapid progression of these disorders leads to functional disability. However, the phenotypic presentations of patients carrying GDAP1 mutations are heterogeneous. In most cases patients can present with vocal cord paresis, diaphragmatic paralysis, and facial weakness. In contrast, dominant inherited GDAP1 mutations are less severe and associated with a later onset. Interestingly, GDAP1 knockout mice present with an age-related hypomyelinating peripheral neuropathy. Furthermore, loss of GDAP1 impairs mitochondrial morphology and axonal transport in peripheral neurons [140, 141].

7.4.2 Autosomal Dominant Optic Atrophy

Autosomal dominant optic atrophy (ADOA) is a hereditary optic neuropathy characterized by a bilateral degeneration of optic nerves causing symmetrical visual loss, typically starting during the first decade of life. The disease primarily affects the retinal ganglion cells (RGCs) and their axons which form the optic nerve [142]. ADOA is mainly linked to *OPA1* mutations [32, 49] and is a relatively common form of inherited optic neuropathy; its prevalence is around 3 cases in 100,000 people [143, 144]. In 2007, two independent groups generated mice models expressing a different mutated version of *OPA1*. These studies showed that OPA1 was required during early mouse embryonic development. Interestingly, heterozygous *OPA1* mutants are viable, but exhibit an age-dependent loss of RGCs that eventually progresses to a severe degeneration of ganglion cells and nerve fiber layer [145, 146]. These works demonstrate that the phenotype was not caused by a specific OPA1 proteolytic processing defect, but was associated with a concerted decrease of both L-OPA1 and S-OPA1 levels. In addition, loss of OPA1 was associated with abnormal mitochondrial cristae morphology, mitochondrial swelling, and a reduced

number of optic nerve axons. These mouse models showed that mitochondrial defects caused by the loss of OPA1 affect high-energy glutamatergic synapses which lead to dendritic degeneration of ganglion cells [147].

7.4.3 Neuropathy Linked to DLP1

Human diseases linked to DRP1/DLP1 mutations are extremely rare. In 2007, a de novo mutation in one DLP1 allele was identified in a neonate patient presenting microcephaly, abnormal brain development, optic atrophy, and elevated plasma concentration of lactic acid as well as very long-chain fatty acids causing their death at 37 days of age [148]. Despite the drastic elongation of the mitochondrial and peroxisomal networks, OXPHOS activities were not affected in skin fibroblasts and skeletal muscle biopsies. This mutation was later reported to prevent higher-order assembly of DLP1, thus precluding organelle fission [149]. Interestingly, independent mouse knockouts showed that DRP1 was required for embryonic and brain development. Neuron-specific *Drp1* knockout presents aberrant mitochondrial morphology and distribution preventing proper dendritic and axonal development [98, 150]. Loss of DRP1 in dopaminergic neurons affects mitochondrial mobility and depletes axonal mitochondria. These mitochondrial defects cause degeneration of synaptic terminals and cell loss [151].

The pathological spectrum associated with disturbed mitochondrial fission has recently expanded to include Parkinson's, Huntington's, and Alzheimer's diseases. Pathogenic mutations involved in Parkinson's and Huntington's diseases have been associated with an increased recruitment of DRP1 to mitochondria resulting in excessive mitochondrial fragmentation [152, 153]. Furthermore, DRP1 has also been shown to interact with a Parkinson disease-related protein, LRRK2 (leucine-rich repeat kinase 2) [154]. This interaction enhances mitochondrial translocation of DRP1 to promote mitochondrial fragmentation. In the case of Alzheimer's disease, mitochondrial fragmentation is progressively increased during the progression of the disease both in patients and in transgenic mouse models [155–157]. However, the molecular mechanism involved is still unclear. Interestingly, it has been reported that DRP1 posttranslational modifications such as S-nitrosylation and phosphorylation hold a crucial role in Alzheimer's disease [80, 158].

7.5 Conclusion

Overall, it is clear that perturbations in mitochondrial dynamics and activity are directly or indirectly involved in neurodegenerative diseases. However, although in vitro studies have provided crucial information regarding mutations, structure, and molecular response, almost nothing is known about the in vivo regulation of mitochondrial dynamics in healthy adult axons or synapses. Furthermore, it is

becoming increasingly clear that multiple factors can affect mitochondrial dynamics, and the strong interdependence between mitochondrial activity, dynamics, and transport introduces additional complexity. A future challenge will be to unravel the molecular nature of these interactions. To this end, availability of established disease models will allow rapid progress in our understanding of the physiological regulation of mitochondrial dynamics and will open promising new avenues to test both in vitro and in vivo efficacy of potential new agents to find treatment options for these progressive neurodegenerative diseases.

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