

Review

Mitochondrial dynamics in neurodegeneration: from cell death to energetic states

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Abstract: From Parkinson's disease to an ischemic stroke, a consistently reoccurring theme in the context of neuronal degeneration is the dysfunction of mitochondria as the underlying factor. Insight into the mechanistic basis for mitochondrial dysfunction in neurodegenerative disorders has allowed the theme of mitochondrial dynamics to be highlighted as a central player. The precise balance of mitochondrial dynamics is among the most critical features for the juxtaposed processes of cell death and survival. More recently, studies have allowed mitochondrial shape to emerge as a key regulator of respiratory efficiency that can enforce the bioenergetic status of cells and thereby determine cell fate. Here we review the most current advances that provide an explanation for the long-standing question of how mitochondrial shape can impact cellular metabolism. Furthermore, we discuss the implications of an imbalance in mitochondrial dynamics in neurodegenerative disorders.

Keywords: mitochondrial dynamics; cristae architecture; bioenergetics; ATP production; cell survival; neurodegeneration

1. Introduction

Mitochondria are considered the powerhouse of the eukaryotic cell. Classically known to be the cellular energy producer, the mitochondrion has gained even more attention over the years with the cumulative discoveries of additional functions. The modern day view of mitochondria instills upon it an array of functions, from the traditional ATP production to more recent implications in cell signaling [1]. Despite the diversity of functions, mitochondria remain best acknowledged as the chief energy providers for the cell. This is most relevant in high-energy consuming cells. Neurons, in particular, are sensitive to alterations in mitochondrial ATP production mainly due to their high-energy consumption properties and their low glycolytic capacity [2,3]. In this sense, the

biological relevance of sustained and efficiently functional mitochondria in the neuronal population becomes clear.

Studies from the past decade have been focused on understanding the nature of mitochondria and the regulatory mechanisms that impinge on their functional output. These studies led to major discoveries revealing that mitochondria are highly dynamic organelles that undergo continuous cycles of fission and fusion [4-6]. It is the disruption of this fine balance in mitochondrial dynamics that appears as an important factor in neurodegenerative disorders [7-9]. The equilibrium of fission and fusion events not only dictates the structural morphology of mitochondria, but also regulates metabolism [10-12]. However, it has been unclear as to how mitochondrial shape can affect ATP production through oxidative phosphorylation (OXPHOS). Recent studies in the field now reveal that mitochondrial dynamics are directly involved in the energetic output of mitochondria [13-17]. These dynamic architectural changes allow cells to thrive under stress conditions and can ultimately impose life and death decisions. In this review, we will discuss the latest evidence supporting a role for mitochondrial dynamics as a regulatory mechanism that can dictate the bioenergetic status of cells. We will also discuss how mitochondrial restructuring is an absolute essential component of the cellular adaptation to stress, not only to mute cell death signaling but also to modify energy production.

2. Mitochondrial dynamics

Mitochondria are one example of an organelle whose shape and structure can act as a functional regulatory factor. Contrary to the textbook view of mitochondria as static rod shaped organelles, mitochondria are in fact highly dynamic both at the structural and ultra-structural levels [4]. At the structural level, mitochondria are constantly undergoing cycles of fission and fusion, whereby the equilibrium of these two opposing processes dictates the overall length and connectivity of mitochondria. At the ultra-structural level, mitochondria are able to modify their cristae architecture [18]. The fusion of two mitochondria requires the coordinated process of outer and inner membrane fusion [19,20]. Mitochondrial fusion is mediated by three dynamin related large GTPases: Mitofusin 1 (MFN1), Mitofusin 2 (MFN2) and Optic atrophy protein 1 (Opa1) [21,22]. During outer membrane fusion, the transmembrane MFN1 and MFN2 form homo- and hetero-oligomeric complexes to tether the outer membranes of two mitochondria[21]. Meanwhile, the intermembrane OPA1 tethers the inner membranes to direct inner membrane fusion[20]. In addition to its role in inner membrane fusion, OPA1 is a master regulator of cristae structure and remodeling [22,23]. The fission process, on the other hand, involves the division of mitochondria at the inner and outer membrane through the action of the large GTPase, dynamin related protein 1 (DRP1), as well as other factors including Fis1, MFF, MiD49 and MiD51 [24,25]. In addition to these proteins, recent studies provide evidence for the involvement of cellular components in the division of mitochondria, namely the endoplasmic reticulum (ER) and the actin cytoskeleton [26-28].

3. A regulated balance of mitochondrial dynamics

Mitochondrial length and ultrastructural morphology, as dictated by the rates of fission, fusion and cristae modifications, are far from random events. Recent studies have shown that dynamic changes in mitochondrial architecture have a major impact on the cell's ability to survive stress and

modify their energy production [29-33]. In addition to the steady-state basal dynamics of mitochondria, it is now clear that mitochondria are able to rapidly and efficiently alter their structure in response to a variety of cues [29,30,34]. For this reason, “mitochondrial dynamics” should now reflect the ability of mitochondria to constantly modify their architecture, both basally and in response to changing cellular and environmental cues, in order to elicit changes in length, connectivity, cristae structure and function. In fact, these processes are essential to the well-being of mitochondria, and thus of the cell. Below we will provide a brief overview for the evidence that implicates disruption of mitochondrial dynamics as a major player in the degeneration of multiple neuronal populations.

4. Evidence for abnormal mitochondrial dynamics in neurodegeneration

The importance of mitochondrial dynamics in nervous system function first became apparent by genetic studies that identified mutations in the fusion machinery in neurodegenerative diseases [35-38]. We now know that mitochondrial dynamics are a crucial part in the maintenance of neuronal survival, as pathological imbalances between fusion and fission events develop in many neurodegenerative disorders and acute brain injury [9,39-41]. During aging, neurodegenerative diseases and extreme stress conditions, mitochondria in neurons become fragmented and dysfunctional. This change in mitochondrial morphology is attained by either direct or indirect mechanisms that alter the function of the fission/fusion machinery.

4.1. Neurodegenerative diseases

The pathological spectrum associated with a disturbance in mitochondrial dynamics encompasses a group of neurological disorders, including Parkinson’s disease (PD), Alzheimer’s disease (AD), and Huntington’s disease (HD) [7,9,41]. Studies of genes mediating familial forms of PD have provided compelling evidence, at the genetic level, for a role of mitochondrial dynamics in the development of PD [42,43]. As an example, mutations in proteins related to the familial forms of PD, particularly the autosomal recessive PD proteins PINK1, Parkin and DJ-1 have been shown to regulate mitochondrial dynamics and morphology through modulation of DRP1 expression and activity [44-46]. It has been shown that Parkin interacts with Drp1 and mediates its ubiquitination and subsequent proteasomal degradation [47]. Pathogenic mutations or knockdown of Parkin lead to increased Drp1 levels and aberrant mitochondrial fission [45]. Furthermore, mutations in the autosomal dominant PD protein LRRK2, which represents the most common genetic cause of PD, causes massive mitochondrial fragmentation through alterations of DRP1 [48,49]. In the case of AD, although the pathogenesis for this disease is not well understood, there is accumulating evidence for the implication of mitochondrial dysfunction. The observed extensive mitochondrial fragmentation in concert with changes in gene expression of mitochondrial fission/fusion machinery suggest an imbalance in mitochondrial dynamics [50-52]. Likewise, changes in mitochondrial dynamics have been found in HD patients and animal models of the disease, leading to excessive fragmentation and decreased motility of mitochondria [53]. Of interest is the discovery that mutant huntington (HTT) can potentiate the pro-fission activity of DRP1 [54]. Together these studies provide strong evidence that aberrant mitochondrial fragmentation represents a common axis in neurodegenerative disorders.

4.2. Aging

Aging is one of the most understudied areas in biology that can be envisioned as neurodegeneration set in slow motion. The aging process in mammalian cells compromises the dynamic plasticity of mitochondria through disruption of the regulatory balance of fission and fusion pathways, although the underlying mechanisms are largely unknown [55-57]. As such, dysregulation of mitochondrial dynamics is thought to play a role in the increased incidence of age-related disorders and higher susceptibility of cells to various stress conditions during progressive aging. Studies performed in skeletal muscle of aging individuals have revealed an altered expression of mitochondrial fission/fusion proteins [58]. Furthermore, mice with a muscle-specific deficiency in Fis1 and Drp1, which reduces mitochondrial fission activity, showed a diminished level of muscle atrophy and attenuated activation of atrophy-related genes during fasting. At the ultrastructural level, profound age-dependent loss of cristae structure has been documented in an aging model organism [59]. A recent study has shed light on the outcome of homeostatic regulation of mitochondrial dynamics in the aging brain. Proteomic analysis of synaptosomal mitochondria in aging mice revealed an age-dependent alteration in the expression of the mitochondrial fission protein DRP1 and mitochondrial fusion proteins MFN1 and OPA1, that suggests an attempt to maintain a fission-fusion balance with age [60]. These studies demonstrate a role for mitochondrial-shaping proteins in cellular survival during aging and stress.

4.3. Acute stress conditions

A modification in mitochondrial morphology is a prominent phenotype observed in various neuronal populations in response to pathophysiological conditions. In fact, a large body of evidence indicates that aberrant mitochondrial fission is an early event following acute brain injury and is considered a key contributing factor in the ensuing demise of neurons [61-64]. Several *in vivo* animal and *in vitro* neuronal culture models of brain injury, particularly those relevant to ischemic stroke, show a common activation of the mitochondrial fission pathway. For example, rapid fragmentation of mitochondria has been demonstrated during hypoxia, glutamate toxicity, transient or focal ischemia, OGD (oxygen-glucose deprivation) and oxidative damage through increased levels of NO (nitric oxide) and ROS (reactive oxygen species) [61,63-69]. Regardless of the upstream stress stimulus, DRP1-mediated activation of the fission pathway precedes the initiation of cell death signaling. With this in mind, it can be appreciated how the homeostatic regulation of mitochondrial dynamics is a central player in the survival of neurons during stress.

5. The protective effect of rebalancing mitochondrial dynamics in neurodegeneration disorders

The relevance of altered mitochondrial dynamics as a main mediator of neuronal degeneration is strengthened by the myriad of data demonstrating the protective effect of either inhibiting fission or enhancing fusion. As previously mentioned, activation of DRP1-mediated mitochondrial fission is an important contributing factor in the progression of PD. Neurons lacking PINK or Parkin accumulate DRP1, resulting in excessive mitochondrial fission, increased oxidative stress, and reduced ATP production [70-74]. These defects can be reversed by the inhibition of mitochondrial

fission with the use of mdivi-1, an inhibitor of the DRP1 pathway, or by overexpression of MFN2 or OPA1 [70-72]. Recently, the effectiveness of preventing mitochondrial fission as a therapeutic intervention has been tested using a newly developed selective peptide inhibitor of DRP1, termed P110 [75]. Researchers differentiated iPSC (induced pluripotent stem cells) from PD patients with a mutation in LRRK2 into dopaminergic neurons and treated these cells with P110. This led to a substantial reduction of mitochondrial fragmentation. Even more compelling evidence for the inhibition of fission as a pharmacological strategy has been demonstrated in acute injury models. *In vitro* models of glutamate-toxicity or OGD in mouse hippocampal neurons or *in vivo* mouse models of transient focal ischemia can be protected from enhanced mitochondrial fission and apoptosis by DRP1 knockdown or mdivi-1 inhibition [34,76-78]. Furthermore, overexpression of mitochondrial fusion proteins has significant protective effect under different stress conditions, such as NMDA excitotoxicity, DNA damage and oxidative stress [34,66,67]. Thus overriding mitochondrial fission, regardless of the cause, and enhancing mitochondrial fusion can preserve mitochondrial architecture and neuronal survival. The key question here is, how can mitochondrial shape alter a cell's ability to survive stress.

6. Physiological remodeling of mitochondrial structure and function: a sensor of energy supply and demand

In terms of the role of mitochondrial dynamics in cell survival, much of the focus has been placed on the negative impact of mitochondrial fission. This is mainly due to the elegant studies demonstrating the intimate link between cristae remodeling during the fission process, and the propagation of cell death signaling [62,79-82]. In addition, Drp1 mediated constriction of mitochondria, which promotes tethering and hemifusion of membranes, has been shown to stimulate oligomerization of the pro-apoptotic protein BAX and release of cytochrome c [83]. Currently, mitochondrial fusion has been receiving more attention as several studies are emerging with the concept that elongated mitochondria, through enhanced fusion capacity, play a major role in the cellular response to changing metabolic environment and stress conditions (Figure 1) [29,30,79]. Mitochondria possess complex adaptive responses and can react to the changing microenvironment through modifications of mitochondrial shape and cristae architecture. Stress-induced mitochondrial hyperfusion (SIMH) is a phenomenon present in a variety of mammalian cycling cells that is activated in response to a number of stress stimuli, such as UV irradiation and amino-acid deprivation [30]. As the name implies, SIMH promotes massive hyperfusion of mitochondria through activation of OPA1, MFN1 and SLP2, a mitochondrial inner membrane protein that regulates OPA1. Activation of this pathway confers resistance to cells under stress conditions and allows the maintenance of mitochondrial ATP production [30]. Other studies have demonstrated that metabolic stress in MEFs, such as nutrient deprivation, inhibits DRP1 and results in mitochondrial elongation as well OPA1-dependent cristae remodeling and maintained ATP production [16,29,84]. Although physiological stimuli that modify mitochondrial dynamics have been identified in cycling cells, such mechanisms remained unknown in neurons. Our recent study identifies the first example of a physiological regulator of mitochondrial dynamics in multiple neuronal populations, showing the protective nature of mitochondrial elongation during stress [34]. We observed that hypoxic stress-induced changes in the microenvironment, which causes a mild decrease in the extracellular pH, activates a dual program that inhibits DRP-1 mediated fission and promotes mitochondrial

elongation through activation of SIMH [34]. Mitochondrial remodeling by acidosis protects neurons from cell death during chronic hypoxic exposure, sustains mitochondrial integrity and ATP production despite oxygen limitations. Interestingly, the common theme observed in all cases whereby mitochondrial response elicits an activation of fusion is the maintained or enhanced capacity for ATP production. Thus posing the question of how can mitochondrial length act as a regulator of metabolic output.

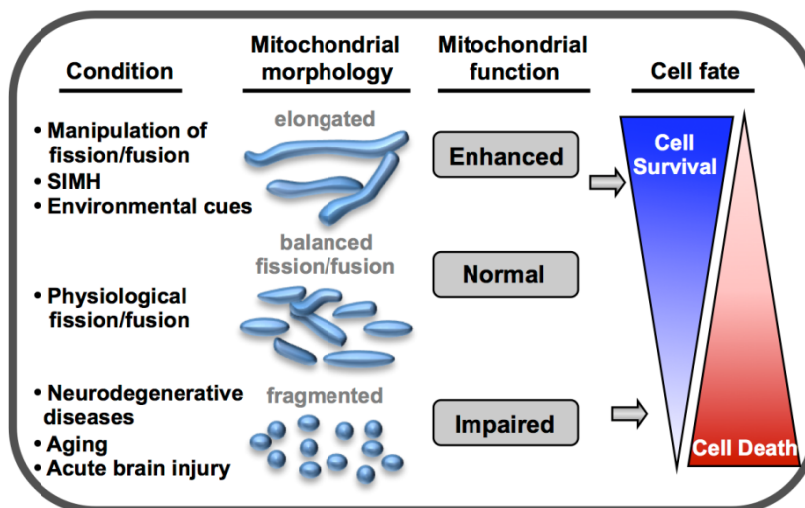


Figure 1. Manipulation of mitochondrial dynamics as a strategy to promote neuronal survival and adaptation to stress conditions. Aberrant mitochondrial fragmentation is a common theme in neurodegeneration leading to impaired mitochondrial function and increased cell death. Promoting mitochondrial fusion, by exogenous or endogenous mechanisms, can sustain mitochondrial function to maintain neuronal survival.

7. The importance of mitochondrial remodeling: the bioenergetics perspective

The existence of a strong interlinking connection between cell survival and mitochondrial dynamics is well established, yet several lingering questions remain. Why is the maintenance of plasticity in mitochondrial dynamics important and how does the alteration of mitochondrial shape regulate functional output? This is of particular importance to the neuronal population since these cells rely on a continuous supply of energy through mitochondrial respiration. In addition, neurons do not possess robust compensatory mechanisms that can allow a shift to glycolytic metabolism while maintaining an efficient supply of energy, as observed in cancer cells [85-90]. Thus a central intriguing question is whether mitochondrial shape changes can impact mitochondrial energy production. New insights from the latest wave of discoveries have influenced our appreciation for mitochondrial dynamics in the regulation of bioenergetics.

7.1. Mitochondrial dynamics drives ETC supercomplex assembly to enhance ATP generation

Under physiological conditions, both OPA1 and MFN2 have been assumed to be involved in maintaining mitochondrial respiration. This is largely based on studies whereby loss of mitochondrial fusion, through genetic loss or mutations in OPA1 and MFN1/2, shows a defect in mitochondrial coupling, decreased membrane potential, impaired mitochondrial-dependent ATP production and disruption of certain ETC complexes [91-95]. The general belief being that dysregulation of mitochondrial fusion would lead to accumulation of defective mitochondria through loss of mtDNA complementation [96,97]. Recently, however, a direct role for OPA1 in the regulation of mitochondrial respiratory efficiency has been established [17]. OPA1-dependent modulation of cristae shape regulates the assembly of the ETC into supercomplexes for maintaining optimal mitochondrial respiration and cell growth [17]. Disruption of cristae shape by acute loss of OPA1 was sufficient to disrupt supercomplex assembly and respiratory capacity prior to any impairment of mtDNA copy number. Meanwhile, a slight elevation in the levels of OPA1 led to tighter cristae, increased activity of respiratory enzymes and enhanced the respiratory efficiency of mitochondria [17]. This provides the first evidence that mitochondrial dynamics, cristae structure and respiratory function are interconnected.

7.2. Mitochondrial reconfiguration during stress dictates cellular bioenergetics and cell survival

Dynamic changes in mitochondrial architecture have a major impact on the ability of cells to survive stress and modify their energy production. Our recent work demonstrates that mitochondria can respond to different environmental cues to modify their energetic output and promote cell survival [16,34]. In essence, the state of the mitochondrial network and cristae organization can be reconfigured to reflect the metabolic demand of a cell under stress conditions [98-100]. OPA1 can respond rapidly to changes in nutrient levels in cycling cells to regulate cristae structure [16]. By forming oligomeric interactions, OPA1 can regulate cristae tightness to enhance the stability of ETC complexes, drive the formation of supercomplexes and increase assembly of the ATP synthase to maintain mitochondrial respiration during cellular starvation (Figure 2). Importantly, in the absence of OPA1 cells were no longer resistant to starvation-induced cell death.

Our recent work shows that mitochondrial elongation and cristae remodeling in neurons, by physiological cues during ischemic conditions, can go so far as to maintain efficient mitochondrial ATP production even amid conditions that cannot support this process, such as severe hypoxia [34]. The remodeling of mitochondria under such conditions can instigate a systemic reconfiguration of mitochondrial efficiency to extract more ATP per oxygen molecule, by driving the supercomplex assembly of ETC complexes and ramping up the respiratory reserve capacity. In doing so, mitochondrial structure can dictate the bioenergetic status of neurons and allows sustained ATP levels without the need for glycolysis. This study provides an explanation into the protective effect of mitochondrial fusion that goes beyond the inhibition of apoptotic signaling. Furthermore, it places the changes in mitochondrial architecture as a regulatory mechanism for the bioenergetic adaptation to metabolic demand that can quickly endorse the fate of cells (Figure 3).

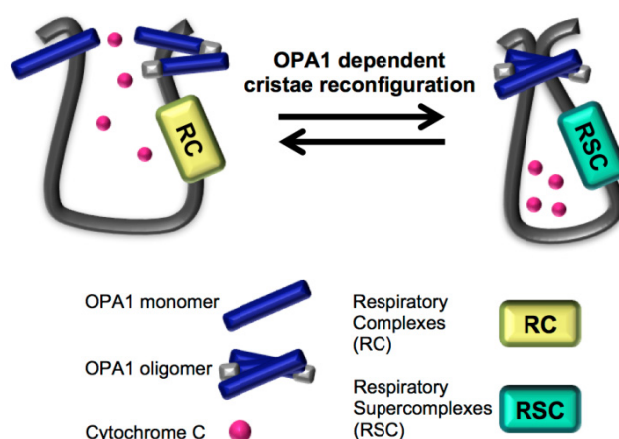


Figure 2. The dual function of OPA1-mediated reconfiguration of mitochondrial cristae architecture. Reversible formation of OPA1 oligomers controls cristae tightness. OPA1-dependent regulation of cristae architecture serves two purposes; 1) to prevent the release of apoptotic factors, such as cytochrome c, and 2) to promote supercomplex assembly of the ETC complexes. This promotes cell survival by maintaining efficient mitochondrial function while preventing cell death.

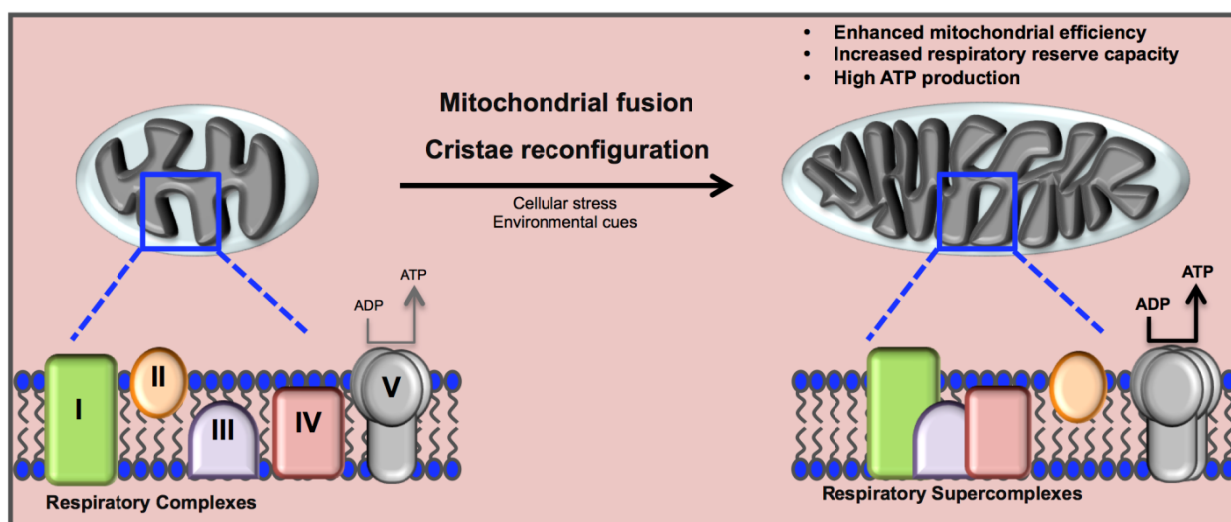


Figure 3. Mitochondrial fusion and cristae reconfiguration regulate the bioenergetic status of cells. Mitochondrial dynamics is a mechanism for the cellular adaptation to stress. In response to stress and different environmental cues, mitochondria can modify fusion activity and cristae architecture to promote the assembly of respiratory complexes into supercomplexes, and the maintenance of ATP synthase complexes. This enhances the respiratory efficiency of mitochondria in order to increase energy production.

8. Clinical implications of targeting mitochondrial dynamics

Recent evidence, from our work and others, demonstrate that mitochondrial dynamics is a strong regulatory point for neuronal survival. The inhibition of mitochondrial fission is a very

important strategy in the prevention of cell death. However, one needs to consider the nature of neurons and the high level of energy consumption that is required for their effective function in the brain. To this end, we propose that targeting mitochondrial fusion and modification of cristae architecture may allow neurons to both survive and thrive during conditions of stress. As such, manipulations of mitochondrial shape as a means to not only prevent cell death but to also enhance energy production for neuronal survival should now be at the forefront in the design of therapeutic disease interventions.

9. Conclusion

The imbalance in mitochondrial dynamics that is observed in many neurodegenerative disorders and during aging and stress conditions is an important element that contributes to neuronal death. In addition to the impact of mitochondrial dynamics on cell death signaling, studies have now revealed that mitochondrial structure can directly regulate cellular metabolism. Therefore, alterations in mitochondrial dynamics and structure can be viewed as a regulatory mechanism for the cellular adaptation to stress, that prevent cell death while maintaining metabolic integrity. The ability of mitochondria to respond to different stresses or environmental cues by reconfiguring their functional efficiency, through modification of fusion activity and cristae architecture, is essential to the continued survival of neurons.

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Conflict of interest

All authors declare no conflicts of interest in this paper.

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