Mitochondrial Dynamics

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Mitochondria are highly dynamic organelles that undergo morphological changes in order to adapt to cellular demands. These changes are orchestrated by the coordinated cycles of fusion and fission, referred to as mitochondrial dynamics, and dysregulation of these processes contributes to disease development.

mitochondrial dynamics fusion fission mitophagy

1. Introduction

Mitochondria represent a tubular, remarkably dynamic system of membrane-bound cell organelles that were first observed in high-resolution electron micrographs in the early 1950s [1]. Since their endosymbiotic biogenesis through the fateful integration of an *alpha*-proteobacterium within an archaeal host cell [2], mitochondria have become indispensable constituents of multicellular life. They are responsible for the production of the chemical energy required for cell metabolism through oxidative phosphorylation (OXPHOS) in the form of adenosine triphosphate (ATP) and thus, are often called the “energy factories” of the cell [3][4]. In the 1890s, the microbiologist Carl Benda coined the term mitochondrion from the Greek words “mitos”, which means “thread”, and “chondrion”, which means “small granule”, as he perceived, under a microscope, hundreds of tiny bodies with the tendency to form long chains in the cytoplasm of eukaryotic cells [5].

As a result of their endosymbiotic origin, mitochondria carry their own genome, which is denoted as mtDNA and encodes 13 components of the OXPHOS system that are synthesized by ribosomes present within mitochondria. The remaining subunits of the system, as well as proteins required for mtDNA replication, transcription and translation, are encoded by nuclear genes [6]. Structurally, mitochondria consist of an outer membrane that encloses the entire content of the organelle and an inner membrane that houses the OXPHOS system and delineates the mitochondrial matrix. The inner mitochondrial membrane (IMM) has a larger surface area than the outer mitochondrial membrane (OMM) and is characterized by a specific spatial arrangement consisting of a series of invaginations known as “cristae”, which extend into the matrix. Between the outer and inner membranes, there is an enclosed compartment, referred to as the intermembrane space [7].

As highly dynamic structures, mitochondria undergo morphological changes and spatial rearrangements in order to adapt to cellular demands and to maintain energy homeostasis. These changes are modulated through the coordinated cycles of mitochondrial fusion and fission, commonly referred to as mitochondrial dynamics, which control mitochondrial number, size, shape and distribution within the cell [8][9]. The delicate equilibrium between fusion and fission confers important benefits that are brought about through the exchange of mitochondrial content,

maintenance of their genome and segregation of dysfunctional organelles that are targeted for autophagic degradation [10], a mitochondrial quality-control process known as mitophagy. This selective form of autophagy acts in concert with mitochondrial biogenesis for the control of mitochondrial turnover. Mitophagy is a crucial process in maintaining mitochondrial homeostasis, and aberrant sequestration of dysfunctional mitochondria due to impaired mitochondrial fission contributes to disease development [11][12].

2. Mitochondrial Dynamics and Associated Diseases

Unequivocally, the steady-state and dynamic equilibrium of the mitochondrial network is critical for preserving optimal function at the organismal level. Disruption of the delicate equilibrium between the two opposing processes of fusion and fission results in a fragmented or elongated mitochondrial network that has been associated with several pathological conditions. Besides the mutations in nuclear or mitochondrially encoded genes that are associated with monogenic diseases of mitochondrial dysfunction [13], aberrations in mitochondrial structure have recently emerged as a pathogenic mechanism of more complex diseases and opened a new perspective in disease pathology (Table 1). Examples of such pathologies include various metabolic conditions, cancer and a broad spectrum of neurodegenerative diseases [14][15][16].

2.1. Defects in Mitochondrial Fusion Mediators and Disease

Systematic studies have shown that a plethora of human diseases are associated with excessive mitochondrial fragmentation as a result of defective fusion.

Neurons are cells of extremely high energy demand and are thus particularly vulnerable to mitochondrial dysfunction. Alterations in the mitochondrial network and consequent mitochondrial dysfunction have been suggested to occur as prominent early features in neurodegenerative diseases [17]. Nowadays, there is an increasing number of neurodegenerative disorders that are associated with mutations in mitochondrial fusion genes. Genetic alterations in the *MFN2* gene represent the most common molecular cause of Charcot–Marie–Tooth disease Type 2A (CMT2A), a dominantly inherited form of peripheral neuropathy. To date, more than 100 different mutations affecting *MFN2* have been reported in patients with CMT2A (available from: uantwerpen.vib.be). The typical clinical symptoms of CMT2A involve the progressive atrophy of distal limb muscles that usually leads to wheelchair dependency in patients and a decrease of deep-tendon reflexes linked to foot deformities and distal sensory loss [18]. Structural studies have shown that the majority of CMT2A-associated mutations in *MFN2* are mapped to four distinct functional zones and are mostly associated with severe CMT2A phenotypes, whereas mutations beyond the functional domains lead to milder symptoms. At the molecular level, MFN2 mutants encoding truncated or dimerization-incompetent proteins are more likely to cause disease due to decreased levels of normal MFN2, whereas mutants capable of dimerization and fusion tend to be pathogenic by hijacking normal MFN1 and MFN2 activity [19]. In a recent study, the pharmacological activation of MFN2 using mitofusin agonists was shown to overcome fusion suppression and reversed mitochondrial defects in cultured neurons expressing CMT2A mutants [20]. Moreover, overexpression of MFN1 in a CMT2A mouse model expressing mutant MFN2 was shown to reverse mitochondrial network defects and mitigate phenotypic abnormalities, supporting the notion that imbalances in

mitofusin function is a key determinant in disease development [21]. *MFN2* mutations have been also linked to another type of CMT disease, designated as hereditary motor and sensory neuropathy (HMSN) Type IV, which is characterized by subacute optic neuropathy, bilateral visual impairment and color-vision defects. Interestingly, mutations in the IMM fusion mediator OPA1 underlie the most prevalent form of autosomal dominant optic neuropathy, suggesting a functional overlap of OPA1 with MFN2. The above further implies that balanced mitochondrial dynamics are of particular importance for the proper function of the optic nerve [22][23][24].

Given their key regulatory role in energy metabolism, mitochondria respond to the availability of nutrients and energy demands by adjusting mitochondrial dynamics to maintain homeostasis. As mentioned earlier, under conditions of nutrient shortage and increased energy demand, the mitochondrial network appears elongated, whereas ample nutrient supply and decreased energy demand are associated with mitochondrial fragmentation [25] [26]. It is therefore not surprising that imbalances in mitochondrial dynamics have been recognized as central players in the pathophysiology of obesity and diabetes. Ultrastructural observations in skeletal muscle of obese and type-2 diabetic subjects revealed perturbed structural organization of the mitochondrial network, characterized by small and fragmented mitochondria as compared to healthy controls [27]. Altered expression of MFN1 and MFN2 has been implicated by several studies for abnormal mitochondrial metabolism and the development of diabetes. A study examining MFN2 expression levels in the skeletal muscle of obese and diabetic patients showed reduced MFN2 expression and decreased insulin sensitivity associated with alterations in mitochondrial morphology and aberrant muscle metabolism [28]. In line with the above, a different study reported reduced mRNA levels and protein expression of MFN2 in the skeletal muscle of obese subjects and high-fat Zucker rats, while subsequent electron microscopy analysis revealed disturbed architecture and fragmentation of the mitochondrial network. In addition, the partial abolishment of MFN2 expression led to abnormal mitochondrial metabolism in vitro [29], which is a key risk factor in the development of diabetes. Additional observations in a mouse model of high-fat-diet-induced obesity associated with mitochondrial dysfunction showed that MFN1 and MFN2 expression in skeletal muscle was significantly decreased, concomitant with an increase in the expression of the mitochondrial fission mediators DRP1 and FIS1, thereby shifting mitochondrial dynamics towards fission [30]. Corroborating data from another in vivo study demonstrated that mice lacking MFN1 in proopiomelanocortin (POMC) neurons exhibit abnormal glucose levels due to perturbations in insulin secretion, unveiling a new role for mitochondrial dynamics in the regulation of insulin signaling and glucose homeostasis [31].

As mentioned earlier, OPA1 mutants are responsible for the autosomal dominant optic atrophy-1 (ADOA), a neuro-ophthalmic condition primarily characterized by impairment of visual acuity and generalized color-vision deficits [32] [33]. Besides ocular symptoms, a large number of OPA1 variants have been associated with additional clinical complications including auditory neuropathy, myopathy and ataxia, which define a new type of disease, termed ADOA-plus syndrome [34]. Since the precise pathomechanism of ADOA is not yet fully clear and given the large number of OPA1 mutants that result in truncated products, it has been suggested that haploinsufficiency may represent one of the major disease-causing mechanisms [35]. Certainly, the broad mutation spectrum and the difficulty to establish phenotype–genotype correlations in ADOA patients support the notion that there are additional genetic factors implicated in disease development that have not yet been elucidated. Regardless of the underlying mechanism, mitochondrial fragmentation has been described as a common feature in ADOA with disease severity

being proportional to the extent of fragmentation, underscoring the involvement of defective mitochondrial fusion in disease development [36][37]. Rare OPA1 mutants have been also reported in patients characterized by parkinsonism and dementia, conferring further evidence of the involvement of abnormal mitochondrial fusion in the pathogenesis of other common neurodegenerative diseases [38][39].

2.2. Defects in Mitochondrial Fission Mediators and Disease

In addition to aberrations in the function of mitochondrial fusion mediators, perturbations of the mitochondrial fission machinery have received special attention with regards to their relevance in the development and progression of human pathologies.

Disturbances in mitochondrial fission and in particular in the function of the DRP1 protein have been proposed to play a principal role in the initiation and progression of cancer, though different cancers are known to have distinct oncogenic backgrounds and etiologies. It has been shown that lung-cancer cell lines and lung adenocarcinoma cells from patients exhibit excessive mitochondrial network fragmentation as a result of increased DRP1 expression and reduced MFN2 levels [40]. Moreover, evidence from the same study revealed that the DRP1 protein was not only overexpressed across two different adenocarcinoma cell lines but that its activity was further enhanced after phosphorylation on Ser-616. In contrast, DRP1 inhibition or MFN2 overexpression resulted in reduced proliferation of cancer cells, increased apoptosis and significant regression of tumor growth in vivo [40]. In a second study, DRP1 and mitochondrial dynamics were shown to have a principal role in brain-tumor development. Brain tumor initiating cells (BTICs), which represent a distinguished subpopulation of tumor cells, displayed an increased rate of small and fragmented mitochondria and DRP1 hyperactivation, as compared to non-BTICs. Selective inhibition of DRP1 eliminated tumor growth and increased tumor latency and survival in vivo [41]. Furthermore, a *DRP1*-based large-scale analysis of cancer genomes across various cancer types revealed a robust association of *DRP1* with cell-cycle genes, postulating a role for DRP1 and mitochondrial fission in the regulation of cell proliferation [42]. It is not yet clear whether mitochondrial fragmentation triggers the transformation of cancerous cells, promotes cell-cycle progression or changes the susceptibility of tumor cells to apoptosis, but certainly mitochondrial division is evidently involved in human tumorigenesis.

Over the last few years, mitochondrial fission has been increasingly implicated in a number of neurodegenerative disorders, including Alzheimer's disease (AD), the leading cause of senile and presenile dementia. Pathologically, AD is characterized by generalized cortical atrophy and aggregations of neurofibrillary tangles and amyloid plaques, the density of which appears to correlate with the clinical presentation [43]. Expression analysis of the primary fusion and fission mediators in postmortem AD brains revealed abnormal levels of DRP1, MFN1, MFN2, FIS1 and OPA1, suggesting that altered equilibrium of mitochondrial dynamics may represent a mechanism underlying neuronal dysfunction in AD [44]. AD-associated Aβ plaques' deposition and cognitive impairment is ameliorated upon DRP1 inhibition, as reported by recent studies [45][46]. The selective inhibition of DRP1-mediated mitochondrial division using mitochondrial-division inhibitor 1 (Mdivi-1) was shown to improve synaptic damage and mitochondrial function due to diminished mitochondrial fission in AD neurons [45]. In a second study, the selective inhibition of DRP1 by Mdivi-1 in Aβ-treated neurons blocked mitochondrial fragmentation and improved

mitochondrial function. Furthermore, DRP1 inhibition led to a significant decrease of Aβ plaques in the brain of an AD mouse model and alleviated cognitive symptoms [46]. More recent evidence from fibroblasts derived from AD patients showed increased interaction of DRP1 with its adaptor protein, FIS1, resulting in excessive mitochondrial fission and dysfunction. Conversely, pharmacological inhibition of DRP1/FIS1 interaction improved mitochondrial function in cultured neurons and significantly mitigated the pathological features in the brain of an AD mouse model [47]. In line with the above, a spectrum of mitochondrial abnormalities, including functional distress and the accumulation of fragmented mitochondria, were identified in close proximity to areas with dense amyloid plaque formation in the brains of transgenic animals with AD pathology [48].

Besides AD, mitochondrial dysfunction in neuronal cells is also regarded as one of the main mechanisms for the development of Parkinson's disease (PD), a degenerative disorder of the central nervous system affecting the motor activity of millions of people worldwide. The histopathological hallmark of PD is the intraneuronal build-up of misfolded proteins such as a-synuclein in the substantia nigra leading to the loss of dopaminergic neurons and concomitant dopamine deficiency [49]. Despite the so far obscure etiology of PD, multiple lines of evidence propose mitochondrial dysfunction as an underlying mechanism with potential deleterious effects on neuronal activity. The discovery of multiple mutations in the mitochondrial quality-control protein PTEN-induced putative kinase 1 (PINK1), which are responsible for the autosomal recessive familial PD [50], and, given the implication of PINK1 in mitochondrial dynamics [51][52], the conclusion is that mitochondrial integrity in PD pathogenesis is of central importance. Indeed, it has been demonstrated that the depletion of PINK1 or expression of a PINK1 mutant protein heavily tipped the balance towards fission and excessive mitochondrial fragmentation, while overexpression of the wild-type protein promoted fusion by increasing MFN2 expression [53]. Corroborating research indicated that PINK1 deficiency in a human dopaminergic cell line leads to increased mitochondrial fragmentation and increased mitochondrial autophagy, resulting in "autophagic stress", a critical determinant of neurodegeneration [52]. Consistent with the previous studies, abnormal mitochondrial fission has been further documented as a key factor in the pathogenic pathway of PD by a different study, which reported increased expression of DRP1 and excessive mitochondrial fragmentation in a cellular model of toxin-induced PD [54]. Additional evidence from in vivo models characterized by mitochondrial dysfunction in the nigrostriatal system suggest that the inhibition of mitochondrial fission by the blocking of DRP1 function rescues dopamine-release deficits and attenuates dopaminergic neurotoxicity, thus providing a neuroprotective effect in the nigrostriatal pathway [55]. Furthermore, more recent data from in vitro and in vivo models suggest that sporadic PD is attributed to excessive mitochondrial fragmentation triggered by elevated levels of DRP1 [56]. Accordingly, inhibition of DRP1 hyperactivation in a mouse model of PD attenuated dopaminergic neuronal loss due to reduced mitochondrial translocation of DRP1 and other proteins involved in programmed cell death [57].

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