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Digest paper

Mitochondrial drug targets in neurodegenerative diseases

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ABSTRACT

Growing evidence suggests that mitochondrial dysfunction is the main culprit in neurodegenerative diseases. Given the fact that mitochondria participate in diverse cellular processes, including energetics, metabolism, and death, the consequences of mitochondrial dysfunction in neuronal cells are inevitable. In fact, new strategies targeting mitochondrial dysfunction are emerging as potential alternatives to current treatment options for neurodegenerative diseases. In this review, we focus on mitochondrial proteins that are directly associated with mitochondrial dysfunction. We also examine recently identified small molecule modulators of these mitochondrial targets and assess their potential in research and therapeutic applications.

Mitochondria are extraordinary organelles that produce ATP, maintain calcium homeostasis and regulate signal transduction. Mitochondria govern cell growth and proliferation but also mediate cell death. As mitochondria are often called 'the powerhouses of the cells', it is not surprising that mitochondrial dysfunction has been linked to a wide variety of disorders, such as cancers, diabetes, and cardiovascular diseases. Particularly, many studies have found that mitochondrial dysfunction is one of the major culprits in neurodegeneration. Considering the fact that neurons have high energy demands, which mostly depend on oxidative metabolism,[1] neurons with impaired mitochondrial function inevitably suffer from oxidative stress, ATP depletion, and eventually cell death.

Mitochondrial dysfunction is caused by diverse elements, and its physiological consequences promote a cascade of pathological events as depicted in Figure 1. Various chemicals and environmental toxins disrupt the electron transport chain and the mitochondrial membrane potential leading to calcium overload and reactive oxygen species (ROS) generation.[2–5] High levels of intracellular calcium concentrations and ROS further damage the mitochondrial structure and invoke apoptotic pathways. Mutations in nuclear and mitochondrial DNA lead to the synthesis of defective mitochondrial proteins and enzymes.[6,7] Age-dependent changes resulting in damage to mitochondrial DNA and morphology significantly alter expression levels and activity of integral proteins and signaling enzymes affecting the pathways related to cell proliferation and death.[8,9]

Mitochondrial dysfunction itself is not a disease; however, mitochondrial dysfunction disrupts cellular calcium and protein homeostasis and promotes accumulation of detrimental proteins in the brain, thereby contributing to the pathogenesis of many neurodegenerative diseases.[10–13] For example, prolonged exposure of neuronal cells to amyloid-β (Aβ) peptides impairs the mitochondrial electron transport chain and aggravates oxidative stress.[14,15] Dysfunctional mitochondria along with oxidative stress not only promote aggregation of Aβ but also produce hyperphosphorylated tau proteins.[16,17] These misfolded proteins eventually form large numbers of senile plaques and neurofibrillary tangles, which are the defining characteristics of Alzheimer's disease (AD). Similarly, α-synuclein accumulates in dysfunctional mitochondria, and aggregates in Lewy bodies seen in Parkinson's disease (PD).[18] Mutant Cu/Zn-superoxide dismutase (SOD1) is localized to the mitochondrial membrane and aggregates to cause apoptosis in amyotrophic lateral sclerosis (ALS).[19] In Huntington's disease (HD), mutant huntingtin protein forms aggregates and directly interacts with mitochondria, disrupting calcium homeostasis.[20]

Since most of the current treatment options for neurodegenerative diseases provide only symptomatic relief rather than targeting the root causes of disease, breaking the vicious cycle caused by mitochondrial dysfunction offers novel therapeutic opportunities. Over the past decade, many studies have found that mitochondrial dysfunction can be caused by a number of different pathways,

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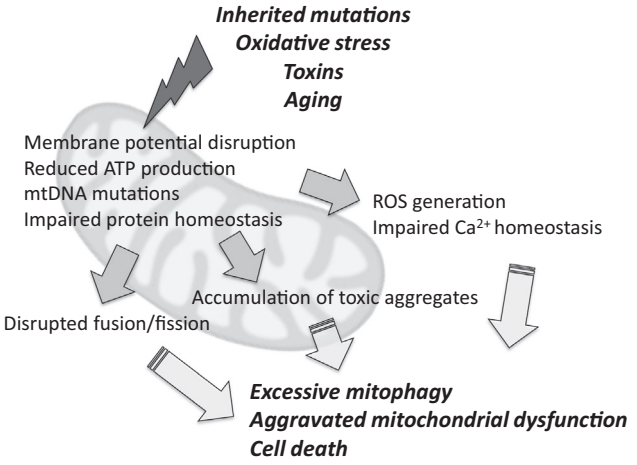

Figure 1. Sources and consequences of mitochondrial dysfunction.

largely taking place inside mitochondria. Restoring normal levels of calcium and ROS by modulating proteins related to the mitochondrial membrane potential can rescue dysfunctional mitochondria. Molecules targeting signaling enzymes and integral proteins may have an opportunity to deactivate these pathways and restore functional mitochondria, thus providing a possible therapeutic potential. Therefore, the main goal of this Letter is to succinctly review mitochondrial proteins that are directly linked to mitochondrial dysfunction, and to assess their therapeutic value in neurodegenerative diseases. In addition, we will discuss recently identified small molecule modulators of each protein target and their possible roles in research and therapeutic applications as summarized in Table 1 and Figure 2.

Mitochondrial permeability transition pore (MPTP): The MPTP is a multimeric protein complex located in the inner mitochondrial membrane and is activated in response to proapoptotic stimuli such as ROS and calcium overload. The opening of the MPTP induces sudden exchange of materials between mitochondria and cytoplasm, leading to the loss of membrane potential; the inner mitochondrial membrane becomes permeable to molecules smaller than 1.5 kDa, resulting in significant mitochondrial swelling.[21,22] Although MPTP was first recognized half a century ago,[23,24] its involvement in neurodegenerative diseases was discovered rather recently,[25–28] mainly because the overall processes of MPTP formation and the mechanisms regulating these processes have not been fully elucidated. The voltage-dependent anion channel (VDAC) in the outer membrane, the adenine nucleotide translocase (ANT) in the inner membrane, and cyclophilin D (CypD) in the matrix are thought to be the major participants in the formation of the MPTP.[29] Additionally, the 18 kDa mitochondrial translocator protein (TSPO)[30] in the outer membrane, hexokinase[31] in the cytosol, and the mitochondrial phosphate carrier (PiC)[32] are known to interact with the MPTP. Giorgio et al. reported that dimers of F_0F_1-ATP synthase form a channel-like structure along with a bound CypD, suggesting that F_0F_1-ATP synthase is a central component of the MPTP.[33–35]

Among the putative components of the MPTP, CypD, a mitochondrial peptidyl-prolyl isomerase, appears to be the key regulator of MPTP formation, thus making it a potential therapeutic target. CypD is located in the mitochondrial matrix; however, under stressful conditions, it translocates into the inner mitochondrial membrane and forms the MPTP.[36,37] It has been reported that specific knockdown of CypD blocks calcium-induced MPTP opening[38] and protects cells from oxidative stress-induced cell death in various neurodegenerative diseases, including AD,[26] ALS,[39] PD,[40] and X-linked adrenoleukodystrophy (X-ALD).[41,42] Du et al. demonstrated that CypD promoted MPTP opening upon binding to Aβ, and CypD deficiency alleviated neuronal cell death and improved cognitive function in AD mice.[26] In addition to genetic ablation of CypD, inhibition of CypD, by cyclosporin A (CsA), protects neuronal cells from oxidative stress by inhibiting MPTP formation.[43–45] Chemical inhibitors of CypD, such as CsA, are particularly useful for the development of therapeutic agents; however, reports on CypD-specific inhibitors are relatively scarce in the literature. While CsA is the most specific inhibitor of CypD to date, it also binds to other isoforms of cyclophilins non-selectively and possesses immunosuppressive activity. To overcome these limitations, several attempts have been made to develop selective inhibitors of CypD. Guo et al. developed quinoxaline derivatives that bind to CypD with K_d values in low micromolar

Table 1
List of mitochondrial proteins and their small molecule ligands*

Categories	Proteins	Possible pathogenesis	References for identified ligands	Diseases
MPTP	CypD	Activates the MPTP under stress conditions	46,48,49	AD, PD, ALS
	TSPO	Activates the MPTP under stress conditions; inhibits neurosteroid production under oxidative stress	60,62,65	AD, PD, ALS
Kinases	PINK1	Mutant PINK1 impairs mitophagy	72	PD
	LRRK2	Mutant LRRK2 promotes Lewy body formation	83,84,87,88	PD
	Drp-1	Promotes mitochondrial fragmentation and apoptosis	76,78	PD
Chaperones	Mortalin	Downregulation of mortalin disrupts mitochondrial integrity	100,101	AD, PD
	DJ-1	Cells with DJ-1 mutants are more susceptible to oxidative stress-induced neurotoxicity	106	AD, PD, ALS
Proteases	hPreP	Decreased hPreP activity impairs degradation of Aβ	117	AD
	HTRA2	Mutant HTRA2 impairs mitophagy	NA**	AD, PD
Other	ABAD	Promotes ROS generation and cell death upon binding to Aβ	136,137,139,141	AD
	MitoNEET	Down-regulation of mitoNEET promotes excessive ROS accumulation	147,149	PD
	SOD1	Mutant SOD1 forms toxic aggregates	156,157	ALS

* *Abbreviations:* AD, Alzheimer's disease; ABAD, Aβ binding alcohol dehydrogenase; ALS, amyotrophic lateral sclerosis; CypD, cyclophilin D; Drp-1, dynamin-related protein 1; HTRA2, high temperature requirement A2; LRRK2, leucine-rich repeat kinase 2; MPTP, mitochondrial permeability transition pore; PD, Parkinson's disease; PINK1, PTEN-induced kinase 1; SOD1, superoxide dismutase 1; TSPO, translocator protein.
** NA, not available.