神经退行性疾病中线粒体动态变化研究进展

秦思月, 高举, 王兴龙*, 苏擘*

山东大学基础医学院, 细胞与神经生物学系, 济南 250012

* 联系人, E-mail: wangxinglong@sdu.edu.cn; bxs103@sdu.edu.cn

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摘要 线粒体是真核细胞中最常见的细胞器, 具有高度动态性, 伴随持续性的融合、分裂和运输, 其动态性不但影响线粒体的形态与数量, 同时调控其定位与功能. 线粒体也是维持神经元功能与生存的基础. 线粒体动态异常出现在多种神经退行性疾病的早期, 包括阿尔兹海默症、帕金森综合征、肌萎缩性脊髓侧索硬化症和亨廷顿舞蹈症等. 本文就线粒体动态变化的分子机制进行了简述, 分析了线粒体多态性与神经元功能的关联; 详述了不同疾病中线粒体动态变化的特点, 探讨了以调控线粒体动态为基础的新型治疗策略.

关键词 神经退行性疾病, 阿尔兹海默症, 帕金森综合征, 肌萎缩性脊髓侧索硬化症, 亨廷顿舞蹈症, 线粒体动态变化, 线粒体碎裂, 线粒体分裂与融合

线粒体是绝大多数真核细胞所共有的细胞器, 具有高度动态性, 伴随着持续性的分裂、融合与运输, 这些动态变化不仅维持线粒体的完整性和合理的分布, 同时也是保证线粒体正常功能的根本. 线粒体还参与细胞内的多种信号通路, 包括ATP的合成、代谢产物的加工、活性氧类(reactive oxygen species, ROS)的生成、钙离子平衡、细胞凋亡与坏死等^[1~3]. 作为细胞的“能量工厂”, 线粒体负责整个生命体的能量供给. 大脑是人体内的能耗器官, 重量占体重的2%, 却消耗着20%的能量. 为维持有效的糖酵解与活跃的生理代谢, 大脑内的神经元需要充分地利用线粒体产生的能量^[4]. 此外, 由于神经元拥有树突、轴突等多种复杂的胞体延伸结构, 为了满足不同位置的能量需求, 还要依靠线粒体合理的运输与分布. 线粒体还参与稳定细胞

内钙离子储量, 是突触传导、轴突和树突内物质运输以及突触小泡循环等多项神经元活动顺利进行的基础^[5,6].

神经退行性疾病是一种无法治愈的恶性神经障碍性疾病, 其主要特征是中枢神经系统和周围神经系统中神经元的退化与死亡. 常见的神经退行性疾病包括阿尔兹海默症(Alzheimer's disease, AD)、帕金森综合征(Parkinson's disease, PD)、肌萎缩性脊髓侧索硬化症(amyotrophic lateral sclerosis, ALS)、亨廷顿舞蹈症(Huntington's disease, HD)等. 研究表明, 神经退行性疾病病人患病早期, 即出现大脑内新陈代谢率下降、线粒体功能紊乱等病理特征^[7], 说明线粒体功能紊乱在神经退行性疾病的发病过程中扮演着重要的角色. 另据发现, 神经退行性疾病病患的神经元中普遍存在线

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粒体碎裂现象,同时还伴随异常的线粒体分布^[8,9]。这些现象提示,异常的线粒体动态变化可能是造成线粒体功能紊乱及退行性神经病变的关键诱因之一。本文着眼于几种常见的神经退行性疾病,分析了其中的线粒体异常的动态变化。

1 线粒体动态变化

1.1 线粒体分裂

线粒体分裂与融合是两个相反的生物学过程,二者的平衡性对整个线粒体网络形态的维护至关重要。融合和分裂过程受多种动力相关GTP酶的调节。线粒体分裂蛋白1(Drp1/DLP1)是一种大分子GTP酶,定位于细胞质中^[10]。在线粒体分裂过程中,Drp1被线粒体表面受体蛋白Mff, Fis1, MiD48/51等招募至线粒体外膜,通过自我装配,形成寡聚化的环状结构,利用GTP水解酶活力实现对线粒体膜的切割^[11~14](图1A)。最新研究指出,在Drp1募集和装配后,另有动力蛋白Dyn2参与后期膜分裂过程^[15]。分裂结束后,Drp1复合物滞留在其中一个子线粒体上^[16],丧失继续切割线粒体的能力^[17,18]。失活的Drp1寡聚复合物被空泡蛋白VPS35优先结合,从线粒体直接运输至溶酶体降解^[19]。目前,针对线粒体分裂的分子机制研究已取得不小的进展,但引发线粒体分裂的诱因至今不明。有研究显示,内质网与肌动蛋白微丝可能对Drp1在线粒体表面富集位点的选择起到决定性作用^[20,21]。另外,溶酶体与线粒体的接触位置也可能是线粒体分裂的起始位点^[22]。

1.2 线粒体融合

线粒体融合包括内膜融合和外膜融合两部分。这一过程主要通过3种大分子GTP酶调控,包括促进外膜融合的Mfn1和Mfn2,以及协助内膜融合的OPA1^[23]。与Drp1类似,这3种蛋白也是利用GTP酶活性和蛋白质自我组装能力,实现对线粒体膜结构的重编辑。在线粒体外膜融合过程中,Mfn1或Mfn2的卷曲螺旋域通过相互作用结合,形成纯合或杂合的寡聚体复合物,从而促进膜融合^[24,25](图1B)。除此之外,线粒体膜上的磷脂质也参与膜融合过程。MitoPLD是磷脂酶D家族的一员,它通过水解双磷脂酰甘油产生磷脂酸,调节线粒体融合^[26]。另有MIGA通过促进MitoPLD二聚体的形成,间接调控线粒体的融合^[27]。

图1 哺乳动物细胞线粒体动态变化示意图

A: 胞质中的Drp1被多个线粒体表面受体蛋白招募至线粒体外膜,形成寡聚化的环状结构,切割线粒体膜; B: 线粒体外膜蛋白Mfn1或Mfn2通过卷曲螺旋域相互作用结合,形成纯合或杂合的寡聚体复合物将细胞膜捆绑在一起,实现外膜的融合;内膜蛋白OPA1参与嵴的形成以及内膜的融合; C: 协助正向运输的Kinesin-1复合物,以及参与逆向运输的Dynein/Dynactin复合物,分别与线粒体表面Miro1/2和Milton1/2蛋白复合物相互结合,带动线粒体沿微管朝固定方向运动

1.3 线粒体运输

为满足不同的生理需求,线粒体被运送至细胞内的特定位置发挥功能。按照运动速度,线粒体运输分为通过微管进行的快速运输和由肌动蛋白丝实现的缓慢运输。按照运动方向分为远离胞体的正向运输和靠近胞体的逆向运输。正、逆向运输的实现,主要依靠线粒体选择性结合不同的马达蛋白复合物^[28]。例如,协助正向运输的Kinesin-1复合物,以及参与逆向运输的Dynein/Dynactin复合物,它们与线粒体表面Miro和Milton蛋白直接相互作用,带动线粒体沿微管朝固定方向运动^[29,30](图1C)。线粒体还能在Myo2, Myo19等肌动蛋白的帮助下,在微丝上进行短距离运输^[31,32]。另外,线粒体在细胞内的分布也受其动态变化的影响^[33]。例如,线粒体动态相关蛋白Drp1和Mfn2就曾被报道参与调节线粒体在轴突中的运输^[34,35]。敲除细胞中线粒体融合相关蛋白Maf和OPA1,明显抑制了线粒体在轴突中的运输,此时若同时敲除Drp1将逆转线粒

体运输缺陷^[36]。除了细胞内的运输,线粒体还能在不同类型的细胞之间进行运输。例如,损伤的线粒体被神经元释放,运输至星形胶质细胞中并通过自噬清除^[37,38]。反之,星形胶质细胞也能够利用特殊机制释放功能正常的线粒体,然后被神经元吸收利用^[39]。

2 线粒体动态变化与线粒体功能和神经元功能的关联

线粒体动态变化除了能直接影响线粒体的形状、数量和定位之外,还参与维护线粒体完整性和功能性。线粒体融合可以实现膜脂质和线粒体内容物在不同线粒体之间的交换,有利于代谢产物的平均分配和线粒体DNA(mtDNA)的相互补偿,从而有效避免基因突变,保证线粒体的正常功能。反之,线粒体分裂可以隔离受损伤的线粒体,促进其通过自噬途径降解^[40-42]。线粒体动态失衡可能导致线粒体延长或缩短,最终降低线粒体的代谢活力。例如,抑制Drp1表达可促使线粒体延长,导致氧化磷酸化(oxidative phosphorylation, OXPHOS)复合物IV活力下降,ATP合成受阻^[43]。在出现线粒体碎裂的细胞中,线粒体钙离子吸收能力和线粒体内钙离子扩散能力均有下降,说明线粒体动态平衡异常影响钙离子稳态^[44,45]。还有证据显示,线粒体形态变化与OXPHOS复合物的装配、嵴的重塑、基质空间的凝聚以及ROS的产生都密切相关^[46-49]。另外,线粒体动态平衡还与线粒体非折叠蛋白应答反应(mitochondrial unfolded protein response, mtUPR)一同参与维护线粒体内蛋白质的稳态^[50,51]。

鉴于神经元结构与功能的特殊性,其对线粒体动态变化更加敏感。例如,线粒体动态相关蛋白的缺失可干扰线粒体运输与定位功能,导致神经元轴突、树突和突触小体内线粒体的缺失,最终引发树突棘和突触的消失^[52-54]。线粒体动态变化对神经元功能的影响还体现在线粒体动态调节蛋白突变引发的各类遗传性神经类疾病,如与Mfn2相关的2A型腓骨肌萎缩病^[55,56],以及由于OPA1突变引发的1型视神经萎缩症^[57,58]等。线粒体动态变化异常还是多种神经损伤性疾病的早期病理特征,如脑缺血、中风、脑外伤等,这一特征在神经退行性疾病中尤其明显,如ALS, AD, PD和HD等^[7,59,60]。以下综述了几种常见的神经退行性疾病中线粒体异常动态变化的情况及相关的研究

进展。

3 神经退行性疾病中的异常线粒体动态变化

3.1 AD中的线粒体异常动态变化

AD是一种常见于老年人中的痴呆症,患病者大脑内的记忆、学习、意识思维和语言区域的神经元持续退化与死亡。患者脑内出现的老年斑(senile plaque, SP)和神经纤维缠结(neurofibrillary tangle, NFT)是AD的两个最主要的病理特征,其中NFT是由超磷酸化的微管相关蛋白Tau组成的细胞内聚集体,SP是细胞外的 β -淀粉样(amyloid- β , A β)沉积。目前,针对AD病人中线粒体动态性的研究已取得初步进展。研究发现,除了AD病人,在过表达A β 或Tau的AD动物模型中,线粒体碎裂和膜结构不完整是非常典型的早期病理特征之一^[61-66],且伴随Drp1, OPA1, Mfn1/2和Fis1等蛋白表达量的改变。早老素蛋白(presenilin, PS)突变是引发AD的诱因之一,携带PS1 E280A突变的AD病人大脑中,从颞叶区到海马区的神经元中都出现了线粒体形态的异常变化^[67],说明PS可能涉及调控线粒体动态。APP是A β 的前体蛋白,在APP转基因小鼠(*Mus musculus*)模型中,研究人员发现碎裂线粒体以及线粒体产能缺陷等现象先于SPs出现^[68,69]。近期另两项研究还发现,在APP或Tau转基因老鼠模型中,通过降低Drp1含量抑制线粒体碎裂的发生,能缓解线粒体功能紊乱以及防止突触的丢失^[70,71]。暗示线粒体形态异常对疾病进程产生关键性影响,线粒体动态变化可作为潜在的治疗靶点。

在AD实验模型中,除了形态的异常变化,线粒体分布也受到影响。超磷酸化或突变(P301L)的Tau蛋白可导致神经元中线粒体运输异常^[72,73]。在AD病人和APP转基因小鼠中, Parkin介导的线粒体自噬途径是引起线粒体运输缺陷的潜在原因^[74,75]。另外,在A β 处理或过表达APP的神经元内,线粒体在轴突中的运输能力和密度均有所下降^[76,77],这一现象可以通过抑制线粒体分裂而缓解^[65,77],说明线粒体运输功能的减弱很可能是由于线粒体碎裂引发的。在AD病人中,线粒体动态变化异常还出现在神经元的胞体、轴突、突触末梢等各个不同区域。由此可能造成局部能量的缺乏,触发神经元功能紊乱及死亡。目前,AD患者中线粒体动

态变化异常的具体机制还不明确, 但有证据显示, A β 和Tau皆能在线粒体中与Drp1等线粒体融合、分裂调节蛋白相结合, 暗示其可能直接影响线粒体动态平衡, 从而引起神经毒性, 诱发退行性病变^[61,64,78]。线粒体内A β 的积累不仅影响线粒体动态平衡, 还是线粒体功能异常的重要诱因之一。激活线粒体内蛋白酶水解活力, 能够促进A β 的清除并恢复线粒体正常功能^[79]。

3.2 PD中的线粒体异常动态变化

PD是全球第二大神经退行性疾病, 仅次于AD, 罹患PD的病人, 出现特有的运动能力障碍, 临床表现为运动迟缓、静止性震颤、机体僵硬等症状。PD的病理学特征主要表现为黑质区多巴胺能(dopaminergic, DA)神经元的退化和死亡, 以及DA神经元胞质中由 α -synuclein组成的包涵体的出现^[80]。最早期的PD分子病理研究主要依赖于1-甲基-4-苯基-1,2,3,6-四氢吡啶(1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, MPTP)的毒理学模型。MPTP作为一种嗜神经毒性物质, 在大脑内转化为高毒性的MPP⁺, 并在DA神经元中富集, 通过多巴胺转运体特异性抑制线粒体OXPHOS复合物I^[81], 诱发DA神经元的神经退行性病变^[82]。有趣的是, MPP⁺还能够促进线粒体分裂, 并导致线粒体碎裂现象, 而该过程发生在神经元死亡之前^[83]。说明线粒体动态失衡可能是MPP⁺引起神经毒性的重要诱因之一。

不仅在DA神经元内, PD病人的其他细胞中的线粒体也呈现多态性变化和功能紊乱情况^[84-86]。过去10年, 不断有关于PD相关蛋白失活引发线粒体碎裂的研究。例如, 在PD病人的肌肉和DA神经元中, PINK1, Parkin或DJ-1等PD相关蛋白的减少都能引起异常的线粒体多态性^[87,88]。此外, 在PD相关实验模型中, 突变的 α -synuclein蛋白错误定位于线粒体上, 诱发线粒体功能紊乱和线粒体碎裂^[89,90]。LRRK2基因突变作为引起PD病发的另一关键性因素也会诱发线粒体碎裂^[91]。另有PD相关蛋白VPS35突变后通过促进线粒体上无活性的Drp1寡聚物的清除, 导致线粒体碎裂^[92]。

在PD相关遗传和毒理模型中, 不仅有线粒体形态的异常, 同时轴突中的线粒体运输功能也受到影响, 这一现象可通过抑制线粒体分裂而得到缓解^[83,91]。推测在PD中线粒体运输功能损伤是线粒体分裂、融合的下游效应。研究人员还发现Parkin和PINK1参与介导Miro1降解途径, 更进一步地证实线粒体运输功能可

能受到PD相关蛋白的直接调控^[93]。

已知的多数PD相关蛋白, 如 α -synuclein, PINK1, Parkin, LRRK2, DJ-1和VPS35等都能够定位在线粒体或线粒体相关膜结构上^[91,92,94-97], 推测这些蛋白很可能是线粒体分裂、融合等动态变化的直接参与者。例如, Parkin和PINK1参与介导包括Drp1, Mfn1, Mfn2和Miro1在内的多个线粒体动态性调节蛋白的降解^[93,98-100]; LRRK2和VPS35可分别与Drp1发生直接相互作用, 调节线粒体动态变化和功能。现已有越来越多的证据显示, 线粒体动态变化异常可能是导致线粒体功能紊乱和神经元退化的常规机制之一^[101]。

线粒体动态变化与线粒体自噬也密切相关。多项研究证实, 线粒体碎裂先于自噬过程发生^[42,102-105]。抑制线粒体分裂将阻碍线粒体自噬过程^[102]。PINK1/Parkin介导的线粒体形态变化是线粒体自噬过程中的早期步骤。随着线粒体膜电势的下降, 蛋白激酶PINK1在线粒体表面积累, 通过招募并活化Parkin, 选择性降解线粒体融合相关分子, 瓦解受损伤线粒体的正常融合机制, 避免其与健康线粒体的融合^[106-109]。在PINK1/Parkin缺失或者突变的细胞和动物模型中, 线粒体形态异常和受损伤线粒体的积累是其典型的病理特征^[110-112]。鉴于其在PD发生发展中的重要作用, 线粒体自噬将会成为治疗PD的新型药物开发靶点。

3.3 ALS中的线粒体异常动态变化

ALS又被称为Lou Gehrig's病, 患者脑干和脊髓内的运动神经元退化, 导致肌无力、肌萎缩以及言语、吞咽和呼吸困难等症状。ALS的典型病理标志是运动神经元内出现以RNA/DNA结合蛋白TDP-43为主要成分的包涵小体^[113]。遗传学上, *SOD1*, *TDP-43*, *FUS*, *C9orf34*等基因的突变均可诱发ALS的产生。研究发现, ALS病人的神经元和其他细胞中均出现线粒体形态异常现象^[114-116]。除此以外在多种ALS动物模型中也可观察到线粒体碎裂情况的发生。Cu/Zn超氧化物歧化酶1(SOD1)是第一个从ALS病人中检验出的遗传性突变。在突变*SOD1*转基因实验模型中, 线粒体呈现碎裂现象, 且线粒体分裂、融合调节因子Drp1, OPA1, Mfn1和Fis1的表达量发生改变。*FUS*突变和*TDP-43*突变也能造成线粒体碎裂, 以及线粒体分裂、融合调节因子的表达量变化^[117-121]。有趣的是, 多功能干细胞诱导产生的携带*TDP-43*和*C9orf72*突变的人运动神经元

内也被证实发生线粒体碎裂现象^[115,122]。综上所述,线粒体动态变化异常在ALS病人和ALS模型中具有一定的普遍性^[123]。

在ALS病人中,线粒体运输出现异常,导致其聚集在脊髓运动神经元的胞体和近胞体轴突丘中^[124]。此外,在*SOD1*突变或*TDP-43*突变的转基因动物中,神经元细胞核周围以及近胞体的轴突也出现异常的线粒体簇^[119,120,125~127]。在体外培养的神经元中,表达突变的*SOD1*或*TDP43*蛋白,导致轴突内线粒体运输功能损伤^[119,120,128,129]。在ALS病人以及突变的*SOD1*或*TDP-43*转基因动物的脊髓中*Miro1*的表达量大大降低^[130],说明在ALS中*Miro1*表达量的下降可能是造成线粒体运输异常的关键因子。有趣的是,在表达*TDP-43*或*SOD1*突变基因的运动神经元中,通过过表达无活性的Drp1或Mfn2抑制线粒体分裂,能有效防止线粒体运输缺陷的发生^[120,131]。说明在ALS中,除了*Miro1*缺乏之外,线粒体分裂融合的异常也是导致线粒体转运功能损伤的诱因之一。未来针对线粒体动态变化对ALS疾病进程的影响将是很有价值的研究方向。

3.4 HD中的线粒体异常动态变化

HD是遗传性神经退行性疾病,患病者伴有多种神经、认知和运动方面的病症。HD是由突变的*CAG*基因编码的N端携带多聚谷氨酰胺链的Htt蛋白所引发^[132]。HD的主要病理特征包括纹状体和大脑皮层内神经元的退化与死亡以及细胞内包涵小体的出现。这类包涵体由泛素化蛋白和带有多聚谷氨酰胺链的截短型Htt蛋白组成^[133]。大量证据显示,HD病人的细胞内存在线粒体碎裂现象^[134,135]。在HD病人的大脑中,线粒体分裂、融合调节蛋白Drp1, MFN和Fis1的表达量或翻译后修饰发生极大的改变^[135~137]。另外,在HD病人和突变Htt转基因小鼠模型的纹状体中,S-亚硝基化Drp1的表达量上升,该形式的Drp1拥有更加高效的GTPase活力,导致线粒体碎裂情况越发明显,最终引起树突棘的消失以及突触损伤的加重^[138,139]。线粒体动态异常现象还在多种HD相关动物模型中被发现。例如,3-NP是线粒体OXPHOS复合体II的抑制剂,用3-NP处理神经元,可见线粒体碎裂和线粒体功能紊乱相继发生,最终诱发类似HD病理的纹状体神经退行性病变和运动能力

损伤^[140~142]。有趣的是,在3-NP毒理模型中,抗氧化剂的使用能抑制线粒体动态异常的发生,暗示线粒体动态变化异常也可能是线粒体产能缺乏的结果^[141,142]。在这些HD毒性或遗传性模型中,除了线粒体形态的变化之外,同时伴有线粒体运输功能障碍。

近期一些关于突变Htt和线粒体动态调节蛋白的相互作用的研究,进一步揭示了Htt与线粒体动态性之间可能的直接联系。突变的Htt蛋白能和Drp1在线粒体上发生相互作用^[38,135],而在表达突变Htt基因的神经元中Drp1的失活,以及Fis1和Drp1相互作用的减弱都能缓解线粒体异常动态变化的发生。另外,突变Htt蛋白能选择性地隔离和失活肌动蛋白Kinesin和Dynactin,或通过与HAP1的相互作用干扰肌动蛋白与微管之间的联系,从而导致线粒体运输功能损伤^[143,144]。综合多项发现,说明突变的Htt能对线粒体的动态变化产生多种不同形式的干扰,导致线粒体形态和功能的紊乱,以及神经元死亡,这一过程可能是引起HD发生与发展的主要途径之一。

4 总结与展望

AD, PD, ALS, HD以及多种其他神经退行性疾病的主要特征都是神经元的退化和死亡。而线粒体是维持神经元存活的必要条件。现如今,已在多种神经退行性疾病中发现了线粒体多态性现象,这一早期常见的病理特征可能是线粒体和神经元功能紊乱的主要诱因之一^[145]。虽然引发线粒体动态异常的诱因众多,但多项新兴的研究显示,在多种神经退行性疾病模型中,抑制线粒体碎裂,皆能有效减少神经元死亡,改善运动能力。例如,在表达*Tau*或*APP*的转基因AD模型动物中,通过降低Drp1的表达量抑制线粒体碎裂,可实现对神经元的保护以及行为能力的改善^[70,71]。Drp1的小分子抑制剂Mdivi-1也能在PD动物模型中成功抑制线粒体碎裂,恢复多巴胺的释放,阻止DA神经元的死亡^[146]。除此之外,封闭Drp1和Fis1相互作用的抑制剂P110,也实现了改善HD神经毒性和行为缺陷的目的^[146](图2)。这些以调控线粒体动态为基础的病理研究成果,为未来神经退行性疾病的研究和治疗提供了良好的新方向。

图2 线粒体在神经元退行性病变中的动态变化趋势

由于外界刺激(MPTP, A β)或基因突变(*TDP-43*, *SOD1*, *LRRK2*, *mHtt*等)的作用, 神经元中的线粒体动态发生异常, 产生碎裂和不合理分布等多种异常现象, 伴随线粒体功能紊乱, 从而引发神经元退行性病变, 导致神经元的死亡。使用Mdivi-1或P110等药物抑制线粒体分裂能有效减少神经元的死亡, 改善个体行为能力

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Mitochondrial dynamics in neurodegenerative diseases

QIN SiYue, GAO Ju, WANG XingLong & SU Bo

Department of Cell Biology and Neurobiology, School of Basic Medical Sciences, Shandong University, Jinan 250012, China

Mitochondria are highly dynamic organelles along with continuous fission, fusion and transport. Mitochondria dynamics not only control their morphology and number, but also affect their distribution and function. Mitochondria are also the basis for neuronal survival and involved in numbers of neuronal functions. Mitochondrial dynamic abnormalities accompanied by dysfunction have been reported in a wide range of neurological disorders, especially neurodegenerative diseases such as Alzheimer’s disease (AD), Parkinson’s disease (PD), amyotrophic lateral sclerosis (ALS) and Huntington’s disease (HD). In this review, we will briefly describe the molecular mechanisms of mitochondrial dynamics and their critical roles in regulating neuronal function. We will also review the studies about mitochondrial dynamic abnormalities found in neurodegenerative diseases, and discuss the possibility of targeting mitochondrial dynamics as a likely novel therapeutic strategy for treating neurodegenerative diseases.

neurodegenerative diseases, Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis, Huntington’s disease, mitochondrial dynamics, mitochondrial fragmentation, mitochondrial fission and fusion

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