



线粒体未折叠蛋白反应在神经退行性疾病中的作用*

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摘要 线粒体作为真核生物能量代谢的核心枢纽, 参与多种细胞活动, 如细胞基质代谢调节、细胞凋亡、激活信号转导通路等关键生命活动, 其代谢状态与多种疾病的发生及进展密切相关。神经退行性疾病以神经元进行性丢失和功能障碍为主要病理特征, 线粒体功能障碍被认为是其重要诱因之一。线粒体未折叠蛋白反应 (mitochondrial unfolded protein response, mtUPR) 作为线粒体内一种应急防御机制, 主要通过调控分子伴侣和蛋白酶表达, 高效促进错误折叠蛋白的识别和降解来维持线粒体蛋白质稳态, 以保证细胞乃至整个机体的正常生理健康状态。mtUPR 的异常激活或抑制与阿尔茨海默病、帕金森病等多种神经退行性疾病的发生发展密切相关, 深入探究 mtUPR 的动态调控作用和深层分子机制对神经退行性疾病的发病机理具有重要意义。本文综述了 mtUPR 的基本概念、主要诱导因素和信号转导通路, 重点探讨了 mtUPR 与神经退行性疾病之间的内在关系与调控规律, 有助于神经退行性疾病的靶向治疗的研发。最后, 本文展望了 mtUPR 的研究在神经退行性疾病中面临的挑战与未来, 旨在为神经退行性疾病的治疗带来新的突破。

关键词 线粒体功能障碍, 线粒体未折叠蛋白反应, 神经退行性疾病, 帕金森病, 阿尔茨海默病

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神经退行性疾病对人类健康造成严重威胁, 在中国其患者人数呈上升趋势。这类疾病以神经元的逐渐丧失及其功能障碍为特征, 涵盖了阿尔茨海默病 (Alzheimer's disease, AD)、帕金森病 (Parkinson's disease, PD)、亨廷顿舞蹈病 (Huntington's disease, HD) 和肌萎缩侧索硬化病 (amyotrophic lateral sclerosis, ALS) 等多种类型。目前, 对神经退行性疾病的病因研究主要集中在遗传因素和环境因素两个方面。这类疾病的发病机理难以预测, 涉及多种细胞内的异常过程, 其中线粒体功能障碍被认为是一个重要因素。线粒体作为一个高效的生物能量转换器, 是细胞代谢活动的核心, 线粒体功能障碍不仅与衰老过程紧密相关, 还与神经退行性疾病、癌症等多种疾病的发生有重要关联^[1-3]。因此, 维持线粒体的功能稳定性对于细胞的存活和人体的正常生理功能非常重要。随着在秀丽隐杆线虫中发现的线粒体蛋白质结构异常所触发的独特线粒体未折叠蛋白反应 (mitochondrial

unfolded protein response, mtUPR) 分子机制逐渐被揭示, mtUPR 通路在线粒体功能及神经退行性疾病的作用中日益凸显^[4-6]。因此, 本文主要总结近年来不同研究模型中 mtUPR 最新分子机制的研究进展, 并探讨 mtUPR 调控神经退行性疾病发生发展的分子机制。

1 mtUPR 的概述

1.1 mtUPR 的定义

当外部环境或代谢状况发生改变, 线粒体内未折叠与错误折叠的蛋白异常累积, 会触发线粒体应激, 称为 mtUPR, 旨在处理并清除异常蛋白质, 维系线粒体正常的生理功能。作为线粒体质量控制

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的一环, mtUPR 主要通过诱导线粒体伴侣蛋白和蛋白酶的表达来精细调控蛋白质的折叠、组装及降解过程, 以此来维持线粒体蛋白质组的稳态^[7-8]。其中, 热休克蛋白 (heat shock protein, Hsp) 60、Hsp10、线粒体热休克蛋白 70 (mitochondrial heat shock protein 70, mtHsp70)、线粒体 Lon 蛋白酶 1 (mitochondrial lon peptidase 1, LONP1) 等伴侣蛋白能够帮助蛋白质正确折叠并防止蛋白质聚集体的形成, 而蛋白酶 (主要包括基质型 AAA 蛋白酶和膜间隙型 AAA 蛋白酶) 则负责清除受损或折叠错误的蛋白质, 减少其在线粒体中的积累^[9]。

1.2 mtUPR 的诱发因素

1.2.1 线粒体结构损伤导致 mtUPR

在哺乳动物中通过溴化乙锭 (ethidium bromide, EtBr) 去除线粒体 DNA (mitochondrial DNA, mtDNA) 后, 会引发线粒体内的 Hsp60 和 Hsp10 大量表达, 这一发现奠定了 mtUPR 的研究基础^[10], 后续研究发现, mtDNA 的突变及拷贝数的改变均与 mtUPR 有关。在培养的原代成纤维细胞和癌细胞中, 使用阿霉素损伤 mtDNA 会激活 mtUPR, 并通过激活转录因子 5 (activating transcription factor 5, ATF5) 信号通路传递至细胞核, 该通路进一步诱导 I 型干扰素 (interferon 1, IFN-1) 的产生, 增强核脱氧核糖核酸 (nuclear DNA, nDNA) 修复能力。此外, 线粒体转录因子 (transcription factor A mitochondrial, TFAM) 缺陷小鼠黑色素瘤细胞中的 mtDNA 应激产生的肿瘤在体内对阿霉素更具耐药性^[11]。在携带线粒体 DNA 3243 位腺苷酸突变为鸟苷酸 (m.3243A > G) 突变的患者中分离和扩增尿液来源于干细胞 (urine-derived stem cells, USCs) 中发现, m.3243A > G 突变水平高的 USCs 表现出异常的线粒体形态和功能, 以及 ATF5 依赖性 mtUPR 升高^[12]。Surfeit 基因座蛋白 1 (surfeit locus protein 1, SURF1) 是线粒体复合物 IV 的结构蛋白, 与野生型小鼠相比, 该基因突变小鼠的原代成纤维细胞中, mtUPR 相关蛋白 Hsp60, 酪蛋白线粒体基质肽酶的水解亚单位 (caseinolytic mitochondrial matrix peptidase proteolytic subunit, CLPP), Lon 蛋白酶的表达升高^[13]。

线粒体电子传递链的轻度损伤在多种模式生物中均可诱发 mtUPR, 甚至能延长动物的寿命^[14-16]。一些研究表明, 电子传递链抑制剂如鱼藤酮 (复合物 I 抑制剂)、抗霉素 A (复合物 III 抑制剂) 和寡

霉素 (复合物 V 抑制剂), 可通过损害线粒体功能来诱导 mtUPR。其作用机制是影响电子传递链亚基的组装, 进而导致未组装的孤立亚基积累^[17]。与此发现一致的是, 通过 *cco-1* 基因的 RNA 干扰 (*cco-1* gene RNA interference, *cco-1* RNAi) 和 *clk-1* 基因突变体对电子传递链复合物的下调, 同样会引起未组装孤立亚基的积聚并激活 mtUPR。

1.2.2 线粒体内蛋白质稳态失衡引起 mtUPR

线粒体中的蛋白质大部分由细胞核编码, 在细胞质中合成后经由线粒体外膜上的通道被转运进线粒体内, 极少部分是由 mtDNA 编码且在线粒体内部合成。在细胞内利用该鸟氨酸转氨甲酰酶 (ornithine transcarbamylase, Δ OTC) 突变蛋白模拟线粒体基质中蛋白积累的情况, 引起强烈的 mtUPR^[18]。后续研究表明, 小鼠中的 Δ OTC 也可以激活 mtUPR, 证实了线粒体蛋白稳态失衡对 mtUPR 的诱导作用^[19]。线粒体内蛋白稳态依赖蛋白运输复合体的正常功能, 通过核糖核酸干扰 (RNA interference, RNAi) 在秀丽隐杆线虫中降低线粒体内膜转位酶 23 (translocase of the inner mitochondrial membrane 23, TIMM-23) 蛋白水平, 阻断内膜转位酶复合物的功能可以强烈诱导 mtUPR^[20]。此外, 启动 mtUPR 的关键信号分子还包括线粒体活性氧类 (reactive oxygen species, ROS) 和细胞质中的线粒体蛋白前体 (c-mitochondrial precursor proteins, c-mtProt), 它们通过由 DnaJ 热休克蛋白家族 (Hsp40) 成员 A1 (DnaJ heat shock protein family (Hsp40) member A1, DNAJA1) 介导的分叉信号级联激活热休克因子 1 (heat shock factor 1, HSF1), 形成调控机制并启动线粒体分子伴侣和蛋白酶的转录^[21]。

在哺乳动物的神经母细胞瘤细胞系 (SH-SY5Y) 内, 富含亮氨酸的五肽重复序列蛋白 (leucine-rich pentatricopeptide repeat-containing protein, LRPPRC) 的敲除会导致线粒体编码和核编码的复合物 IV 亚基间数量失衡, 并且这种失衡是触发线粒体 mtUPR 的重要因素。同样, 在秀丽隐杆线虫中, LRPPRC 样基因多种黑色素瘤抗原 1 (multiple melanoma antigen 1, *mma-1*) 的功能丧失也能诱导 mtUPR 的发生^[22]。有相关研究建立了 PD 多巴胺能神经元样细胞模型, 该模型过表达过氧化物酶体增殖物激活受体 γ 共激活因子 1 α (peroxisome proliferator-activated receptor gamma coactivator 1 alpha, PGC-1 α) 时可激活 mtUPR,

通过 LRPPRC 信号转导来减少氧化应激损伤, 从而对细胞具有保护作用^[23]。

1.3 mtUPR 的信号转导

线粒体与细胞核之间存在着一种细胞器间信号转导机制, 称为线粒体-细胞核通讯, 该机制主要通过线粒体至细胞核的信号通路介导 mtUPR 的信号传递, 从而实现对线粒体蛋白质稳态的有效调控, 以恢复线粒体功能或启动细胞凋亡。

在秀丽隐杆线虫体内, mtUPR 的调控主要由 CLPP 执行, CLPP 剪切蛋白质后产生的多肽片段通过转运蛋白 1 被转运到线粒体外部, 随后这些多肽片段在细胞质中广泛扩散^[24]。被释放的多肽与碱性亮氨酸拉链 (basic leucine zipper, bZIP) 家族的应激激活转录因子 1 (activating transcription

factor associated with stress-1, ATF5-1) 发生相互作用, 进而触发一系列信号级联反应^[24]。泛素样蛋白 5 (ubiquitin-like protein 5, UBL-5) 和同源结构域线虫背腹轴发育调控因子 1 (dorsal ventral organizer 1, DVE-1) 复合物结合, 从而激活相关伴侣蛋白与蛋白酶的基因表达, 以维持线粒体的蛋白质稳态。此外, LIN-65 蛋白、甲基转移酶 2 (methyltransferase-2, MET-2) 也参与 mtUPR 的转录激活过程^[25]。

研究显示, 相较于秀丽隐杆线虫, 哺乳动物中的 mtUPR 信号转导机制展现出更为复杂的特性, 且尚未完全明晰。有趣的是, 这两个物种在 mtUPR 信号转导的机制层面存在显著的重叠 (图 1)。哺乳动物中最重要的 mtUPR 调控因子是

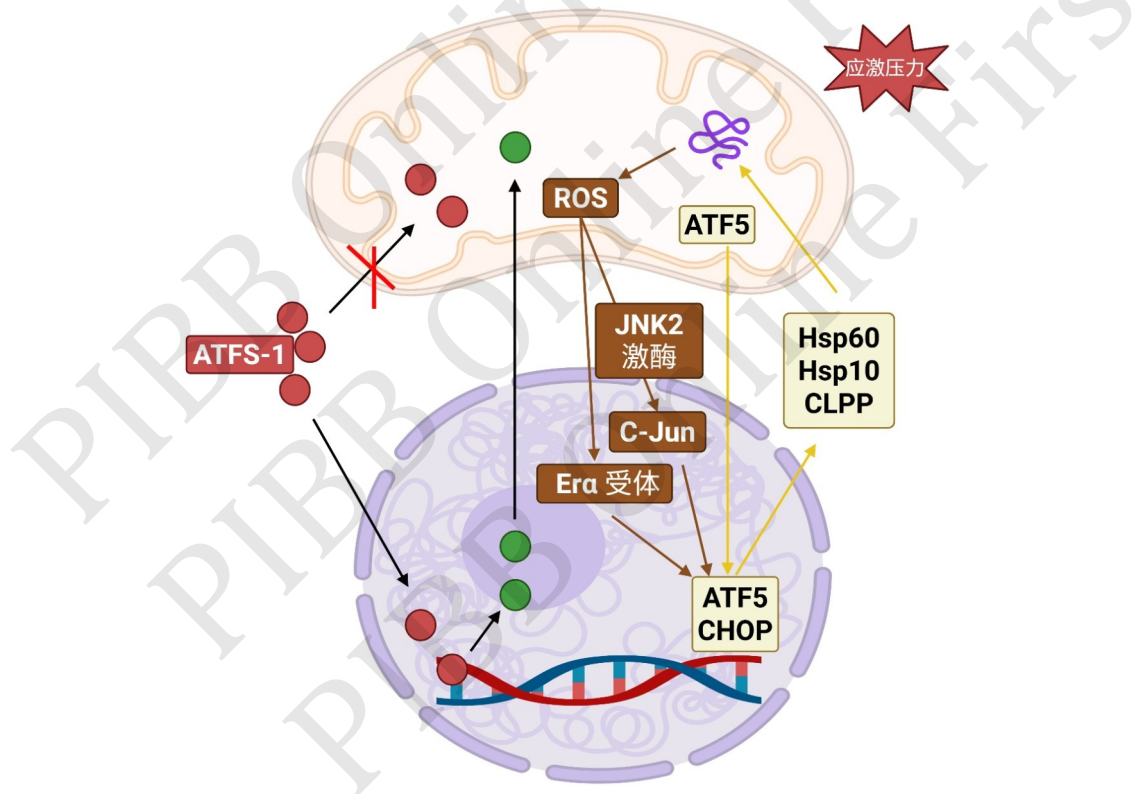


Fig. 1 Regulatory mechanism of the mtUPR in *C. elegans* and mammalian cells

图1 线虫及哺乳动物细胞内线粒体未折叠蛋白反应的调控机制

线虫中正常情况下 ATF5-1 定位在线粒体中, 当未折叠蛋白堆积或其他线粒体应激出现时, ATF5-1 进入细胞核, 引起相应的基因转录。线粒体受到损伤后, 如错误折叠蛋白的堆积, 会导致线粒体内活性氧类水平升高, 引起 ATF5 等转录因子进入细胞核, 在 JNK2 激酶的作用下, CHOP 和 ATF5 等转录因子促进细胞核内 Hsp60、Hsp10、CLPP 等蛋白质的表达, 这些蛋白质进入线粒体内清除错误折叠的蛋白, 维持线粒体的蛋白质稳态。ATFS-1: 应激激活转录因子 1 (activating transcription factor associated with stress-1)。ATF5: 激活转录因子 5 (activating transcription factor 5)。ROS: 活性氧类 (reactive oxygen species)。C-Jun: 细胞 Jun 原癌基因 (cellular Jun proto-oncogene)。CHOP: CAAT 增强子结合蛋白同源蛋白 (CAAT enhancer-binding protein homologous protein)。Hsp60: 热休克蛋白 60 (heat shock protein 60)。Hsp10: 热休克蛋白 10 (heat shock protein 10)。CLPP: 酪蛋白线粒体基质肽酶的水解亚单位 (caseinolytic mitochondrial matrix peptidase proteolytic subunit)。其中, 红色圆圈代表 ATF5-1 或其同源物如 ATF5, 绿色圆圈代表 ATF5-1 或其同源物在核内发挥转录调控作用的功能形式或协同因子。

ATF5, 作为 ATFS-1 的同源蛋白质, 它是一种受线粒体导入效率调控的 bZIP 转录因子, 与 ATFS-1 功能相似, 并且也具备线粒体靶向序列^[26]。除了 ATF5 外, 还有两种 bZIP 家族转录因子-应激激活转录因子 4 (activating transcription factor 4, ATF4) 和 CAAT 增强子结合蛋白同源蛋白 (CAAT enhancer-binding protein homologous protein, CHOP) 同样参与 mtUPR 的激活过程^[27]。这 3 个转录因子的表达均依赖于整合应激反应 (integration of stress response, ISR) 的参与, 结果是减少线粒体内错误折叠蛋白的累积^[28]。沉默信息调节因子 (silence information regulator, sirtuin, SIRT) 家族在调控线粒体质量控制及线粒体生物学功能方面具有潜在的研究价值, 该家族中的 SIRT1 表达在细胞核、细胞质基质和线粒体中, 是目前已知家族成员中在 mtUPR 调控过程中参与度最高的一个分子^[29]。SIRT1 调控 mtUPR 有两条途径, 第一条是 SIRT1 通过去乙酰化叉头框蛋白 O (forkhead box O, FOXO), 如线虫的 DAF-16 转录因子^[30]、哺乳动物的 FOXO3^[31], 促进 FOXO 核转位, 激活 mtUPR 靶基因 (如线粒体伴侣蛋白 Hsp60, Hsp10) 的表达, 缓解蛋白质聚集, 协同增强应激抵抗; 第二条是 SIRT1 去乙酰化 PGC-1 α , 增强核基因编码的线粒体蛋白 (如电子传递链复合物亚基) 的转录, 恢复线粒体蛋白稳态^[32]。

近期研究发现, 多种非编码核糖核酸 (non-coding RNA, ncRNA) 参与 mtUPR 调控。长链非编码核糖核酸 (long chain non-coding RNA, lncRNA) 如长链非编码 RNA ND5 (lncRNA ND5, lncND5)、长链非编码 RNA ND6 (lncRNA ND6, lncND6)、长链非编码 RNA 细胞色素 b (lncRNA Cytochrome b, lncCytb) 等定位于线粒体附近, 应激时表达改变, 通过碱基互补配对、招募染色质修饰复合物等方式, 影响线粒体基因转录^[33, 34]。微 RNA (microRNA, miRNA) 如 miRNA-382 会影响线粒体与细胞核之间蛋白质数量的平衡, 沉默 miRNA-382-5p 显示线粒体核糖体蛋白和呼吸链蛋白的集体下调, 这种效应伴随着 nDNA 和 mtDNA 编码的线粒体蛋白之间的不平衡和 Hsp60 蛋白的诱导, 提示 mtUPR 的激活^[35]。

2 mtUPR 与神经元退行性疾病的关系

多种神经退行性疾病, 包括 AD、PD、HD 和

ALS, 具有一套共同的病理机制, 其核心在于变性或错误折叠蛋白的聚集和累积, 这些过程共同驱动了神经退行性疾病的进行性发展^[36]。在动物模型到人类脑组织中都发现随着年龄的增长, 出现氧化损伤加剧、膜电位损坏、钙离子失衡等线粒体功能异常现象^[37]。线粒体功能损伤的发生早于神经退行性疾病, 且可能是引起疾病发生的原因。研究表明, 在线虫^[38]、果蝇^[39]、小鼠^[40]等模式生物中, 均发现 mtUPR 与延缓衰老进程密切相关, mtUPR 可以帮助减轻在衰老过程中线粒体负担的应激压力, 如受损蛋白的累积、ROS 的过量产生等 (表 1), 因此 mtUPR 可能在不同种神经退行性疾病的发生发展中发挥相似的作用。

2.1 mtUPR 与阿尔茨海默病

大脑内细胞外的毒性 β 淀粉样蛋白 (amyloid beta, A β) 与细胞内的微管相关蛋白 (microtubule-associated protein Tau, Tau) 神经原纤维缠结是 AD 的主要病理特征^[57]。研究表明, 线粒体功能失调与 AD 起始及进展阶段密切相关, 线粒体呼吸链扰动^[58], 线粒体氧化应激^[59], mtDNA 的释放^[60]等均参与 AD 的发生发展过程^[61]。这些线粒体功能障碍最终会导致线粒体稳态调控失衡, 进而引发细胞生理功能及超微结构的病理性重塑, 表明线粒体功能障碍在 AD 发病机制和过程中发挥重要作用。在 AD 中, 淀粉样前体蛋白 (amyloid precursor protein, APP) 的异常高表达可促使裂解出的 A β 蛋白先在细胞的胞质中积累^[62]并定位于线粒体基质, 形成特征性线粒体靶向沉积^[63], 诱发线粒体超微结构损伤, 从而触发氧化应激级联反应, 其表现为: 大量 ROS 突破细胞抗氧化屏障后, 损伤电子传递链, 抑制三羧酸循环, 选择性攻击 mtDNA, 通过蛋白质碳化与脂质过氧化等修饰反应, 最终引发线粒体能量代谢崩溃^[64]。同时, 膜通透性的改变使 mtDNA 释放至胞质可激活环鸟苷酸-腺苷酸合成酶 (cyclic GMP-AMP synthase, cGAS) /干扰素基因刺激因子 (stimulator of interferon genes, STING) 通路, 触发干扰素的产生^[65], 这种由 A β 启动的病理级联不仅造成突触信号传递功能障碍, 更通过线粒体介导的凋亡通路诱导神经元程序性死亡。AD 中 mtDNA 损伤通过氧化应激-免疫激活轴这一核心机制来加剧神经退行性病变。

HtrA 丝氨酸蛋白酶 2 (HtrA serine peptidase 2, HTRA2) 位于线粒体膜间腔, 是分解处理错误折

表1 不同物种 ND 疾病模型中 mtUPR 的研究进展
Table1 Research development of mtUPR in ND models of different species

物种	疾病	mtUPR 的功能	参考文献
人	AD	减少细胞内的A β 沉积	[41-42]
	PD	降低细胞内氧化应激水平, 稳定线粒体膜电位	[23, 43-44]
	HD	改善线粒体神经突的运输, 维持细胞存活	[45]
	ALS	减少突变CHCHD10、异常TDP-43毒性蛋白的产生和堆积	[46-47]
小鼠	AD	减少细胞内的A β 沉积	[48-49]
	PD	减少 α -syn寡聚物, 缓解多巴胺能神经元退化, 降低细胞内氧化应激水平	[50]
	HD	减少突变HTT导致的线粒体蛋白堆积	[51]
	ALS	提高NAD ⁺ 代谢, 清除突变hSOD1神经毒性蛋白, 维持神经干细胞/神经前体细胞池	[52]
线虫	AD	减轻A β 的神经元毒性并抑制线粒体损伤	[53]
	PD	缓解多巴胺能神经元退化	[54]
	HD	减弱多谷氨酰胺诱导的凋亡	[55]
	ALS	升高丝氨酸蛋白酶水平, 抑制线粒体损伤	[56]

AD: 阿尔茨海默病 (Alzheimer's disease)。PD: 帕金森病 (Parkinson's disease)。HD: 亨廷顿舞蹈病 (Huntington's disease)。ALS: 肌萎缩侧索硬化症 (amyotrophic lateral sclerosis)。A β : β 淀粉样蛋白 (amyloid β)。CHCHD10: 卷曲螺旋-螺旋-卷曲螺旋-螺旋结构域蛋白 10 (coiled-coil-helix-coiled-coil-helix domain containing 10)。TDP-43: TAR DNA 结合蛋白 43 (TAR DNA-binding protein 43)。 α -syn: α 突触核蛋白 (α -synuclein)。HTT: 亨廷顿蛋白 (huntingtin)。NAD⁺: 烟酰胺腺嘌呤二核苷酸 (nicotinamide adenine dinucleotide)。hSOD1: 人超氧化物歧化酶 1 (human superoxide dismutase 1)。

叠蛋白质的重要蛋白酶, 因此也是 mtUPR 的一个重要调控因子。缺乏 HTRA2 或者表达突变 HTRA2 的小鼠表现出神经退行表型^[66]。对大规模的数据进行孟德尔随机化分析, 发现线粒体丝氨酸蛋白酶 HTRA2 是延缓 AD 的保护性蛋白^[67]。

SIRT 已经被证实是 mtUPR 的重要调节因子, 同时也参加 AD、PD、HD 等神经退行性疾病过程, 但是 SIRT 参与神经退行性疾病过程的机制还不清楚^[68]。研究发现, 在线虫 PD 模型中, 利用 RNA 干扰敲低 sir-2.2 蛋白/SIRT4, 发现 α -syn 及多巴胺转运体 1 (dopamine transporter 1, dat-1) 的表达水平均降低, 与此同时, mtUPR 的水平受到相应抑制^[69]。

此外, 衰老被认为是 AD 的首要风险因素, 伴随着人体正常衰老过程, 线粒体的质量与活性也逐渐减退。相较于其他细胞类型, 神经元具有较高的能量代谢需求, 这使得它们对年龄相关的线粒体功能衰退尤为敏感。在衰老过程中, mtDNA 突变会积累, 导致线粒体功能下降^[70-71], 且伴随着线粒体自噬的减少, 并导致受损线粒体的积累、氧化应激的增加和细胞铁死亡的诱导^[72]。在 AD 的早期进展阶段, 已观察到线粒体功能障碍的迹象, 表现为 mtDNA 突变增加和膜损伤引起的氧化应激水平升高^[73-74]。衰老与 AD 均会引发 mtDNA 的结构与功能改变, 但驱动机制、变化特征及病理效应存在

本质差别。衰老导致的 mtDNA 改变是生理性、渐进性的退变, 为 AD 的发生提供了病理基础, 而 AD 早期的 mtDNA 改变是病理性、加速性的细胞损伤, 是 AD 病理进程的重要组成部分^[75]。线虫与哺乳动物中, mtDNA 点突变或大片段缺失会触发 mtUPR, 通过核转录程序上调分子伴侣的生物合成, 提升 mtDNA 修复与复制效率^[76]。与此同时, mtUPR 对 mtDNA 的调控保护与风险并存, 持续激活的 mtUPR 会促进异常 mtDNA 的增殖与扩散^[77]。

在 AD 的线虫模型中, A β 通过上调 E3 泛素连接酶 SIAH-1, 促进其与 E2 泛素连接酶协同作用, 介导转录因子 DVE-1 的第 48 位的赖氨酸残基, 连接的多聚泛素化和蛋白酶体降解, 从而破坏 mtUPR。DVE-1 的降解加剧了 A β 聚集和线粒体功能障碍, 而敲除 E3 泛素连接酶 SIAH-1 或过表达 DVE-1 则能恢复线粒体稳态, 减轻 A β 毒性^[78]。另有研究表明, 在过表达外源 A β 的线虫模型中, 诱导 mtUPR 的关键转录因子 ATFS-1 对于维持线粒体蛋白质稳态和机体健康至关重要; 通过多西环素抑制线粒体翻译或使用烟酰胺核糖 (nicotinamide riboside, NR) 等 NAD⁺ 增强剂可以增强 mtUPR 和线粒体自噬, 从而改善线虫的运动能力、延长寿命, 并减少 A β 聚集。同样, 在 APP/早老素 1 (presenilin 1, PS1) AD 转基因小鼠中, NR 治疗

能减少大脑中的A β 斑块,改善情境记忆^[79]。研究表明,A β 聚集会破坏线粒体功能,而细胞通过激活mtUPR和线粒体自噬等应激反应进行补偿,增强相关通路能够有效刺激mtUPR可有效促进A β 降解^[78],从而延缓痴呆的发生发展。然而关于mtUPR与AD不同临床病理亚型之间的直接关联性尚待进一步探索。

2.2 mtUPR与帕金森病

PD的遗传性与线粒体相关基因突变密切相关,包括调控线粒体质量控制的核编码基因,如PTEN诱导激酶1(PTEN-induced kinase 1, PINK1)^[80],帕金森蛋白/Parkin E3泛素连接酶(Parkin RBR E3 ubiquitin protein ligase, Parkin)^[80]及14个线粒体功能基因^[81]。抑制PGC-1 α 活性是PINK1和Parkin突变诱导的家族PD的主要原因,PGC-1 α 的过表达可能会激活mtUPR,通过LRPPRC信号转导减少氧化应激损伤,从而维持线粒体稳态^[23]。某些mtDNA,比如生长停滞及DNA损伤诱导蛋白34(growth arrest and DNA damage-inducible protein 34, GADD34)^[43]的单倍群表达可能会延长mtUPR过程,从而有利于保持蛋白质稳态并促进细胞对PD发展的抵抗。

线粒体电子传递链蛋白与PD的发生发展也有关联^[82],电子传递链复合物I抑制剂鱼藤酮和超氧化物诱导物百草枯,在引起线粒体功能障碍的同时,也会强烈诱导mtUPR^[83-84]。此外,线粒体发生的多种与PD相关的功能损伤均可引起mtUPR的激活^[43]。在类PD模型中,转基因秀丽隐杆线虫过表达的 α -syn及其他与PD相关的线虫突变体,均出现诱导mtUPR的现象,不仅如此, α -syn过表达和ATFS-1突变引起的mtUPR失调也可协同加剧多巴胺能神经损伤^[85]。

在PD中,SIRT1通过去乙酰化PGC-1 α ,调节线粒体自噬,调控 α -syn的磷酸化水平,并参与mtUPR通路,以此来减轻 α -syn病理聚集^[86]。SIRT3可上调线粒体自噬水平,对抗 α -syn诱导的线粒体功能障碍,同时,下调亲环蛋白(cyclophilin D, CypD)的乙酰化水平,减轻由线粒体蛋白稳态失衡引起的mtUPR^[50, 87]。SIRT2是一种NAD⁺依赖的去乙酰化酶,抑制或敲除SIRT2可显著减轻1-甲基-4-苯基-1, 2, 3, 6-四氢吡啶(1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine, MPTP)诱导的PD小鼠黑质多巴胺能神经元死亡

和运动功能障碍,对环境因素和遗传因素所致PD均有保护作用^[88],然而这种保护神经元功能是否通过mtUPR通路尚无直接证据。线粒体质量控制失衡是PD的核心特征,适度激活mtUPR增强线粒体质量控制和蛋白质稳态,极有可能减少 α -syn沉积,保护神经元的活力。

2.3 mtUPR与亨廷顿舞蹈病

HD的病因是编码亨廷顿蛋白的基因中出现CAG重复序列扩增,导致所编码蛋白的多聚谷氨酰胺(polyglutamine, polyQ)序列异常延长。研究表明,HD与线粒体功能存在密切关联。突变型亨廷顿蛋白(mutant huntingtin, mHTT)的polyQ结构域与动力相关蛋白1(dynamitin-related protein 1, Drp1)结合,通过Drp1促进线粒体过度分裂,导致轴突中线粒体碎片化及运输停滞增强^[89]。在秀丽隐杆线虫HD早期模型中,长度超过40个谷氨酰胺残基的PolyQ在线粒体上聚集时,会激活5-羟色胺依赖的mtUPR信号通路以维持线粒体稳态^[90],而被紫苏醛激活的mtUPR信号通路则会降低polyQ的聚集程度^[91]。而在哺乳动物的HD晚期模型中,ATP结合盒转运蛋白B亚家族成员10(ATP-binding cassette subfamily B member 10, ABCB10)通过转录因子CHOP抑制mtUPR过程^[92],在HD细胞模型中,线粒体伴侣蛋白(如Hsp60、Hsp10)水平显著降低,提示mHTT可能通过干扰线粒体蛋白稳态,抑制mtUPR的激活^[93]。诸多研究表明,HD早期激活mtUPR增强线粒体蛋白稳态发挥保护作用,HD晚期mtUPR衰竭或过度激活则加剧蛋白质稳态失衡,加剧病理损伤。因此,增加mtUPR利用基因编辑或小分子化合物激活相关通路,或可促进mHTT清除及线粒体自噬,有望为HD研究提供新思路。

2.4 mtUPR与肌萎缩侧索硬化症

ALS是一种进行性神经退行性疾病,其特征是脊髓、脑干和运动皮层运动神经元的逐渐退化,最终导致肌肉无力、萎缩和瘫痪^[94]。线粒体功能障碍在ALS的疾病进程中扮演着关键角色^[95],而mtUPR作为细胞应对线粒体应激的适应性机制,与ALS的发生发展密切相关。

研究发现,ALS中的关键病理蛋白TAR DNA结合蛋白43(TAR DNA-binding protein 43, TDP-43)可以诱导线粒体损伤并激活mtUPR^[47, 96]。在ALS模型小鼠中,NAD⁺的补充被发现可以减轻神

经退行性疾病, 并激活脑部的 mtUPR 信号, 从而增强线粒体蛋白质稳态并促进成年神经发生^[52]。

综上所述, 这些研究结果均表明 mtUPR 在神经退行性疾病发病机制中发挥重要作用 (图2)。

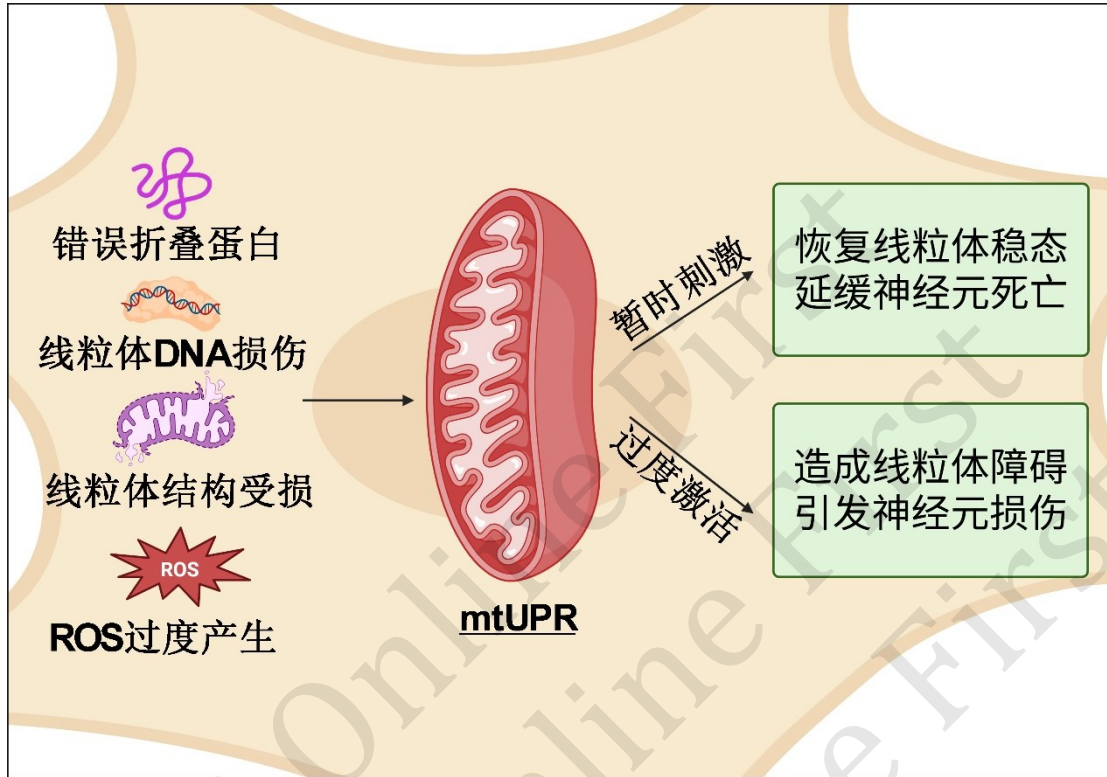


Fig. 2 The Double-Edged molecular mechanisms underlying the regulation of NDs progression by the mtUPR

图2 线粒体未折叠蛋白反应调控神经退行性疾病进程的双刃剑分子机制

神经退行性疾病中常见的表现包括错误折叠蛋白的积累、线粒体功能损伤、以及神经元的退化。其中错误折叠蛋白的堆积和线粒体结构损伤都会引起 mtUPR 的激活, 通过一系列细胞核转录事件来清除包括 A β 在内的蛋白质, 恢复并维持线粒体功能, 起到对神经元的保护作用。ROS: 活性氧类 (reactive oxygen species)。

3 总结

mtUPR 作为一种保守的线粒体质量控制机制, 其在不同疾病模型中的激活途径在分子水平上具有高度相似性。然而, 这种应激反应的下游反馈调节网络却展现出明显的疾病特异性, 受到特定疾病环境中独特分子事件的精细调控。AD 中, A β 可能会直接结合 LONP1 等 mtUPR 效应蛋白, 阻碍其蛋白酶活性, 恶化线粒体中的蛋白质稳态^[4]。类似的, 线虫 PD 模型中, 易聚集的 α 突触核蛋白 A53T 突变体 (alpha-synuclein A53T mutant, A53T) 突变 α -syn 蛋白比野生型引发的 mtUPR 更强烈, 进而加剧神经元的损伤^[85]。HD 中, 线粒体中分子伴侣蛋白表达量下降, 预示着较低水平的 mtUPR, 可能会加速疾病进程^[93]。ALS 中, TDP-43 对 mtUPR 的靶向激活可能会延缓神经元的退化及疾病症状的

发展^[47]。

相较于其他体细胞, 神经元对线粒体功能的依赖性具有显著的特异性。mtUPR 是维持线粒体完整性和功能性的重要机制。研究表明, mtUPR 与延缓衰老进程密切相关, 而神经退行性疾病风险与衰老呈高度相关^[2]。当前 mtUPR 的研究主要聚焦在模式生物秀丽隐杆线虫, 跨物种差异提示未来更多的研究重心应转移至探索哺乳动物 mtUPR 的多样化应激通路上。mtUPR 在神经元退行性疾病的进程中扮演着至关重要的角色, 然而, 在病理状态下 mtUPR 的激活和持续时间并没有确切的规律性, 如早期 HD 模型适度激活机制能够保护神经元免受线粒体功能障碍时带来的损伤, 进而减轻疾病的症状, 但慢性或过度激活反而通过 mtUPR 触发凋亡信号, 这种双向调控特性更需要精准解析。控制线粒体蛋白质质量稳态是保证线粒体功能的前提。如

何利用 mtUPR 控制蛋白质稳态, 发挥线粒体最佳功能也需要进一步探究, 同时也需重点关注 mtUPR 与核-线粒体通讯网络的交互调控, 以及其在衰老相关神经退行性病变中的时序性作用。

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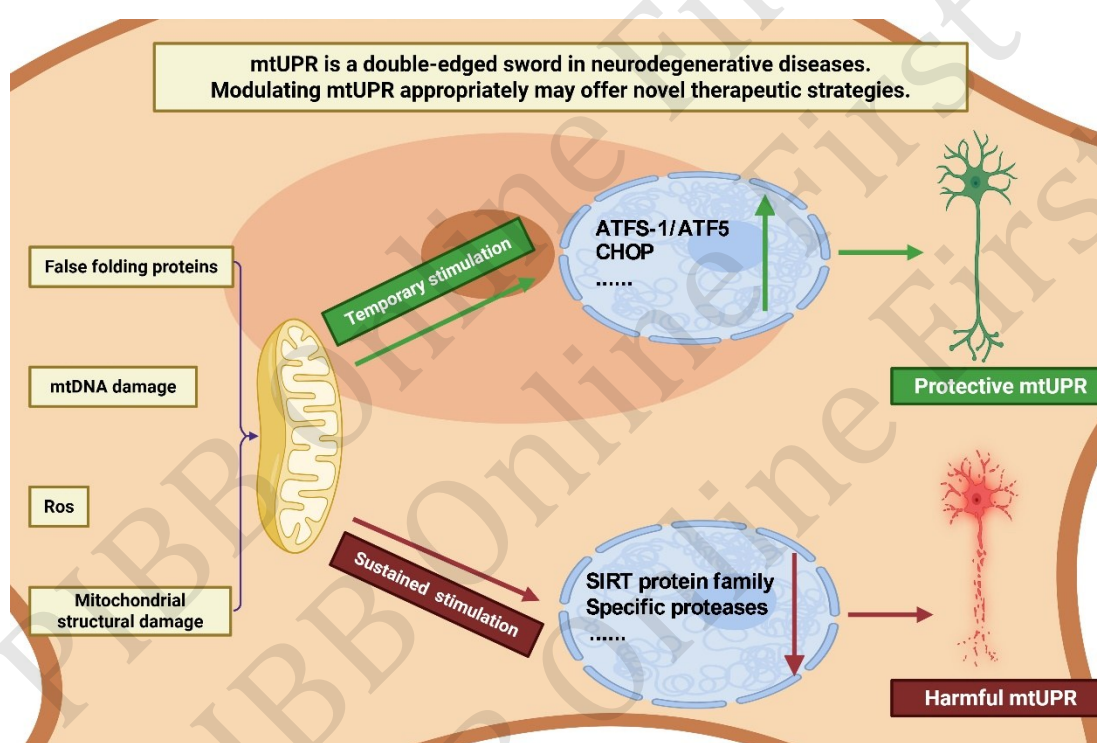
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The Role of The Mitochondrial Unfolded Protein Response in Neurodegenerative Diseases*

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Graphical abstract



Abstract As the core hub of energy metabolism in eukaryotes, mitochondria participate in a variety of cellular activities, including metabolic regulation of the cell matrix, apoptosis, and the activation of signal transduction pathways. Their functional status is closely linked to the initiation and progression of various diseases. Neurodegenerative diseases are primarily characterized by the progressive loss and dysfunction of neurons, and mitochondrial dysfunction is considered one of the key triggers in this process. The specific mechanisms by which mitochondrial dysfunction contributes to neurodegenerative diseases have attracted widespread attention. When misfolded or unfolded proteins are detected, a process known as the mitochondrial unfolded protein response (mtUPR) is activated to promote proper protein folding or degradation, thereby restoring mitochondrial function. As a mitochondrial stress defense mechanism, mtUPR primarily regulates the expression of nuclear-encoded genes, such as chaperones and proteases, to alleviate mitochondrial stress. Studies have shown that, in addition to misfolded and unfolded proteins, other mitochondrial stresses—such as mitochondrial DNA abnormalities and reactive oxygen species (ROS)—can also induce mtUPR. The biological functions of mtUPR extend beyond mitochondria and are crucial for the health of the entire cell and even the whole organism. The mtUPR process

involves communication between mitochondria and the nucleus, a phenomenon that is highly conserved and has been observed across different species. Abnormal activation or inhibition of mtUPR is closely associated with the development of various neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease. An in-depth exploration of the dynamic regulatory role and molecular mechanisms of mtUPR is therefore of great significance for understanding the pathogenesis of these disorders. In addition to neuron loss, neurodegenerative diseases are characterized by the accumulation of misfolded proteins in the brain, including insoluble fibrils of amyloid beta, phosphorylated tau, or α -synuclein. While the molecular pathways of mtUPR are largely conserved across different diseases, the possibility of differential regulatory factors cannot be excluded. Although mtUPR activation is predominantly recognized for its cytoprotective role, it may exert deleterious effects when overstimulated or sustained. Chronic mtUPR activity has been linked to mitochondrial dysfunction and increased neuronal vulnerability, contributing to the pathogenesis of various neurodegenerative diseases. This review summarizes the fundamental concepts, major inducers, and signaling pathways of the mitochondrial unfolded protein response (mtUPR). We focus on the intrinsic relationship and regulatory patterns between mtUPR and neurodegenerative diseases, providing insights that may aid the development of targeted therapies. Finally, we discuss the challenges and future directions of mtUPR research in this field, aiming to pave the way for new therapeutic breakthroughs. A major limitation arises from the experimental models currently used; most findings rely on model organisms or cultured cells, which cannot fully replicate the complexity of human neurons. Future research should therefore focus on three main directions: (1) defining the molecular switches that determine whether mtUPR acts in a protective or detrimental manner; (2) elucidating differences in mtUPR molecular pathways across various models of neurodegenerative diseases; and (3) establishing robust biomarkers for mtUPR activity.

Key words mitochondrial dysfunction, mitochondrial unfolded protein response, neurodegenerative diseases, Parkinson's disease, Alzheimer's disease

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