# 线粒体DNA拷贝数与人类疾病相关性研究进展

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**摘要** 线粒体是细胞的能量转换中心, 并参与细胞凋亡、钙调控、自由基代谢、铁代谢、信号传递等多种生理活动, 线粒体发挥功能依赖于正常的线粒体基因组。过去对于线粒体基因组的研究多集中在线粒体DNA突变引起线粒体功能异常导致疾病发生, 然而近些年线粒体DNA拷贝数的变异引起了研究人员的关注。线粒体DNA拷贝数是线粒体活性的指标之一, 其变异反映了线粒体的生物发生以及线粒体的功能。多种人类疾病中存在线粒体DNA拷贝数的变异, 但调节线粒体DNA拷贝数的机制尚未被完全阐明。该文讨论了线粒体DNA拷贝数与线粒体病、衰老和年龄相关神经退行性疾病、癌症等疾病的相关性, 以及线粒体DNA拷贝数的调控机制, 以期为相关疾病的治疗、诊断和研究提供参考信息。

**关键词** 线粒体DNA拷贝数; 线粒体病; 衰老; 神经退行性疾病; 癌症

# Research Progress on the Relationship between Mitochondrial DNA Copy Number and Human Disease

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**Abstract** Mitochondria are the energy conversion center of cells, and participate in many physiological activities such as apoptosis, calcium regulation, free radical metabolism, iron metabolism, signal transmission, etc. The function of mitochondria depends on the normal mitochondrial genome. In the past, most studies on mitochondrial genome focused on mitochondrial DNA mutation leading to mitochondrial dysfunction and disease. However, in recent years, the variation of mitochondrial DNA copy number has attracted the attention of researchers. Mitochondrial DNA copy number is one of the indicators of mitochondrial activity, and its variation reflects the biogenesis and function of mitochondria. Mitochondrial DNA copy number variation exists in a variety of human diseases, but the mechanisms regulating mitochondrial DNA copy number have not been fully elucidated. This paper discusses the relationship between mitochondrial DNA copy number and diseases such as mitochondrial diseases, aging and age-related neurodegenerative diseases, cancer, and the regulatory mechanism of mitochondrial DNA copy number. This paper provides theoretical basis for the treatment, diagnosis and research of related diseases.

**Keywords** mitochondrial DNA copy number; mitochondrial disease; ageing; neurodegenerative diseases; cancer

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哺乳动物细胞在进化过程中，线粒体内的遗传信息大多数都转移到了细胞核，但线粒体仍保留了一个残留的基因组，即线粒体基因组(mitochondrial genome/mitochondrial DNA, mtDNA)[1]。线粒体参与ATP和GTP等生物能量中间体的产生以及Fe-S簇、血红素和氨基酸的合成，钙离子调节，炎症和细胞凋亡等生理活动[2]。线粒体DNA拷贝数(mitochondrial DNA copy number, mtDNA-CN)是线粒体活性的指标之一，与细胞能量储备、氧化应激和线粒体膜电位的变化直接相关[3]。异常的mtDNA拷贝数会造成线粒体内氧化应激水平升高，从而导致mtDNA损伤，进而影响线粒体发挥正常功能[3]。而线粒体功能障碍与线粒体病、年龄相关神经退行性疾病、癌症等多种人类疾病密切相关。因此，阐明mtDNA拷贝数与疾病发生发展之间的关系对相关疾病的诊断、治疗、预后有重大意义，mtDNA拷贝数可能会作为相关疾病发生发展和预后的潜在标志物。近年来，mtDNA拷贝数的调节机制也已成为研究热点。

## 1 线粒体DNA拷贝数

每个细胞中都有成百上千个mtDNA拷贝，mtDNA拷贝数在每个细胞内与其能量需求保持一致，具有高能量需求的组织细胞内mtDNA通过复制产生更多拷贝数以提供更多的能量，但在衰老、细胞分化、激素治疗和疾病中mtDNA拷贝数可能会发生显著变化[4]。异常的mtDNA拷贝数导致mtDNA氧化应激水平升高以及mtDNA基因表达缺陷，从而影响线粒体功能，包括氧化磷酸化(oxidative phosphorylation, OXPHOS)、ROS产生、信号转导、细胞凋亡、细胞生长和线粒体到细胞核逆行信号的转导等，mtDNA拷贝数动态稳定的调控对于细胞维持正常的运转具有重要意义[5]。

mtDNA分子通过复制来实现线粒体中的多个mtDNA拷贝，与核染色体不同的是mtDNA复制与细胞周期无关，mtDNA复制的具体机制尚未明确，目前存在三种模型，即链置换模型、滞后链核糖核酸渗入模型和链耦合模型，其中链置换模型受到广泛认可[6]。人mtDNA具有重链起始位点($O_H$)和轻链起始位点($O_L$)两个复制起始位点，mtDNA的复制从$O_H$开始，mtDNA被TWINKLE线粒体DNA解旋酶解旋，H链与线粒体DNA单链结合蛋白(mitochondrial single-stranded DNA-binding protein, mtSSB)结合，线粒体RNA聚合酶(mitochondrial RNA polymerase, POLRMT)结合在轻链的轻链启动子(light strand promoter, LSP)上进行转录，生成一条几十个核苷酸大小的引物RNA[7]。引物帮助引导线粒体DNA聚合酶γ(mitochondrial DNA polymerase subunit gamma, POLG)生成新的H链。新生成的H链和原L链通过氢键结合，将原重链置换出来，形成D环复制中间物。当新生重链合成约2/3时，D环不断膨胀，导致原重链上的$O_L$暴露出来，POLG经过原L链的OL之后，原H链会折叠成茎环结构，避免与mtSSB结合的同时与POLRMT结合，以原H链为模板合成约25个核苷酸大小的引物RNA，在POLG作用下合成新的L链。此后，两条新生成的链继续合成，直到POLG再次通过$O_H$或者$O_L$，新复制的链完成[6]，再经过拓扑异构酶3α(topoisomerase 3α, Top3α)的作用，缠绕的新复制mtDNA分子相互释放[8]，mtDNA分子完成复制(图1)。

## 2 线粒体DNA拷贝数的测量

迄今为止，许多研究已经确定了组织和外周血样本中mtDNA拷贝数的水平。值得注意的是，外周血中的mtDNA拷贝数改变可能是线粒体功能和有氧代谢的潜在指标，并已发现外周血中的mtDNA拷贝数与癌症风险显著相关[5,9]。然而，由于细胞中线粒体数量和mtDNA拷贝数在组织类型中不同，因此使用准确的方法测量mtDNA拷贝数至关重要。

目前有几种方法可用于定量mtDNA拷贝数。评估人体样本和模式生物细胞中mtDNA拷贝数使用最广泛的方法是实时荧光定量聚合酶链式反应(quantitative real-time PCR, qPCR)，然而，绝大多数研究将mtDNA水平与核基因水平的比值作为相对mtDNA拷贝数[10-12]，这使得不同研究之间mtDNA拷贝数水平的比较非常困难。最近，微滴式数字PCR(droplet digital PCR, ddPCR)依靠大量样品分配和泊松统计来测量绝对mtDNA拷贝数[13-14]。然而，由于ddPCR通量有限，对于高拷贝数样本的测量结果可能会不准确[15]。

最近的研究表明，mtDNA拷贝数的定量可以通过下一代测序(next-generation sequencing, NGS)计算出来，NGS包括全外显子组测序(whole-exome sequencing, WES)和全基因组测序(whole-genome

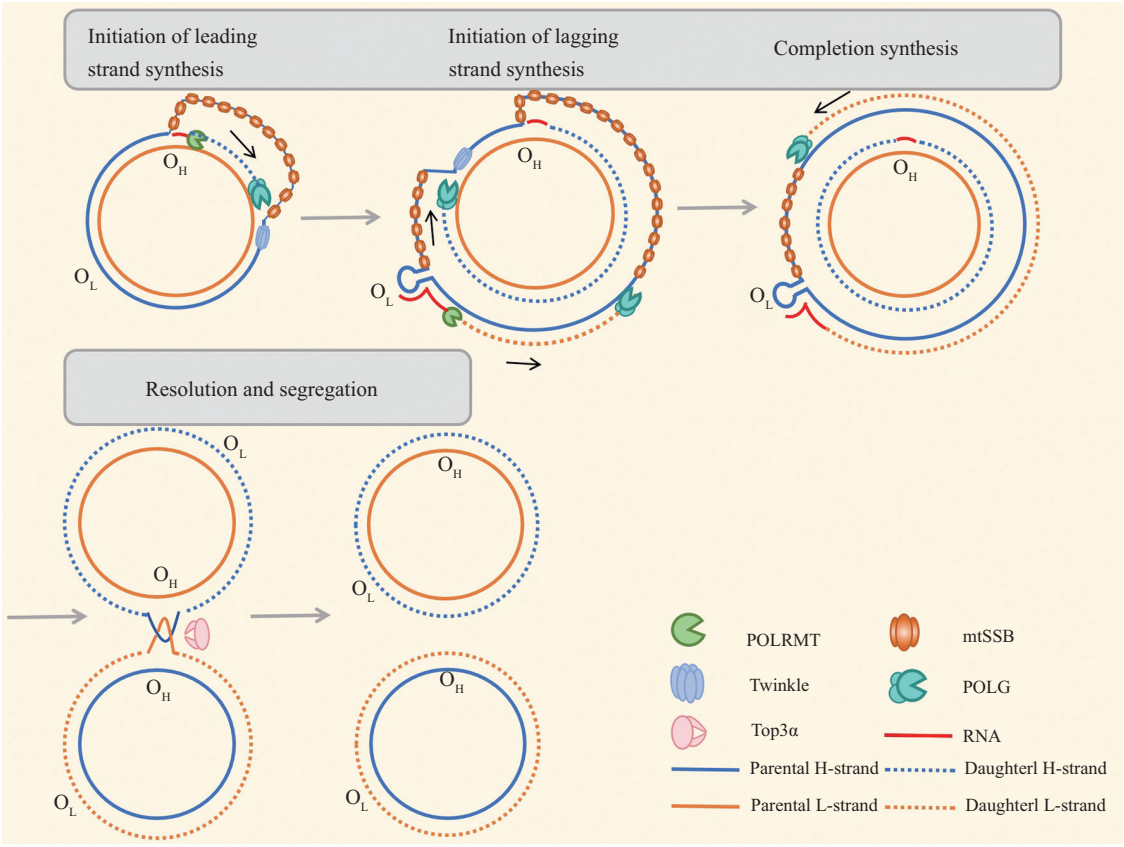



**图1 mtDNA复制的链置换模型**

**Fig.1 The asymmetric strand-displacement model**

sequencing, WGS)[16-17]。NGS技术能够对mtDNA水平进行高通量、高灵敏度和准确的评估[17]。WES或WGS将来可能会成为评估mtDNA拷贝数和mtDNA异质性水平的金标准。

此外, 纯化DNA的方法对于评估mtDNA含量也至关重要。由于mtDNA是环状结构以及mtDNA排列紧凑的特征, 提取DNA时可能会破坏mtDNA的完整性[16,18]。为了建立更准确的mtDNA拷贝数测量方法, 近年来已经进行了许多关于mtDNA提取方法的研究[19-21]。LONGCHAMPS等[16]发现使用基于裂解的方法提取mtDNA具有较低的变异性, 并且比其他方法更准确。

## 3 疾病与线粒体DNA拷贝数异常

线粒体DNA拷贝数是衡量每个细胞线粒体基因组数的指标, 是线粒体功能障碍的生物标志物, 与能量储备、氧化应激和线粒体膜电位的变化密切相关[22-23]。mtDNA拷贝数的改变可引起线粒体功能紊乱从而导致线粒体病、衰老、神经退行性疾病以及癌症的发生[4]。

### 3.1 线粒体病中的mtDNA拷贝数

线粒体病是一组以OXPHOS缺陷为特征的遗传性疾病, 可由核基因突变导致mtDNA表达水平降低, 或由原发性mtDNA突变直接改变mtDNA编码基因产物的功能或丰度引起[24]。mtDNA耗竭综合征(mtDNA depletion syndrome, MDS)是由于参与各种mtDNA维持过程(包括线粒体核苷酸代谢、mtDNA复制、线粒体动力学和质量控制)的核基因突变, 从而导致mtDNA拷贝数显著降低[25-26], 并造成肝功能障碍、发育迟缓、肌张力底下、胃肠道运动障碍以及代谢紊乱等一系列症状, MDS中低mtDNA拷贝数和病理状况之间有直接联系, 然而在其他相关线粒体病中mtDNA拷贝数和病理状况之间的联系尚不明确。对于由mtDNA缺失导致的Pearson综合征或卡恩斯−塞尔综合征(Kearns-Sayre syndrome, KSS)患者进行mtDNA拷贝数测定, 发现大多数患者的mtDNA拷贝数增加, 且mtDNA拷贝数与mtDNA缺失的大小或位置无关[4]。在携带异质m.3243A>G突变的线粒体脑肌病伴高乳酸血症和卒中样发作(mitochondrial encephalomyopathy with lactic acidosis

and stroke-like episodes, MELAS)患者中的研究显示，高mtDNA拷贝数与较轻的疾病症状相关[27]。mtDNA拷贝数的水平也与肌阵挛癫痫伴破碎红纤维病(myoclonic epilepsy and ragged red fibers, MERRF)患者的不同表型有关。此外，在携带同质突变的Leber遗传性视神经病变(Leber's hereditary optic neuropathy, LHON)患者中，mtDNA拷贝数在疾病的外显率中起作用，m.11778G>A或m.3460G>A突变的无症状携带者比视障患者具有更高的mtDNA拷贝数[28]。

上述研究和表1中总结的其他数据表明mtDNA拷贝数可能与线粒体病的发病和进展有关。然而，在这些疾病中，mtDNA拷贝数的增加可能是一种维持OXHPOS活性、延缓疾病发作和减弱表型表达的补偿机制[29]。

### 3.2 衰老和年龄相关退行性疾病中的mtDNA拷贝数

对衰老和年龄相关性退行性疾病的相关研究表明了mtDNA突变和OXPHOS功能障碍在这些疾病中扮演的角色[4]，然而mtDNA拷贝数在衰老和年龄退行性疾病中的作用尚不清楚。

衰老与mtDNA拷贝数相关性研究显示，mtDNA拷贝数在淋巴细胞和血液样本中随着年龄的增长而显著下降[38-39]，且mtDNA拷贝数的下降在老年受试者中更为明显[39]，另外，外周血中低mtDNA拷贝数与高死亡率以及认知和身体机能的下降有关[39]。然而对血液和淋巴细胞以外的样本进行的研究产生了不同的结果，在骨骼肌和心脏组织中未观察到与年龄相关的mtDNA拷贝数降低。此外一项研究报道称，老年受试者的骨骼肌细胞mtDNA拷贝数减少，肝脏细胞mtDNA拷贝数增加[40]。关于帕金森病(Parkinson's disease, PD)患者mtDNA拷贝数的一些研究表明，PD患者血液和黑质中mtDNA拷贝数降低[41-42]，有研究表明PD患者血液中mtDNA拷贝数增加[43-44]，也有研究表明PD患者mtDNA拷贝数与健康人比没有变化[45-46]。mtDNA拷贝数的测量也在阿尔茨海默病(Alzheimer's disease, AD)患者中进行，与对照组相比AD患者额叶皮层的mtDNA拷贝数降低了30%~50%，在血液、脑脊液、死后脑组织标本中mtDNA拷贝数也降低[47]。一项对人类大脑组织中mtDNA序列变异和拷贝数的研究，进一步支持mtDNA拷贝数与AD之间的相关性[41]。

对PD和AD的新型诊断和预后生物标志物的需求促进了评估外周血和脑脊液中mtDNA拷贝数的研究工作。这里讨论的大多数数据(表2)表明，在与

**表1 线粒体病与mtDNA拷贝数变异**

**Table 1 Mitochondrial disease and mtDNA copy number variation**

| 疾病 Disease | 核基因/线粒体基因突变 Nuclear gene/mitochondrial gene mutation | 样本类型 Sample type | mtDNA拷贝数 mtDNA copy number | 定量方法 Quantification method | 参考文献 References |
|---|---|---|---|---|---|
| MDS | *ANT1* | Skeletal muscle | Down | qPCR | [30] |
| | *FBXL4* | Skeletal muscle | Down | qPCR | [31] |
| | *PLOG* | Blood | Down | qPCR | [32] |
| | *TWNK* | Blood | Down | qPCR | [32] |
| | *DGUOK* | Blood | Down | qPCR | [32] |
| | *TYMP* | Blood | Down | qPCR | [33] |
| | *SUCLG1* | Leucocytes | Down | qPCR | [34] |
| | *mtSSB* | Muscle/blood/kidney | Down | qPCR | [35] |
| | *TWNK* | Blood | Down | WES | [36] |
| Pearson's syndrome | mtDNA deletion | Blood | Up | qPCR | [4] |
| KSS | mtDNA deletion | Blood/muscle | Up | qPCR | [4] |
| MERRF | m.8344A>G | Leucocytes | Up/unchanged/down | qPCR | [4] |
| MELAS | m.3243A>G | Leucocytes | Up/unchanged/down | qPCR | [4] |
| LHON | m.11778G>A | Blood | Up/unchanged | qPCR | [28,37] |
| LHON | m.3460G>A | Blood | Up/unchanged | qPCR | [28,37] |

WES: 全外显子组测序; qPCR: 实时荧光定量PCR。

WES: whole-exome sequencing; qPCR: quantitative real-time PCR.

表2 衰老和神经退行性病变与mtDNA拷贝数变异

Table 2 Aging and neurodegenerative lesions and mtDNA copy number variation

| 疾病 Disease | 样本类型 Sample type | mtDNA拷贝数 mtDNA copy number | 定量方法 Quantification method | 参考文献 References |
|---|---|---|---|---|
| Ageing | Lymphocytes | Down | qPCR | [38] |
| | Blood | Down | WGS | [48] |
| | Liver | Up | NGS, ddPCR | [40] |
| | Skeletal muscle | Down | NGS, ddPCR | [40,49] |
| | Substantia nigra | Up | qPCR | [50] |
| PD | Blood | Down | ddPCR | [43] |
| | Blood | Unchanged | qPCR | [45] |
| | Substantia nigra | Down | qPCR | [51] |
| | Cerebellum | Unchanged | WES | [41] |
| | Cerebellar cortex | Unchanged | WES | [41] |
| | Cerebrospinal fluid | Up | ddPCR | [52] |
| AD | Cerebrospinal fluid | Down | qPCR | [53] |
| | Blood | Unchanged | qPCR | [54] |
| | Blood | Down | qPCR | [47] |
| | Cerebellar cortex | Down | WES | [41] |
| | Frontal cortex | Down | WGS | [55] |

WGS: 全基因组测序; WES: 全外显子组测序; qPCR: 实时荧光定量PCR; ddPCR: 微滴式数字PCR。
WGS: whole-genome sequencing; WES: whole-exome sequencing; qPCR: quantitative real-time PCR; ddPCR: droplet digital PCR.

年龄相关的疾病和衰老中观察到的线粒体功能下降与mtDNA拷贝数的逐渐减少有关。但这些研究的结果也可能因标本的质量和组成而产生严重偏差。因此, mtDNA水平与年龄相关疾病之间可能存在的因果关系需要进一步的实验验证。

### 3.3 癌症中的mtDNA拷贝数

mtDNA拷贝数与线粒体基因组中的氧化损伤水平显著相关, 并通过参与ROS产生来调节细胞凋亡以及细胞分化。异常的mtDNA拷贝数可导致mtDNA氧化应激水平升高, 氧化应激损伤mtDNA, 进而使得线粒体功能紊乱, 例如OXPHOS的紊乱可能导致细胞内ATP生成减少, 从而触发癌细胞糖酵解的代偿性增加[5]。异常的mtDNA拷贝数降低线粒体生物发生速率, 改变正常细胞的功能, 最终导致肿瘤的出现, 因此, mtDNA拷贝数可作为多种癌症的潜在标志物。

外周血标本中mtDNA拷贝数的变化在肿瘤类型之间存在差异, 与非肿瘤组织相比, 乳腺癌、膀胱癌、食管癌、头颈部鳞状细胞癌、肾癌和肝癌中观察到mtDNA拷贝数增加[5]。在肾透明细胞癌、肝细胞癌和骨髓增生性肿瘤中发现mtDNA拷贝数降低[5]。mtDNA拷贝数变异与癌症进展风险的关联也有报道, 血液中高mtDNA拷贝数与淋巴瘤[56]、乳腺癌[57]、皮肤癌[58]、肺癌[59]和胰腺肿瘤[60]的进展风险增加相关, 也有研究表明高mtDNA拷贝数对骨癌、肾癌等癌症类型有保护作用[4]。外周血细胞中mtDNA拷贝数的基线水平极低和极高都与肝癌发病风险增加有关, 但其潜在机制需要进一步阐明[61]。通过比较几种癌症类型中正常和肿瘤组织样本, mtDNA的拷贝数也被评估为预后因素, mtDNA拷贝数的增加和减少都与疾病的严重程度相关。结直肠癌的进展与mtDNA拷贝数的增加[62]和减少[63]有关。肺癌、胃癌和肾细胞癌中也有类似的发现, 研究发现疾病严重程度与高mtDNA拷贝数有关[64], 然而早期研究发现两者呈反比关系[65]。

以上的数据以及表3中的数据表明, mtDNA拷贝数可能是多种癌症的潜在标志物。然而, mtDNA拷贝数在不同癌症类型中的差异, 可能是不同癌症组织中能量代谢需求不同的结果。大多数研究只探究了mtDNA突变或mtDNA拷贝数与疾病的关系, 对于未来的研究, 同时评估mtDNA突变和mtDNA拷贝数, 并将这些参数与mtDNA表达和OXPHOS能力的评估联系起来对于预测癌症的发病风险以及预后至关重要。

## 4 线粒体DNA拷贝数调控

目前mtDNA拷贝数的调控机制尚未完全明确,

**表3 癌症疾病严重程度与mtDNA拷贝数变异**

**Table 3 Cancer disease severity and mtDNA copy number variation**

| 疾病<br>Disease | mtDNA拷贝数<br>mtDNA copy number | 严重程度<br>Disease severity | 定量方法<br>Quantification method | 参考文献<br>References |
|---|---|---|---|---|
| Primary breast tumour | Down | Increased | WGS | [65] |
| Colorectal carcinoma | Up | Increased | qPCR | [62] |
| Squamous cells carcinoma | Down | Increased | WGS, WES | [65] |
| Renal carcinoma | Down | Decreased | WGS | [64] |
| Renal oncocytomas | Up | Decreased | qPCR | [66] |
| Hepatocellular carcinoma | Down | Increased | qPCR | [64] |
| Lung adenocarcinoma, small cells lung cancer | Up | Increased | qPCR | [64] |
| Non-small cell lung cancer | Down | Increased | qPCR | [67] |
| Lymphocytic leukaemia | Up | Increased | WGS | [64] |
| Pancreas tumour | Up | Increased | WGS | [64] |
| Primary prostate cancer | Up | Increased | WGS | [64] |
| Thyroid cancer | Up | Increased | WGS | [64] |

WGS: 全基因组测序; WES: 全外显子组测序; qPCR: 实时荧光定量PCR。

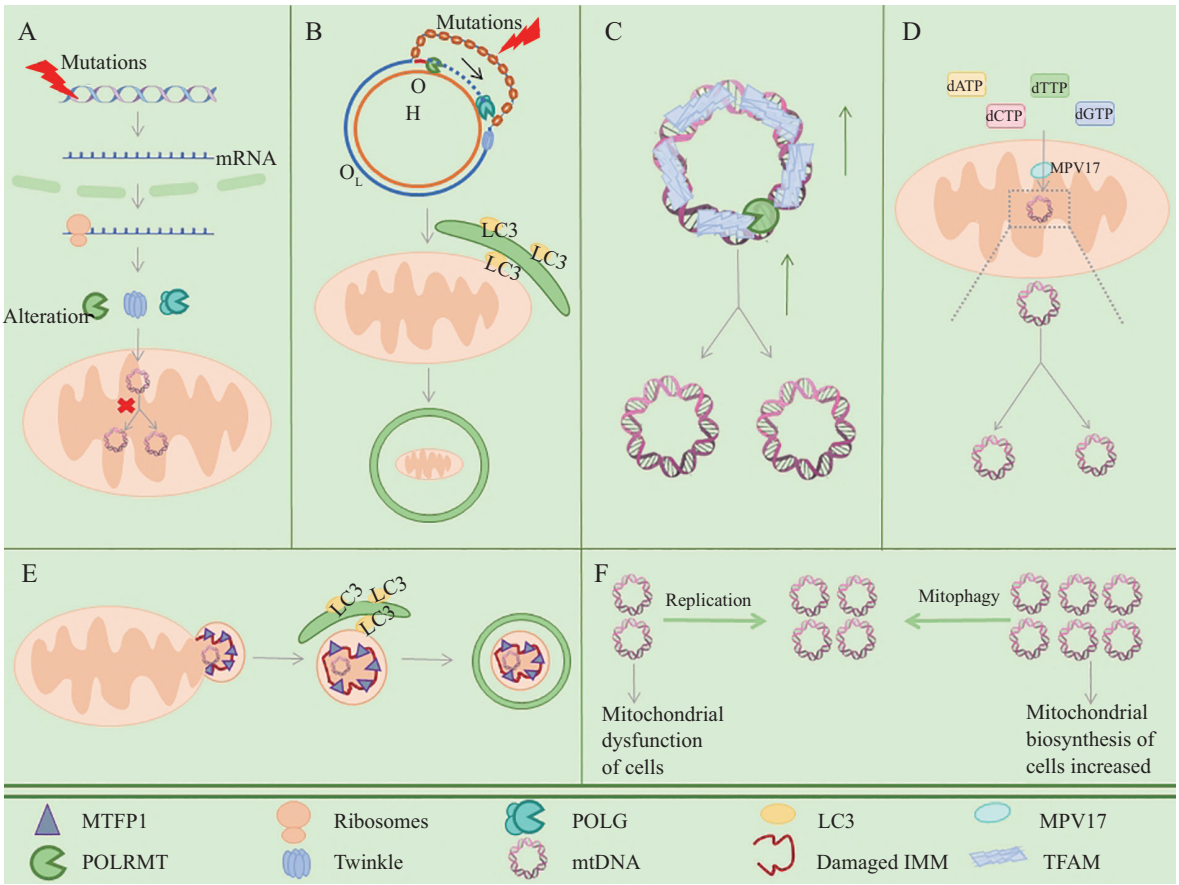
WGS: whole-genome sequencing; WES: whole-exome sequencing; qPCR: quantitative real-time PCR.

但有几种理论和模型来解释mtDNA拷贝数的调控。参与mtDNA复制和维持的蛋白可能是维持和调节mtDNA水平的关键因素。POLG与mtDNA拷贝数密切相关, MEDEIROS等[68]的研究表明线粒体依靠自噬的稳态功能来平衡POLG的合成和降解模式, 从而控制mtDNA拷贝数。Twinkle可调节细胞中mtDNA拷贝数水平, 在mtDNA复制过程中, Twinkle决定是否将全长mtDNA复制[69], 在转基因小鼠中Twinkle解旋酶的过表达会导致mtDNA拷贝数增加[70]。mtDNA突变经常发生在mtDNA的D环区域内, D环中的突变可能会改变mtDNA调控位点上核编码DNA的几个调节因子的结合亲和力, 从而改变mtDNA转录, 导致氧化磷酸化和ROS产生的紊乱[71]。受损的mtDNA通过线粒体自噬去除, 进而导致mtDNA拷贝数减少[72]。因此, D环区域的改变会严重影响mtDNA拷贝数的调控。在线粒体基质中, 线粒体转录因子A(mitochondrial transcription factor A, TFAM)将mtDNA包装成线粒体类核, 每个线粒体类核平均包含1.4个mtDNA分子[73], 转基因小鼠中TFAM的过表达导致mtDNA拷贝数增加[70]。尽管与mtDNA复制和维持过程相关的调控因子任何突变或缺失都可能扰乱mtDNA拷贝的调控, 但参与该机制的蛋白质的过表达不会不断增加mtDNA的拷贝数[69]。

除了蛋白调节mtDNA拷贝数外, mtDNA拷贝数的调节还可能取决于dNTP池的可用性, 线粒体中DNA复制依赖于dNTP的平衡供应, 有研究表明增加线粒体dNTP合成可以挽救POLG缺陷的成纤维细胞中mtDNA拷贝数的减少[74]。MPV17是一种线粒体内膜蛋白, 该蛋白参与线粒体脱氧核苷酸稳态, MPV17缺失导致线粒体脱氧核苷酸不足进而导致mtDNA拷贝数降低[75]。

最近的一项研究表明, 细胞通过调节线粒体内膜(the inner mitochondrial membrane, IMM)上的线粒体分裂过程蛋白1(mitochondrial fission process 1, MTFP1)水平来操纵线粒体融合从而调节mtDNA拷贝数。MTFP1抑制线粒体融合, 使得线粒体网络中分离出富含MTFP1的小线粒体(small MTFP1-enriched mitochondria, SMEM), 而SMEM中含有mtNDA, SMEM通过线粒体自噬降解, 进而降低了细胞内的mtDNA拷贝数[76]。

此外, mtDNA拷贝数调控的阈值模型表明, 当拷贝数降到下限时, 未知因素会触发mtDNA复制机制的上调, 从而推动mtDNA拷贝数回升。当拷贝数升高到阈值时, 会诱导线粒体自噬的发生进而导致mtDNA降解, 从而将mtDNA拷贝数降到正常水平, 以维持细胞内mtDNA相对稳定的水平[5]。当偏离正常mtDNA拷贝数的状态持续太久或偏离正常mtDNA拷贝数细胞的积累, 可能会增加患相关疾病的风险。相关研究表明外周血细胞中mtDNA拷贝数的基线水平极低和极高都与肝癌发病风险增加有关[61]。随着对mtDNA拷贝数在疾病中扮演角色的认识, 明确mtDNA拷贝数调节机制将有助于对线粒




A: mtDNA复制调控mtDNA拷贝数。由内源性攻击引起的编码mtDNA复制相关蛋白的核基因突变, 导致mtDNA复制异常进而改变mtDNA拷贝数。B: D环区域基因突变调控mtDNA拷贝数。受损的mtDNA通过线粒体自噬去除, 进而导致mtDNA拷贝数减少。C: TFAM调控mtDNA拷贝数。TFAM的过表达导致mtDNA拷贝数增加。D: dNTP池调控mtDNA拷贝数。MPV17的缺失导致线粒体脱氧核苷酸不足进而导致mtDNA拷贝数降低。E: 线粒体分裂调控mtDNA拷贝数。细胞通过调节MTFP1水平来操纵线粒体分裂, 进而通过线粒体自噬调节mtDNA拷贝数。F: mtDNA拷贝数调控的阈值模型。当拷贝数降到下限时, 细胞触发mtDNA复制机制的上调, 从而推动mtDNA拷贝数回升。当拷贝数升高到阈值时, 会诱导线粒体自噬的发生进而导致mtDNA降解。

A: mtDNA replication regulates mtDNA copy number. Mutations in nuclear genes encoding mtDNA replication-associated proteins induced by endogenous attacks lead to abnormal mtDNA replication and consequently to altered mtDNA copy number. B: mutations in the D-loop region regulate mtDNA copy number. Damaged mtDNA is removed by mitophagy, leading to mtDNA copy number decreased. C: TFAM regulates mtDNA copy number. Overexpression of TFAM leads to an increase in mtDNA copy number. D: dNTP pool regulates mtDNA copy number. Deletion of MPV17 leads to a shortage of mitochondrial deoxyribonucleic acid, which in turn leads to a decrease in mtDNA copy number. E: mitochondria segregation regulates mtDNA copy number. Cells manipulate mitochondrial fission by regulating MTFP1 levels, which in turn regulates mtDNA copy number through mitophagy. F: threshold model of mtDNA copy number regulation. When the copy number drops to the lower limit, the cell triggers the upregulation of the mtDNA replication mechanism. When the copy number elevated to the upper limit, the cell induces mitophagy.

**图2 mtDNA拷贝数的调控**

**Fig.2 Regulation of mtDNA copy number**

体病、神经退行性疾病以及癌症等相关人类疾病的治疗(图2)。

## 5 与mtDNA相关的疾病治疗

线粒体内mtDNA异质性与拷贝数水平可能是人类患病与否的关键因素, 直接或间接控制mtDNA水平或者mtDNA异质性可能是治疗或预防疾病进展的有效措施, 目前控制mtDNA水平或者mtDNA异质性的治疗主要集中在原发性线粒体疾病, 但对于其他相关疾病是一种潜在的有效治疗策略。

### 5.1 控制mtDNA异质性

目前, 改变mtDNA异质水平的最有效策略是线粒体靶向核酸内切酶技术, 如转录激活因子样效应核酸酶技术(mitoTALENs)和锌指核酸酶技术(mitoZFNs)[77-78]。在具有异质性mtDNA突变的小鼠模型中, 通过注射腺相关病毒(adeno-associated

virus, AAV)载体递送的mitoTALENs或mitoZFNs, 可将mtDNA异质水平降低到阈值以下, 从而改善心脏和骨骼肌中的分子表型[79-80]。该领域正在快速发展, 为临床治疗相关mtDNA异质突变导致得疾病带来了希望。需要指出的是, mitoTALENs和mitoZNFs的使用仅限于异质mtDNA突变, 例如点突变和缺失, 不能用于治疗一些常见的同质致病突变, 例如引起LHON的突变。

增加mtDNA拷贝数可能会治疗由异质性mtDNA突变引起的人类疾病, 尽管mtDNA拷贝数调控的分子机制尚不清楚, 但mtDNA的量与TFAM蛋白水平成正比。因此, mtDNA拷贝数的操纵可以通过调节TFAM表达实现。研究表明, 过表达TFAM使得mtDNA拷贝数增加, 从而改善由异质mtDNA缺失或tRNA致病点突变引起的线粒体疾病的症状[29]。通过操纵TFAM水平来调节mtDNA拷贝数可能为治疗原发性线粒体疾病以及干预以线粒体损伤为特征的其他人类疾病提供潜在的治疗策略。

### 5.2 控制mtDNA拷贝数

有关线粒体自噬缓解相关疾病症状的研究显示, 肠道微生物群产生的尿石素A可选择性降解功能失调的线粒体, 从而增强线粒体氧化磷酸化能力, 延长线虫和啮齿动物的寿命, 并提升老年小鼠的肌肉功能和运动能力[81]。此外, 肌动蛋白和烟酰胺腺嘌呤二核苷酸补充剂诱导AD小鼠和线虫模型线粒体自噬, 逆转了AD小鼠和线虫模型的记忆障碍[82-83]。阿拉伯糖素促进PINK1-PRKN介导的线粒体自噬, 延缓小鼠的细胞衰老[84]。通过线粒体自噬将受损线粒体选择性降解能够缓解相关疾病症状, 而线粒体自噬的同时又间接降低了mtDNA拷贝数, 线粒体自噬能够缓解疾病症状是否通过调节mtDNA拷贝数水平实现还有待进一步研究。

通过促进线粒体生物发生来增加mtDNA水平能够抵消由mtDNA或核基因突变引起的生物能量缺陷, 线粒体生物发生的刺激需要核DNA和mtDNA编码基因产物的同步表达。过氧化物酶体增殖受体γ辅激活因子1α(peroxisome proliferator-activated receptor gamma coactivator 1α, PGC1α)通过与多种核转录因子相互作用从而促进线粒体的生物发生, PGC1α的过表达改善了复合IV组装缺陷小鼠的肌病表型, 并改善了部分mtDNA突变体小鼠的过早衰老表型[85], 说明线粒体生物发生的增加可以降低线粒体病的严重程度。线粒体生物发生促进剂, 如苯扎贝特、烟酰胺核苷和烟酸, 也已在人体试验中进行[86], 促进线粒体生物发生可能是治疗线粒体疾病的有效治疗策略(图3)。

## 6 问题与展望

在线粒体病、神经退行性疾病以及癌症等多种人类疾病中都存在着mtDNA拷贝数的变异, mtDNA拷贝数与相关疾病的发生发展密切相关, 并可能是相关疾病诊断以及预后的潜在标志物, mtDNA拷贝数的相关研究成为了当前研究的热点领域之一。然而mtDNA水平与疾病严重程度以及发病风险仍然只是存在相关性, 对于mtDNA水平如何影响疾病发生发展的具体分子机制以及细胞调节mtDNA拷贝数的具体分子机制仍然不完全清楚, 有待进一步研究。随着日后相关研究的深入, 将阐明不同疾病不同发展阶段的mtDNA拷贝数的变化、mtDNA拷贝数在疾病中扮演的角色以及调节mtDNA拷贝数的具体机制, 以期为预防和治疗线粒体病、神经退行性疾病以及癌症带来新的方向。

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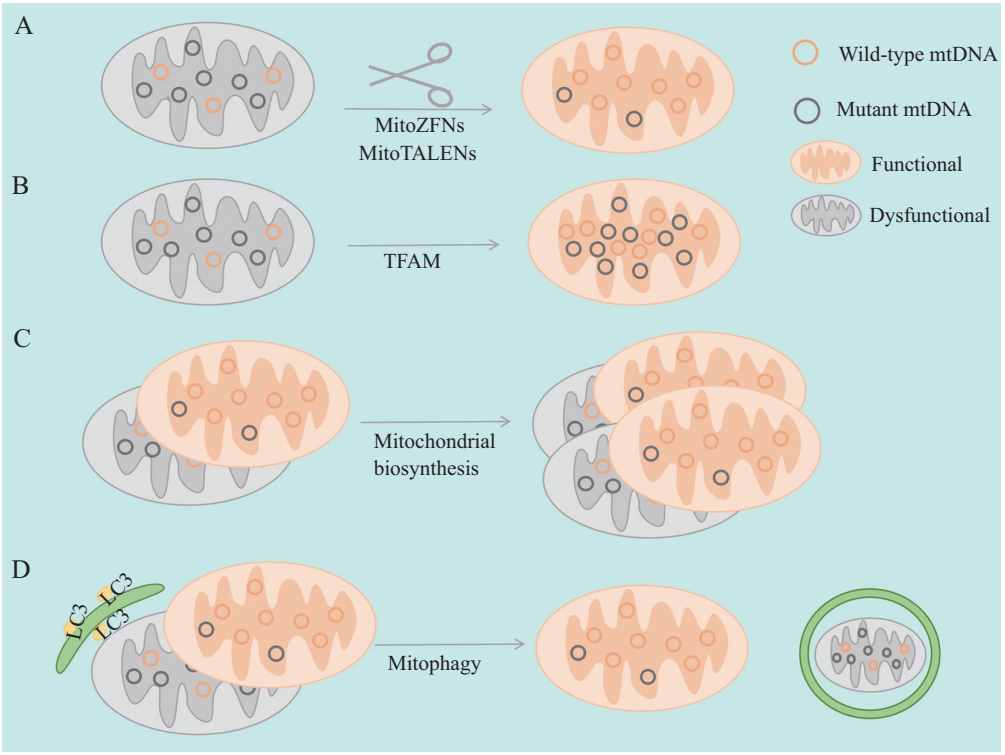


A: mitoTALENs和mitoZNFs选择性切除mtDNA。将突变的mtDNA选择性切除, 残留的野生型mtDNA进行复制进而恢复线粒体功能。B: 通过调节TFAM表达水平增加mtDNA拷贝数。由于功能性mtDNA的量的绝对增加, 线粒体功能可以部分恢复从而缓解疾病症状。C: 促进线粒体生物发生。通过促进线粒体生物发生, 可以实现所有线粒体成分以及mtDNA水平的普遍增加, 以挽救细胞OXPHOS的缺陷。D: 促进线粒体功能障碍的线粒体进行线粒体自噬。通过将功能障碍的线粒体清除, 具有功能的线粒体经过生物发生后挽救细胞OXPHOS的缺陷。

A: mitoTALENs and mitoZNFs selectively excise mtDNA. Mutant mtDNA is selectively excised and the residual wild-type mtDNA is replicated to restore mitochondrial function. B: increase mtDNA copy number by regulating TFAM expression level. Due to the increase in functional mtDNA, mitochondrial function can be partially restored to alleviate disease symptoms. C: promoting mitochondrial biogenesis. By promoting mitochondrial biogenesis, a general increase in all mitochondrial components as well as mtDNA levels can be achieved to save the cell's OXPHOS. D: promote mitochondrial autophagy in mitochondria with mitochondrial dysfunction. By removing the dysfunctional mitochondria, the mitochondria function.

**图3 与mtDNA相关的疾病治疗**

**Fig.3 Disease treatment associated with mtDNA**

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