DOI: 10.13376/j.cbls/2022086

文章编号：1004-0374(2022)07-0778-12

线粒体基因组转录调控机制研究进展

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摘　要：线粒体是半自主细胞器，具有自身的基因组 (mtDNA) 和独特的复制转录机制。线粒体不仅是细胞能量工厂，也是细胞代谢、信号转导和表观调控的枢纽。目前对核基因组编码线粒体基因的转录调控已有较多认识，mtDNA 的转录调控机制研究则处于起步状态。线粒体转录复合体包括线粒体 RNA 聚合酶 POLRMT (mitochondrial RNA polymerase)、转录因子 TFAM (mitochondrial transcription factor A) 以及 TFB2M (mitochondrial transcription factor B2) 等。近年研究发现，线粒体转录复合体互作因子调节 mtDNA 的转录强度。此外，线粒体转录复合体的翻译后修饰或 mtDNA 的化学修饰也是调控线粒体转录的重要机制。一些核因子在转位至线粒体后也会调控线粒体转录过程，最终影响线粒体代谢和细胞呼吸水平。由于 mtDNA 编码电子传递链的关键蛋白，线粒体转录异常与肿瘤、心血管疾病、糖尿病、衰老等多种人类疾病密切相关。现阶段对 mtDNA 转录复合体的结构和生化活性已有初步认识，但细胞如何协调 mtDNA 转录和线粒体代谢活性仍是尚待解决的生物学问题。本文旨在总结近年线粒体转录调控机制的研究进展及其生理病理意义，并展望可能的药物靶点及临床前景。

关键词：线粒体转录；线粒体基因组；线粒体 RNA 聚合酶；线粒体转录复合体；线粒体转录相关疾病

中图分类号：Q343；Q75　　**文献标志码：**A

Advances on the regulatory mechanisms of mitochondrial genome transcription

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Abstract: Mitochondria are semi-autonomous organelles with specific genomes (mtDNA). They maintain machineries that are specialized for mtDNA replication and transcription. In addition to their role as cellular powerhouses, mitochondria are also hubs for cell metabolism, signal transduction and epigenetic regulation. To date, the transcriptional regulation of nuclear genome-encoded mitochondrial genes has been extensively understood. However, the knowledge of transcriptional regulation of mtDNA is still in its infancy. Mitochondrial transcription complex consists of POLRMT (mitochondrial RNA polymerase), TFAM (mitochondrial transcription factor A) and TFB2M (mitochondrial transcription factor B2). Recent studies found that protein interactors of

收稿日期：2022-03-16；修回日期：2022-04-27

基金项目：国家自然科学基金项目(81790251，81790250，81772946，81502379)；上海市青年科技启明星计划(20QA1401700)；上海市自然科学基金项目(22ZR1414200)；上海市青年人才托举工程(2018QNRC001)；上海市晨光计划(14CG15)

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transcription complex regulated mtDNA transcription efficiency. Post-translational modifications of mitochondrial transcription complex and chemical modifications of mtDNA were also important mechanisms for regulating mitochondrial transcription. Some nuclear factors were found to translocate into mitochondria and alter mtDNA transcription, ultimately affecting mitochondrial metabolism and cellular respiration. mtDNA encodes key proteins in the electron transport chain, hence mitochondrial transcription abnormalities are closely related to multiple human diseases, such as tumors, cardiovascular diseases, diabetes and aging. At present, the structure and biochemical activity of mitochondrial genome transcription complex have been preliminarily recognized. How cells coordinate mtDNA transcription and mitochondrial metabolic activity remains a key biological question. This review summaries recent progresses in mitochondrial transcriptional regulation and its pathophysiological significance, with a highlight of potential druggable targets and their clinic potential.

Key words: mitochondrial transcription; mitochondrial genome; mitochondrial RNA polymerase; mitochondrial transcription complex; mitochondrial transcription related diseases

线粒体是真核细胞能量生产的核心，它通过氧化磷酸化 (oxidative phosphorylation, OXPHOS) 途径产生 ATP。线粒体被认为起源于 15 亿年前的内共生事件，该事件使宿主细胞拥有了区室化的生物能量和生物合成的“工厂”，同时内共生菌获得了宿主的各种代谢物。有趣的是，线粒体在进化过程中保留了它们的基因组，线粒体基因组 (mtDNA) 所携带的遗传信息对细胞的正常生命活动是不可缺少的。与核基因不同，mtDNA 的转录和复制发生在同一时空。mtDNA 转录复制的有序进行依赖于多种因子的协助以及精密的调控机制。

线粒体位于细胞代谢网络的关键位置 [1]，mtDNA 表达与细胞几乎所有代谢活动相关，而 mtDNA 转录调控是尤为关键的一步。线粒体转录会直接或间接影响线粒体呼吸和细胞代谢。在漫长的生物进化过程中，细胞演化出了复杂的线粒体生物合成调控体系，通过多层次的调节机制控制线粒体转录的活性来满足自身需要。近年的研究对 mtDNA 的转录调控机制及其生理病理作用有了初步的认识，细胞可通过调节信号通路诸如 AMPK (AMP-activated protein kinase) 和 mTOR (mammalian target of rapamycin) 等的活性改变线粒体基因转录，核转录调控因子如 PGC-1α (peroxisome proliferator-activated receptor-γ coactivator-1α)、NRF2 (nuclear factor erythroid 2-related factor 2)、SIRT7 (Sirtuin 7) 等则直接调控核编码线粒体基因表达 [2]。然而，mtDNA 的转录调控研究相对较少，线粒体自身转录调控和细胞代谢的协同机制也是近年研究热点之一。本文将重点围绕 mtDNA 转录调控机制及其在代谢性疾病中的生理病理作用展开综述，并初步探讨通过靶向线粒体转录干预线粒体相关疾病的可能性。

1 mtDNA及其转录分子机器概述

mtDNA 位于线粒体基质，大小约 16.5 kb，属于环状双链 DNA，可结合其他分子形成拟核 [3-4]。mtDNA 编码 13 个氧化磷酸化蛋白、2 个 rRNA 及 14 个 tRNA。mtDNA 唯一的非编码区是 D 环 (displacement loop, D-loop)，也是转录复制的关键调控区域 [5]。控制 mtDNA 转录的 DNA 元件包括轻链启动子 (light strand promoter, LSP) 和重链启动子 (heavy strand promoter, HSP)。线粒体的转录发生在基质中，主要由线粒体 RNA 聚合酶及其辅助因子完成 [6]。

线粒体 RNA 聚合酶 (mitochondrial RNA polymerase, POLRMT) 是负责 mtDNA 转录的 RNA 聚合酶，在转录和复制中均担任关键的角色。POLRMT 需要线粒体转录因子 B2 (mitochondrial transcription factor B2, TFB2M) 和线粒体转录因子 A (mitochondrial transcription factor A TFAM) 来共同启动 mtDNA 转录 [6]。POLRMT 的 C 端结构域 (carboxyl-terminal domain, CTD) 包含了酶的活性位点，负责催化核苷酸链的合成，而且对与 DNA 的结合至关重要 [7]。N 端结构域 (NTD) 包含识别启动子的结构元件。POLRMT 与 mtDNA 结合时碱基特异性较弱，更多依赖于与启动子预先结合的转录因子识别 mtDNA，这种依赖性拓宽了线粒体基因转录的调控层次。此外，POLRMT 还包含 N 端延伸域 (N-terminal extension, NTE)，NTE 负责结合 mtDNA 和 TFAM，从而维持转录的特异性 [8-9]。

TFAM 在 mtDNA 的转录、维持和复制中都发挥关键作用 [10-12]。在转录起始时，TFAM 结合 mtDNA 将其弯曲成 U 型构象 (U-turn) 从而激活转录 [13-16]。

转录起始前，TFB2M 会被招募到 POLRMT 上，两者协同识别并融化启动子，启动子双链在转录复合体作用下解链并开始特异的转录起始 [6, 17]。

2 mtDNA转录起始、延伸和终止的分子生物学过程

负责线粒体转录的分子机器主要包含催化转录的 POLRMT 和一些辅助因子，这一体系负责调控 mtDNA 上的启动子识别、转录起始、转录延伸和终止。近年的研究对转录分子机器的工作原理和调控机制已有一定认识，但和细胞核基因组转录调控机制研究相比，仍处于起步阶段。

POLRMT 与 mtDNA 启动子结合后引发转录起始，位于启动子附近的转录因子和 POLRMT 组装成封闭的转录起始复合物，整个转录起始过程都发生在这一复合物中。有意思的是，只有 TFAM 具备单独与轻链启动子 LSP 特异性结合的能力，POLRMT 和 TFB2M 均不能单独识别启动子 [18-20]。TFAM 与 POLRMT 率先结合于 mtDNA 上 [21]，由 TFAM 介导的 mtDNA 构象变化能够帮助转录复合物的组装和激活 [18]。随后，TFB2M 进入转录起始复合体，引发启动子区域 mtDNA 解链，形成转录起始泡 [18-20]。转录起始位点的模板链被 POLRMT 捕获，非模板链则与 TFB2M 结合 [22-23]。也有研究表明存在非经典的转录复合体装配机制：POLRMT 和 TFB2M 形成复合物结合到 mtDNA 启动子上后，招募 TFAM 进而引发转录起始 [24-28]。在转录起始阶段，POLRMT 以 mtDNA 为模板合成 RNA。新生 RNA 的长度从 2 nt 延长到 8~10 nt 时，POLRMT 仍稳定结合 mtDNA 启动子，随后 RNA:DNA 杂交链引发的构象变化将起始复合体转化为延伸复合体 [29-32]。

线粒体 DNA 转录起始过渡到转录延伸阶段时，与 POLRMT 结合的起始因子 TFB2M 被延伸因子 (mitochondrial transcription elongation factor, TEFM) 取代 [33-34]。TEFM 可与转录泡的非模板链结合 [22, 35]。虽然 POLRMT 具有单独催化转录延伸的活性，但仅能合成约 500 nt 的 RNA 转录本，更长的转录本则需要 TEFM 存在才能顺利合成 [22, 35-36]。因此，TEFM 与转录泡和 RNA 的相互作用可以稳定延伸复合体，对线粒体 DNA 的转录完整性是必需的 [36-39]。

线粒体 DNA 通过 LSP 和 HSP 引发的转录过程产生多顺反子 RNA 转录本。转录完成时需要线粒体转录终止因子 (mitochondrial transcription termination factor 1, mTERF1) 协助实现转录本合成的终止 [40]。随后，转录本经加工后形成单个的 mRNA、tRNA 和 rRNA 分子，进一步参与线粒体遗传信息流动和生物合成过程。

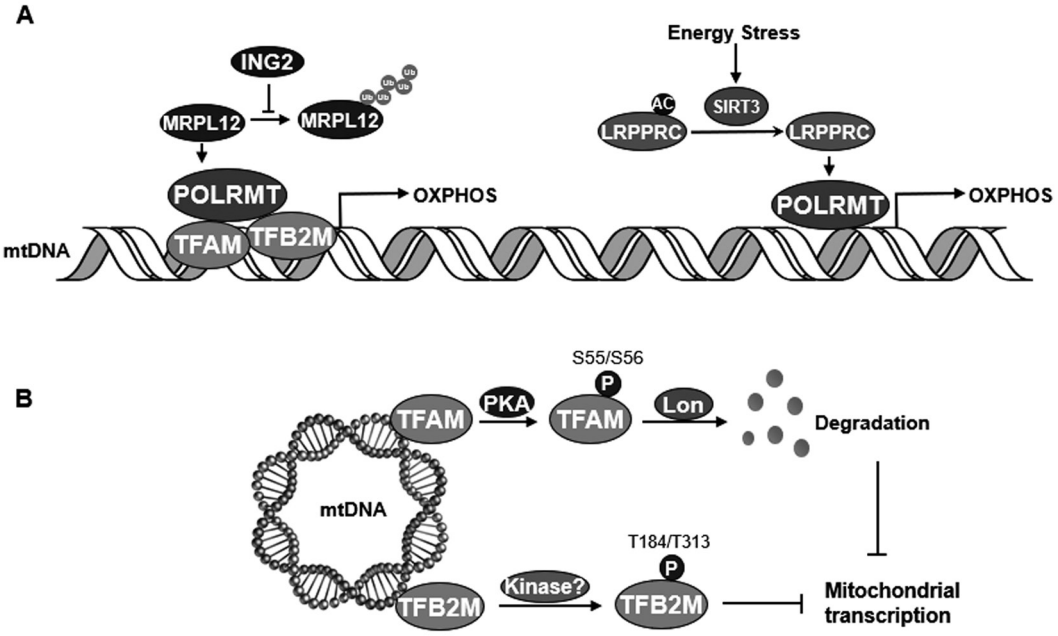
3 线粒体调控自身DNA转录的机制

3.1 线粒体转录复合体互作因子对转录的调控

近年研究发现，转录复合体与多种蛋白质相互作用，这些相互作用蛋白发挥着重要的转录调控作用 (图 1)。首先，线粒体核糖体蛋白 L12 (mitochondrial ribosomal protein L12, MRPL12) 是线粒体核糖体大亚基的结构组分之一，MRPL12 在其非核糖体形式时可直接与 POLRMT 相互作用并调节线粒体转录活性 [41]。RNAi 介导的 MRPL12 敲低会使 POLRMT 不稳定并显著降低 mtDNA 转录水平 [42]，表明 MRPL12 维持 POLRMT 的稳定性。细胞核蛋白 ING2 (inhibitor of growth family member 2) 可转位到线粒体影响 MRPL12 泛素化水平，从而调控 POLRMT 活性和线粒体转录速率 [43](图 1A)。其次，富亮氨酸 PPR 模体蛋白 (leucine-rich PPR motif-containing protein, LRPPRC) 可结合 POLRMT 介导转录激活 [44](图 1A)，在细胞系中过表达 LRPPRC 会增加线粒体 DNA 编码转录本的表达 [44-45]，而 LRPPRC 的缺失会导致转录产物减少以及线粒体功能障碍。值得注意的是，LRPPRC 也在线粒体 RNA 的加工过程中发挥作用，LRPPRC 基因缺陷会导致新生儿神经系统疾病 [46-47]。值得一提的是，线粒体 DNA 单链结合蛋白 (mitochondrial single-stranded DNA binding protein, mtSSB) 在 mtDNA 复制中是必需的。在 mtDNA 解旋后，mtSSB 不仅可以防止单链 DNA 重新配对或被核酸酶降解，也会阻止 mtDNA 转录的非特异性起始，从而发挥转录调控作用 [48]。

3.2 翻译后修饰对转录的调控

质谱研究表明转录复合体广泛存在翻译后修饰 [49]，因此蛋白质翻译后修饰也是调控线粒体转录的重要机制 (图 1B)。线粒体转录因子 TFAM 和 TFB2M 的翻译后修饰可直接干预线粒体转录 [50-54]。TFAM 可被蛋白激酶 PKA 磷酸化，进而被定位于线粒体基质的 Lon 蛋白酶降解，从而降低线粒体 DNA 的转录强度 [52, 55](图 1B)。TFB2M 也可被未知激酶磷酸化。TFB2M 的关键苏氨酸残基被磷酸化后，TFB2M 与线粒体 DNA 启动子的亲和力显著下降 (图 1B)。晶体结构提示，这些磷酸化修饰也可能干扰 TFB2M 与 POLRMT 的相互作用从而减弱转录起始 [56]。近年，高通量蛋白质谱技术鉴定出了



(A) POLRMT结合蛋白是重要的线粒体转录调控因子，如MRPL12可直接与POLRMT相互作用，维持线粒体转录复合体的稳定性以促进mtDNA转录，ING2蛋白又可以与MRPL12相互作用来抑制MRPL12泛素化，从而增强线粒体转录及OXPHOS水平；LRPPRC与POLRMT相互作用也可以增加mtDNA转录活性，在能量应激状态下SIRT3蛋白可以降低LRPPRC乙酰化水平以增强其与POLRMT的相互作用。(B)翻译后修饰调控线粒体转录活性，转录因子TFAM在S55/S56位点经PKA磷酸化后与mtDNA解离，最终被Lon蛋白酶降解，导致转录抑制；TFB2M的T184/T313位点被磷酸化后同样失去结合mtDNA的能力，导致转录抑制。

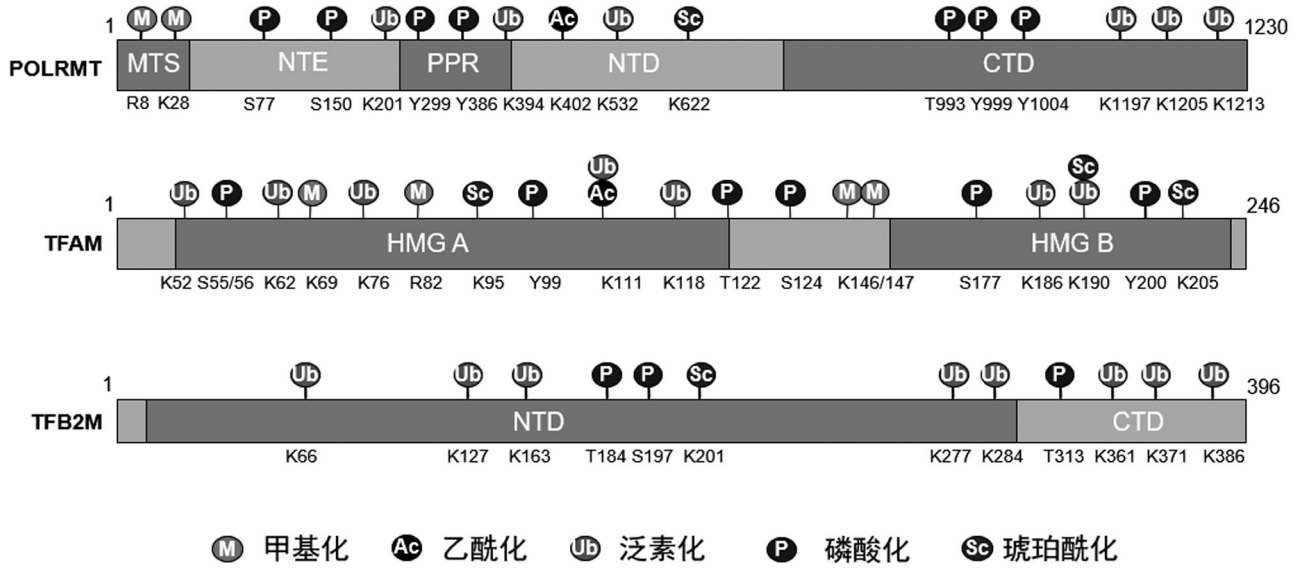
图1 线粒体转录起始的调控机制

POLRMT、TFAM、TFB2M 的多种翻译后修饰，包括磷酸化、乙酰化、甲基化、泛素化、琥珀酰化等 (图 2)[49, 57-59]，且其中很多位点在进化上是保守的。这些发现提示，蛋白质的翻译后修饰在线粒体转录过程中发挥着潜在的调控作用。介导和去除线粒体转录复合体翻译后修饰的酶类及调控方式将具有重要的研究前景。

3.3 mtDNA自身化学修饰及拟核形成对转录的调控

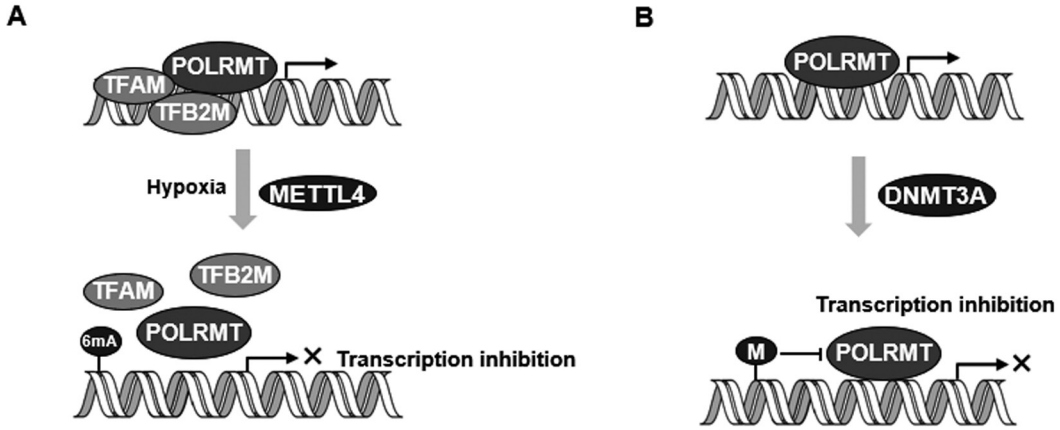
除了线粒体转录复合体层面的调控方式，mtDNA 自身的化学修饰也是调控线粒体转录的重要机制。研究发现，mtDNA 中胞嘧啶和腺嘌呤可被甲基化 [60-61]。胞嘧啶甲基化可发生在 CpG、GpC 和非 CpG 位点 [61-67]，mtDNA 中 D 环的调控区域发生甲基化的频率最高，这一区域的高甲基化会降低 mtDNA 的转录水平，说明甲基化在调控线粒体转录中具有重要作用。mtDNA 甲基化在发育、衰老、缺氧应激过程中均有不同程度改变 [60, 67-68]，但调控机制尚待解析。有趣的是，将 GpC 甲基转移酶表达到线粒体中介导 mtDNA 的 GpC 甲基化后，线粒体转录本显著减少，但 mtDNA 拷贝数没有明显变化 [64]。这些发现提示，mtDNA 甲基化直接和转录相关联，并且甲基化一定程度上会抑制转录。此外，mtDNA 的甲基化修饰也会调控线粒体转录因子的活性。mtDNA 甲基化会减弱 TFAM 与基因组的结合以改变其转录活性，并可能通过 TFAM 的招募机制间接调节 TFB2M 和 POLRMT 的活性 [69]。另外，核甲基转移酶，如 DNMT1 (DNA methyltransferase 1)、DNMT3A (DNA methyltransferase 3A) 和 METTL4 (methyltransferase like 4) 已被鉴定可定位于线粒体 [60, 67-68]，引起 mtDNA 甲基化进而调控转录。其中，METTL4 可以通过甲基化腺嘌呤 6mA 位点，导致 TFAM 从 mtDNA 上解离，且不能与其他转录因子形成复合物，转录被抑制 [60](图 3A)；DNMT3A 可以特异性甲基化 mtDNA 中 ND2-COX3 编码区域，抑制 POLRMT 的转录 (图 3B)[67]。mtDNA 除了甲基化以外是否同细胞核 DNA 一样存在其他修饰仍待进一步研究 [60, 67-68]。

值得注意的是，mtDNA 并非直接裸露于线粒体基质，而是与多种蛋白质相互结合以拟核的状态存在 [3, 70]。拟核的形成可以降低线粒体基因突变率，也因此拟核蛋白可通过与 mtDNA 结合影响转录。TFAM 是哺乳动物线粒体拟核蛋白的重要组分。研



图中分别标注了POLRMT、TFAM及TFB2M可发生翻译后修饰的部分位点(来源：phosphositeplus.org)，提示翻译后修饰可能对线粒体转录调控有重要作用。图中出现的同排标注，如TFAM的K111位点，表示该位点既可发生乙酰化也能被泛素化。MTS (mitochondrial targeting sequence)：线粒体靶向序列；NTE (N-terminal extension)：N端衍生结构域；PPR (N-terminal pentatricopeptide repeat)：N端五肽重复结构域，此结构域通常介导RNA与酶的相互作用，并通过一个富含脯氨酸的连接体连接到N端结构域，影响POLRMT核心的移动性；HMG A/HMG B (high mobility group A/B)：HMG框结构域A/B，TFAM中的两个HMG结构域负责与mtDNA结合并使DNA发生弯折。

图2 线粒体转录起始蛋白可发生多种翻译后修饰



(A)低氧状态下，METTL4能使mtDNA上的腺嘌呤发生甲基化(6mA)，导致部分位点TFAM与mtDNA发生解离且不能与其他转录因子形成复合物，从而引起转录抑制。(B) DNMT3A可以将mtDNA中特定区域甲基化，抑制POLRMT介导的mtDNA转录。

图3 mtDNA甲基化调控线粒体转录

究表明，TFAM 数量足以包裹 mtDNA。TFAM 与 mtDNA 的比值越高，表明包装越紧密，转录和复制的可能性越低[70-71]，因此 TFAM 在转录调控中的作用具有多面性。此外，mtDNA 结构能够形成 G-四链体 (G-quadruplex, G4)，特别是富含鸟嘌呤的重链[72]。体外研究表明，TFAM 与形成 G4 的 DNA 序列具有较高的亲和力[73]。因此，mtDNA 结构和拟核组织状态的变化也是调控线粒体转录复合体的重要机制。

4 核因子调控mtDNA转录

许多核因子会直接或间接影响 mtDNA 转录，由于线粒体转录复合体的主要组分均由核基因编码，所以核因子调控线粒体转录的一个关键机制就是控制转录复合体的表达。NRF2 和 PGC-1α 等核转录因子是已经被鉴定出的调控线粒体生物合成

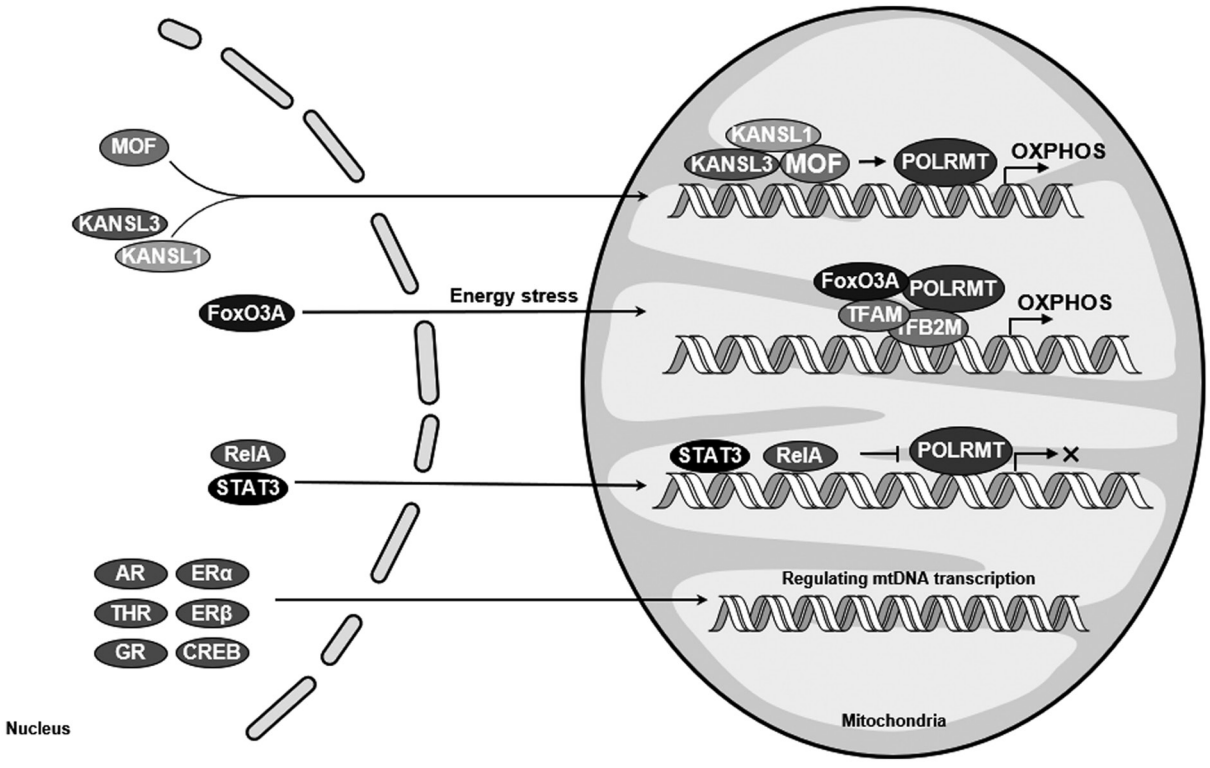
的主要因子，控制包括 POLRMT、TFAM、TFB2M 和 mTERF1 在内的多种因子的表达 [74-78]。

除核转录因子通过影响线粒体转录复合物表达调控线粒体转录外，一些核因子可发生线粒体转位并直接结合 mtDNA 以调控 mtDNA 转录，如 THR (thyroid hormone receptor)、GR (glucocorticoid receptor)、CREB (cyclic-AMP response binding protein)、MEF2D (myocyte enhancer factor 2) 等 [79-83] 已被发现可与 mtDNA 直接结合并影响线粒体转录。下面列举了这一领域的一些最新进展。

雄激素受体 (androgen receptor, AR) 和雌激素受体 (estrogen receptor，包括 ERα/ERβ) 是配体依赖的核转录因子，在细胞功能和发育中发挥多种作用。在前列腺肿瘤细胞中，AR 可定位于线粒体基质，进而下调线粒体 OXPHOS 亚基基因的表达 [80]。进一步研究提示，雄激素受体和雌激素受体均具有潜在结合 mtDNA 的能力 [84]。

FoxO (forkhead box protein O) 转录因子家族蛋白在细胞核中参与能量稳态、葡萄糖代谢、凋亡和细胞周期阻滞基因的转录 [85]。该家族成员 FoxO1 被证实在基础代谢条件下可与 mtDNA 的 D 环结合。在白色和棕色脂肪细胞中的研究表明，营养限制会导致 FoxO1 从 mtDNA 解离，进而穿梭到细胞核并与细胞核 DNA 结合，最终降低线粒体转录和呼吸水平 [86]。在肿瘤细胞中，低糖培养可以促进 FoxO3A 的线粒体转位。FoxO3A 与 SIRT3 (Sirtuin 3)、TFAM 和 POLRMT 形成复合物，进而促进 mtDNA 转录 [87] (图 4)。

NF-κB (nuclear factor-kappa B) 转录因子家族在炎症、细胞分化和细胞存活的信号通路中发挥作用 [88]。在 2018 年，研究发现 NF-κB 家族的 RelA (RELA proto-oncogene) 及其抑制分子 IκBα (inhibitor kappa B alpha) 也定位于线粒体中 [79]；RelA 进入线粒体基质后与 mtDNA 相互作用，进一步阻碍 POLRMT 与 mtDNA 的结合，从而下调 mtDNA 编码的两个 OXPHOS 基因的表达水平 [89]。STAT (signal transducer and activator of transcription) 蛋白是一类参与调节细胞生长和存活的核转录因子 [90]。在小鼠角质细胞中，



由上至下：MOF蛋白由细胞核进入线粒体并在KANSL1和KANSL3辅助下结合在mtDNA上，增强POLRMT的转录活性；在能量应激的状态下，FoxO3A进入线粒体与mtDNA转录起始复合体结合，增强mtDNA转录及OXPHOS水平；STAT3或RelA等核蛋白进入线粒体后会和mtDNA结合并抑制线粒体转录；其他核因子AR、ER、THR、GR、CREB等也可转位至线粒体结合mtDNA，调控线粒体转录。

图4 核因子转位至线粒体调控mtDNA转录

STAT3 可转位至线粒体，结合 TFAM 和 mtDNA；敲除 STAT3 则增强多个 mtDNA 编码基因的转录，表明 STAT3 发挥抑制 mtDNA 转录的作用 [89](图 4)。

TEA 结构域转录因子 (TEA domain family member, TEAD) 是 Hippo 信号通路下游的转录因子，在细胞增殖中起重要作用。该家族成员之一 TEAD4 参与维持早期胚胎发育中的能量稳态 [91-92]。研究发现，TEAD4 与 mtDNA 转录控制有关 [93]。在早期胚胎细胞中，TEAD4 的缺失导致线粒体转录水平下降和 OXPHOS 受损，免疫荧光和染色质免疫沉淀实验证实 TEAD4 直接结合在 mtDNA 的 D 环等区域 [93]。TEAD4 与结合于 mtDNA 上的 POLRMT 相互作用进而调控转录 [93]。

原癌基因 *MDM2* (mouse double-minute 2 proto-oncogene) 因其对核转录因子 p53 的调控而闻名。MDM2 也可以与核染色质结合进而改变转录 [94]。研究发现，氧化应激驱动 MDM2 向线粒体基质的转位，并与 mtDNA 的轻链启动子结合 [95]。MDM2 在正常细胞和肿瘤细胞中抑制 TFAM 与 mtDNA 的相互作用，从而下调轻链启动子介导的转录 [95]。有趣的是，MDM2 与 mtDNA 的结合具有启动子特异性。因为许多研究表明 MDM2 不与重链启动子结合，也不改变 mtDNA 重链编码基因的转录。机制研究表明，MDM2 结合轻链启动子后会抑制 NADH 脱氢酶 6 的转录，从而削弱线粒体呼吸链复合物 Ⅰ 的活性 [95]。这些研究表明，MDM2 可以特异性调控线粒体转录过程从而影响肿瘤发生发展。

核因子组蛋白乙酰转移酶 MOF (males-absent on the first) 及参与调控的搭档蛋白 KANSL1 (KAT8 regulatory NSL complex subunit 1) 和 KANSL3 (KAT8 regulatory NSL complex subunit 3) 可定位于线粒体中结合 mtDNA 并调控转录及呼吸 (图 4)。MOF 在线粒体中与 mtDNA 结合，当 MOF 敲除后会影响到 mtDNA 表达，并导致 mtDNA 上 TFB2M 和 POLRMT 的积累，可能造成线粒体转录停滞 [96]，提示 MOF 可能乙酰化转录体系中的蛋白以调控其功能以及转录进程。

5 mtDNA转录失调与多种人类疾病发生发展密切相关

mtDNA 的正常转录不仅维持线粒体代谢活性，更重要的是确保细胞整体能量调度和代谢稳态。mtDNA 转录异常会导致线粒体功能失调和代谢紊乱，进而参与发育缺陷、糖尿病、心血管疾病、帕金森病、衰老和肿瘤等疾病的进程 [97-102]。

5.1 线粒体转录复合体的突变引发多种先天性疾病

线粒体转录调控蛋白的突变直接阻碍 mtDNA 转录的正常进行。例如，POLRMT 的突变会造成多种遗传疾病的发生。C1696T (Pro566Ser) 突变的患者会出现肾小管疾病、佝偻病、Fanconi 综合征，并且伴有发育迟缓和肌肉张力减退等临床表现；C748G (His250Asp) 突变会造成智力障碍、听力损伤、眼睛斜视等症状；POLRMT 突变还会引起畸形发育、肌肉张力减退、身材矮小、贫血、眼球运动异常等症状 [103]。作为直接负责线粒体转录的 RNA 聚合酶，POLRMT 缺陷引发的这类症状也侧面提示线粒体基因转录在维持机体功能中发挥重要作用。

mtDNA 突变会直接导致 mtDNA 功能异常，引起个体发育、神经、肌肉等功能异常 [104]。mtDNA 突变也有可能直接调控转录。例如，mtDNA 基因组 $tRNA^{Leu}$ 基因 A3243G 位点突变可以引发遗传性糖尿病和听力缺失，该突变发生于线粒体转录终止因子 mTERF1 与 mtDNA 结合的作用位点 [40, 105]，提示这一突变会影响到线粒体转录终止从而参与疾病发生。

5.2 线粒体转录异常参与代谢综合征和神经系统疾病等的发生发展

TFAM 和 TFB2M 作为关键的线粒体转录因子，其功能失调同样与多种临床疾病密切相关。在帕金森病、阿尔茨海默病、亨廷顿病以及衰老的患者中，TFAM 的表达水平均显著降低 [106-109]。在阿尔茨海默病模型中，过表达 TFAM 会显著降低 mtDNA 甲基化和氧化水平，改善神经认知功能 [110]；在衰老患者细胞中过表达 TFAM 会增加呼吸链复合体 Ⅰ 和 Ⅳ 的活性 [111]，并且降低年龄依赖的脂质过氧化反应。此外，TFAM 的缺失会导致过度肥胖，并且会使胰岛素代谢紊乱，增加患糖尿病和继发性心肌病的风险 [112-113]。对 TFB2M 疾病相关性的研究较少，少量研究表明 TFB2M 突变可能与自闭症的发生相关 [114-115]。

值得一提的是，mtDNA 转录复合体结合蛋白也可能通过改变线粒体转录参与多种病理过程。例如，MRPL12 在糖尿病肾病中的表达显著减少，并且线粒体氧化磷酸化和 mtDNA 拷贝数降低 [116]。*MRPL12* 突变同样会造成发育迟缓、神经退化等症状 [117]。另外，*LRPPRC* 基因突变或表达异常与 Leigh 氏综合征和帕金森综合征等神经疾病密切相关 [118-120]。

5.3 线粒体转录失调影响肿瘤进程

快速增殖的细胞高度依赖线粒体代谢[9, 14, 22]。线粒体除提供大量能量外，还会为肿瘤生长提供代谢前体，维持肿瘤细胞的氧化还原和钙离子稳态，调控信号通路活性来满足肿瘤的代谢需求。肿瘤细胞和肿瘤干细胞通常高度依赖氧化磷酸化，因此也高度依赖线粒体转录。实验发现在多种快速增殖的肿瘤细胞中，mtDNA 拷贝数以及线粒体转录水平都显著高于其他正常组织细胞[121-123]，线粒体转录相关因子表达水平也明显上升。多种肺癌细胞均高表达 POLRMT，敲除或沉默 POLRMT 基因会明显降低肺癌细胞的增殖、转移和浸润能力，并诱导肿瘤细胞凋亡[124]。在骨肉瘤细胞中，POLRMT 的表达水平显著高于正常组织[125]；在急性髓细胞白血病中 POLRMT 水平也显著上升[126-127]。类似地，TFAM 在多种肿瘤中也处于表达异常状态，如宫颈癌、前列腺癌、结直肠癌、乳腺癌、白血病等[128-131]。有意思的是，*TFAM* 的单核苷酸多态性 (rs3900887) 调控着肿瘤细胞的体积大小。在 K-Ras (Kirsten rat sarcoma 2 viral oncogene homolog) 突变肺癌细胞中敲低 TFAM 后，线粒体呼吸减弱，肿瘤生长也被显著减缓[53]。TFB2M 在肿瘤中的研究较少，其在肝癌细胞中维持有氧糖酵解，通过介导代谢重塑促进肿瘤细胞的增殖[132]。

6 未来可能的研究方向和展望

得益于结构生物学、蛋白质谱和高通量测序的技术进步，目前对线粒体转录起始、延伸和终止等关键步骤的复合体装配、构象变化和 DNA 识别结合机制已有较为清晰的认识；而对调控线粒体转录的生理病理信号及其分子细胞生物学机制的认识仍然较为匮乏。在可预见的未来，线粒体转录调控机制将得到系统解析，基于线粒体转录设计线粒体功能异常相关疾病的靶向药物也将成为可能，将来可能的研究方向如下。

6.1 系统挖掘线粒体转录复合体结合蛋白和mtDNA结合蛋白

线粒体转录复合体结合蛋白和 mtDNA 结合蛋白极有可能调控 mtDNA 的转录、复制、修复和拟核组装等过程。因此，采用免疫沉淀等技术发掘线粒体转录复合体相互作用的生物大分子将为线粒体转录研究提供极大助力。现有研究已经初步鉴定出了与 POLRMT、TFAM 和 TFB2M 结合的蛋白。对 mtDNA 结合蛋白的发掘和功能注释也正在进行。

与此同时，线粒体转录相关蛋白的翻译后修饰也将是线粒体转录调控研究的热点之一。作为重要的代谢性细胞器，线粒体生物合成过程与细胞代谢高度偶联[133]，而翻译后修饰是联系细胞代谢和蛋白质功能的重要节点。解析线粒体转录的翻译后修饰调控机制有助于解析线粒体转录调控的生物学意义。

6.2 基于线粒体转录的药物设计和开发

由于线粒体转录在多种疾病的发生发展中发挥着重要的调节作用，靶向线粒体转录的药物将在肿瘤和线粒体异常相关疾病的治疗中体现巨大的潜力。近年研究发现，靶向 POLRMT 的小分子药物在体外和体内表现出广谱的抑癌效果[134-135]。这些小分子抑制剂以非竞争性结合的方式抑制 POLRMT 活性，并进一步降低 mtDNA 的转录强度和细胞呼吸水平[134]。类似的针对线粒体转录的小分子药物开发将具有广阔的应用前景。

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