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评 述

线粒体稳态失衡与心脏衰老及相关疾病

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摘要 随着年龄的增长, 衰老的心脏会发生左室肥厚、舒张功能不全、瓣膜功能下降、心肌纤维化增加、电传导异常等病理变化. 线粒体作为真核细胞中调控代谢的关键细胞器, 是细胞内合成ATP的重要场所. 由于心脏一刻不停地收缩需要大量ATP提供能量, 线粒体稳态对于维持正常的心脏功能至关重要, 而线粒体稳态失衡则会导致心脏功能发生异常. 本文主要阐述了衰老心脏中线粒体的异常变化, 探讨了线粒体形态与数量变化、线粒体代谢异常、线粒体质量控制失衡、线粒体基因组和转录组改变等线粒体稳态失衡在常见衰老相关心脏疾病发生发展中的重要作用, 总结了靶向线粒体干预衰老相关心脏疾病的现状与前景, 为研究线粒体相关心脏疾病的细胞分子机制, 治疗衰老相关的心脏疾病提供新的思路.

关键词 线粒体稳态, 衰老, 心脏疾病

随着我国人口老龄化的加剧, 衰老相关的心血管疾病已成为我国居民的一大健康威胁, 其发病率呈逐年增加的趋势[1]. 研究表明, 线粒体稳态失衡在衰老相关心血管疾病的发病机制中起着重要作用. 深入研究线粒体稳态失衡的机制, 充分了解线粒体在衰老相关心脏疾病中的变化特征, 将有助于人们理解线粒体稳态与心脏疾病之间的复杂关系. 本文综述了线粒体稳态和衰老相关心脏疾病研究的最新进展, 探讨了心脏疾病中线粒体稳态失衡的具体分子机制, 为靶向线粒体治疗衰老相关心脏疾病提供了理论依据和研究思路.

1 衰老相关心脏疾病与线粒体的关系

线粒体作为细胞中ATP生成的主要场所, 在心脏中发挥着重要的作用[2]. 线粒体在心肌细胞中密集分布, 在人类中约占心肌细胞总体积的25%左右[3]. 除参与氧化磷酸化外, 线粒体还参与诸多细胞反应, 包括脂肪酸

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氧化、类固醇合成、细胞氧化还原稳态、离子稳态、氧感应、钙储存和程序性细胞死亡的调节等[4]. 因此, 线粒体稳态的维持对心脏正常功能维持至关重要.

心脏的衰老是心脏结构和功能发生变化的动态过程, 可能伴随炎症、心脏肥大、纤维化以及收缩功能障碍, 从而引起高血压、缺血性心肌病、心衰等常见心脏疾病[5~8]. 在衰老过程中, 心脏线粒体可出现形态和数量的变化、代谢的变化、质量控制失衡以及基因组和转录组的变化, 伴随和推动衰老相关心脏疾病的发生发展(图1).

1.1　衰老过程中心脏线粒体形态、结构和数量变化

心脏线粒体主要包括两种线粒体——位于肌膜下的肌膜下线粒体(subsarcolemmal mitochondria, SSM)和位于肌纤维之间的肌间线粒体(intrafibrillar mitochondria, IFM). 研究显示, 衰老相关的线粒体形态改变和数量减少主要发生于肌间线粒体, 而肌膜下线粒体未见有随年龄明显改变的证据[9].

衰老心肌细胞中线粒体结构的改变主要包括线粒体肿胀、基质紊乱、嵴缺失等[10~12]. 与6周龄组Wistar大鼠相比, 24月龄组大鼠左右心室的线粒体体积均有减少, 线粒体嵴的密度也显著降低[13]. 同样, 在病理性衰老OXYS大鼠模型中, 与同年龄对照组相比, 心肌细胞线粒体超微结构分析显示其线粒体嵴的密度降低, 单个线粒体体积缩小, 线粒体数量也有所下降[14].

心磷脂(cardiolipin, CL)是一种主要存在于线粒体内膜的二磷脂酰甘油脂, 通过参与线粒体膜形态和结构的完整性维持及线粒体酶的活性调节, 影响线粒体的能量生成[15]. 部分研究表明, 心磷脂含量随年龄增加而降低, 导致线粒体内膜流动性的异常改变[16]. 另有研究发现, 与成年大鼠相比, 24月龄的Fischer 344大鼠心肌线粒体心磷脂的含量并未发生改变, 其酰基组成和分子构成也未发生改变[9,17]. 因此, 心磷脂含量在心脏衰老相关电子传递障碍机制中的变化规律和作用仍存在一定争议. 进一步的研究发现, 在缺血条件下老年心脏心磷脂发生特异性氧化, 导致电子传递链复合物(electron transport chain, ETC)功能降低和内膜双层排列的破坏, 促进了细胞色素c的释放, 从而引发细胞死亡[18], 为心磷脂调控衰老心脏线粒体稳态与功能提供了新的分子机制.

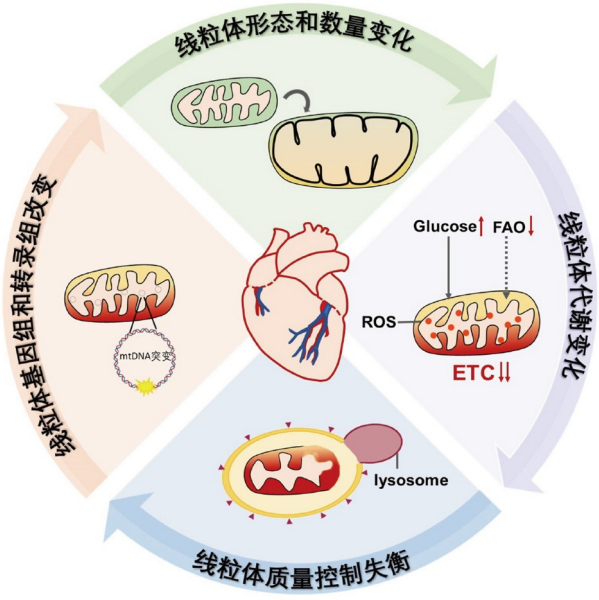

图 1　线粒体引起心脏衰老的机制. 在心脏衰老过程中, 线粒体的形态功能变化、线粒体质量控制系统失调以及线粒体基因组和转录组改变影响线粒体的功能和稳态, 进而影响心脏的功能(网络版彩图)

Figure 1　Mitochondria-related molecular mechanisms of cardiac aging. Multiple factors are involved in affecting the function and homeostasis of mitochondria in the process of cardiac aging, including the changes in the morphology, genome and transcriptome as well as the disorders in the quality control system of mitochondria (color online)

1.2　衰老过程中心脏线粒体代谢的变化

在心脏线粒体中, 脂肪酸和碳水化合物是通过氧化磷酸化(oxidative phosphorylation, OXPHOS)生成ATP的两种主要底物. 生理条件下, 成年心脏大约70%的能量来自脂肪酸氧化, 30%来自葡萄糖代谢. 这一比例随年龄增加而变化, 衰老的心脏表现出氧化脂肪酸的能力降低, 对葡萄糖代谢的依赖性增强[19~21]. 其中, 丙酮酸脱氢酶复合物(pyruvate dehydrogenase complex, PDC)是调节脂肪酸和碳水化合物代谢竞争的关键酶复合物. 在衰老过程中, 丙酮酸脱氢酶激酶(pyruvate dehydrogenase kinase, PDK)通过磷酸化修饰增加PDC的含量, 从而使线粒体氧化葡萄糖的能力增强, 脂肪酸氧化比例减少[9,22].

衰老心肌细胞往往产生更多的活性氧(reactive oxygen species, ROS), 并且其对ROS的清除能力也随年龄下降. 氧化物歧化酶、谷胱甘肽转移酶和氧化还原酶等主要参与细胞内ROS的清除, 而这些蛋白的编

码基因在大鼠和人类心脏中随年龄增长而显著下调[23]. 通过对老年人和年轻人心房组织中线粒体蛋白编码基因的转录谱检测发现, 1/10的线粒体蛋白编码基因表达发生显著变化, 其中大部分为表达下调与线粒体能量代谢通路相关, 导致线粒体氧化磷酸化能力以及复合物Ⅰ活性显著降低[24]. 衰老心肌的线粒体ROS生成增加, 同时氧化应激损伤敏感性增加, ROS清除能力下降, 导致ROS与线粒体损伤之间的恶性循环.

烟酰胺腺嘌呤二核苷酸(nicotinamide adenine dinucleotide, NAD^+)是线粒体电子传递链上的一个电子载体, 在多种细胞过程中发挥重要作用. NAD^+可以从色氨酸开始从头合成(*de novo* biosynthesis pathway), 也可以从NAD^+前体如烟酸(nicotinic acid, NA)、烟酰胺(nicotinamide, NAM)或烟酰胺核苷(nicotinamide riboside, NR)开始的补救途径(salvage pathway)合成. 在心脏组织中, NAD^+主要通过后者产生. 其在氧化(NAD^+)和还原形式(NADH)之间的相互转化, 参与细胞氧化还原、能量代谢和线粒体生物发生(mitochondrial biogenesis)等多项反应. 在衰老等慢性应激环境下, 线粒体DNA(mitochondrial DNA, mtDNA)损伤增加, NAD^+水平降低, 导致线粒体蛋白去乙酰化减少, 进一步促进线粒体功能障碍并导致心肌重构[25,26]. 此外, NAD^+还作为信号分子及多种酶(如SIRTs, PARPs, CD38 和CD157)的共同底物, 调节基因表达、DNA修复、钙信号通路和昼夜节律等, 影响心脏的稳态和衰老[27]. 例如, SIRTs是NAD^+依赖性去乙酰化酶[28]. 其中, SIRT3, SIRT4和SIRT5通过调节能量代谢关键酶的活性, 成为线粒体的"应激传感器". 在心肌梗死[29]、缺血再灌注损伤[30]以及肥胖相关心衰模型[31]中, SIRT3和SIRT4表达下调; 在AngII或压力过载诱导的心肌肥厚模型[32]中, SIRT3和SIRT4表达上调. 此外, 在小鼠心脏衰老过程中, NAD^+水平下降[33], SIRT3表达下调[34], 而*Sirt3*基因敲除小鼠心脏在13个月龄时提前出现心肌肥厚和纤维化等衰老表型[35].

mTOR(mammalian target of rapamycin)信号通路也是调控线粒体代谢的重要途径之一. mTOR是PI3K家族中的一个丝氨酸/苏氨酸激酶, 根据对雷帕霉素的敏感性区分为两个不同的复合物: mTOR复合物1(mTORC1)和复合物2(mTORC2)[36]. 雷帕霉素敏感的mTORC1包含mTOR的支架蛋白调控相关蛋白RAPTOR, 而雷帕霉素不敏感复合物mTORC2包含mTOR的支架蛋白雷帕霉素不敏感伴生蛋白RICTOR[37]. mTOR通路参与从胚胎期心血管发育到出生后心脏稳态维持和病理生理变化等多个过程, 其信号失调与许多年龄相关的心脏病理表型有关, 如心力衰竭. 对mTOR通路的研究表明, mTORC1主要通过其下游底物调控蛋白质合成、自噬和线粒体功能等关键细胞过程, 从而调控衰老、健康寿命和自然寿命[38]. 降低mTORC1活性可增强对应激反应的耐受性, 增强线粒体呼吸和代谢, 减缓衰老速度, 延长小鼠寿命. 在果蝇中, mTORC1可以激活下游磷酸化4EBP, 暴露eIF4E的磷酸化位点(4EBP是eIF4E的结合蛋白)[39], 过表达4EBP则可促进心脏应激抵抗和维持正常心率[40]. 在老年小鼠模型中, mTORC1及其下游分子磷酸化水平增强, 伴随心脏线粒体受损, 氧化还原标志物升高, 葡萄糖和脂肪酸氧化通路异常[41]. mTORC2主要在细胞存活、代谢、增殖和细胞骨架组织中起到重要作用. mTORC2抑制可能对心脏产生不利影响, 在果蝇心脏中过表达mTORC2可以延缓衰老相关的心脏功能下降, 延长寿命[42].

1.3 衰老过程中的心脏线粒体质量控制失衡

哺乳动物成体心肌细胞的再生能力极为有限, 心肌线粒体的质量控制对维持线粒体和心肌细胞稳态十分重要[43]. 线粒体的质量控制系统由多种互相关联的途径组成, 包括线粒体未折叠蛋白反应(mitochondrial unfolded protein response, mtUPR)、线粒体分裂和融合、线粒体自噬和线粒体生物发生等(图2). 线粒体的质量控制异常可以严重影响心肌细胞的功能, 导致心脏的功能异常.

(1) 线粒体未折叠蛋白反应. mtUPR可维持线粒体完整性和功能性, 在调节线粒体内蛋白质稳态和维持正常细胞功能中起到关键作用. 在细胞应激条件下, 线粒体中错误折叠或未折叠蛋白质积累会激活mtUPR, 继而激活核编码的线粒体蛋白酶(CLPP, LONP1等)、线粒体伴侣蛋白(HSP60, HSP70, HSP10等)等, 以保护线粒体蛋白质组的功能完整性[44~46]. mtUPR对心脏疾病的影响有两面性: 一方面, mtUPR对慢性和急性心脏损伤具有保护作用, 在心脏应激反应中, 增强的mtUPR可减轻线粒体功能障碍和心脏收缩功能障碍[47]; 另一方面, mtUPR促进心脏疾病的发

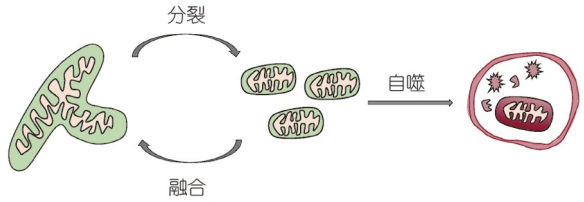

图 2　线粒体的分裂、融合与自噬(网络版彩图)
Figure 2　Mitochondrial fission, fusion and mitophagy (color online)

展，其相关蛋白HSP60的高表达与心力衰竭中心肌细胞损伤有关[48]．抑制mtUPR激活因子c-JUN的表达可以延缓心力衰竭的发展[49]．在老年小鼠心脏中，敲除线粒体融合和分裂基因可以导致mtUPR蛋白HSP60, AFG3L2, LONP1的丰度上调[50]．由于mtUPR在衰老心脏模型中的研究较少，其如何影响心脏衰老有待进一步研究．

(2) 线粒体动力学．线粒体的分裂和融合分别由线粒体分裂蛋白(DRP1，MFF)和线粒体融合蛋白(OPA1，MFN1，MFN2)介导，对于线粒体稳态维持和心脏功能调控具有重要的作用[51]．线粒体融合可促使部分受损的线粒体之间实现功能互补；线粒体分裂则可通过分离受损与未受损的线粒体组分，产生功能相对正常的线粒体并促进损伤部分的及时清除，从而维持线粒体的整体功能和细胞的稳态[52]．线粒体的分裂和融合的失衡会导致心脏功能的异常．敲除小鼠心肌细胞中的线粒体分裂基因*Dnm1L*(编码DRP1)，可导致心肌细胞线粒体伸长，线粒体自噬的过度激活以及线粒体缺失，致使心肌细胞坏死并发生扩张型心肌病[53,54]．敲除小鼠心肌细胞中的线粒体外膜融合基因*Mfn1*和*Mfn2*则会由于线粒体自噬障碍，导致受损线粒体的异常积累和肥厚型心肌病的发生[55]．此外，线粒体外膜融合基因还参与介导内质网和线粒体之间的Ca^{2+}信号传导，*Mfn2*心肌特异性敲除的小鼠心脏线粒体Ca^{2+}吸收减少，线粒体生物能量平衡受到破坏并导致心脏功能异常[56]．

衰老可以引起心脏中线粒体融合与分裂失衡，从而引发心脏功能障碍[51,57]．在仓鼠和人的研究中发现，衰老的心肌中存在形态异常的巨型线粒体，提示线粒体融合增多或线粒体分裂减少[10,11]．DRP1可以调控衰老心脏中线粒体自噬水平; 在D-半乳糖(D-galactose)诱导的衰老H9C2细胞中，过表达DRP1可以抑制PINK1/PARKIN介导的线粒体自噬，从而减少衰老引起的心肌细胞凋亡[58]．

(3) 线粒体的自噬．线粒体自噬是指线粒体选择性地被自噬体吞噬并被传递到溶酶体进行降解的过程. 线粒体自噬和线粒体分裂与融合协同作用, 维持线粒体数量和功能的稳定性[59]．目前，激活线粒体自噬的主要途径有三种: PTEN诱导激酶1(PINK1)/PARKIN信号通路、BCL2相互作用蛋白3(BNIP3/NIX)通路以及线粒体外膜蛋白FUN14 domain-containing 1 (FUNDC1)信号通路.

目前, PINK1/PARKIN信号通路的研究最多[60], 其异常与心脏疾病密切相关．PINK1作为受损线粒体的分子传感器，触发线粒体自噬的起始信号．当线粒体损伤达到一定阈值时，PINK1通过磷酸化MFN2将PARKIN募集至线粒体外膜; PARKIN作为线粒体自噬信号的“增强子”，通过对线粒体蛋白进行泛素化修饰, 介导线粒体自噬[61,62]．此外，去泛素化酶和PTEN-long蛋白也参与调控该过程，对维持线粒体稳态具有重要作用[63]．诸多研究证明, PARKIN在多种心血管疾病中下调，包括心肌梗死、糖尿病性心肌病和心力衰竭[64]．在果蝇中，敲除*park*(*Parkin*的同源基因)可使果蝇的心脏管发生扩张，同时伴随甜甜圈状空心扩大的线粒体的积累[65]．在小鼠中，围产期心肌细胞特异性*Parkin*敲除则会导致胚胎期线粒体的驻留并阻碍成年期线粒体的生物发生，从而引发致死性心肌病[66]．在小鼠心梗模型中，*Parkin*敲除还会使小鼠心肌细胞线粒体自噬水平降低，受损线粒体累积，从而导致凋亡的心肌细胞数量增加，加重心肌重构，生存率降低[67]．此外，由于线粒体外膜融合基因*MFN2*参与介导PARKIN向线粒体外膜的招募，围产期心肌细胞特异性*Mfn2*敲除也会导致PARKIN介导的线粒体自噬通路受到抑制，导致受损线粒体的过度积累、ROS生成增加，从而引起心力衰竭[68]．在成年小鼠中，线粒体分裂基因*Dnm1L*的心肌细胞特异性敲除则会抑制线粒体分裂，导致线粒体自噬过度增加，造成线粒体缺失，从而因心肌能量缺乏而发生细胞坏死和扩张型心肌病; 而通过敲除*Parkin*抑制线粒体自噬，可以延缓*Dnm1L*敲除所引起的线粒体缺失和扩张型心肌病[69]．诸多因子会通过PINK1/PARKIN途径调控线粒体自噬，包括AMPKα2, PTEN-L，SIRT3等．在心衰患者和主动脉缩窄心衰小鼠样本中存在AMPKα2向AMPKα1亚型转移，并伴有线粒体功能和线粒体自噬的降低，导致心衰进一步恶

化; 小鼠心脏中过表达*Ampkα2*基因可通过增强心肌线粒体自噬和改善线粒体功能, 延缓心衰的进展[70]. SIRT3缺失可引起内皮细胞炎症和血管细胞肥大[71], 其过表达可以增强心脏中微血管内皮细胞的线粒体自噬, 并促进血管生成, 改善高血压导致的心脏重构[72].

由于受损线粒体的积累与衰老相关疾病有关, 而选择性处理受损线粒体依赖于线粒体自噬, 因此线粒体自噬在衰老相关疾病中起到关键作用. PARKIN在老年小鼠的心脏中下调, 而*Parkin*的过表达减轻了老年小鼠的功能下降[73]. 与此一致的是, 在晚期糖基化终末产物AGEs诱导的心肌细胞衰老模型中发现, PINK1/Parkin介导的自噬参与心肌细胞衰老的进程, 降低线粒体自噬活性可能成为阻断心肌细胞衰老状态的一种有效途径[74]. 此外, 在衰老的心脏中, PARKIN从细胞质向线粒体的易位减少, 同时其磷酸化水平下降. 衰老心肌细胞中骨架蛋白*Shank3*敲低可上调PINK1和PARKIN的表达, 并促进PARKIN的线粒体易位及其磷酸化, 促进线粒体自噬, 恢复线粒体功能; 而正常心肌细胞中*Shank3*的抑制显著阻碍了PARKIN的易位和磷酸化, 提示线粒体自噬过强或过弱均会导致线粒体稳态的破坏和进一步的心脏损伤[75]. 在小鼠主动脉组织的研究表明, 衰老会使白介素-6(interleukin 6, IL-6)水平升高, 损害主动脉细胞内的线粒体功能, 引起衰老相关动脉粥样硬化的发生, 这一现象与线粒体自噬增强和Parkin水平增加相关[76].

除PINK1/Parkin通路以外, BNIP3L/NIX通路也是线粒体自噬相关通路之一. BNIP3是细胞死亡调节因子BCL-2蛋白家族的一员, 是一种具有双向作用的线粒体外膜蛋白. 与其他线粒体自噬受体类似, BNIP3的N端区域存在LIR基序, 该区域的突变会阻断与LC3的相互作用, 导致线粒体自噬缺陷. 缺氧诱导因子1α (hypoxia-inducible factor 1α, HIF-1α)可以结合到BNIP3启动子上诱导BNIP3表达, 促进PINK1转位, 进而诱导线粒体自噬. 心脏在缺血再灌注条件下, BNIP3表达水平升高, 线粒体自噬增加[77]. 在衰老相关研究中发现, 与野生型小鼠相比, *BNip3*/*Nix*双敲除小鼠心脏中功能障碍线粒体的积累速度随着年龄的增长而加快, 提示这类线粒体自噬受体在维持线粒体稳态预防衰老中起着关键作用[78].

此外, 线粒体外膜蛋白FUN14 domain-containing 1 (FUNDC1)相关通路也是调控线粒体自噬的重要途径. FUNDC1是一种线粒体外膜蛋白, 它通过与LC3相互作用诱导缺氧时受体介导的线粒体自噬. 诸多证据已表明, FUNDC1的水平和磷酸化状态与包括心脏病在内的多种疾病的发生、进展和预后密切相关[79]. 在*Fundc1*敲除的小鼠模型中发现, 缺氧预处理可诱导血小板中FUNDC1依赖的自噬, 并减少心脏缺血再灌注损伤[80]. 过氧化物酶体增殖物激活受体(peroxisome proliferator-activated receptors, PPARs)的缺失与FUNDC1去磷酸化和线粒体自噬激活密切相关, 引起线粒体电子传递链复合物(electron transport chain, ETC)活性增加、线粒体呼吸功能增强和ATP产生增加. *Akt2*和*AMPK*同时敲除的小鼠易发生心脏早衰, 检测其心脏发现包括BNIP3和FUNDC1在内的几种线粒体自噬蛋白水平降低, 提示其心脏早衰表型可能由线粒体自噬缺陷引起[81]. 在成人心脏祖细胞(cardiac progenitor cells, CPCs)分化的研究中发现, 在分化过程中, BNIP3L和FUNDC1均显著上调, 破坏BNIP3L-和FUNDC1-介导的线粒体自噬导致线粒体形成甜甜圈状线粒体, 更容易因氧化应激引起细胞死亡, 并减少CPCs在体内的滞留[82].

(4) 线粒体生物发生. 线粒体生物发生是核基因组与线粒体基因组共同调控的复杂过程, 对线粒体的更新十分重要, 当生物发生出现障碍时, 线粒体会出现数量的下降、ROS、氧化脂质、氧化蛋白质以及突变mtDNA的累积, 使呼吸链活性下降, 细胞衰老加剧[83]. 线粒体生物发生由一系列转录因子及转录共激活因子参与调控, 其中增殖激活受体γ(PPARγ)共同激活剂1α (PPARγ coactivator-1α, PGC-1α)起到关键作用.

研究发现, 小鼠中心脏特异性过表达*Ppargc1α*可引起新生阶段核编码线粒体基因表达增加, 线粒体生物发生增加[84]. 在小鼠主动脉缩窄(transverse aortic constriction, TAC)诱发心衰模型中发现, PGC-1α蛋白及mRNA水平均下调[85], PGC-1α缺失可使心衰加剧[86].

随着啮齿类动物和人类的衰老, 心脏线粒体的数量逐渐减少, 且主要局限于肌膜下线粒体[87,88]. 心肌PGC-1α表达降低使幼年小鼠线粒体基因表达出现和老年小鼠类似的变化, 但PGC-1α的过度激活也可加速野生型老年小鼠的心脏衰老并缩短寿命, 适度过表达PGC-1α可抑制老年心脏的病理性重塑, 减少细胞凋亡, 提示PGC-1α在心脏线粒体质量控制方面存在着微

妙的调控作用[89,90].

1.4　衰老过程中线粒体基因组和转录组的变化

线粒体是一种半自主性细胞器, 其生物合成和功能调控受核基因组和线粒体基因组两套系统共同作用. mtDNA为环状DNA, 不同物种的mtDNA长度不同, 哺乳动物细胞mtDNA长度约为16.5 kb[91]. 在人类细胞中, mtDNA编码22个tRNA和2个rRNA, 以及13个多肽, 这些多肽包含ETC复合体Ⅰ, Ⅲ, Ⅳ和Ⅴ的核心亚基, 这些亚基对OXPHOS活性至关重要[92]. 由于组蛋白缺乏、有限的DNA修复能力以及mtDNA靠近线粒体ROS产生位点, mtDNA与核DNA相比更容易受到损伤[93], 且突变率高, 而修复能力有限, 这一特点使其被称为"衰老时钟(aging clock)", 一些研究者认为它的启动引发了整个生物的衰老[94]. 这可能导致线粒体功能障碍, 并引起多种疾病的发生.

衰老引起的心脏mtDNA的变化包括mtDNA点突变、点缺失以及拷贝数(mtDNA-CN)减少[95,96], 这些变化影响了线粒体电子传递链中部分蛋白质复合物的合成和超复合物的装配, 从而导致线粒体功能受损, 能量产生不足, 进而影响心脏的正常功能[97,98]. 借助单细胞mtDNA靶向测序技术, 科学家们发现老年人体细胞中mtDNA突变极为普遍, 且具有高度异质性及有害性, 提示mtDNA突变及其引起的线粒体功能下降是衰老及相关疾病的重要基础[99]. mtDNA的复制依赖于核编码酶, 如DNA聚合酶(Polγ), 其在mtDNA复制中起着参与合成和校对的重要作用. 过度产生的ROS可降低Polγ的校对能力, 导致mtDNA复制错误[100]. 在Polγ缺陷的小鼠研究中发现, 其所有组织中均存在mtDNA突变或缺失, 其中心脏出现心肌肥厚和功能障碍等心脏早衰表型[98,101]. 线粒体DNA拷贝数(mtDNA-CN)虽然不能直接反映mtDNA损伤情况, 但与线粒体酶活性和ATP的产生有关, 因此可以作为线粒体功能的生物标志物[102], 且与多种衰老相关疾病相关[103]. mtDNA-CN随着年龄的增长而下降[104], 且外周血mtDNA-CN与冠心病严重程度之间存在关联, 可用于预测心血管事件风险[105]. mtDNA-CN影响衰老相关疾病的机制可能是通过核DNA甲基化修饰来调节核基因的表达[103]. 另外, 最近的证据表明, 线粒体基因组的表观遗传修饰也与心血管疾病相关[106]. 尽管与核DNA中可检测到的甲基化水平相比较, mtDNA甲基化水平较低, 但研究显示mtDNA的甲基化与线粒体损伤相关. 通过对10名冠心病患者和17名健康个体的血小板线粒体进行研究, 研究者发现冠心病患者中*MT-CO1*, *MT-CO2*, *MT-CO3MT-TL1*基因和健康人相比甲基化程度更高[107]. 为了进一步探究mtDNA甲基化是否与冠心病的不同表型有关, 研究人员检测了稳定型冠状动脉疾病(stable coronary artery disease, SCAD)和急性冠状动脉综合征(acute coronary syndrome, ACS)患者线粒体的差异, 并发现SCAD患者外周血白细胞mtDNA-CN较高, D环区甲基化水平较低[108]. 在mtDNA与衰老相关的研究中发现, 慢性氧化应激/低血清可诱导人胎儿心脏的间充质干细胞(mesenchymal stem cells, MSCs)衰老, mtDNA的CpG位点甲基化与之密切相关[109].

2　线粒体稳态失衡导致的心脏衰老相关疾病的细胞和分子机制

心脏衰老主要表现为心肌细胞功能的改变引起心脏结构异常和功能减退. 线粒体稳态失衡与许多心脏衰老相关疾病相关, 例如缺血性心肌损伤、心律失常、心肌肥厚和心力衰竭等. 本文对线粒体稳态失衡在衰老相关常见的心脏疾病中的细胞和分子机制进行了总结, 了解这些疾病模型中线粒体稳态失衡发生和发展的具体机制将为未来进行靶向线粒体干预及延缓心脏衰老提供理论依据和基础.

2.1　线粒体稳态失衡与缺血性心肌损伤

缺血性心肌损伤是指由于冠状动脉血供减少或中断所致的部分短暂或永久的心肌坏死, 多由粥样硬化所致. 心肌梗死是威胁全球人口健康的疾病之一, 其发病率随着年龄的增长而增加, 全世界每年有700万人受此影响, 其五年生存期只有30%, 甚至远低于大部分恶性肿瘤[110]. 由于心肌细胞在成年心脏中再生能力非常低, 缺血所致的不可逆的心肌损伤最终可引起心力衰竭.

衰老相关的心脏生理结构和功能恶化导致缺血等应激条件下ROS生成失控, 氧化还原稳态紊乱可进一步触发相关信号通路, 导致线粒体功能障碍, 最终引起心肌细胞死亡. 老年人发生心梗等缺血性心肌损伤的风险更大, 且死亡率更高[111]. 研究发现, 小鼠心肌耐缺血能力从中年(12个月)开始逐渐减弱, 并且随年

龄增长(从18个月至24~28个月)而愈发明显[112]. SIRTs是NAD^+依赖性去乙酰化酶, 是线粒体的“应激传感器”, 可以通过激活心脏保护分子来减少氧化应激, 并抑制心肌缺血再灌注损伤相关信号通路. 由于SIRTs在延缓细胞衰老和延长寿命方面同样起着至关重要的作用, 近年来科学家评估了SIRTs对衰老动物心肌缺血再灌注损伤的保护作用. 结果显示, SIRT3缺乏可加重心脏对缺血再灌注损伤的易感性, 且程度随年龄增长而加重[113].

衰老引起的心肌线粒体的稳态失衡除了加重心肌缺血再灌注损伤外, 还可削弱心脏对缺血预处理的反应. 在30分钟缺血及120分钟再灌注之前给予短暂的缺血预处理(10分钟)可以对幼龄小鼠心脏产生保护作用, 而对老年小鼠未能产生保护作用; 通过将冠心病患者右心房组织肌小梁结构置于体外有氧Tyrode's溶液(95% O_2/5% CO_2)和缺氧无底物Tyrode's溶液(95% N_2/5% CO_2)中模拟缺氧复氧, 研究者发现, 和年轻人相比, 预处理对老年冠心病患者心房组织的心肌缺血后功能恢复并无保护作用[114]. 与缺血预处理类似的是, 在大鼠心肌缺血再灌注模型中观察到, 药物预处理(如吸入麻醉药)对于老年大鼠心脏也未能产生保护效果[115]. 预处理的心肌保护作用在老年患者中的减弱可能与衰老心脏线粒体稳态失衡、氧化磷酸化作用减弱、预处理相关心肌保护分子通路中的相关因子缺失有关[116]. 例如, 心肌线粒体缝隙连接蛋白CX43可以通过增加复合酶Ⅰ的活性, 增加线粒体ATP生成, 而与幼龄小鼠心肌线粒体相比, 老年小鼠左室CX43蛋白含量降低40%, 提示衰老引起的线粒体蛋白改变可能会削弱老年小鼠抗心肌缺血再灌注损伤的能力[117].

2.2 线粒体稳态失衡与代谢性心脏疾病

目前, 代谢性心血管疾病在中国人群发生率随年龄增加逐渐升高. 衰老加重糖脂代谢紊乱, 最终可引起心脏受累. 患有心脏疾病的老年人, 通常伴有多种代谢相关疾病, 如糖尿病、高血脂、肥胖等. 患者合并危险因素越多, 疾病进程越快, 预后越差. 影响心脏疾病发生和发展过程的代谢性因素中, 糖脂代谢紊乱是多重代谢紊乱的核心.

在65岁以上老年人群中, 患有糖尿病的老年人发生冠心病、脑梗、充血性心力衰竭等心脑血管疾病风险明显高于无糖尿病的老年人[118]. 胰岛素抵抗与高胰岛素血症增加全身代谢紊乱, 激活交感神经系统和肾素-血管紧张素-醛固酮系统, 导致心肌纤维化、心肌肥厚、心肌细胞凋亡和冠脉微循环障碍, 最终引起心力衰竭. 研究发现, 心脏特异性胰岛素受体基因敲除和胰岛素受体底物基因敲除小鼠在胰岛素刺激下的葡萄糖摄取减少, 同时心功能受损. 另外, 心脏特异性敲除葡萄糖转运蛋白4基因(*Glut4*)使小鼠心脏出现钙离子稳态失衡, 心肌细胞肥大和纤维化, 提示胰岛素抵抗可损害心功能[119]. 线粒体功能障碍可能是代谢紊乱和胰岛素抵抗产生相关心脏病的潜在原因[120]. 在胰岛素抵抗的情况下, 心肌将葡萄糖作为能量来源的能力降低, 脂肪酸氧化利用相对增加; 在线粒体层面, 心肌线粒体对底物的利用能力下降, 线粒体呼吸受到抑制[121,122]. 在糖尿病大鼠模型中, 出现呼吸功能下降的线粒体数量及范围随年龄增大而增加, 1月龄糖尿病大鼠心脏仅心外膜下心肌细胞线粒体呼吸受到抑制, 而2月龄糖尿病大鼠心脏心内膜下和心外膜下心肌细胞线粒体呼吸均受到抑制[123], 提示衰老可加重糖尿病引起的心肌细胞线粒体功能障碍. 在代谢和衰老相关疾病过程中, NAD^+起着至关重要的作用. 在糖尿病心肌病研究中, 通过构建心肌特异性NADH泛素氧化还原酶亚基S4敲除模型和烟酰胺磷酸苷转移酶NAMPT过表达小鼠模型,研究者发现NAD^+氧化还原失衡可促进小鼠心脏超氧化物歧化酶(superoxide dismutase 2, SOD2)乙酰化、肌钙蛋白S150磷酸化和能量受损. 烟酰胺磷酸苷转移酶(nicotinamide phosphoribosyltransferase, NAMPT)可以通过提高心脏NAD^+水平恢复NAD^+氧化还原平衡, 减轻心功能障碍, 提示NAD^+氧化还原在调控糖尿病心肌病进展中起到重要作用[124]. 同时, NAD^+也可调控胰岛素敏感性和胰岛素分泌, 在给糖尿病小鼠补充NMN的研究中发现, NAD^+水平的恢复也伴随胰岛素分泌的恢复[125]. Sirtuins作为NAD^+消耗酶, 也在衰老与代谢疾病研究中被广泛关注. 在STZ诱导的糖尿病小鼠模型中发现, 糖尿病小鼠心肌*Sirt3*表达明显低于非糖尿病小鼠, 敲除*Sirt3*的糖尿病小鼠和普通糖尿病小鼠相比, 血清乳酸脱氢酶(lactate dehydrogenase, LDH)水平升高, ATP水平降低, ROS产生增多, 心功能障碍更加显著[126]. 这些研究为通过调控线粒体NAD^+代谢治疗糖尿病及延缓心脏衰老提供了新的思路.

肥胖是代谢性心脏病的一大危险因素, 这类人群

在体重增加的同时常伴有胰岛素抵抗、高血糖、高血压和血脂异常. 肥胖可加速和加剧心脏衰老, 在年轻肥胖人群中观察到的诸多心脏表型变化和病理机制也存在于衰老心脏中, 例如, 肥胖本身(不合并糖尿病)直接导致年轻人群心肌细胞线粒体生物发生和呼吸链功能出现障碍, 线粒体ROS产生增加以及端粒缩短[127]. 在D-半乳糖(D-galactose)诱导的衰老模型中, 通过比较D-galactose处理的正常饮食大鼠、高脂饮食(high-fat diet, HFD)大鼠和D-galactose处理的HFD大鼠的心功能, 研究者发现, 8周后D-galactose处理的HFD大鼠心功能障碍以及线粒体功能、自噬损害最严重. 衰老通过加重心肌线粒体功能, 影响自噬, 增加细胞凋亡等方式加重肥胖大鼠的心功能障碍[128].

2.3　线粒体稳态失衡与心律失常

线粒体对于维持正常心脏电传导功能至关重要, 一方面, 维持心肌细胞电活动的离子通道和转运体需要线粒体提供ATP; 另一方面, 过量的ROS可以通过调节这些通道的表达或改变它们的翻译后修饰来影响离子电流[129]. 衰老引起的线粒体功能障碍(ATP降低及ROS升高)可破坏细胞内离子稳态和膜兴奋性, 从而引起心律失常.

心房颤动(atrial fibrillation, AF)是心房的一种快速不规则节律, 是最常见的与衰老相关的心律失常[130]. 衰老引起的线粒体功能障碍与心房颤动的发生和进展密切相关, 其机制包括线粒体电子传递链功能的下降、线粒体能量代谢紊乱、mtDNA损伤以及mtDNA有害突变的增加等. 通过对房颤和非房颤老年患者右心耳组织氧化磷酸化的检测发现, 房颤与线粒体电子传递链活性的降低和氧化应激的增加有关[131]. 在线粒体能量代谢方面, 房颤患者心房组织总体脂质过氧化水平较高, 线粒体超氧化物产生增多, 参与线粒体能量代谢的各种酶表达下调[132]. 在老年患者永久性房颤中, 线粒体代谢向胎儿期表型转变, 即从脂肪酸β氧化转为糖酵解, 糖酵解的代偿性增加降低了细胞内pH值, 进一步导致细胞内Na^+和Ca^{2+}超载[133]. 在衰老引起的线粒体能量代谢方面, PGC-1α被认为是调节线粒体生物发生和能量代谢的关键分子. 研究发现, 老年房颤患者血清PGC-1α和ΔΨm水平降低[134]. 衰老导致的端粒缩短可以抑制PGC-1α, 引起线粒体功能障碍和氧化应激、细胞内Ca^{2+}超载等一系列反应, 最终诱发房颤[135]. 另外, mtDNA拷贝数变化、mtDNA突变和损伤均与房颤的发生相关. 临床前瞻性队列研究发现, 外周血mtDNA拷贝数水平与房颤风险呈负相关, 且独立于其他危险因素[136]. 房颤患者心房肌mtDNA的7900~16500核苷酸位置之间的大规模缺失发生频率很高, 其中房颤患者心房肌4977 bp缺失的mtDNA平均比例是非房颤患者的3.75倍. 此外, 8-羟基脱氧鸟苷(8-hydroxydeoxyguanosine, 8-OHdG)是DNA氧化损伤最常见的产物之一, 与非房颤患者相比, 房颤患者mtDNA中8-OHdG的出现频率更高, 提示mtDNA的改变与房颤的发生相关[137].

2.4　线粒体稳态失衡与心力衰竭

心力衰竭是由心脏结构和功能性疾病导致的心肌收缩和舒张功能障碍, 是上述所述各种心脏病理变化的最终结局. 衰老相关的心力衰竭中, 压力负荷型(如高血压所致)及缺血型(如心梗所致)心力衰竭最为常见. 线粒体质控动态平衡的破坏、线粒体自噬的异常、线粒体生物发生减少以及线粒体代谢异常在衰老相关心衰的发生和发展机制中起到重要的作用.

线粒体质控平衡的破坏与心脏衰竭密切相关. 在小鼠TAC诱导的压力负荷型心衰模型中, *Drp1*缺失可抑制线粒体自噬, 并加剧TAC诱导的线粒体功能障碍和心力衰竭的进展[138]. 在AngII诱导的高血压小鼠模型中, *Mfn2*过表达下调小鼠心肌细胞肥厚相关基因*Anf*的表达并抑制AKT的活化, 使AngII诱导的心肌肥厚被明显抑制[139]. 线粒体肽酶YME1L和OMA1参与线粒体融合蛋白OPA1的合成, 小鼠心脏特异性*Yme1l*基因敲除可加速线粒体融合蛋白OPA1水解, 触发线粒体碎裂并导致扩张型心肌病和心力衰竭, 而敲除*Oma1*基因可以抑制这一过程, 从而挽救心脏功能和线粒体形态[140]. 在心衰的犬和人类的心肌组织中也发现, 线粒体分裂相关蛋白水平增加, 融合相关蛋白水平降低[141].

线粒体自噬被证明在心衰的机制中起到重要作用. 终末期心衰患者左心室E3泛素连接酶Mule的表达明显下降, 敲除小鼠*Mule*基因可使原癌基因*c-myc*累积, 导致PINK1表达下调, 线粒体功能异常, ROS生成增多, 小鼠出现左心室功能障碍. 敲除*c-myc*基因可以抑制*Mule*缺失导致的PINK1下调、线粒体功能障碍和心肌损[142]. 此外, P53与衰老和阿霉素引起的心力衰竭密切相关. P53通过与Parkin结合, 干扰Parkin迁移至受

损线粒体的表面, 从而抑制线粒体自噬, 导致心功能受损. 敲除*p53*, 可明显减少老年小鼠和阿霉素引起的心功能损害[143]. 此外, 心衰患者FUNDC1表达明显下调, 敲除小鼠心肌细胞*Fundc1*基因可导致心肌细胞线粒体形态和功能异常[144], 加剧高脂饮食引起的心肌重塑、心功能下降, 同时三磷酸肌醇受体(inositol triphosphate receptor 3, IP3R3)水平升高, 心肌细胞内发生钙超载[145]. 另外, 敲低自噬相关基因*Atg5*也可抑制线粒体自噬, 导致巨噬细胞中ROS和炎症因子增多, 加重AngII诱导的心脏炎症和心肌纤维化[146].

线粒体生物发生受损是心力衰竭机制中的重要因素. 在啮齿类动物[85]、犬[147]和人类[148]中的研究均表明, 线粒体生物发生的破坏是心力衰竭病理生理的早期事件, 如果及时逆转对心脏可产生保护作用. AngII诱导的小鼠高血压心衰模型中, 线粒体生物发生基因*Ppargc1a*, *Ppara*, *Pparg*等相关表达基因均下调[149]. 通过检测心衰患者心外膜脂肪组织的基因谱发现, 与非心衰患者相比, 其心外膜脂肪中线粒体PGC-1α表达水平下降[150]. 在人类左心室活检组织标本中发现, 与正常对照组相比, 心衰患者DRP-1表达增加, PGC-1α表达减少[151].

在心衰发病机制中, 线粒体的代谢异常也是一个关键的驱动因素. 通过对正常和缺血所致的心衰心脏线粒体进行蛋白质谱分析, 研究人员鉴定出27个参与能量代谢的差异表达蛋白. 三羧酸循环酶和丙酮酸脱氢酶复合体亚基表达增加, 脂肪酸氧化和OXPHOS相关蛋白表达减少. 这一变化表明在心力衰竭过程中, 代谢从脂肪酸氧化向糖酵解代谢转换[152]. 从终末期心衰患者中分离出来的心脏成纤维细胞中脱乙酰化酶SIRT3水平降低, SIRT3的缺乏会加剧心肌肥厚并诱导间质纤维化; SIRT3的过表达可以抑制心脏成纤维细胞中纤维化标志物的表达[153]. 这些研究提示NAD^+水平下降、线粒体脱乙酰化受损在心衰过程中起到关键作用. NAD^+及其前体NR可以通过逆转脂肪酸氧化的高乙酰化状态, 改善线粒体功能而产生心肌保护作用, 这一过程依赖于SIRT3[154].

3 靶向线粒体改善心脏衰老相关疾病的干预措施

在过去的几十年中, 相关研究已揭示了线粒体稳态失衡在衰老相关心脏疾病中的重要地位, 进而推动了诸多关于靶向线粒体改善衰老相关心脏疾病的探索, 包括改善线粒体代谢, 维持线粒体质控稳态, 减轻线粒体氧化应激与炎症反应, 修复核编码和线粒体编码DNA突变, 探究线粒体衍生多肽(mitochondrial derived peptide, MDPs), 开发线粒体移植技术等多个方向.

3.1 线粒体代谢

NAD^+在心脏线粒体代谢及衰老过程中起到重要作用, 通过补充NAD^+前体或激活NAD^+依赖的去乙酰化酶(SIRTs)等调节NAD^+相关代谢稳态可以改善心脏功能, 这一作用已在动物模型中得到验证[27]. 在临床试验中, 补充NAD^+前体NA[155]及其类似物[156]已被证明能够提高NAD^+水平和线粒体氧化磷酸化能力, 显著降低低密度脂蛋白水平, 增加高密度脂蛋白水平. 通过补充NAD^+另一前体NR也可以提高NAD^+水平, 降低老年人的收缩压, 改善主动脉硬化, 且目前认为口服NR具有良好的耐受性, 尚未发现不良事件[157,158]. 最新的将NR应用于心衰治疗的临床随机对照试验表明, NR约使全血NAD^+水平增加一倍, 且血中NAD^+水平的相对增加与外周血单个核细胞线粒体呼吸功能增强和NLRP3相关炎症小体表达降低相关[159].

如前文所述, SIRTs是NAD^+依赖的去乙酰化酶, 其活性依赖于NAD^+合成. 一些证据表明, 二者与线粒体代谢密切相关, 并且随衰老发生改变. 在大鼠缺血再灌注损伤模型中发现, SIRTs激活剂白藜芦醇可以通过诱导自噬以及上调SIRT1和SIRT3, 改善心功能, 减少心肌梗死面积[160]; 在阿霉素诱导的大鼠心脏毒性模型中, 白藜芦醇可以减轻左心室重构及纤维化[161]. 临床研究显示, 白藜芦醇可上调2型糖尿病合并冠心病患者外周血单个核细胞中的PPARγ和SIRT1. 2型糖尿病和冠心病患者补充白藜芦醇4周对血糖控制、胆固醇水平和丙二醛(malondialdehyde, MDA)水平均有有益影响[162]. 运动锻炼也可以通过调控SIRTs的表达水平及活性起到心肌保护作用. 在运动过程中, SIRT1和SIRT3在心脏中表达上调, 通过FOXO3a依赖的信号通路, 增加超氧化物歧化酶和过氧化氢酶的水平, 发挥心脏保护作用[163].

针对线粒体代谢的另一条重要通路mTOR通路, 其抑制剂雷帕霉素在延缓心脏衰老方面的作用已被诸

多研究证实. 雷帕霉素通过抑制mTOR通路, 逆转衰老心脏脂肪酸氧化减少, 并增强线粒体代谢, 这一过程与雷帕霉素增加衰老心脏的AMPK磷酸化有关[164]. 在人类心脏成纤维细胞中观察到, 雷帕霉素可改善衰老所致的线粒体氧化代谢的减弱, 并且增加线粒体代谢中利用底物的灵活性[165]. 由于雷帕霉素对mTORC2的抑制作用可以产生代谢和免疫方面的副作用, 科学家研发了新型雷帕霉素类似物DL001, 通过其对mTORC1的高选择性使其在有效抑制mTORC1活性的同时明显减少对脂质代谢和免疫系统的副作用[166]. 除了雷帕霉素以外, 卡路里限制也可以通过抑制mTOR通路发挥抗衰老作用. 由于mTORC1在营养和胰岛素感应中起到关键作用, 因此认为卡路里限制主要通过抑制mTORC1通路发挥抗衰老作用. 通过抑制酵母、线虫中mTORC1的表达发现卡路里限制无法延长寿命, 进一步验证了这一观点[167]. 在大鼠高脂饮食模型中, 卡路里限制可提高端粒酶活性, 增强自噬, 改善大鼠左室舒张功能, 这些影响可能对维持正常的心脏功能和延缓心脏衰老起到重要作用[168]. 为研究卡路里限制对心脏的保护作用是否与年龄有关, 研究者使不同年龄段小鼠接受3个月的卡路里限制饮食(比随意饮食少40%), 最终卡路里限制显著逆转了中老年小鼠的心脏衰老表型, 包括心脏重塑(心肌细胞肥大和心肌纤维化)、炎症、线粒体损伤、端粒缩短以及与衰老相关的标志物, 但在年轻小鼠中卡路里限制反而加速心脏衰老. 卡路里限制使年轻小鼠*AMPKa2*, *AMPKβ2*和*AMPKγ1* mRNA水平显著降低, 叉状头转录因子(fork-head box subgroup O, FOXO)的下游转录物, 如BCL2/腺病毒E1B相互作用蛋白3(BNIP3)和微管相关蛋白1轻链3β(MAP1lC3B, 又称LC3)下调, 但在中年和老年小鼠中未见这一变化, 因此卡路里限制诱发APMK的激活并引起对FOXO信号通路的调控与年龄相关[169]. 卡路里限制开始前的营养状态同样也可以影响这一干预对心脏衰老的保护效果. 在小鼠模型中, 和之前正常饮食的小鼠相比, 长期进行高脂饲养的小鼠卡路里限制抑制心脏重构的作用明显被削弱[170].

3.2　线粒体质量控制体系

线粒体质量控制体系对于维持衰老过程中线粒体网络的稳定性至关重要, 通过干预线粒体融合与分裂、线粒体自噬以及生物发生等, 可以改善衰老相关心脏疾病的预后.

研究表明, 抑制线粒体分裂可以减轻心肌缺血/再灌注损伤. 线粒体分裂抑制剂Midivi-1可以有效降低缺血/再灌注小鼠模型的心肌梗死面积[171]. 与Mdivi-1类似, P110也可以通过阻止DRP1与DRP1受体分裂蛋白(fission protein 1, FIS1)结合, 有效地抑制线粒体过度分裂, 减小心梗面积, 并防止发生心梗后心力衰竭[172]. 然而, 在猪心肌梗死模型中, 通过再灌注开始时冠状动脉内注射Midivi-1并不能减少心肌梗死面积或维持心脏功能[173]. 近年来, 研究者们开发了两种新型抑制剂Drpitor1和Drpitor1a, 其相较于Midivi-1对Drp1 GTPase具有更高的特异性和更强的药效, 在大鼠模型中被证明可以显著改善心脏再灌注损伤期间的心室功能[174]. 此外, 生长分化因子GDF11可通过TGF-β受体信号通路促进线粒体融合, 从而增强心脏间充质干细胞活力, 可用于干细胞治疗心肌梗死[175]. 由心梗引起的不利微环境中, 瘦素可通过靶向线粒体融合蛋白OPA1信号通路维持线粒体形态和功能, 维持线粒体的完整性并延长人间充质干细胞(human MSCs, hMSCs)的存活时间, 提升hMSCs对心梗等心血管疾病的治疗效果[176].

通过提高自噬促进受损线粒体的清除是维持心血管系统稳态、延缓心脏衰老的基础, 目前已有多种靶向线粒体自噬的药物正处于研究阶段. 由于抑制PINK1可引起线粒体功能障碍, 是促进衰老相关疾病的一个重要特征. 因此科学家利用*Parkin*过表达可通过促进缺陷线粒体并入自噬体, 诱导衰老小鼠心脏的线粒体自噬, 减轻衰老引起的心功能下降[143]. 此外, 口服亚精胺可减轻心肌肥厚, 并通过改善心肌细胞线粒体呼吸功能和促进线粒体自噬来维持衰老过程中的心功能[177]. 褪黑素的心肌保护作用被证实与调控PPAR/FUNDC1/线粒体自噬通路有关. 接受冠状动脉旁路移植术(coronary artery bypass grafting, CABG)的急性心肌梗死患者和缺血再灌注损伤模型的小鼠中均发现PPAR的表达下调, 褪黑素通过恢复PPAR含量、阻断FUNDC1介导的线粒体自噬减少心脏缺血再灌注损伤[178]. 除直接作用于心脏, 降低其他风险因素也可减少心脏病的发生. 比如, FUNDC1及其互作蛋白FBXL2共同维持高脂饮食状态下的心脏稳态, 可作为肥胖型心肌病的潜在防治靶点[145]. 在糖尿病治疗领域, 钠-葡萄糖协同转运体(sodium-glucose co-transporter-2, SGLT2)抑制剂通过独特的非胰岛素依赖型降糖

机制，为2型糖尿病的治疗开辟了新途径. 目前，关于SGLT2抑制剂的临床研究显示，SGLT2抑制剂的应用不仅可改善2型糖尿病患者的血糖控制，而且还可降低心血管事件和心力衰竭住院发生率，其机制与激活SIRTs、促进自噬和调节线粒体融合和分裂有关[179~181]. 目前已经有多种药物在实验动物模型中显示出有通过调节线粒体自噬延缓衰老的效果，但这些药物是否能通过调节自噬在人类身上发挥延缓心脏衰老的作用仍有待进一步探索[182].

3.3 线粒体氧化应激

在过去的20多年中，已有大量动物及临床研究尝试使用抗氧化剂治疗心脏疾病, 如辅酶Q(coenzyme Q, CoQ)、维生素E、抗坏血酸(vitamin C, VitC)和β-胡萝卜素等[183~188]. CoQ是一种普遍存在于细胞膜和线粒体中的因子，在心脏、肾脏和肝脏等代谢较快的器官中含量很高, 但可能会因衰老、遗传因素、药物(如他汀类)、心血管疾病、退行性肌肉疾病和神经退行性疾病而降低. 临床研究发现: 对于有高血压、胰岛素抵抗、血脂异常和肥胖等相关危险因素的患者，补充外源性CoQ10可能有助于降低心力衰竭、心房颤动和心肌梗死等心血管疾病的发生率[183].

大多数临床研究发现，通过膳食补充或者注射给药尽管可以使患者的外周循环中抗氧化剂达到较高水平, 但并未明显改善疾病的严重程度. 由于一般的抗氧化剂无法跨越线粒体磷脂双分子层而减少线粒体内ROS的产生，因此靶向线粒体的抗氧化剂是目前的研究热点. Mitoquinone(MitoQ)是一种基于亲水性三苯基膦(triphenylphosphine, TPP)的线粒体靶向抗氧化剂, TPP阳离子促进MitoQ进入线粒体, 特异性地减轻线粒体的氧化应激损伤[189]. 研究发现，给予MitoQ10可延缓高血压大鼠高血压的进展，改善内皮功能，抑制心肌肥厚[190,191]. 这一效果在心血管内皮功能损伤患者的临床研究中也已得到证实[192]. Mito-Tempol与MitoQ有类似作用机制, 一旦进入线粒体, 它被泛醇迅速转化为Mito-Tempol-H, 产生抗脂质过氧化的作用[193]. Mito-Tempol可通过恢复自噬通量抑制低密度脂蛋白LDL诱导的泡沫细胞形成, 激活自噬, 改善动脉粥样硬化[193]. 另外，Mito-Tempol还可通过控制线粒体Ca^{2+}平衡和抑制自发电位改善老年大鼠的心律失常[194], 并且可以减少老年小鼠心肌细胞ROS的产生，改善心脏收缩功能障碍[195]. Elamipretide(亦称SS-31，MTP 131或Bendavia)是一种新的线粒体靶向四肽，可增加线粒体产能, 它并不直接清除ROS，而是通过干扰心磷脂从而阻止其氧化，减少线粒体中ROS的形成[196]. 大鼠缺血再灌注模型中，Elamipretide预处理可显著降低缺血再灌注损伤时心肌脂质过氧化，减少梗死面积[197]. 在一项小型临床研究中发现，Elamipretide用于射血分数降低的心衰患者耐受性良好，单次输注4小时Elamipretide可降低其左室舒张末期容积[198], 而在之后一项样本量较大且随访时间较长的临床研究中发现，使用Elamipretide治疗的患者在4周时左室收缩末期容积并未见明显改善[199]. 由于研究发现Elamipretide治疗8周可以逆转老年小鼠的蛋白质组氧化状态，Elamipretide在近年来也被用于干预衰老相关心脏疾病[200]. 在高糖饮食的老年小鼠模型中，给予Elamipretide可以预防高糖饮食引起的心脏肥厚[201]. 目前认为，其机制与其改变蛋白翻译后修饰、增强肌球蛋白结合蛋白(cardiac myosin binding protein C, cMyBP-C)磷酸化和降低S-谷胱甘肽水平有关[202,203].

线粒体呼吸链是氧化应激的重要场所，保持线粒体呼吸链的完整性有助于降低氧化应激，减少心肌损伤, 因此有学者对2-磺酰嘧啶衍生物(TC9-305, 作用于线粒体呼吸链复合物Ⅱ)[204,205]、PARP1抑制剂(如3-氨基苯甲酰胺[206])以及线粒体膜通透性转换(mitochondrial permeability transition, MPT)诱导的坏死抑制剂(一种作用于转位蛋白TSPO的小分子TRO40303[207])的保护作用进行了研究. 由于特异性或生物利用度问题，这些分子中的大多数从未进入临床开发阶段，仅有TRO40303和环孢素A在急性心肌梗死后接受PCI治疗的患者中开展过临床试验[208,209], 但未发现有明显的临床疗效[210~213].

3.4 线粒体编码DNA突变修复

大多数衰老相关线粒体疾病由于存在mtDNA突变而难以逆转[214]. 如何穿过线粒体内膜进入含有mtDNA的线粒体基质，如何利用特异性靶向突变的mtDNA进行修复，是目前mtDNA突变修复的难点. 由于向导RNA(guide RNA, gRNA)不能特异性靶向线粒体，经典的CRISPR-Cas9系统不能用于修复mtDNA突变[215]. 科学家随后开发了无需向导RNA的mitoZFN[216]和mitoTALEN[217]技术: 前者向小鼠尾静脉

中注射含有靶向线粒体的ZFN腺相关病毒(adeno-associated virus, AAV), 两个多月后检测到心脏组织中突变mtDNA的水平下降40%; 后者将含有靶向线粒体的TALEN腺相关病毒(AAV)注射到携带着mtDNA突变的小鼠肌肉中, 六个月后检测到小鼠肌肉组织中的突变mtDNA的水平下降了50%以上(低于导致线粒体疾病的突变水平). 鉴于这两种方法难以包装成病毒载体, 且在高突变载荷下剩余的正常mtDNA不足以维持线粒体正常功能[218], 科学家们开发了细菌毒素DDdA衍生的胞嘧啶碱基编辑(bacterial toxin DddA-derived cytosine base editors, DdCBEs)系统, 该系统可以在一定程度上实现特定碱基的替换[219], 该技术已实现对小鼠胚胎线粒体DNA的编辑, 为治疗mtDNA突变导致的疾病带来了新的思路和方向[220]. 由于DdCBEs诱导的核基因组中普遍存在脱靶突变[221], 最新的研究设计了HiFi-DdCBEs, 使其脱靶活性最小化, 提高了编辑效率和准确性, 在未来研究中可能成为治疗的理想选择[222].

3.5　线粒体衍生多肽

MDPs是由mtDNA编码的一组多肽, 具有与线粒体相似的功能, 在应激状态下可以维持线粒体功能和细胞活力. 近年来研究发现, MDPs可以通过降低各种心脏病相关危险因素, 如衰老、胰岛素抵抗、高脂血症和动脉粥样硬化等, 发挥心脏保护作用, 为心血管疾病的治疗提供了新的思路[223]. MDPs通过抗氧化、抗凋亡和抗炎症反应, 以及通过减少内质网应激, 发挥其心脏保护作用[224]. 目前有三种研究最多的MDPs, 即Humanin, MOTS-c(mitochondrial ORF of the 12S rDNA type-c)以及SHLP1-6(small Humanin-like peptide)[225,226]. 动物研究表明, 外源性给予Humanin可减少衰老小鼠心肌纤维化和细胞凋亡[227], Humanin通过降低复合物 I 活性, 直接保护心脏线粒体免受氧化应激引起的功能障碍[228]. 但由于Humanin比较短小, 作用持续时间短, 科学家们开发了比Humanin效力更强的类似物S14G-humanin(HNG), 并在猪模型中验证了其预防心脏缺血再灌注损伤的作用[229]. 与Humanin作用类似, MOTS-c可降低血管紧张素1型受体(angiotensin type 1 receptor, AT1 receptor)和内皮素B受体(endothelin Receptor B, EDNRB)表达水平, 提高磷酸化AMPK水平, 防止心脏重构和心肌收缩功能障碍的进展[230]. 在人类研究中发现, 人类血浆MDPs(Humanin, MOTS-c和SHLP2)水平随年龄的增长而下降, 并与线粒体功能障碍、线粒体产生的氧化损伤和年龄相关疾病的发展相关[225,231], 但将MDPs最终用于临床治疗仍有许多工作要做.

3.6　线粒体移植

线粒体移植是一种将外源性线粒体移植到线粒体缺陷细胞中的治疗方法, 可以克服药物治疗的局限性以预防或恢复线粒体疾病, 用健康的线粒体替换受损的线粒体可以保护细胞免受进一步的损伤[232,233]. 线粒体移植最初被用于缺血再灌注损伤模型中, 研究人员从未缺血组织中分离出线粒体, 然后在再灌注之前将其注入缺血区域, 可使肌酸激酶(creatine kinase-MB, CK-MB)和肌钙蛋白I(cardiac troponin，cTnI)的水平显著降低, 并且可以增强细胞活力, 促进组织功能恢复[234]. 在随后的临床试验中, 通过将无缺血的腹直肌中的线粒体自体移植到心脏, 有80%缺血再灌注损伤的患者心室功能得到恢复, 且未出现与线粒体移植相关的心律失常、心肌内血肿、瘢痕产生等短期并发症[235]. 在肺动脉结扎致右心衰竭的猪模型中, 移植健康小牛的心肌线粒体至猪右心室游离壁, 可使心肌细胞凋亡减少, 右心室对压力负荷适应性增强, 收缩功能和非移植组相比明显增强[236].

线粒体移植对心脏功能的改善很大程度上取决于所移植的线粒体的完整性和活性, 因此近年来科研人员在不断寻找提高线粒体移植效果的方法. 体外实验发现, 在移植前用Alda-1治疗激活线粒体乙醛脱氢酶2(mitochondrial aldehyde dehydrogenase 2, ALDH2), 可以提高线粒体移植治疗心肌细胞缺氧复氧的效果[237]. 另外, 研究人员发现, 人诱导的多能干细胞来源的心肌细胞(human induced pluripotent stem cells-derived cardiomyocytes, hiPSC-CMs)可以分泌富含功能性线粒体的外泌体, 可有效地将线粒体转移到受体心肌细胞中, 改善心肌细胞缺氧所致线粒体损伤; 在小鼠缺血/再灌注损伤模型中, 也发现直接在心肌内注射iCMs衍生的外泌体可产生心脏保护作用[238], 这一方法比裸线粒体移植可行性更高. 然而, 线粒体移植通常是通过将线粒体输注到冠状动脉中或在胸骨切开后将线粒体直接注射到缺血心肌中来实现的, 这些有创操作极大地限制了线粒体移植的临床应用. 因此, 更

多的研究开始探索临床上更为可行的线粒体递送途径. 最新研究利用结合三苯基磷离子(TPP^+)的多肽CSTSMLKAC(PEP)形成PEP-TPP-线粒体化合物, 将线粒体靶向递送到缺血心肌区域[239]. PEP可以有效地结合线粒体, 并对缺血心肌有优先选择性, 其缺血感知特性促进其靶向转运到缺血心肌, 且很容易从PEP-TPP-线粒体化合物中解离, 从而允许移植的线粒体被心肌细胞有效地内化或由内皮细胞转移到心肌细胞. 移植的线粒体可增强心肌细胞能量产生, 促进心肌收缩, 减少细胞凋亡, 减少巨噬细胞浸润和炎症反应, 减弱缺血再灌注损伤.

在老年心脏病患者中, 线粒体移植能否产生保护作用或者能发挥多大程度的保护作用尚未见报道. 将线粒体移植用于治疗仍然面临一系列挑战. 例如, 单次给予线粒体并不能维持长期的治疗效果. 线粒体的分离方法和来源以及给药途径和剂量的多少均影响线粒体移植的效果[2,240,241]. 因此, 如何为不同疾病制定最佳的线粒体移植标准方案有待进一步研究.

4 总结与展望

随着我国人口老龄化的加剧, 如何降低衰老相关心脏疾病的发生率, 延长老年人群的寿命已成为亟待解决的问题. 在国家政策的大力支持下, 我国科研人员在心血管衰老及相关疾病研究领域已获得一系列重要发现. 其中, 关于线粒体稳态在衰老引起的心脏疾病的机制中起到的重要作用已获得证实, 但在靶向线粒体的心脏疾病的防治和干预手段开发方面仍然面临诸多挑战. 线粒体稳态调控机制的任何部分的失衡都会对整个心脏产生影响, 仅仅从一个分子或一条信号通路入手难以在整体层面起到延缓心脏衰老的效果.

针对人体心血管结构功能的内在复杂性与生物医药研究临床转化之间的矛盾, 迫切地需要研究人员开发先进的人细胞培养系统和多种动物模型构建. 其中, 结合人干细胞定向分化与心血管类器官培养的研究模型, 具有从人的进化性、异质性、系统性、可变性、动态性等方面模拟心血管系统衰老和疾病状态的潜力, 可能为心血管衰老及相关疾病的机制研究、药物和其他干预手段的评价等提供开放式、场景化的研究平台, 有望助力突破制约心血管衰老和相关疾病研究的体系瓶颈, 从结构与功能动态发展的视角阐释心血管衰老及相关疾病发生发展的基本调控规律, 为研究人类心血管衰老及相关疾病机理提供新平台, 为开发防治和干预心血管衰老的有效手段提供新思路.

随着单细胞测序技术、多组学技术以及生物信息学的发展, 未来有望从宏观上更加明确线粒体稳态对心脏衰老的整体调控网络, 进而发现更多延缓心脏衰老的关键分子和细胞标志物, 有助于推动我国衰老相关心脏疾病的早期评估、预警和开发更多的新型有效治疗手段. 维持衰老过程中的心脏稳态, 同时延长老龄人群寿命.

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Mitochondrial dyshomeostasis in cardiac aging and related diseases

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Cardiac aging is characterized by cardiac functional decline and pathophysiological myocardial remodeling over time, which is one of the major risk factors for cardiac diseases. An increasing number of studies have elucidated the critical role of mitochondrial dysfunction in the pathobiologies of aging-related cardiac diseases. This review mainly focuses on mitochondrial dyshomeostasis in cardiac aging and summarizes the remarkable progress in understanding the impacts of mitochondrial dyshomeostasis on aging-related cardiac diseases and the potential perspectives of mitochondrial-targeted interventions and therapeutic strategies for aging-related cardiac disease.

mitochondrial homeostasis, aging, cardiac disease

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