·综 述·

线粒体功能障碍、细胞衰老与心血管衰老

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摘要：线粒体功能障碍及细胞衰老会通过多种途径加速心血管衰老，进而导致年龄相关心血管疾病的发生、发展。现有证据表明，二者均有潜力成为延缓心血管衰老的有效靶点。该文就线粒体功能障碍及细胞衰老在心血管衰老中的作用机制作简要综述，以期为今后心血管疾病的诊断、管理及治疗药物的研发提供参考。

关键词：心血管系统；衰老；线粒体功能障碍；细胞衰老
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Mitochondrial dysfunction, cellular aging and cardiovascular aging

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Abstract: Mitochondrial dysfunction and cellular aging can accelerate cardiovascular aging through various pathways, leading to the occurrence and development of age-related cardiovascular diseases. Existing evidence suggests that both have the potential to become effective targets for delaying cardiovascular aging. This article reviewed the mechanisms of mitochondrial dysfunction and cellular aging in cardiovascular aging, in order to provide reference for the diagnosis, management and development of therapeutic drugs for cardiovascular diseases in the future.

Key words: cardiovascular system; aging; mitochondrial dysfunction; cellular aging

线粒体功能障碍在衰老及其相关慢性疾病的发生、发展中起关键作用[1]，尤其在严重依赖线粒体代谢和信号传导的心血管系统中表现得更为明显。除心肌能量代谢外，线粒体在细胞内钙稳态、氧化还原平衡、合成和分解代谢反应以及心血管系统中几乎所有细胞的炎症和重要信号启动中均发挥至关重要的作用[2—3]。故与年龄相关的线粒体缺陷会首先影响心血管系统[4—5]。线粒体功能障碍是心血管疾病中关键病因之一[6—7]。细胞衰老通常指细胞周期永久停滞，导致复制能力不可逆的丧失及特定细胞功能降低，同时产生促炎特征。衰老不被细胞类型限制，不仅会发生在内皮细胞和成纤维细胞等细胞中，也会影响心肌细胞。本文将讨论线粒体功能障碍和细胞衰老在心血管衰老中的作用机制，以期为今后心血管疾病的诊断、管理及治疗药物的研发提供参考。

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1 线粒体功能障碍

在心脏中，衰老与线粒体含量的显著降低有关[8—9]。心脏中老化线粒体的结构、功能受损，表现为直径增加、基质变形、嵴缺失以及氧化磷酸化减少，这是线粒体呼吸链复合物，特别是复合物IV55213的活性及稳定性降低所致[10]。虽然上述异常主要影响纤维间线粒体[4,11—12]，但心脏代谢亦会严重受损。

线粒体缺陷在老化血管中亦十分明显[13—14]，这是因为血管内皮细胞和平滑肌细胞的线粒体生物发生受损，加之线粒体漂移量和呼吸减少[15—16]。血管老化还与线粒体产生的活性氧（reactive oxygen species，ROS）增加有关，ROS 可直接清除一氧化氮并降低一氧化氮生物利用度，从而损害内皮依赖性血管舒张[17—18]。此外，抑制核转录因子红系 2 相关因子 2（nuclear factor-erythroid 2-related factor 2，NRF2）的抗氧化活性会使衰老的血管细胞更易受到 ROS 诱导的损伤[19—20]。动物试验显示，*NRF2* 缺陷小鼠血管衰老加速，且血管功能障碍易感性增加[21—22]。线粒体 ROS 的过量产生可能会增加线粒体 DNA（mitochondrial DNA，mtDNA）突变、缺失的速率，甚至导致线粒体释放 mtDNA，从而激活促炎信号通路。因此，ROS 激活核因子（nuclear factor，NF）-κB，而胞质 mtDNA 触发 DNA 传感器环状鸟苷一磷酸 - 腺苷一磷酸合成酶（cyclic guanosine monophosphate and adenosine monophosphate synthase，cGAS），进而触发干扰素基因刺激蛋白（stimulator of interferon genes，STING），以启动Ⅰ型干扰素反应[14,23]。这些促炎途径的激活导致与年龄相关的内皮功能障碍[24—26]。此外，烟酰胺腺嘌呤二核苷酸（nicotinamide adenine dinucleotide，NAD）这一关键代谢辅因子水平降低也会导致线粒体功能障碍，从而诱导心血管衰老[27—28]。

从机制上讲，年龄相关的线粒体自噬丧失会降低线粒体质量，从而导致功能失调细胞器的积累以及心血管稳态的降低[29—31]。Billia 等[32] 研究发现，PTEN 诱导假定激酶 1（PTEN-inducible kinase 1，PINK1）敲除小鼠在幼年即会出现心肌肥大。推测是由于线粒体自噬受损，PINK1 增加了功能失调线粒体的积累所致[33]。另有动物试验显示，尽管心肌细胞过表达过氧化物酶体增殖物激活受体 -γ 辅激活因子 -lα 可在早期改善线粒体功能及心功能，但其最终仍会加速心脏衰老，缩短模型动物寿命，其原因可能为线粒体自噬缺陷及受损线粒体积累[34]。此外，线粒体融合及分裂亦会影响线粒体自噬，消除线粒体融合及分裂会严重损害线粒体自噬，进而加速心脏衰老[35]。Wang 等[36] 的研究结果可验证上述观点。

近来研究显示，线粒体丙酮酸载体蛋白 1、2 缺乏亦会导致线粒体缺陷，从而加速心脏衰老，使模型动物心肌肥大、收缩异常[37—38]。此外，线粒体肉碱 O- 棕榈酰转移酶 2 的条件性缺失会破坏体内内皮脂肪酸氧化，导致心脏瓣膜增厚，并增加器官的血管通透性[39]。

多种靶向线粒体功能障碍的干预措施已被证实可延缓心血管衰老，发挥心血管保护作用。Hoshino 等[31] 发现，诱导心肌细胞 *Parkin* 基因过表达不仅能维持线粒体的完整性及心肌功能，还可减轻心血管衰老及炎症。而促 *Twinkle* 基因过表达可改善载脂蛋白 E 敲除小鼠的 mtDNA 损伤，通过增加纤维帽厚度、减少坏死核心形成来改善线粒体功能，从而提升动脉粥样硬化（atherosclerosis）斑块的稳定性[40]。抗氧化剂 SS-31 及甲磺酸米托醌（mitoquinone methanesulfonate）可使老化血管的氧化应激正常化，并恢复内皮细胞的血管舒张功能[41—42]。补充 NAD 前体可促进线粒体氧化代谢，从而发挥细胞保护作用[43]，并延缓心血管衰老[44—45]。此外，通过抑制 NAD 消耗酶来恢复 NAD 水平也可获得心血管益处[46—47]。

2 细胞衰老

衰老通常被定义为细胞周期的永久停滞，导致复制能力的不可逆丧失及特定细胞功能的降低。心血管系统中的细胞衰老与多种心血管疾病的发生、发展密切相关[48—49]。多种因素可诱导细胞衰老的发生[50]，而衰老的细胞会分泌一系列促炎因子、趋化因子及基质蛋白酶等，进而诱发“二次衰老”，导致年龄相关疾病的发生[51]。虽然细胞衰老在正常发育、伤口愈合及肿瘤抑制中具有积极作用，但衰

老细胞的过度积累会导致机体衰老及多种年龄相关心血管疾病，包括动脉粥样硬化、缺血性心肌病及射血分数保留的心力衰竭（heart failure with ejection fraction preservation）等[52—56]。

由于血管内皮细胞特殊的解剖位置，其直接暴露于各种衰老诱导因子[57—58]。与正常内皮细胞相比，衰老的内皮细胞表现出形态异常及体积增大，与基底膜的黏附增加，与血流方向一致的能力降低[57—59]；从功能上讲，衰老的内皮细胞可致血管舒张功能降低[60]。与内皮细胞相似，心肌细胞衰老也会导致结构及功能异常，如心肌肥大、促纤维化信号转导，进而导致心肌壁增厚、僵硬[61]。成纤维细胞衰老在伤口愈合中具有重要作用[62]，但其亦会导致心肌纤维化，并损伤心功能[63]。

现有证据表明，清除衰老的细胞能延缓衰老、延长寿命[61,64—65]。动物试验显示，组蛋白去乙酰化酶抑制剂能通过清除衰老的细胞，减轻心肌肥大及纤维化，改善心功能[66]。p16Ink4a 表达与细胞衰老相关，清除其表达物可提高心脏抵御应激的能力，并改善心肌重塑[61]。长期使用 senolytic 亦被证实可延缓血管衰老，改善内皮依赖性血管舒张[67]。此外，考虑到端粒断裂、缩短会加速心血管衰老，导致心肌肥大、纤维化、舒张功能障碍以及内皮功能障碍等[34,60,68]，以其为靶点或能改善年龄相关的血管内皮功能障碍[69]。

3 结语

线粒体功能障碍及细胞衰老均参与心血管衰老，从而导致多种年龄相关心血管疾病的发生、发展。现有证据表明，以上述二者为靶点进行干预可延缓心血管衰老，进而改善相关症状，延长机体寿命。但目前相关研究尚以动物试验为主，亟需开展相关临床研究，以促进临床转化，为心血管疾病患者提供更多治疗选择。

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