·综 述·

心血管衰老机制：巨自噬功能受损和表观遗传学改变

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摘要：心血管系统在持续的机械和代谢压力下运行，随着年龄的增长，在分子、细胞和器官水平上发生功能障碍的风险逐渐升高。特别是巨自噬功能受损和表观遗传学改变，其中包括 DNA 甲基化、组蛋白修饰和非编码 RNA。这些心血管衰老机制紧密交织，个别机制的加强或减弱会影响其他机制。了解心血管衰老机制，有望为今后心血管疾病的诊断及新药研发提供新的思路和方向。

关键词：心血管系统；衰老；巨自噬功能；表观遗传学
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Mechanism of cardiovascular aging: impaired macroautophagy function and epigenetic changes

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Abstract: The cardiovascular system operates under continuous mechanical and metabolic pressure, and as age increases, the risk of functional impairment at the molecular, cellular, and organ levels gradually increases. Especially with impaired macroautophagy function and epigenetic changes, including DNA methylation, histone modifications, and non-coding RNA. These cardiovascular aging mechanisms are closely intertwined, and the strengthening or weakening of individual mechanisms can affect other mechanisms. Understanding these cardiovascular aging mechanisms is expected to provide new ideas and directions for the diagnosis of cardiovascular diseases and the development of new drugs in the future.

Key words: cardiovascular system; aging; macroautophagy function; epigenetics

正常的循环功能是无病预期寿命的关键决定因素，而心血管疾病是目前全球致残、致死的主要原因之一[1]，故维持心血管健康对促进机体健康、延长寿命十分必要。现已知心血管衰老机制包括巨自噬功能丧失、蛋白稳态丧失、基因组不稳定、表观遗传学改变、线粒体功能障碍、细胞衰老、神经激素信号失调及炎症[2]。本文就巨自噬功能受损及表观遗传学改变作简要综述，以期为今后心血管疾病诊断及新药研发提供新的思路及方向。

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1 巨自噬功能受损

巨自噬是一种关键的细胞控制机制，对功能失调的细胞质成分的清除至关重要。在巨自噬过程中，蛋白质聚集体及老化细胞器被隔离在双膜囊泡中（即自噬体），随后与溶酶体融合，以酶促降解其内容物，从而为生物能量及合成代谢反应提供代谢产物。因此，巨自噬不仅有助于促变性，还可靶

向其他大分子，如胞质溶胶中的异位 DNA、脂滴（脂吞噬）、部分内质网（网状噬）、整个细胞器（包括线粒体和过氧化物酶体）以及入侵病原体（异噬）。此外，巨自噬机制有助于异噬[3]。因具有重要的稳态作用，巨自噬与心血管健康状态相关[4—6]。

现有研究表明，巨自噬功能失调与心血管疾病的发生密切相关，包括动脉粥样硬化（atherosclerosis）、冠状动脉粥样硬化性心脏病（coronary atherosclerotic heart disease）、心律失常（arrhythmia）、心力衰竭（heart failure，HF）及化疗相关心脏毒性[5,7—8]。同时，部分具有心脏保护作用的药物亦被证实能调节巨自噬活性，如阿司匹林（aspirin）、β 受体阻断剂及钙离子通道阻断剂[9—12]。越来越多的证据表明，巨自噬会随个体年龄的增长而减少[13—14]，从而导致与年龄相关的慢性疾病的发生[15]。但对于衰老影响心血管巨自噬的具体机制尚未达成一致[16]，目前主要认为与自噬蛋白的抑制性高乙酰化、Sirtuin 脱乙酰酶及其必需底物烟酰胺腺嘌呤二核苷酸在 T 细胞中的活性降低有关[17—18]。

蛋白质乙酰化会导致过高的乙酰辅酶 A 水平及胰岛素 - 丝氨酸 / 苏氨酸蛋白激酶哺乳动物雷帕霉素靶蛋白信号通路的过度激活，尤其是在伴内脏脂肪过多和代谢综合征（metabolic syndrome）的情况下；钙离子信号转导也被认为可调节巨自噬[19]，并在内皮细胞及心肌细胞中得到证实[20—21]。亚精胺水平会随年龄增长而逐渐降低[22—23]，从而损害自噬蛋白的鸟嘌呤依赖性翻译[24]。多项研究证实，外源性补充亚精胺能重新激活血管巨自噬，逆转动脉老化，从而发挥心脏保护作用，延长模型小鼠寿命[25—26]。

自噬相关基因（autophagy-related gene，ATG）亦是影响巨自噬的重要因素。如 *ATG5* 缺失小鼠心脏结构及功能存在明显异常[27—28]。在血管平滑肌细胞中，敲除 *ATG7* 会损害钙离子稳态，加速衰老，并加剧动脉粥样硬化[29—30]。敲除 *ATG5* 及 *ATG7* 小鼠的内皮细胞巨自噬功能受损[31]；敲除 Kruppel 样因子 4 基因会导致内皮功能障碍，表现为体内乙酰胆碱诱导的血管舒张减少[32]。

以上述机制作为靶点或能有效延缓心血管衰老，延长寿命[4]。Fernández 等[33]研究发现，敲除 *Beclin-1* 基因的小鼠巨自噬普遍被激活，心肌纤维化、肥大显著减轻。限制热量摄入被多项研究证实能有效诱导巨自噬，从而延缓心血管衰老，减轻舒张功能障碍、心脏纤维化和肥大及全身炎症[34—36]。在动物模型中，额外补充亚精胺被证实具有心脏保护作用，能减轻心肌增厚、僵硬和舒张功能障碍，改善血管内皮功能障碍，调节血压，并减少炎症[22,25—26]。其他促自噬的化合物，如雷帕霉素（rapamycin）和海藻糖，也对心血管系统具有抗衰老作用[37—39]。上述证据均支持巨自噬功能受损是心血管疾病潜在治疗靶点这一观点。

2 表观遗传学改变

心血管系统中的基因表达水平受多种表观遗传学因素影响，包括 DNA 甲基化、组蛋白修饰及非编码 RNA（non-coding RNA，ncRNA）[40—41]。

2.1 ncRNA

NcRNA 与心血管疾病高度相关[42]。NcRNA 亚族包括环状 RNA、微 RNA（micro RNA，miRNA）及长链 ncRNA（long ncRNA，lncRNA），均与心血管衰老相关机制有关。例如环状 RNA 叉头框蛋白 O3（circular RNA forkhead box protein O3，circFOXO3）在小鼠及人类心脏中高度表达，且其与心脏衰老密切相关[43]。

多种 miRNA 的心脏表达谱随年龄增长而变化[44]。MiRNA-34a 在心肌中高度表达[45]，其与促进衰老和 DNA 损伤有关[45—46]。敲除小鼠 *miRNA-34a* 可减轻心肌肥大及凋亡，并改善心功能[45]。此外，在老年小鼠主动脉中 miRNA-34a 表达亦上调[47]，能在体外发挥抗衰老作用[48]，并改善模型小鼠冠状动脉闭塞后的心脏恢复情况[44]。敲除小鼠 *miRNA-34a* 能减少维生素 D 诱导的血管钙化[48]。

MiRNA-22 是一种具有促心肌肥大、抑制巨自噬作用的 ncRNA，其表达水平随年龄增加而升高[49—50]。动物试验证实，抑制 miRNA-22 表达能促进心肌细胞的巨自噬，减轻心肌梗死后的心脏结构及功能异常[50]。

lncRNA Sarrah 在老年小鼠心脏及缺血性心肌病（ischemic cardiomyopathy）、射血分数保留的 HF 啮齿动物模型中表达下调，其过表达可抑制心肌细胞凋亡，提高心肌细胞存活率，促进内皮细胞增殖及心肌缺血后的心功能恢复，但该作用是否在老年小鼠中存在仍有待确定[51]。

2.2 组蛋白修饰

组蛋白的翻译后修饰在表观遗传调控中起重要作用。例如，组蛋白赖氨酸残基的乙酰化通过改变染色质结构缩合来调节基因转录活性。沉默信息调节因子（silence infor-mation regulator，SIRT）1 是一种烟酰胺腺嘌呤二核苷酸依赖的去乙酰化酶，其表达水平随年龄增长而降低[52—53]，适当提高 SIRT1 表达水平可延缓心脏衰老[54]。与之相似，增强内皮 SIRT1 表达可预防早期血管老化，维持血管舒张反应[55]。敲除 *SIRT6* 会导致早发性血管功能障碍[56]，且血管平滑肌细胞中 SIRT6 表达减少与血管钙化风险增加有关[57]。此外，动物试验表明，SIRT6 与心肌肥大及 HF 的进展有关[58]。

组蛋白脱乙酰酶（histone deacetylase，HDAC）家族成员 HDAC1、HDAC2、HDAC3、HDAC5、HDAC7 及 HDAC9 对心肌细胞发育、成熟及生长至关重要[59]。现有证据表明，HDAC 抑制剂能有效改善心脏舒张功能[60—62]，但仍需进一步明确 HDAC 各亚型在其中的具体作用。目前已知不同亚型 HDAC 在心血管稳态及心血管疾病病理机制中均有其独特作用[63]。例如 *HDAC6* 缺陷小鼠对肺动脉高压（pulmonary hypertension）以及应激诱导的收缩功能障碍的易感性降低[64—66]，表现为舒张功能障碍的过早发作，并随年龄增长而进展[66]。敲除 *HDAC9* 则可减少主动脉钙化[67]，但会加重模型动物的病理性肥大[68]。故而，优化 HDAC 亚型的靶向性或能减少脱靶效应及不良反应。

大量研究表明，组蛋白甲基化对心脏稳态具有重要作用[69—72]，而靶向组蛋白甲基化已被认为是动脉粥样硬化及肥厚性心肌病（hypertrophic cardiomyopathy）的潜在治疗靶点[72—74]。目前还需要进一步研究，以明确衰老过程中是否伴随心血管系统中可靶向的组蛋白甲基化的改变。

2.3 DNA 甲基化

尽管 DNA 甲基化已被用于心血管健康评估，但其在心血管疾病中的具体作用尚存争议[75—78]。研究证实，DNA 甲基化与 HF 的心脏结构改变有关[78—80]，但与血液及其他组织相比，心脏中 DNA 甲基化的测量结果可能较实际年龄低约 10 岁[81—82]。这一发现表明，人类心脏可能对与年龄相关的 DNA 甲基化具有相对抵抗力。但有动物试验显示，与维持 DNA 甲基化有关的 DNA 甲基转移酶（DNA methyltransferase，DNMT）1 心脏表达水平随年龄增长而降低，而敲除成年小鼠 *DNMT1* 未引起任何明显不良后果，且在心脏毒性模型中表现出心脏保护作用[83]。

DNA 从头甲基化所需的其他 DNMT 亚型（如 DNMT3A、DNMT3B）的作用亦存议。尽管在 HF 患者中 DNMT3A 及 DNMT3B 表达水平上调[80]，但动物试验显示，*DNMT3A* 和（或）*DNMT3B* 缺失小鼠并未有明显心脏结构改变或严重心肌病[84—85]。虽然目前已知 DNMT 与心脏发育异常有关[86]，但其具体作用机制依旧有待明确。相类似的现象在血管中亦存在。动脉粥样硬化与血管衰老之间存在密切联系[87]。老年人群整体血管 DNA 甲基化水平较低[88]，而动脉粥样硬化血管则显示出局灶性高水平 DNA 甲基化[89]，DNMT1 抑制剂能减轻动脉粥样硬化病变[90]。故需开展进一步研究，以明确血管 DNA 甲基化在自然衰老中的具体机制，有望为心血

管疾病的防治提供新思路。

3 结语

随着年龄增长，心血管疾病发生风险逐渐增加。巨自噬功能受损及表观遗传学改变（包括 DNA 甲基化、组蛋白修饰和 ncRNA）在心血管衰老及心血管疾病中均具有重要作用，且相互紧密交织在一起、相互影响。了解心血管衰老机制，有望为今后心血管疾病的诊断及新药研发提供新的思路及方向。

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