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M6A甲基化在心衰中的研究进展

王春艳[1,2]，杨　光[2*]，付青青[1,2]

[1]西安医学院研究生处，陕西　西安
[2]陕西省人民医院心血管内科，陕西　西安

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摘　要

随着经济的发展，心力衰竭(HF)患者的死亡率仍持续增长。导致HF的病因众多，其中表观遗传和基因表达异常成为了HF的重要发病机制之一。N6-甲基腺苷(m6A)是真核细胞中最常见的内部RNA修饰，本篇综述将介绍m6A甲基转移酶(编码器writer)，m6A去甲基化酶(消码器eraser)，m6A识别蛋白(读码器reader)通过一系列调节最终导致HF的发生。本篇综述还会介绍甲基化通过调节钙稳态、自噬及炎症反应、氧化应激以及铁死亡等介导HF的发生发展。

关键词

心力衰竭，M6A甲基化，钙稳态，自噬及炎症反应，氧化应激，铁死亡

Research Progress of M6A Methylation in Heart Failure

Chunyan Wang[1,2], Guang Yang[2*], Qingqing Fu[1,2]

[1]Division of Graduate Studies, Xi'an Medical University, Xi'an Shaanxi
[2]Department of Cardiovascular Medicine, Shaanxi Provincial People's Hospital, Xi'an Shaanxi

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Abstract

With the development of the economy, the mortality rate of patients with heart failure (HF) remains high. There are many causes of HF, among which epigenetic and gene expression abnormalities have become one of the important pathogenesis of HF. N6-methyladenosine (m6A) is the most common internal RNA modification in eukaryotic cells, and this review will introduce m6A methyltransferase (encoder writer), m6A demethylase (decoder eraser), and m6A recognition protein (barcode

*通讯作者。

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reader) eventually lead to the development of HF by a series of modulations. This review will also cover that methylation may mediate the development of HF by modulating calcium homeostasis, autophagy and inflammatory responses, oxidative stress, and ferroptosis.

Keywords

Heart Failure, M6A Methylation, Calcium Homeostasis, Autophagy and Inflammatory Response, Oxidative Stress, Ferroptosis

1. 简要介绍

HF 的发病率逐年上升，影响着全球超过 6400 万人。因此，减轻其社会和经济负担已成为全球公共卫生的首要任务[1]。HF 是一种有临床症状和/或心脏结构和/或功能异常且伴有钠尿肽水平升高和/或肺部或全身充血的疾病[2] [3]。m6A 修饰是真核细胞中最常见的内部 RNA 修饰，可通过剪接、降解、翻译和易位调节来完成 RNA 修饰[4]。其中 m6A 甲基化可能通过调控钙稳态、自噬及炎症反应、氧化应激以及铁死亡等介导 HF 的发生发展。为 HF 的诊治及靶向治疗提供新思路。

2. M6A 的研究

N6-甲基腺苷(m6A)首次发现于 20 世纪 70 年代。m6A 的存在与 mRNA 不稳定性密切相关[5]。m6A 修饰是真核细胞中最常见的内部 RNA 修饰，可通过剪接、降解、翻译和易位调节来完成 RNA 修饰。m6A 包括：m6A 甲基转移酶(编码器 writer)，m6A 去甲基化酶(消码器 eraser)，m6A 识别蛋白(读码器 reader)。M6A 甲基转移酶(编码器，writer)包括(METTL3/5/14/16、WTAP、ZC3H13、KIAA1429、RBM15/15B、HAKAI、DNMT3B 和 83 ZCCHC4) [4]。甲基转移酶样 3 (methyltransferaselike 3, METTL3)、甲基转移酶样 14 (methyltransferase-like 14, METTL14)催化的 RNA 修饰的关键[6]。其中，METTL3 为催化核心[7]，而 METTL14 是稳定剂、激活剂[8]。M6A 去甲基化酶(消除器，eraser)可介导 m6A 表观转录组[9]。m6A 去甲基化酶的发现揭示了 m6A 修饰的可逆性，因此 m6A 修饰是一个动态调控的过程[10]。肥胖相关(FTO)基因是真核细胞中的一种 RNA N6-甲基腺苷(m6A)去甲基酶[11]。FTO 能使 N6,2’-O-二甲基腺苷(m6Am)-二甲基修饰的 mRNA 去甲基化并降低其化学稳定性[12]。m6A 是一种高度动态且可逆的修饰[13]。M6A 识别蛋白(阅读器，reader)是 YTH 大家族的成员，该家族包括包含 YTH 结构域的家族蛋白 1-3 (YTHDF1/2/3)和包含 YTH 结构域的蛋白 1-2 (YTHDC1/2)亚科[14]。含有 YTH 结构域的蛋白质是第一个被发现的 m6A 结合蛋白[15]。M6A Reader 结合位点与 m6A 定位重叠，均位于 CDS 终止密码子和 mRNA 上的 3’UTR 附近[16]。

3. M6A 甲基化与心力衰竭

m6A 参与各种基本的生物功能，尤其在 HF 中发挥重要作用。研究表明 m6A 与 HF 存在密切关系。METTL3 在心肌细胞凋亡中起重要作用，当沉默 METTL3 时可增强缺血缺氧处理后心肌细胞的自噬并抑制细胞凋亡，METTL3 在 m6A 的两个残基 3’-UTR 处甲基化 TFEB (溶酶体生物合成和自噬基因的主要调节因子)，促进了 RNA 结合蛋白 HNRNPD 与 TFEB 前 mRNA 的结合，从而使 METTL3 促进了细胞凋亡。

m6A 甲基化酶 METTL3 在体内外均可促进心肌细胞肥大[17] [18] ALKBH5 与 METTL3 起相反作用，ALKBH5 可抑制缺血性缺氧诱导的心肌细胞的凋亡[19]。WTAP 与 METTL14 类似，WTAP 不表现出甲基转移酶活性；然而，它的敲低显着降低了 RNA 中 m6A 修饰的水平，其程度甚至比 METTL14 敲低还要严重。这表明 WTAP 对于 m6A 修饰至关重要[20]。我们发现 Wilms'tumor 1 相关蛋白(WTAP，m6A RNA 甲基转移酶复合物的关键调节蛋白)是心脏功能和心脏病的关键调节蛋白。WTAP 通过维持心肌细胞特定基因的染色质可及性，在心脏发育和心脏功能中发挥关键作用[21]。FTO 和 ALKBH5 对于心脏稳态至关重要。研究证实，FTO 和 ALKBH5 在胚胎心脏和心血管疾病的发生发展中发挥着重要作用，如动脉粥样硬化、冠心病(CHD)和 HF [19] [22]。

4. M6A 甲基化在心力衰竭发生机制中的作用

4.1. m6A 甲基化和钙稳态

心肌细胞钙稳态失调是 HF 的主要原因之一。在心肌细胞的收缩、舒张功能及心电信号的传递中起重要作用。当 HF 发生时，SERCA2a (肌浆/内质网 Ca^{2+} ATP 酶 2a，心肌细胞中表达的 SERCA 的主要亚型)功能降低[23]。SERCA2a 是一种 SR 膜蛋白，通过将 Ca^{2+}从细胞质转运到 SR 来维持较低的细胞质 Ca^{2+}水平。SERCA2a 泵分别负责人类和大鼠舒张期 Ca^{2+}心室 CM 周转的约 70%和 92% [24]。在 HF 发生的过程中，心肌细胞中 m6A 去甲基化酶 FTO 表达减少，METTL4/14 等书写蛋白表达增加，衰竭心脏和缺氧心肌细胞中 m6A 含量增加[25] [26]。通过影响收缩蛋白 SERCA2a 的转录表达，导致钙稳态调节异常，从而降低心肌收缩功能。体内外研究表明，FTO 可提高 Ca^{2+}振幅，加速 Ca^{2+}衰减，缩短肌小节，减少由 Ca^{2+}引起的 m6A 增加缺血，改善心肌细胞相应的收缩功能障碍。经过通路富集和筛选后，FTO 可以选择性作用于心脏肌节组织、肌原纤维组装、钙治疗和收缩等相关通路，可引起多种心脏疾病，如肥厚型心肌病、室间隔缺损、房室缺损、心律失常和 CHD 等疾病[25] [27]。

4.2. m6A 甲基化和炎症反应及巨噬细胞自噬

近期有证据表明，在 HF 中，可以发现高水平的炎症生物标志物，如 IL-1β、IL-6、IL-10、CRP、TNF-α 等炎症因子[28]。其中，IL-6 在无症状左心室功能障碍到有症状左心室功能障碍的演变中发挥作用，对于有发生临床心力衰竭(尤其是 HFpEF)风险的患者来说，它是一个有前途的生物标志物[29]。IL-10 是一种主要的抗炎细胞因子。炎症在心脏肥大的发展和 HF 的发展中起着重要作用。IL-10 可以在心脏组织中表达，并且可能在心脏重塑中发挥重要作用[30]。各种慢性炎症性疾病刺激冠状动脉微血管功能障碍(CMD)的发生和发展[31]。干扰素调节因子-1 (IRF-1)在调节动脉粥样硬化的免疫、炎症和细胞凋亡中发挥重要作用[32]。郭等人表明 IRF-1 的过度表达通过上调 circ_0029589 上的 m6A 甲基化水平和 METTL3 的表达来促进动脉粥样硬化巨噬细胞的凋亡和炎症[33]。METTL3 通过抑制 NF-κB 通路来降低脂多糖诱导的巨噬细胞的炎症反应[34]。简等人表明，敲除 METTL14 可通过减少内皮细胞的炎症反应来抑制动脉粥样硬化斑块的形成。STAT1 是一个关键的转录因子，可启动信号级联反应，从而激活促炎巨噬细胞。METTL3 已被证明可以直接甲基化 STAT1 mRNA 以提高 mRNA 稳定性，从而上调 STAT1 的表达并促进 M1 巨噬细胞的极化[35]。METTL3-STAT1 介导的 M1 巨噬细胞的极化可能导致动脉粥样硬化、肥胖相关脂肪重塑、腹主动脉瘤等疾病的发生和进展，使其成为潜在的抗炎靶点[36]。

4.3. m6A 甲基化和氧化应激

氧化应激被定义为氧自由基产生和清除之间的不平衡，在心脏重塑和心力衰竭的病理生理学中发挥着重要作用[37]。氧化应激是由于活性氧产生和抗氧化防御之间的不平衡导致自由基积累而发生的。在心

脏中，ROS 激活参与心肌细胞肥大、间质纤维化、收缩功能障碍和炎症的信号通路，从而影响细胞结构和功能，并导致心脏损伤和重塑[38]。

有研究表明，去甲基化酶 ALKBH5 的活性和总体 m6A 甲基化水平直接受 ROS 调节。ROS 可以通过激活 ERK/JNK 信号通路诱导 ALKBH5 的翻译后修饰，从而抑制其活性，有助于增加 mRNA m6A 水平并维持细胞基因组完整性。同样，氧化应激对 m6A 阅读器产生不同的影响[39]。RNA 甲基转移酶 METTL3/METTL14 介导的 N6-甲基腺苷(缩写为 m6AinRNA)和 NSUN2 介导的 5-甲基胞苷(缩写为 m5CinRNA)修饰的增强加剧氧化应激[40]。

4.4. m6A 甲基化和铁死亡

铁死亡已被确定在心肌梗死和心肌病等各种情况下的 HF 的发生和进展中发挥重要的病理生理作用[41]。目前认为铁死亡的基本机制是脂质过氧化氢积累，导致谷胱甘肽过氧化物酶(GPX)限度降低。然后，细胞中的游离铁离子通过芬顿反应与脂质过氧化物相互作用，产生脂质自由基，导致细胞死亡。因此，铁死亡的机制主要涉及以下三个过程：脂质过氧化、GSH 合成和消耗以及铁代谢异常[42]。

Yunfan Yang 等人研究发现，FTO 对 P21/Nrf2 的激活与 P53、P21/Nrf2 mRNA 的 m6A 去甲基化相关，表明 FTO 以 P53 依赖和独立的方式激活 P21/Nrf2。HuR 对于铁死亡和 P53、P21/Nrf2 中 FTO 的调节至关重要[43]。甲基化是由 METTL4 主导的 YTHDF2 识别并降解甲基化的 Nrf2 沉默 METTL4 可以通过抑制 Nrf2 的下调来抑制铁死亡，从而减轻败血症诱导的 ALI [44]。

5. 总结与讨论

m6A 甲基化的调节与 HF 的发生发展紧密相关，越来越多的研究揭示了 m6A 甲基化以不同的作用方式对 HF 的发生发展产生重大影响。本文综述了 m6A 甲基化与 HF 之间的关系，及 m6A 甲基化在 HF 过程参与调节了钙稳态、自噬及炎症反应、氧化应激以及铁死亡等关键机制。目前仍有部分调控机制尚未阐明，需要通过更多的探索研究来增加对 m6A 甲基化参与 HF 调节作用的认识，及其作用的具体机制，最终将其应用到 HF 诊治的临床实践中，为 HF 的诊治提供理论支持。

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