Advances in Clinical Medicine 临床医学进展, 2025, 15(3), 2020-2030
Published Online March 2025 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2025.153833

Hans汉斯

METTL家族与代谢性疾病调控

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收稿日期：2025年2月19日；录用日期：2025年3月12日；发布日期：2025年3月21日

摘　要

随着经济和社会的发展，代谢性疾病的患病率逐年升高，已为全球带来巨大的疾病负担。甲基转移酶样蛋白(Methyltransferase-Like Proteins, METTLs)可调控表观遗传学机制，已成为近年来新兴的研究热点。文章就METTL家族调控三大代谢性疾病的分子机制作一综述，涉及调控胰岛β细胞功能、胰岛素抵抗、脂肪生成、脂质代谢、血糖稳态等多个方面。希望未来可继续进行更为广泛和深层次的研究，为多种代谢性疾病的诊疗提供理论依据。

关键词

METTL甲基转移酶样蛋白，表观遗传学，2型糖尿病，非酒精性脂肪肝，肥胖症

The METTL Family in Metabolic Disease Regulation

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Received: Feb. 19th, 2025; accepted: Mar. 12th, 2025; published: Mar. 21st, 2025

Abstract

With the advancement of socioeconomic development, the prevalence of metabolic diseases has been steadily increasing, imposing a significant disease burden globally. Methyltransferase-Like Proteins (METTLs), which regulate epigenetic mechanisms, have emerged as a burgeoning research focus in recent years. This review comprehensively summarizes the molecular mechanisms by which METTL family members regulate three major metabolic diseases, including their roles in modulating pancreatic β-cell function, insulin resistance, adipogenesis, lipid metabolism, and glucose

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文章引用: 刘一鸣, 周嘉强. METTL 家族与代谢性疾病调控[J]. 临床医学进展, 2025, 15(3): 2020-2030.
DOI: 10.12677/acm.2025.153833

homeostasis. We anticipate that further extensive and in-depth investigations will provide a theoretical foundation for the diagnosis and treatment of diverse metabolic disorders.

Keywords

Methyltransferase-Like Proteins, Epigenetics, Type 2 Diabetes Mellitus, Non-Alcoholic Fatty Liver Disease, Obesity

1. 前言

代谢性疾病是由于体内糖类、脂质等代谢过程紊乱所引起的一大类疾病。常见的代谢性疾病诸如 2 型糖尿病、肥胖症、非酒精性脂肪肝等患病率逐年升高，已成为现代社会影响人类健康的主要威胁，但目前其病理生理机制仍未完全阐明，各类治疗手段的疗效有限[1]。表观遗传学修饰能够整合环境因素的变化影响细胞内的基因表达和信号转导等生物过程，可能在调控代谢性疾病的发病过程中发挥着重要作用。表观遗传学修饰包括 DNA 甲基化、组蛋白修饰、RNA 修饰、基因组印记和染色质重塑等多个方面[2]。METTL 家族是一类编码甲基转移酶的基因家族，其成员通过催化甲基基团转移至 DNA、RNA 或蛋白质，从而调控 DNA 复制、转录及翻译等过程，其广泛分布于细胞核、细胞质和线粒体中，在维持正常细胞活动以及某些疾病的发生发展中发挥着重要作用[3]。目前关于 METTL 家族的大多数研究主要集中在肿瘤领域中，而在代谢性疾病中的研究相对较少，本综述对 METTL 家族中各亚型及其在多种代谢性疾病中的调控作用进行阐述，旨在为代谢性疾病的病理生理机制及诊断治疗提供新思路。

2. METTL 家族成员概述

2.1. METTL1

METTL1 位于染色体 12q14.1 上，由 276 个氨基酸组成 8 个 α 螺旋和 7 个 β 折叠结构[4]，通过其 N 端 SAM 结合域和 C 端 RNA 结合域催化 7-甲基鸟嘌呤(7-Methylguanosine, m7G)向 tRNA、mRNA、微小 RNA (microRNA, miRNA)和长链非编码 RNA (Long Non-Coding RNA, lncRNA)转移[5]-[8]，从而影响细胞生物学行为及免疫微环境等[9] [10]。METTL1 与 WD 重复域 4 (WD Repeat Domain 4, WDR4)协同作用形成一个支架结构，该结构通过其 αC 和 α6 螺旋与 tRNA 的可变环相结合，并催化 tRNA 上 G46 位点的甲基化修饰，进而稳定 tRNA 的结构[11]。

2.2. METTL2A/2B、METTL6、METTL8

人及其他哺乳动物中存在 METTL2A 及 METTL2B，前者位于染色体 17q23.2 上，后者位于染色体 7q32.1 上[12]。METTL2A/2B 参与细胞质和线粒体 tRNA 反密码子环上第 32 位碱基的 3-甲基胞嘧啶(3-Methylcytosine, m3C)，主要修饰 tRNA-Arg 和 tRNA-Thr 家族[13]，可调节基因翻译、细胞稳态和肿瘤生长[14]，缺失 METTL2 可导致 tRNA m3C 甲基化减少 30%~40% [15]。

METTL6 位于染色体 3p25.1，也是一种 m3C 甲基转移酶[15] [16]，修饰 tRNA-Ser 家族。然而只有在联合缺失 METTL2A/2B/6 的情况下才能观察到 tRNA-Ser-GCT 等编码器上的 32 位 m3C 减少，而 METTL2A/2B/6 联合缺陷的细胞呈现出细胞周期受阻、增殖减慢和顺铂敏感性增加等表型[13]。

METTL8是一种多功能RNA甲基转移酶，通过mRNA的交替剪接可产生多种异构体，其中METTL8-iso1主要定位于线粒体，而METTL8-iso4则分布于核仁[17]。其核心功能是催化线粒体tRNA (Mitochondrial tRNA, mt-tRNA)反密码子环第32位m3C的修饰，主要修饰mt-tRNA-Thr和mt-tRNA-Ser (UCN) [18]，直接影响线粒体蛋白质翻译的效率和呼吸链功能[19]。

2.3. METTL3/METTL14

6-甲基腺嘌呤(6-Methyladenosine, m6A)是真核生物mRNA中最常见的RNA修饰，广泛参与RNA的剪接、转运、稳定性和翻译等过程，METTL3和METTL14主要负责催化mRNA上的m6A修饰[20]。两者既可以单独发挥作用，又可以形成METTL3-METTL14复合物共同调控细胞功能，其中METTL3充当催化亚基，包含一个甲基转移酶结构域(Methyltransferase Domain, MTD)和一个锌指结构域(Zinc Finger Domain, ZFD)，其中MTD负责与SAM结合，而ZFD则负责特异性识别RNA序列GGACU [21]。METTL14无催化活性[22]，提供RNA结合支架，激活并增强METTL3的催化活性[23]。两者在DNA甲基化[24]、DNA损伤修复[25] [26]和维持RNA稳定性[26]方面都发挥着至关重要的作用，是METTL甲基转移酶样蛋白家族中研究最为广泛的分子。

2.4. METTL4

METTL4属于甲基转移酶A70 (Methyltransferase A70, MT-A70)家族，其核心结构包含保守的MTA结构域，与METTL3/14具有同源性[27]。METTL4在细胞核内特异性修饰U2小核RNA (Small Nuclear RNA, snRNA)的N6,2'-O-二甲基腺苷(N6,2'-O-Dimethyladenosine, m6Am)位点，通过调控RNA剪切影响基因表达。敲除METTL4会导致数百个基因的可变剪切异常，涉及细胞周期和代谢相关通路[28]。METTL4在线粒体基质中催化线粒体DNA (Mitochondrial DNA, mt-DNA)的6mA修饰，参与线粒体DNA复制与呼吸链功能。METTL4敲低会显著降低mt-DNA的6mA水平，并影响线粒体复合体I (ND1/ND6)的组装，导致能量代谢失衡[27]。

2.5. METTL5

METTL5位于染色体2q31.1，主要在细胞核中表达，与核糖体RNA (Ribosomal RNA, rRNA)加工复合物共定位，提示其参与核糖体生物合成与翻译调控[29]，缺失METTL5会导致多聚体形成减少80%，从而改变多聚体数量和结构，最终导致mRNA翻译和蛋白质合成速度减慢[30]。METTL5需与tRNA甲基转移酶激活子亚基11-2 (tRNA Methyltransferase Activator Subunit 11-2, TRMT11-2)蛋白形成异源二聚体以稳定结构与功能，这两种蛋白形成异二聚体复合物可促进18S rRNA上1832位m6A修饰[31]。

2.6. METTL7A/7B

METTL7A及其同源蛋白METTL7B同为硫醇甲基转移酶A/B (Thiol Methyltransferase 1A/B, TMT1A/B)，分别位于染色体12q13.12和12q13.2。这两种酶均可催化SAM向含有烷基和酚基硫醇的受体底物转移[32]，两者均在内质网中表达。在脂肪细胞中，METTL7A利用其甲基转移酶活性对lncRNA进行m6A修饰，从而增加它们释放到外泌体中的稳定性[33]。

2.7. 其他

METTL13位于染色体1q24.3，是一种赖氨酸特异性甲基转移酶，包含两个甲基结合域MT13-N和MT13-C [34]，其中MT13-N能够特异性地对真核翻译延伸因子1A (Eukaryotic Elongation Factor 1A, eEF1A)

的赖氨酸 55 位点进行甲基化修饰，提高翻译效率，增加蛋白质合成，从而促进肿瘤发生[35]。METTL15 位于染色体 11p14.1，是一种 4-甲基胞嘧啶(4-Methylcytosine, m4C)甲基转移酶，其在 12S mt-rRNA 第 839 位碱基的 m4C 甲基化方面发挥着关键作用，这种修饰促进 12S rRNA 的折叠，影响线粒体小亚基的组装和线粒体的呼吸作用[36]。METTL16 位于染色体 17p13.3，由 562 个氨基酸组成，包括一个甲基转移酶结构域和两个 RNA 结合结构域，主要参与催化 rRNA、mRNA、lncRNA 以及 snRNA 的 m6A 甲基化[37] [38]。METTL17 位于染色体 14q11.2，可与线粒体 12S rRNA 和小亚基协同作用，促进线粒体核糖体的组装[39]，同时作为一个 Fe-S 簇检查点，促进富含铁硫簇氧化磷酸化蛋白的翻译[40]。METTL17 调控线粒体 RNA 甲基化(包括 m4C，m5C，m3C，m7G 和 m6A)，影响线粒体蛋白翻译，敲低 METTL17 可导致线粒体功能紊乱，增强线粒体内脂质过氧化及活性氧(Reactive Oxygen Species, ROS)水平[41]。METTL12 可以调节呼吸链中的通道蛋白，从而影响代谢过程中蛋白与蛋白之间的相互作用[42]。METTL18 能够对 60S 核糖体蛋白 L3 (Ribosomal Protein L3, RPL3)上第 245 位组氨酸残基(Histidine 245, His245)的 τ-N 位点进行甲基化修饰，从而有效减缓核糖体在酪氨酸密码子上的移动速度，为肽链的正确折叠提供了足够的时间，进而有助于功能域的形成[43]。METTL20 能够对电子传递黄素蛋白(Electron-Transferring Flavoprotein, ETF) β 亚基(ETFB)的赖氨酸 200 和 203 位点进行三甲基化修饰，降低 ETF 从乙酰辅酶 A 脱氢酶(Acetyl-CoA Dehydrogenase, ACAD)和戊二酰辅酶 A 脱氢酶(Glutaryl-CoA Dehydrogenase, GCDH)中提取电子的能力，进而影响线粒体的氧消耗率[44]。METTL21 可催化分子伴侣和 eEF1A 的赖氨酸甲基化，与人类健康及多种疾病密切相关[45] [46]。

3. METTL 家族在代谢性疾病中的调控作用

3.1. METTL 家族与 2 型糖尿病

2 型糖尿病(Type 2 Diabetes Mellitus, T2DM)是一种常见的慢性疾病，其发病机制较为复杂，主要由环境与遗传等多种因素引发外周组织出现胰岛素抵抗，同时合并胰岛素分泌减少，进而使机体处于胰岛素相对不足的状态，葡萄糖的摄取与利用也随之减少[47]。

大量研究已表明 T2DM 的发生进展与胰岛 β 细胞数量密切相关，m6A 甲基化酶 METTL3/14 能够通过调控胰岛 β 细胞的数量与功能及其分化发育进程，进而参与 T2DM 的调控。De Jesus 等[48]研究发现敲低 METTL3/14 导致胰岛素和胰岛素样生长因子 1 (Insulin-Like Growth Factor 1, IGF1)刺激的蛋白激酶 B (Protein Kinase B, AKT)磷酸化减少和胰十二指肠同源盒 1 (Pancreatic and Duodenal Homeobox 1, PDX1)蛋白水平下降，使 β 细胞功能障碍。Men 等[49]发现小鼠 β 细胞中 METTL14 缺失引起 m6A 修饰异常，并通过激活内质网应激肌醇需求酶 1α (Inositol-Requiring Enzyme 1 alpha, IRE1α)通路及剪接型 X 盒结合蛋白 1 (Spliced X-Box Binding Protein 1, sXBP-1)通路，使小鼠胰岛素分泌显著下降，出现葡萄糖不耐受。同时，METTL3/14 可以通过调控 mRNA 的稳定性进而影响胰岛 β 细胞转录因子的表达水平，以及胰岛 β 细胞的分化[50]。METTL3 还可以通过调控组蛋白去乙酰化酶 1 (Histone Deacetylase 1, HDAC1) mRNA 的 m6A 修饰，激活其下游 Wnt 及 Notch 信号通路并阻断胰腺发育与内分泌分化[51]。除胰岛 β 细胞功能外，机体组织器官的胰岛素抵抗也是 T2DM 发病的一个重要机制，高脂条件下 METTL3 表达上调增加 m6A 修饰促进代谢相关 mRNA 降解，加剧肝脏脂质积累和胰岛素抵抗，敲除 METTL3 可改善这一代谢表型[52]。砷暴露是 T2DM 发生的独立危险因素，可诱导胰岛 β 细胞功能障碍。Qiu 等[53]发现砷通过抑制 METTL3/14 的表达减少谷胱甘肽特异性 γ-谷氨酰环基转移酶(Glutathione Specific Gamma-Glutamylcyclotransferase 1, CHAC1) mRNA 的 m6A 修饰，从而增加其稳定性，导致 CHAC1 蛋白水平上升加速谷胱甘肽分解，最终引发铁死亡和 β 细胞功能障碍。而 METTL14 介导的 m6A 甲基化在砷诱导核苷酸结合寡聚结构域样受体蛋白 3 (Nucleotide-Binding Oligomerization Domain-Like Receptor Protein 3, NLRP3)炎症小体

激活导致肝胰岛素抵抗的过程中起关键作用[54]。这些研究均为开发针对砷相关 T2DM 的新疗法提供了潜在的分子靶点。

糖尿病肾病(Diabetic Nephropathy, DN)是糖尿病患者最常见的并发症，也是导致终末期肾病的主要原因，DN 的病理特征涉及氧化应激、线粒体功能障碍、细胞外基质积累和足细胞损伤等多个方面。Jin 等[55]研究发现，脂肪干细胞(Adipose-Derived Stem Cells, ADSCs)衍生的外泌体通过释放 miRNA-204 抑制 METTL7A 介导细胞死亡诱导 DFFA 样效应物 C (Cell Death Inducing DFFA like Effector C, CIDEC)的 m6A 修饰，可缓解 DN 中氧化应激诱导的线粒体功能障碍。此外，METTL3 不仅可以通过调控一种环状 RNA (Circular RNA, circRNA)的甲基化水平来调节足细胞自噬[56]，也可以通过 m6A 修饰上调组织金属蛋白酶抑制因子 2 (Tissue Inhibitor of Metalloproteinase 2, TIMP2) mRNA 的稳定性进而激活 Notch 信号通路促进足细胞的炎症和凋亡[57]。糖尿病视网膜病变(Diabetic Retinopathy, DR)是糖尿病微血管并发症的一种，也是糖尿病患者视力残疾和失明的主要原因，周细胞功能障碍是其主要的病理表现。METTL3 可通过 YTH N6-甲基腺苷 RNA 结合蛋白 2 (YTH N6-Methyladenosine RNA Binding Protein 2, YTHDF2)依赖的 mRNA 降解机制抑制蛋白激酶 Cη (Protein Kinase C Eta, PKCη)、FAT 非典型钙粘蛋白 4 (FAT Atypical Cadherin 4, FAT4)及血小板衍生生长因子受体 α (Platelet-Derived Growth Factor Receptor Alpha, PDGFRA)的表达，从而影响周细胞的功能[58]。除此之外，METTL 还参与了其他糖尿病并发症，如糖尿病足[59]、糖尿病性骨质疏松[60]、糖尿病认知障碍[61]、糖尿病性白内障[62]等的病理生理过程。

METTL 家族不仅与 T2DM 的发生发展有关，还涉及 T2DM 的药物治疗机制。胰高血糖素样肽-1 (Glucagon-Like Peptide-1, GLP-1)受体激动剂艾塞那肽通过上调 METTL3 的表达增加 m6A 甲基化水平，从而抑制过氧化氢(Hydrogen Peroxide, H_2O_2)诱导的胰岛 β 细胞凋亡[63]。此外，近期的一项研究还发现新型 GLP-1 受体激动剂 Semaglutide 显著增加了小鼠胰岛中 METTL14 和 PDX1 的表达，后者对于胰岛 β 细胞的发育和成熟至关重要[64]。

3.2. METTL 家族与非酒精性脂肪性肝病

非酒精性脂肪性肝病(Non-Alcoholic Fatty Liver Disease, NAFLD)是一种排除酒精和其他已知肝损伤因素后，以肝细胞内脂肪过度沉积为主要特征的临床病理综合征，其发病机制与胰岛素抵抗及遗传易感性密切相关，包括单纯性脂肪肝(Non-Alcoholic Fatty Liver, NAFL)、非酒精性脂肪性肝炎(Non-Alcoholic Steatohepatitis, NASH)以及由此引发的肝硬化，病情严重时可能发展为肝癌[65]。

近年来，表观遗传学调控与 NAFLD 之间的联系日益受到关注。Peng 等[66]发现在高脂诱导的 NAFLD 小鼠模型和游离脂肪酸(Free Fatty Acid, FFA)处理的人肝癌细胞系 G2 (Hepatocellular Carcinoma Cell Line G2, HepG2)中，m6A 甲基化水平显著增加，这与 METTL3 的上调有关，过表达 METTL3 可以通过 m6A 修饰增加 Rubicon 自噬调节因子(Rubicon Autophagy Regulator, RUBCN) mRNA 的稳定性，抑制自噬体与溶酶体的融合，阻断肝细胞中脂滴的清除。与之相反的是，Xu 等[67]在 FFA 处理的小鼠正常肝细胞系(Alpha Mouse Liver 12, AML12)中发现 METTL3 蛋白水平显著降低，而敲低 METTL3 通过下调细胞色素 P450 4 家族 F 亚家族成员 40 (Cytochrome P450 Family 4 Subfamily F Member 40, CYP4F40)介导的脂肪酸代谢过程，加剧了 AML12 细胞的脂肪变性。Li 等[68]发现高脂和蛋氨酸胆碱缺乏饮食同时诱导的 NASH 小鼠模型和人类 NASH 患者的肝组织中 METTL3 在细胞核中的表达显著降低，而在细胞质中的表达增加，这种变化与肿瘤坏死因子 α (Tumor Necrosis Factor alpha, TNFα)和周期蛋白依赖性激酶 9 (Cyclin-Dependent Kinase 9, CDK9)介导的 METTL3 磷酸化导致 METTL3 从细胞核转移到细胞质有关，过表达 METTL3 通过招募 HDAC1/2 至 CD36 和趋化因子配体 2 (C-C Motif Chemokine Ligand 2, CCL2)基因的启动子区域，导致组蛋白去乙酰化从而抑制这些基因的转录，减少游离脂肪酸摄取，降低炎症反应，保护

肝脏免受 NASH 的侵害。引起这些实验结果差异的原因可能是使用了不同实验模型及实验条件，例如 HepG2 肝癌细胞系中已存在基础代谢重编程，其脂质代谢调控网络与正常肝细胞存在显著差异，而 AML12 细胞保持正常代谢稳态，对 METTL3 调控的敏感性更高；TNFα/CDK9 介导的 METTL3 核质转运机制在早期脂肪变性阶段，核内 METTL3 通过 HDAC1/2 调控表观遗传沉默，但持续炎症刺激导致细胞质 METTL3 积累又可能通过 m6A 非依赖性途径如蛋白互作网络等调控 mRNA 翻译效率，需进一步开发亚细胞特异性敲除模型进行深入机制解析。

目前在 NAFLD 的治疗方面仍缺乏有效药物，低分子量柑橘果胶(Low-Molecular-Weight Citrus Pectin, LCP)通过上调 METTL7B 的表达，增强脂肪组织甘油三酯水解酶(Adipose Triglyceride Lipase, ATGL)和肉碱棕榈酰转移酶 1 (Carnitine Palmitoyltransferase-1, CPT-1)的活性，从而抑制肝细胞脂质积累，具有预防 NAFLD 早期阶段向 NASH 进展的潜力[69]。肉桂醛增加 METTL3 表达并通过 CYP4F40 途径缓解肝脏脂肪变性[67]。这些新兴分子通过 METTL 对 NAFLD 的作用机制有待进一步深入研究。

3.3. METTL 家族与肥胖症

肥胖症(Obesity)是一种以机体脂肪总含量过多和/或局部含量增多及分布异常为特征的慢性代谢性疾病，是由遗传、心理和环境等多种因素共同作用而导致。WHO 定义成人体重指数(Body Mass Index, BMI) ≥ 30.0 kg/m^2 时为肥胖，肥胖可增加心血管疾病、2 型糖尿病和癌症等疾病的发病风险，为全球带来了极大的疾病负担[70]。一项大规模跨种族的全基因组关联分析(Genome-Wide Association Study, GWAS)新发现 METTL15 位点与儿童肥胖显著相关，为理解儿童肥胖的遗传基础提供了重要线索[71]。

白色脂肪组织(White Adipose Tissue, WAT)和棕色脂肪组织(Brown Adipose Tissue, BAT)是哺乳动物体内两种主要的脂肪组织，WAT 以甘油三酯的形式储存机体过剩的能量而导致肥胖，抑制 WAT 的形成或促进 WAT 向米色脂肪转化(WAT 褐变)均可以治疗肥胖症。而 BAT 通过解偶联蛋白 1 (Uncoupling Protein 1, UCP1)调控机体在寒冷环境中消耗能量产热，BAT 的高代谢活性使其在代谢调节中发挥重要作用，有助于防止肥胖和相关代谢疾病。Xie 等[72]发现脂肪组织特异性 METTL3 敲除小鼠在冷暴露下无法诱导 WAT 褐变，脂滴更大，产热和脂解基因表达显著降低。Wang 等[73]发现 BAT 特异性敲除 METTL3 会导致 BAT 发育异常，产热能力降低，进而促进高脂饮食诱导的肥胖和系统性胰岛素抵抗。而 Qin 等[74]则发现髓系细胞特异性 METTL3 敲除小鼠在年龄相关和饮食诱导的 NAFLD 和肥胖模型中，表现出更低的体重、脂肪积累和肝脏损伤，以及改善的炎症和代谢表型。另有最新的一项研究表明，特异性敲除 METTL14 的 BAT 可以通过其内分泌功能分泌前列腺素激活 AKT 信号通路进而改善全身胰岛素敏感性，同时也具有促进 WAT 褐变的作用[75]。由此可见，不同组织与细胞中 METTL 表达水平的变化所带来的脂质代谢表型变化可能并不完全相同，需要针对 METTL 在不同靶器官中的作用机制继续开展研究。

脂肪细胞分化是一个复杂的过程，涉及多种细胞内信号通路和基因表达的调控。敲低 METTL4 可导致胰岛素受体(Insulin Receptor, INSR)基因启动子区域的 6mA 水平显著下降，减少细胞葡萄糖摄取和消耗，最终影响脂肪细胞的分化，表现为脂质生成减少和主要脂肪生成因子表达下调[76]。WT1 相关蛋白(WT1 Associated Protein, WTAP)、METTL3 和 METTL14 组成的 RNA 甲基转移酶复合体通过促进有丝分裂克隆扩张(Mitotic Clonal Expansion, MCE)中的细胞周期过渡来正向调控脂肪细胞分化，WTAP 的减少可以保护小鼠免受高脂饮食诱导的肥胖，改善胰岛素敏感性，并减少脂肪细胞的大小和数量[77]。miRNA 可通过转录后调控在脂肪细胞分化和脂质代谢中发挥重要作用。Yi 等[78]通过转录组测序技术筛选出 hsa-miR-4663 靶向 METTL7A 参与脂滴的形成过程。这些发现为理解脂肪细胞分化的分子机制提供了新的见解，并为开发包括肥胖症在内的代谢性疾病的治疗策略提供了潜在的靶点。

4. 总结与展望

随着对 METTL 家族研究的深入，逐步揭示了其在代谢性疾病中的多维动态调控机制。作为催化 DNA、RNA 及蛋白质甲基化修饰的核心酶类，METTL 家族成员通过以 m6A 为主的多种甲基化修饰参与调节胰岛 β 细胞功能、胰岛素抵抗、脂肪生成、脂质代谢、血糖稳态等多个生物过程，与 2 型糖尿病、非酒精性脂肪肝、肥胖症等多种代谢性疾病密切相关，可为阐明其病理生理机制及诊断治疗提供新思路。

然而，现有的研究多聚焦于胰岛、肝脏或脂肪组织，METTL 家族成员在肌肉、肠道等关键代谢器官中的功能异质性尚未被阐述，可继续建立条件性敲除动物模型来解析组织器官特异性效应。此外，目前对于 METTL 家族的研究大多集中在 METTL3/14 及其所调控的 m6A 修饰上，其他家族成员中诸如 METTL2/6/8 可通过调控 tRNA 甲基化修饰影响蛋白质合成、METTL5 可通过 18S rRNA 修饰调控核糖体解码速率、METTL7 可影响细胞外泌体内 lncRNA 的稳定性等均存在进一步深入研究的潜力。未来可利用组学测序技术继续开发多种甲基化的联合检测，绘制代谢组织的全修饰图谱，或开发外泌体递送系统，实现对 METTL 成员的靶向调控，甚至可以采用器官芯片技术，实现甲基化修饰的动态可视化监测。

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