植物多酚通过microRNA调控脂质代谢研究进展

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摘要 microRNA(简称miRNA)是长度18~25个核苷酸的非编码RNA分子, 具有调控mRNA的翻译和/或稳定性的功能, 从而在转录后水平调节不同基因的表达。人体内约60%编码蛋白的基因的表达受到miRNA调节, 其中包括脂质代谢调控相关基因。植物多酚具有良好的生物活性, 可以通过调节脂质代谢相关miRNAs, 如miR-122和miR-33的表达进而发挥降血脂等活性。该文综述了miRNA调控脂质代谢相关mRNA的作用机制以及植物多酚在这一过程中的可能作用。

关键词 miRNA; miR-122; miR-33; 多酚; 脂质代谢

Review: Plant Polyphenols Modulate Lipid Metabolism by Regulating MicroRNA

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Abstract MicroRNA (miRNA) is small non-coding RNA molecule, about 21~25 nucleotides in length, which regulates gene expression at the post transcriptional level by decreasing the translation and/or stability of messenger RNA. Approximately 60% genes encoding proteins in human are modulated by miRNAs, including genes modulating lipids metabolism. Plant polyphenols can exert hypolipidemic activity by regulating the lipid metabolism related miRNAs, such as miR-122 and miR-33. This paper reviewed the advances in action mechanism by which miRNAs modulate lipids metabolism related mRNAs and the possible effect of plant polyphenols in such a bioprocess.

Key words microRNA; miR-122; miR-33; polyphenols; lipids metabolism

前言

MicroRNA(简称miRNA)是长度为18~25个核苷酸的非编码单链RNA, 它由DNA转录而来, 但不翻译合成蛋白质, 而是通过与靶基因mRNA 3′UTR(untranslated regions)序列互补结合从而降解mRNA和/或抑制蛋白合成来调节转录后基因的表达[1-4]。最近有报道发现, miRNA也可以通过与5′UTR(untranslated regions)或者基因蛋白编码外显子结合来抑制mRNA翻译[5-7]。单个miRNA可以调节多个靶向mRNA的表达, 而某一特定基因的转录翻译也可能被多个miRNA共同调控[8-9]。miRNA在调节细胞关键进程, 如细胞发育、分化、代谢、生长、

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增殖和凋亡等方面具有重要作用[4,10-11]。miRNA参与多个代谢途径, 如胰岛素分泌、碳水化合物和脂质代谢等[12], 它可能通过调节转录因子、分泌因子、受体和转运子等来影响所有的生命过程。

miRNA自身的表达也受到多种因素的调节, 许多生物活性物质可以通过改变miRNA的表达水平从而间接调节其靶基因mRNA的表达[13-19]。植物多酚是自然界最常见的一大类植物活性物质, 近年来的研究发现, 植物多酚的健康保护作用与其调节miRNA的表达有关[20-28]。已有大量的研究表明, 植物多酚对改善脂质代谢有显著效果[29-32], 作用机制与其调节肝脏酶活进而影响胆固醇吸收、调控甘油三酯合成和分泌以及抑制血浆低密度脂蛋白氧化等有关[33-34]。随着对miRNA研究的逐步深入, 研究者发现, 植物多酚改善脂质代谢作用与其调节miRNA的表达水平有重要关系, 如黄酮类化合物通过调节脂代谢相关miRNA的表达水平来调控编码脂代谢相关蛋白质的基因的表达, 进而发挥其调节脂质代谢和降低血压的作用[14,35]。因此, 有科学家指出, miRNA可以作为预防和治疗脂质代谢相关疾病的潜在生物标记。本文主要综述了miRNA调控脂质代谢的作用机制和植物多酚对脂质代谢调控相关miRNA的影响, 探讨多酚调控脂质代谢的分子机制。

1 miRNA与脂质代谢

miRNA是通过对脂质代谢相关基因和/或转录因子的转录后调控来实现对脂类物质代谢的调节。已报道与脂质代谢调控相关的miRNA有很多, 如miR-122、miR-370、miR-33、miR-103、miR-107、miR-758、miR-106b和miR-146a等, 其中研究较多的是miR-122和miR-33。

1.1 miR-122与脂质代谢

miR-122是第一个被鉴定具有调节脂质代谢功能的miRNA, 它在成人肝脏组织中表达丰度最高, 占肝脏总miRNA表达量的72%[36]。动物实验研究发现, miR-122可影响机体胆固醇和脂肪酸代谢[37-38]。Esau等[37]采用反义寡核苷酸(antisense oligonucleotide, ASO)技术研究miR-122的功能, 发现处理组小鼠与对照组比较血液中脂肪酸含量增加, 而胆固醇含量下降, 同时肝脏脂肪酸和胆固醇合成速度下降。进一步研究发现, miR-122缺失会导致调控脂肪酸代谢相关酶FAS(fatty acid synthase)、ACC1(acyl-CoA carboxylase 1)、ACC2(acyl-CoA carboxylase 2)、SCD1(stearoyl-CoA desaturase 1)、ACLY(ATP citrate lyase)和胆固醇代谢相关蛋白SREBP-1c(sterol regulatory element-binding protein-1c)等含量降低, 从而导致脂肪酸和胆固醇合成减少。抑制*miR-122*基因表达后, 翻译脂肪酸代谢酶FAS、ACC1和ACC2等的mRNA表达水平降低[37]。Elmén等[38]采用ASO技术抑制灵长类动物非洲绿猴肝脏*miR-122*表达, 发现血浆中总胆固醇含量随抑制剂剂量增加而减少。也有研究报道, miR-122受到抑制会导致胆固醇合成关键控制酶HMGCR(3-hydroxy-3-methylglutaryl coenzyme A reductase)活性降低, 进而影响胆固醇合成[39]。这些研究表明, miR-122参与脂质代谢调控。

1.2 miR-370与脂质代谢

miR-370在脂质代谢调控方面与miR-122作用相似, 它是通过调节*miR-122*的表达水平来调节脂质代谢[40]。人肝癌细胞HepG2转染miR-370后, 细胞中*miR-122*表达水平上调; 而抑制miR-370表达则会降低*miR-122*水平。HepG2细胞转染miR-370后, 细胞内*SREBP-1c*、*FAS*、*DGAT2*和*ACC1*等的表达水平明显降低, 而用ASO处理细胞后, 上述基因的表达水平则明显提高[40]。进一步通过ASO抑制HepG2细胞*miR-122*表达后, 发现细胞内miR-370对上述基因表达的影响就会消失。此外, miR-370也能与*Cpt1a*(carnitine palmitoyltransferase 1a)基因3′UTR区靶向结合, 进而使*Cpt1a*基因表达下调, 脂肪酸β氧化率降低。这些研究结果表明, miR-370参与调节脂质代谢。

1.3 miR-33与脂质代谢

miR-33位于*SREBP*基因的内含子中, 在调节脂质代谢平衡中起重要作用[41-43]。它是维持细胞内胆固醇和脂肪酸动态平衡的关键转录后调节因子[41-44]。

miR-33通过靶向调节*ABCA1*、*ABCG1*和*NPC1*等基因的表达来调控胆固醇动态平衡。Marquart等[41]研究miR-33对细胞内胆固醇含量的影响, 发现转染编码miR-33的质粒于HEK293细胞, miR-33过表达细胞内氚标记的胆固醇流向ApoA I减少, 而ASO静默*miR-33*后, 细胞内胆固醇外流增加。Najafi-Shoushtari等[42]报道了胆固醇含量对细胞内miR-33表达的影响, 增加巨噬细胞和肝细胞内胆固醇含量, 胞内miR-33表达下调; 而胞内胆固醇含量降低时, miR-33表达上

调。Marquart等[41]进一步分析了小鼠肝脏*ABCA1*基因及其相关蛋白的表达, 发现miR-33通过靶向调节*ABCA1*来调控胆固醇动态平衡。Rayner等[17]研究证实, 抑制灵长类动物非洲绿猴miR-33表达可以提高肝脏ABCA1水平。也有研究发现, miR-33同时还调控另一胆固醇转运体ABCG1[43]。这些研究结果表明, miR-33调节细胞内胆固醇动态平衡。

miR-33还通过调节脂肪酸β氧化相关mRNA的表达调控脂质代谢。Dávalos等[44]从细胞和动物水平研究抑制内源性miR-33的表达对脂肪酸β氧化相关基因的影响, 发现抑制miR-33表达可以增加脂肪酸β氧化关键酶CROT、CPT1a、HADHB和AMPKα等的含量。灵长类动物实验也证实, 抑制miR-33表达上述脂肪酸β氧化相关基因及蛋白含量增加, 同时脂肪酸合成相关基因*SREBP1*、*FAS*、*ACLY*和*ACACA*等下降。同时, 还观察到小鼠实验未发现的现象—血浆VLDL甘油三酸酯水平显著降低[17]。

1.4 其他miRNA与脂质代谢

miR-103、miR-107、miR-758和miR-106b等也参与脂质代谢的调控。Ramirez等[45]通过ASO静默人神经胶质瘤细胞(H4)和小鼠巨噬细胞(J774)中的miR-758, 发现ABCA1表达上调, 细胞内胆固醇含量下降。Kim等[46]发现, miR-106b通过调控小鼠神经元细胞中ABCA1表达进而阻止细胞中胆固醇外流。可见, miR-758和miR-106b通过调节转录后*ABCA1*基因的表达来调节胆固醇动态平衡, 其作用方式与miR-33类似。

*miR-103*和*miR-107*位于PANK(pantothenate kinase)内含子中。旁系同源基因*miR-103*和*miR-107*与泛酸激酶共同作用, 通过抑制*FAS*等基因的表达来调节脂肪酸含量[47]。此外, Yang等[48]发现, 巨噬细胞内miR-146a过表达可显著降低细胞内低密度脂蛋白胆固醇含量。

2 多酚对脂质代谢相关miRNA的调节

多酚具有抗氧化、抗炎、调节代谢、保护心血管、抑制神经退化和抗癌等生物活性[49-50]。过去认为, 抗氧化功效是其生物活性作用机制[51]。而近年来文献报道了多酚生物活性的miRNA水平作用机制。姜黄素通过干扰细胞信号通路表现其抗肿瘤活性[52]。最新研究发现, 摄入姜黄素, 小鼠黑色素瘤组织变小, 剂量组肿瘤细胞中miR-205-5p表达较对照组显著提高[28]。因此, 推测姜黄素可能是通过改变细胞信号来调节miRNA的表达, 进而体现其抗癌活性。有文献报道, 芹菜素通过抑制MAPK(mitogen-activated protein kinase)Erk来降低TRBP(TAR-binding protein)磷酸化进而抑制miRNA由前体向成熟体转变从而抑制miRNA表达[53]。多酚与细胞信号相互作用发生级联反应, 调节转录因子活性, 从而影响基因表达[50-51]。然而关于多酚调控miRNA表达作用机制的研究报道较少, 文献报道较多的是多酚对miRNA表达水平变化的研究。

植物多酚能够调节生物机体miRNA的表达水平, 而且不同酚类化合物影响miRNA的种类及水平差异较大。Milenkovic等[21]通过miRNA和mRNA表达谱基因芯片技术研究了槲皮素、橙皮甙、柚皮素、花青素、儿茶素、姜黄素、原花色素、咖啡酸和阿魏酸等9种植物多酚对高脂膳食喂饲的*apoE*$^{-/-}$小鼠体内miRNA的影响, 结果发现, 酚酸、黄酮和花青素等不同酚类物质对小鼠miRNA种类数量和表达水平的影响差异较大(表1)。摄入黄酮类化合物无论是上调、下调还是总数发生变化的miRNA均较酚酸类化合物多。需要指出的是, 实验所选酚酸种类较少, 有待进一步考查其他酚酸调节miRNA情况。另外, 酚类化合物所调节的miRNA自身的功能也不能忽视。也有研究报道多酚对某些特定miRNA的调节情况。An等[54]报道没食子儿茶素-3-没食子酸酯(epigallocatechin gallate, EGCG)通过下调特异性miRNA表达来保护紫外光诱导的人类真皮成纤维细胞损伤。Kumazaki等[55]发现, 采用20 μmol/L白藜芦醇处理结肠癌细胞DLD-1能显著提高细胞内miR-

表1 不同酚类物质调节*apoE*基因敲除小鼠体内miRNA的数量(根据参考文献[21]修改)

Table 1 The numbers of miRNA regulated by different phenolics in *apoE* knockout mice (modified from reference [21])

多酚 Polyphenols	下调 Down	上调 Up	总计 Total
Quercetin	22	25	47
Hesperidin	53	44	97
Narangin	33	36	69
Anthocyanin	30	15	45
Catechin	36	44	80
Proanthocyanin	37	18	55
Caffeic acid	18	11	29
Ferulic acid	17	22	39
Curcumin	55	11	66

34a(2.5倍)和let-7a(2倍)的表达, 进而下调其靶基因细胞周期调控因子E2F3及其下游基因脂肪细胞和肌细胞调控因子*Sirt1*(Sirtuin type 1)。

目前已有研究发现, 植物多酚单体及提取物通过上调或下调脂肪酸和胆固醇等代谢相关miRNA的表达水平, 进而调控脂类代谢相关酶的表达, 从而实现其调节脂质代谢的作用。植物多酚调节miRNA影响脂质代谢相关的研究报道归纳如表2。

2.1 植物多酚通过调控miRNA调节脂肪酸代谢

植物多酚提取物具有调节miRNA水平的作用。Joven等[25]发现, 持续摄入玫瑰茄多酚提取物可以降低高脂饲料喂养的LDL受体缺陷小鼠肝脏甘油三酯和中性脂肪水平, 同时提高其多不饱和脂肪酸与单不饱和脂肪酸构成比例。分析其机理发现, 高脂膳食刺激动物体内*miR-103*和*miR-107*基因高表达, 而摄入玫瑰茄多酚提取物能够使miR-103和miR-107降低至与对照组相当的水平, 同时还显著抑制miR-122的表达, 从而调控脂肪酸代谢相关基因*FAS*、*SREBP-1c*和*AMPK*(AMP-activated protein kinase)等的表达, 起到降脂作用。不同植物源多酚调节的miRNA不同。Baselga-Escudero等[56]对葡萄籽原花青素提取物调节miR-122及其靶基因进行系统研究发现, 摄入葡萄籽原花青素提取物可以快速暂时性下调大鼠肝脏以及体外培养的肝细胞中miR-122水平, 从而抑制其靶基因*FAS*表达, 减少脂肪酸合成。在此基础上比较了长期摄入葡萄籽原花青素提取物对血脂代谢异常模型组和剂量组脂肪酸代谢情况的影响, 分析发现大鼠肝细胞中miR-122含量显著降低, 靶基因*FAS*被显著抑制, 另一靶基因*Pparβ*/δ表达上调, 脂肪酸含量降低[57]。Murase等[58]在高脂膳食诱导的C57BL/6肥胖小鼠肝脏中发现, 咖啡多酚通过下调*FAS*、*ACC1*、*SCD1*、*SREBP-1c*、*ACC2*和*PDK4*等基因的表达减少肝脏脂肪蓄积。他们进一步利用小鼠肝癌Hepa 1-6细胞验证了上述结果, 同时还发现经咖啡多酚处理的Hepa 1-6细胞中miR-122的表达水平提高了35%。因此, 推测植物多酚通过调节miRNA表达水平的方式调控脂肪酸代谢。

2.2 植物多酚通过调控miRNA调节胆固醇代谢

植物多酚通过调节miR-33和miR-122表达水平来调控胆固醇代谢。Baselga-Escudero等[56]设计了雄性Wistar大鼠摄入猪油(2.5 mL/kg体重)或含有葡萄籽原花青素提取物猪油(250 mg/kg体重)的急性实验(0, 1, 3 h采集血液, 摘取肝脏), 研究发现葡萄籽原花青素能够显著降低大鼠血液中甘油三酯含量, 肝脏中总胆固醇和总甘油三酯含量, 进一步分子水平研究发现剂量组肝脏中*miR-33*的表达较对

表2 多酚通过调节miRNA表达对脂代谢的调控作用

Table 2 The modulation of polyphenols on lipid metabolism by regulating the expression of miRNA

小RNA miRNA	多酚 Polyphenol	上/下调 Up-/down-regulation	实验情况 Experimental condition	代谢通路 Metabolic pathway	参考文献 References
miR-33	Grape seed proanthocyanidins	Down	250 mg/kg, 1 h Male Wistar rats liver 25 mg/L, 1 h, FAO	Cholesterol efflux HDL biogenesis, and VLDL levels. Fatty acid oxidation	[56]
miR-103/107	Polyphenol extract (*Hibiscus sabdariffa*)	Up	28.6 mg/kg/day 10 weeks Male C57BL/6J (LDLr$^{-/-}$) mice liver	TG storage in adipocytes	[25]
miR-122	Polyphenol extract (*Hibiscus sabdariffa*)	Down	28.6 mg/kg/day, 10 weeks Male C57BL/6J (LDLr$^{-/-}$) mice liver	Cholesterol synthesis Bile acid biosynthesis Fatty acid oxidation	[25,56,58-59]
	Quercetin	Up	2 mg/g diet, 6 weeks, Female C57BL/6J mice liver		
	Coffee polyphenols	Up	0.5%~1.0% for 2-15 weeks Male C57BL/6J mice liver 2.5 g/mL, 24 h, Hepa		
	Grape seed proanthocyanidins	Down	250 mg/kg,1 h Male Wistar rats liver 25 mg/L, 1 h, FAO		
miR-370	Ellagitannin	Down	15 μg/mL, 6 h, HepG2	Fatty acid oxidation	[60]

照组降低, *ABCA1*表达水平提高, 高密度脂蛋白含量显著增加, 同时还采用葡萄籽原花青素孵育大鼠肝细胞FAO验证上述*miR-33*和*ABCA1*的表达情况, 得到与动物实验相似的结果。这些结果提示, 葡萄籽原花青素通过下调*miR-33*基因表达, 提高其靶基因*ABCA1*的表达水平, 实现对胆固醇代谢的调节。在急性实验基础上, Baselga-Escudero等[57]进一步考察长期摄入葡萄籽原花青素提取物对血脂代谢异常雄性肥胖Wistar大鼠脂代谢的影响, 发现剂量组(25 mg GSPE/kg)与模型组比较, 能够显著降低血浆中总甘油三酯和低密度脂蛋白含量, 肝脏中总脂肪、总甘油三酯和总胆固醇含量; 基因分析发现*miR-33*表达被抑制, 其调控的靶基因*ABCA1*和*Cpt1a*水平显著升高。此外, 通过外周血单细胞的验证实验也有类似发现。也有研究报道, 植物多酚通过调节*miR-122*表达, 调控胆固醇代谢。Boesch-Saadatmandi等[59]发现, 摄入含有槲皮素(2 mg/g饲料)的半合成西式膳食的雌性C57BL/6J小鼠肝脏*miR-122*水平较模型组提高61%, 而肝脏中总胆固醇含量显著降低。Wen等[60]发现, 经植物多酚Ellagitannin处理后6 h, HepG2细胞中*miR-370*表达提高2.4倍, 并且随时间延长表达量增加。 综上, 植物多酚能够通过调节miRNA调控机体胆固醇代谢。

3 存在的问题

机体内超过60%的细胞水平的转录和翻译受到miRNA的调控, 而植物多酚具有调节肝脏脂肪代谢相关miRNA表达的作用, 这将为阐释多酚改善机体健康作用提供新的研究视角。然而, 仍有许多问题需要进一步深入研究: (1)目前, 尚缺乏多酚调节miRNA分子机制的直接证据。有研究表明, 多酚可以结合在mRNA和蛋白上, 故而多酚也可能与miRNA或miRNA前体结合进而调节其表达水平和稳定性; 而对于来自于内含子的miRNA, 多酚也有可能通过调节宿主基因的表达, 进而调节miRNA的表达。(2)目前的研究还仅局限于对多酚调节miRNA现象的报道, 关于这一作用与不同种类多酚之间的构效关系还未涉及。多酚种类繁多, 结构复杂, 明确其调节miRNA的构效关系对深入了解和利用多酚的生物活性有重要意义。(3)当前的研究集中在验证多酚对单一miRNA及其靶基因的影响, 缺少多酚对调节脂代谢相关的miRNA网络系统的研究。机体内各miRNA的表达并非孤立, 相互之间可能存在协同作用, 因此从生物学功能角度探讨多酚对miRNA网络的调控可能会更接近其作用的本质。上述问题还需要更多基于细胞和动物体内的研究, 以便更加广泛、深入地评估多酚的靶向miRNA及其作用的分子机制。

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