MicroRNA-206功能的研究进展

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摘要 MicroRNAs是一类非编码的小RNA分子, 通过负调控靶基因参与多种生物学进程。MicroRNA-206作为目前最具研究价值和特征的microRNAs之一, 不仅在发挥生物功能的过程中扮演着关键角色, 而且参与了包括肿瘤在内的多种疾病的致病机制。该文就microRNA-206的研究成果, 尤其在多种疾病中的功能作一综述, 并指出其具有的重要的诊断和治疗潜能。

关键词 microRNA-206; 肿瘤; 靶基因

Research Progress on the Roles of MicroRNA-206

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Abstract MicroRNAs have emerged as small non-coding RNAs that negatively regulate gene expression linked to various biological processes. MicroRNA-206 is one of the most studied and best characterized miRNAs, which plays pivotal roles in biological function and is also involved in the pathogenesis of various diseases including cancer. This review summarized the results of studies of microRNA-206 with emphasis on its function in the pathogenesis of numerous diseases and indicated its significant diagnostic and therapeutic potential in the future.

Keywords microRNA-206; cancer; target gene

MicroRNAs(miRNAs)是一类长度约为22个核苷酸的非编码的调控性小RNA分子, 它可以在转录后水平通过mRNA剪切或抑制蛋白质翻译的方式负调控靶基因[1]。自Ambros等[2]发现首个miRNA——lin-4后, 越来越多的miRNA在多个物种中被发现, 并且它们在人类的生理和病理过程中所充当的神秘角色也被一步步揭开。MicroRNA-206便是众多miRNA研究热点中的一个。MiR-206首次发现时被认为是在骨骼肌中特异性表达的[3]。因此, miR-206的早期研究局限在骨骼肌的生理和病理过程中, 对于miR-206在骨骼肌的发育以及相关疾病中的角色阐述得比较详尽。但近几年的研究发现, miR-206不仅仅在骨骼肌中有表达, 而且在其他多个脏器(如肺脏、心脏和脑等)以及多种肿瘤(如乳腺癌、卵巢癌和胃癌等)的组织中也有表达, 并参与调控了这些组织的生理和病理过程。由此可见, miR-206的研究日趋深入和广泛, 因而有必要对miR-206的研究进展作一综述。本文首先介绍miR-206的结构及其生物学

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特性, 然后对miR-206与肿瘤以及miR-206在各个器官(骨骼肌、肺脏、心脏和脑等)中的作用进行阐述。

1　MicroRNA-206的结构及其生物学特性

MiR-206是一种脊椎动物所特有的miRNA, 因而它具有动物miRNA的共性。MiR-206首先由RNA聚合酶II转录生成原始miRNA转录产物(pri-miRNA-206), pri-miRNA-206在细胞核内经一种称为Drosha的RNA内切酶III加工, 得到茎–环结构的miRNA-206前体(pre-miRNA-206)。随后, pre-miRNA-206被Exportin-5蛋白运输到细胞质中, 再经第二种RNA内切酶III Dicer进一步加工得到成熟双链RNA分子, 其中一条成熟链插入RNA诱导沉默复合物(RNA-induced silencing complex, RISC),与其靶基因mRNA的3′端非翻译区(3′-untranslated regions, 3′-UTR)结合, 裂解其靶基因mRNA或抑制蛋白质表达, 从而发挥它的生物学特性, 调控细胞的增殖、分化、凋亡和迁移等多种生物学行为[4](图1)。MiR-206可以抑制多个靶基因的表达; 同一个靶基因也可以受到多个miRNA的调控[5]。由此形成的分子调控网络在胚胎发育、正常生理功能以及多种疾病的病理过程中发挥着巨大作用。

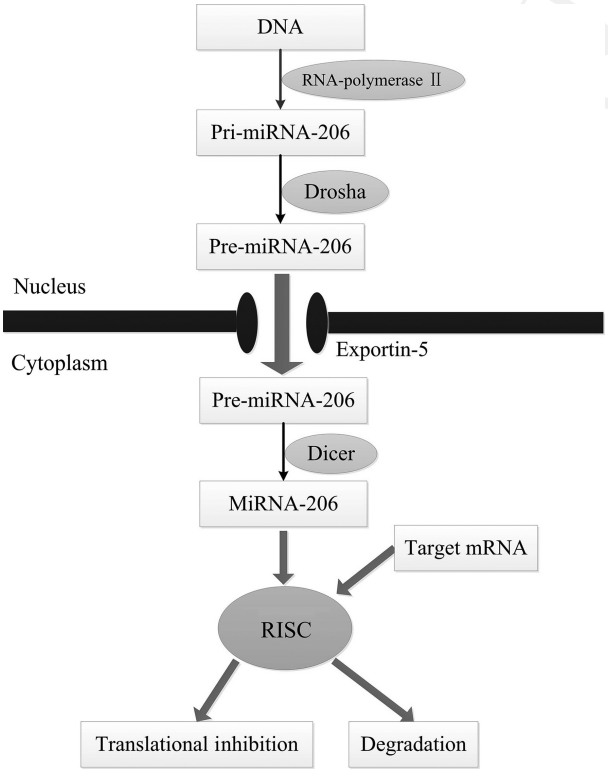

图1 MicroRNA-206生物合成

Fig.1 MicroRNA-206 biogenesis pathway

人的miR-206定位在6号染色体上, 小鼠的定位在1号染色体上, 大鼠的定位在9号染色体上, 但不同物种的miR-206序列是高度保守的[6]。这表明, miR-206可能在哺乳动物的基本生理和病理过程中扮演着重要角色。人的miR-206序列首次是由Lagos-Quintana根据小鼠上已经证实的miR-206序列通过同源性分析预测出来的[7], 随后在人体中得到证实[8]。

MiR-206是肌肉特异性表达的“myomiR”家族成员之一, 其他成员还包括miR-133a-1、miR-133a-2、miR-133b、miR-1-1和miR-1-2[9]。六种miRNA的序列是相似的, 这意味着它们有一些相同或相似的靶基因。其中, miR-1-2与miR-133a-1、miR-1-1与miR-133-a-2、miR-206与miR-133b分别构成作用相反的三个基因簇[10]。通过miRBase Targets、Pic Tar和TargetScan等数据库检索发现, has-miR-206可以跟几百个靶基因结合(如: *TACR1*、*PAX3*、*SDPR*、*GJA1*和*NRP1*等), 而一个靶基因与miR-206作用的结合位点不止一个, 而且与miR-206结合的位点越多, 受miR-206抑制的程度越大。由此可见, miR-206这种可以对下游多个靶基因作用的特性, 揭示了miR-206在复杂的生物分子调控网络中的关键地位, 尤其对多基因调控的生理和病理过程显得更为重要。因此, 以miR-206为靶向的生物治疗可能比以单基因为靶向的治疗更为有效。

2　MicroRNA-206的功能

2.1　MicroRNA-206与肿瘤

MiR-206在ERα阳性乳腺癌中的表达水平是下调的, 而在ERα阴性乳腺癌中的表达是上升的[11-12]。Adams等[13]证实, miR-206在乳腺癌MCF-7细胞系中抑制靶基因*ERα*的表达。随后, Adams等[14]研究指出miR-206不单单直接通过靶基因*ERα*影响ERα的表达, 而且通过抑制其他靶基因(*SRC-1*、*SRC-3*和*GATA-3*)的表达, 进而干扰雌激素相关的信号通路, 影响ERα的表达; 同时, miR-206的表达水平部分通过EGFR/MAPK信号通路受到影响。此外, Ago-2也会促进miR-206的表达, 增高的miR-206将有助于乳腺癌中ERα转为阴性[15]。ERα在乳腺癌中的存在, 为临床诊治乳腺癌提供了一种治疗策略, 因而miR-206为临床个体化治疗乳腺癌提供了一种新的关键性靶点[16]。

MiR-206在人的横纹肌肉瘤(rhabdomyosarcoma, RMS)中处于非常低的表达水平[17]。在RMS细胞系中的miR-206重新表达, 促进了骨骼肌的分化并

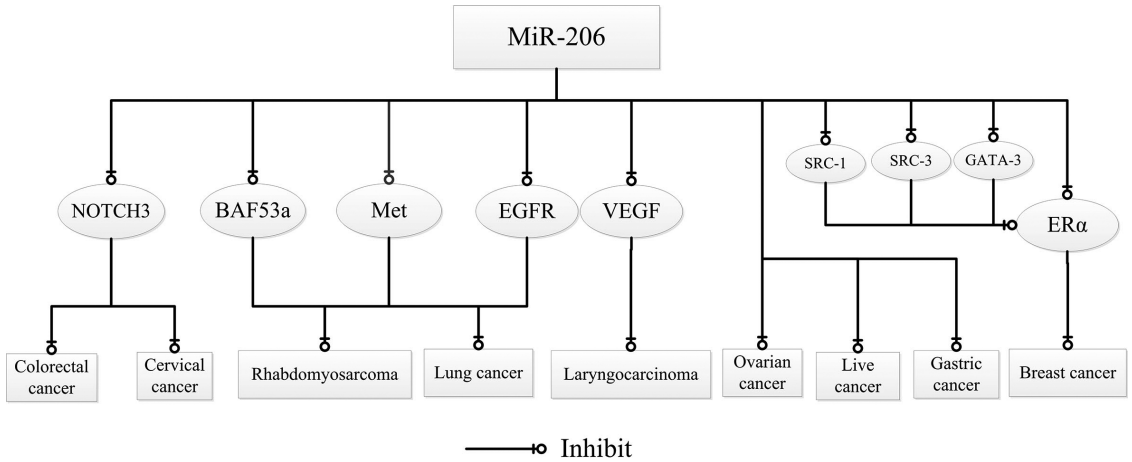

图2　MicroRNA-206在肿瘤中的作用

Fig.2　The roles of microRNA-206 in cancer

且抑制了肿瘤细胞的生长[18]。随后, Yan等[17]证实, miR-206通过靶基因*Met*, 进而抑制RMS的生长和转移。然而, Taulli等[19]研究发现, miR-206通过靶基因*BAF53a*, 进而抑制RMS的进展, 包括RMS的形态学和生物学行为。这表明, miR-206通过多个靶基因发挥肿瘤抑制作用, 更凸显出miR-206在RMS中作为一种肿瘤抑制因子, 可以有效地抑制肿瘤。因此, MiR-206在RMS临床治疗和诊断上具有巨大潜能[20-21]。

MiR-206不仅仅在乳腺癌和横纹肌肉瘤中发挥着独特作用, 而且近几年在卵巢癌[22]、胃癌[23-24]、结直肠癌[25]、喉癌[26]、宫颈癌[27]、肺癌[28]和肝癌[29]中的作用也有相关文献报道。Guo等[22]在CD133阳性的卵巢癌细胞系OVCAR3亚群中用qRT-PCR分析发现, miR-206的表达异常, 这提示miR-206很可能参与卵巢癌的发展。Yang等[23]在98对胃癌和癌旁组织中用qRT-PCR检测对比发现, miR-206的表达下调。对于胃癌患者来说, miR-206的低表达提示了一种不好的预后。Ren等[24]在胃癌细胞系中证实了miR-206对胃癌的抑制作用。MiR-206在结直肠癌中不仅仅可以作为一种疾病预后的生物标志物[25], 而且可以通过下调NOTCH3的表达抑制肿瘤的生长和侵袭[30]。MiR-206还可以通过调控VEGF的表达抑制喉癌的进展[26]。Song等[27]在宫颈癌细胞HeLa中发现, miR-206通过靶基因*NOTCH3*抑制肿瘤生长和引起细胞凋亡。Mataki等[28]研究发现, 在肺鳞状细胞癌中, miR-206可以双重抑制MET和EGFR的致瘤信号通路, 进而发挥作用。在肝癌细胞中, miR-206可以抑制肿瘤细胞的增殖, 促进肿瘤细胞的凋亡[29]。这些研究提示, miR-206是一种有效的肿瘤抑制因子, 参与了多种肿瘤的发生发展过程(图2)。

Singh等[31]在多种癌细胞中研究发现, NRF2可以抑制miR-206和miR-1的表达, 而miR-206和miR-1可以调控磷酸戊糖途径和三羧酸循环相关靶基因(*G6PD*、*PGD*、*TKT*和*GPD2*)的表达, 进而调控肿瘤的糖代谢过程, 从而参与肿瘤的发生。这提示, miR-206通过调控多个靶基因在多种肿瘤的发生发展过程中发挥着重要作用, 而这种抑制肿瘤的效应可能在多种肿瘤中是普遍存在的。

2.2　MicroRNA-206与骨骼肌

MiR-206在骨骼肌发育过程中扮演着重要角色[32]。Takada等[33]研究发现, miR-206的表达水平在胚胎发育过程中稳步上升, 而在出生后3天趋于下降。随后, Koutsoulidou等[32]在从人不同发育阶段分离到的肌肉细胞中, 发现miR-206的表达水平呈上升趋势, 同时伴随着其已知靶基因和上游转录因子MyoD表达水平的变化; 在体外实验中, 异位表达的MyoD诱导了骨骼肌细胞的分化, 同时伴随着miR-206表达水平的增加。这种由MyoD诱导增加的miR-206, 可能通过抑制Fstl1和Utrn的表达发挥作用[34]。MiR-206在骨骼肌发育过程中的重要性由Kim等[35]在小鼠的成肌细胞系(C2C12)中证实, 转染miR-206的C2C12在有血清的培养基中发生分化; 而敲除miR-206的C2C12在无血清的培养基中未发生分化。Pax3是一种调控骨骼肌发育的重要转录因子, 其水平的下调对于启动肌再生程序是必需的[36]。Goljanek等[37]证实, miR-206在转录后水平抑制Pax3的表达, 进而启动骨骼肌发育程序。有趣的是, 处于静止期的骨骼肌卫星细胞在高表达Pax3的同时,

miR-206也处于高表达水平, 这时miR-206却没有发挥抑制作用。研究发现, Pax3受到了选择性多聚腺苷酸化, 使miR-206无法通过Pax3的3′-UTR发挥作用[38]。Pax7是另一种调控骨骼肌发育的重要转录因子, 其在骨骼肌卫星细胞的增殖和分化中具有重要作用。Chen等[39]在骨骼肌卫星细胞中发现, miR-206通过抑制靶基因*Pax7*的表达, 进而促进骨骼肌卫星细胞的分化。有趣的是, 当肌肉受到损伤时, miR-206的表达是下降的, 随之高表达的Pax7使得骨骼肌卫星细胞处于增殖状态。一段时间以后, miR-206又回到了肌肉损伤前的高水平, 随之低表达的Pax7使得骨骼肌卫星细胞从增殖转向分化, 然后替代损伤的骨骼肌。

随后, Nakasa等[40]在骨骼肌损伤的大鼠模型中, 局部注射肌肉特异性的miRNA(miR-1、miR-133和miR-206), 能够显著地加速肌肉的再生, 并且可以有效地防止纤维化。Williams等[41]在肌萎缩性脊髓侧索硬化症(amyotrophic lateral sclerosis, ALS)的小鼠模型中发现, miR-206的缺失会加速ALS的进展。MiR-206通过HDAC4/FGFBP1/FGF信号通路, 促进神经肌肉突触再生[41]。目前的研究表明, 由于miR-206有促进骨骼肌发育和减缓疾病进展的功能, 它很有可能成为治疗肌肉萎缩的靶点[42-43]。

2.3　MicroRNA-206与肺脏

在缺氧诱导的肺动脉高压大鼠上, miR-206的表达是下调的[44-45]; 有趣的是, miR-206在血清中的表达却是上升的[45]。随后, Jalali等[44]通过将miR-206转染到肺动脉平滑肌细胞(pulmonary artery smooth muscle cell, PASMC)中, 发现miR-206抑制NOTCH3的表达, 进而抑制了PASMC的增殖, 并促进了PASMC的分化。而Yue等[45]研究发现, 下调的miR-206通过HIF-1α通路促进了肺动脉高压的进程。在慢性阻塞性肺疾病(chronic obstructive pulmonary diseases, COPD)的患者血清标本中, miR-206的表达是上调的。MiR-206的这种上调跟炎性细胞因子(IL-2、IL-5和TNF)是密切相关的[46]。因而, miR-206很有可能成为COPD的生物标志物之一。此外, miR-206也可能作为生物标记物用于百日咳病人中。Ge等[47]用miR-206同时联合miR-202、miR-342-5p、miR-487b和miR-576-5p作为百日咳的血清标志物, 其特异度和灵敏度可分别达到97.4%和94.3%。Zhang等[48]研究发现, miR-206通过直接抑制靶基因*VAMP-2*的表达, 进而调控肺泡II型细胞分泌表面活性物质。由此可见, miR-206在肺脏疾病中具有重要作用。

2.4　MicroRNA-206与心脏

Shan等[49]首次在小鼠心肌梗死模型中发现, miR-206在梗死的心肌组织中表达增加。MiR-206通过IGF-1的凋亡信号通路, 导致心肌细胞的功能障碍[49]。随后, 同一研究组在高糖诱导的心肌细胞中发现, miR-206在转录后水平抑制Hsp60的表达, 进而加速心肌细胞的凋亡, 而miR-206的增加很有可能是通过MEK1/2通路引起的[50]。Limana等[51]在慢性心衰的小鼠模型中注射HMGB1后发现, HMGB1通过增强心肌再生有效地延缓心衰过程中的心室重构, 并引起了miR-206的表达上调。HMGB1对心脏的效果部分是通过miR-206抑制TIMP-3产生作用的[51]。MiR-206还参与了E2F6诱导的扩张性心肌病[52]。E2F6抑制E2F/Rb信号通路引起miR-206的上调和connexin-43的下调, 进而引起心室重构, 最终导致扩张性心肌病。这些研究表明, miR-206在心脏的生理和病理过程中扮演着重要角色。

2.5　MicroRNA-206与脑

Olsen等[53]通过用基因芯片对成年雄性大鼠不同脑区的检测发现, miR-206在小脑中的表达水平远远比其他脑区高, 这种在不同脑区的分布差异说明, miR-206很有可能参与脑的生理和病理过程。Lehotzky等[54]用miR-206转染少突胶质细胞系(CG-4), miR-206的过表达可以明显抑制p25的表达, 进而通过微管重排抑制少突胶质细胞的分化。Lee等[55]在阿尔兹海默病的小鼠模型上发现, 上调的miR-206可以抑制脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)的表达, 而BDNF可以调节突触可塑性和记忆。由此可见, miR-206参与了阿尔兹海默病的病理过程, 很有可能成为一种潜在的治疗靶点。Liu等[56]在栓塞性脑梗死的患者和动物模型中发现, 血清中miR-206的表达水平跟大脑梗死灶的大小相关, 但具体的调控机制仍不清楚。MiR-206与精神分裂症的发生也是相关的[57], 但具体的分子机制仍需进一步研究。

2.6　MicroRNA-206的其他功能

MiR-206在其他疾病和器官中的作用亦有少量的文献报道。Koba等[58]研究表明, miR-206在区分硬皮病和非硬皮病中具有重要价值。因而, miR-206在硬皮病中具有潜在的诊断价值。Greco等[59]研究发现,

miR-206在神经元细胞中可以抑制神经肽P的合成和释放, 从而参与疼痛的疾病过程。Zhou等[60]研究发现, miR-206是调控生物节律的重要一部分。Walden等[61]研究指出, miR-206在棕色脂肪组织中的表达是丰富的, 而在白色脂肪组织中却是缺失的。这提示, miR-206很可能参与了脂肪能量的释放和储存过程。Zhong等[62]发现, 在肝细胞中miR-206可以抑制LXRα诱导的脂质代谢。Lin等[63]在敲除miR-206的斑马鱼上发现血管异常分支的形成和内皮细胞的增殖。这表明, miR-206可能参与调控血管的发生。在不久的将来, miR-206将会有更多的功能被揭晓。

3 小结与展望

在上述提到的大部分疾病中, miR-206在组织处于病理状态时, 往往处于低表达的水平; 相反, 在正常生理情况下, miR-206处于高表达的水平。由此可见, miR-206的表达对机体展现的是更为有利的一面。在正常生理情况下, 高表达的miR-206起到了一个预防疾病的作用。尤其对于肿瘤来讲, miR-206可以视为一种有效的“抑癌基因”。然而, 有趣的是, 在脑部相关的疾病(如阿尔兹海默病)中, miR-206在病理情况下的表达却是上调的, 这种例外情况的背后或许隐藏着更多关于脑的生命秘密, 这有待于进一步研究。MiR-206作为一种有效的抑癌因子, 在临床肿瘤靶向治疗上显示出巨大的潜力。而且, miR-206在临床诊断和预后评估上是一种有价值的生物标记物。

目前, 针对miR-206在骨骼肌的发育、正常生理和病理过程中的研究更为深入, 具体的调控机制也较为详尽, 未来其在骨骼肌中的研究可能更多地倾向于转化医学方面, 将这一研究应用于临床。而miR-206在其他疾病(尤其是心脏疾病)中的作用及其机制还不清楚, 但初步的研究已展现出miR-206巨大的临床应用潜能。因此, 深入研究miR-206的功能并分析其具体的分子机制, 将为探索miR-206调控人类疾病的研究奠定基础, 为临床靶向治疗疾病提供新的靶点。

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