DNA甲基化调控的miRNA在肺癌发生发展中的作用

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摘要 肺癌是全球发病率和死亡率最高的癌症, 治疗过程受到治愈率低和转移率高的困扰, 亟待了解肺癌在发生发展过程中的分子机制, 以期找到更好的治疗方案。miRNA作为小的非编码RNA, 它可以导致靶基因的mRNA降解或翻译抑制。miRNA受到包括DNA甲基化在内的表观遗传调控, 参与多种细胞过程, 包括细胞分化、增殖和凋亡, 调控癌症等的疾病状态。DNA甲基化作为可逆的表观遗传调控过程, 目前已有DNA去甲基化药物用于癌症的临床治疗, 但是还需寻找特异性较高的药物。以DNA甲基化调控的miRNA为切入点, 该文就DNA甲基化调控的miRNA在肺癌发生发展中的作用, 以及对肺癌化疗和放疗敏感性的研究情况进行综述。

关键词 DNA甲基化; miRNA; 肺癌

Role of DNA Methylation Regulated miRNA in Carcinogenesis of Lung Cancer

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Abstract Lung cancer is the cancer with highest incidence/mortality rate in the world. The treatment process is beset by low cure rate and high metastasis rate. It is urgent to understand the molecular mechanism of lung cancer in the course of occurrence and development in order to find a better treatment plan. As small non coding RNA, miRNA can lead to mRNA degradation or translation inhibition of target genes. miRNA is regulated by epigenetic regulation, including DNA methylation, involved in a variety of cell processes, including cell differentiation, proliferation and apoptosis, and regulating disease status including cancer. DNA methylation is a reversible epigenetic regulation process. Currently, DNA demethylation drugs have been used in the clinical treatment of cancer, but it is still necessary to look for drugs with high specificity. In this paper, the role of DNA methylation regulated miRNA in the occurrence and development of lung cancer, as well as the research on the sensitivity of lung cancer to chemotherapy and radiotherapy are reviewed.

Keywords DNA methylation; miRNA; lung cancer

肺癌作为癌症之王, 是全球范围内发病率与死亡率最高的癌症[1], 小细胞肺癌(small cell lung cancer, SCLC)和非小细胞肺癌(non-small cell lung cancer, NSCLC)是肺癌的2种主要类型。非小细胞肺癌约占肺癌的85%, 包括肺鳞状细胞癌(lung squamous cell carcinoma, LSCC)(40%)、肺腺癌(lung adenocarcino-

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ma, LAC)(40%)和大细胞肺癌(large cell lung cancer, LCLC)(10%)。肺癌的5年生存率约为18%, 约80%的肺癌患者因诊断晚期而不能手术, 同时70%~90%的死亡是由转移引起的[2-3]。因此, 了解肿瘤细胞在不同发展阶段的分子事件, 确定有效的肿瘤生物标志物, 对改善患者预后至关重要。miRNA(microRNA)通过靶向癌基因或肿瘤抑制基因, 参与调节肿瘤的增殖、侵袭和转移过程, 在人类肿瘤的发生发展中起着重要的作用。表观遗传调控被认为是肿瘤发生的重要的早期驱动因素, DNA甲基化是研究最多的表观遗传修饰之一。miRNA作为癌基因或肿瘤抑制基因在肿瘤发生发展中表达异常, 与miRNA启动子区域的DNA甲基化关系密切。本文就DNA甲基化、DNA甲基化调控miRNA对肺癌发生发展过程的影响进行综述。

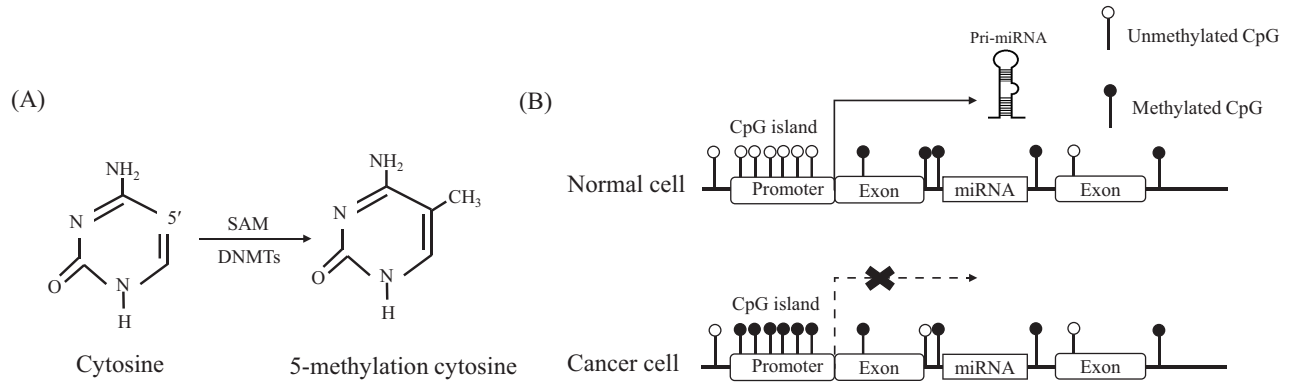
1 DNA甲基化与CpG岛

近年来的研究表明, 表观遗传变化与遗传变化(基因突变、染色体畸变)共同构成了一个复杂的机制。表观遗传机制可以在不改变DNA序列的情况下改变基因表达模式和基因组稳定性, 这些修饰包括DNA甲基化、组蛋白修饰、染色质重塑和非编码RNA的表达改变, 每一个都可能与其他分子过程协同作用[4]。DNA甲基化是表观基因调控机制的重要部分, 是指通过DNA甲基转移酶(DNA methyltransferase, DNMT)作用, 核苷酸序列中的胞嘧啶(cytosine, C)的碳-5位置被*S*-腺苷甲硫氨酸(*S*-adenosine methionine sulfur, SAM)提供的甲基共价修饰为5-甲基胞嘧啶(5-methylation cytosine, 5mC)的过程(图1A)。DNA甲基化在DNA修复、重组、复制以及基因活性调控中起着重要作用。有3种DNMT控制DNA甲基化, 其中DNMT3A和DNMT3B主要负责DNA甲基化的建立, 而DNMT1则负责维持DNA甲基化状态[5]。在哺乳动物基因组序列中, CpG二核苷酸呈不均匀分布, DNA甲基化则发生在基因组上富含高密度CpG的区域, 该区域至少有200 bp, 其中CG的含量大于50%, 被称为CpG岛(CpG island, CpGi)[6]。CpG岛存在于约60%编码蛋白质和miRNA的基因的上游启动子调控区域。在正常细胞中, CpG岛通常是非甲基化的, 然而在肿瘤细胞中, DNA甲基化稳态被破坏, 导致与癌基因和肿瘤抑制基因相关的关键调控区域出现表观遗传修饰。相反, 分散的和非启动子的CpG二核苷酸通常是甲基化的。DNA甲基化水平在肿瘤中比正常组织表现出更高的变异性, 包括低甲基化或高甲基化。通常, 在癌症中可观察到有助于基因组稳定性和沉默癌基因激活的全局低甲基化模式。此外, 肿瘤抑制基因(tumor suppressor gene, TSG)经常由于局部启动子高甲基化而失活, 甲基化被认为是肿瘤转化的主要贡献者[7]。甲基化是一个可逆的变化, DNA甲基转移酶抑制剂如5-氮杂-2′-脱氧胞苷(5-Aza-dC)或与组蛋白脱乙酰化酶抑制剂TSA(trichostatin A)协同可作用于基因的再表达[8]。

2 miRNA与DNA甲基化

miRNA是由19~24个核苷酸组成的小的内源性非编码RNA, 最早被当作转录噪音而被发现。miRNA作为靶基因表达的转录后调节因子, 通过与靶基因3′非翻译区(3′ untranslated region, 3′UTR)不完全互补结合, 抑制靶mRNA的转录或蛋白翻译, 从而调控基因的表达。miRNA可能参与调节高达30%的蛋白质编码基因。根据靶基因mRNA的特性, miRNA可分为肿瘤抑制miRNA和促癌miRNA, 广泛参与细胞增殖、周期进程、衰老、凋亡、侵袭和转移等过程, 也可影响细胞对于药物或辐射的敏感性。一个miRNA可以在相互关联的路径上调节数百个靶mRNA, 而多个miRNA可以调节一个基因。参与癌症中miRNA表达异常的表观遗传学机制, 包括DNA甲基化和组蛋白修饰, 甲基化沉默miRNA可以通过影响miRNA调控的基因和途径, 深刻地影响肿瘤的发展, 特别是启动子区域内CpG岛的甲基化是恶性肿瘤中miRNA失活的重要机制[9]。

KUNEJ等[10]分析了45篇实验论文, 发现14.0%的被检测的受表观遗传调控的miRNA完全位于CpG岛内, 11.6%的miRNA容易表观遗传失活, 包括23种肿瘤病理类型。其中, 45.0%的miRNA在多个肿瘤类型的细胞中受到表观遗传调控。比如miR-124a、miR-1/2/3、miR-127和miR-199-1/2至少在7种肿瘤中受到DNA甲基化的表观遗传调控, miR-34s则在12种肿瘤中受到DNA甲基化的表观遗传调控。miR-34甲基化是肿瘤发生过程中与肿瘤相关的常见事件, 在肺、胃、卵巢、结肠、胰腺、喉、肾和其他组织的肿瘤中都可以观察到miR-34b/c和miR-34a的甲基化位点[11]。作为肿瘤抑制miRNA, miR-34a直接靶向



A: DNA甲基化过程。B: 正常细胞和癌细胞中DNA甲基化调控的miRNA表达的机制。虚线和×表示miRNA的转录被阻断。

A: DNA methylation process. B: mechanism of miRNA expression regulated by DNA methylation in normal and cancer cells. Dashed line and × indicate that miRNA transcription is blocked.

图1 细胞中受DNA甲基化调控miRNA特征

Fig.1 Patterns of miRNA silenced by DNA methylation in cells

E2F3(E2F transcription factor 3)、*MYCN*(V-Myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog)、*Bcl-2*(B-cell lymphoma-2)、*NOTCH1*、*JAG1*(Jagged 1)、*MET*(mesenchymal-epithelial transition)、*AXL*(Anexelekto)、*IL-6R*(interleukins-6 receptor)、*YY1*(Yin-Yang)等基因参与了广泛的生理过程, miRNA-34s的失活促进了肿瘤的增殖、运动、上皮–间质转化(epithelial-mesenchymal transition, EMT)和侵袭[11-12]。还有一些受DNA甲基化调控的miRNA, 如miR-203在多种实体瘤和造血系统恶性肿瘤中下调[13-14], 而miR-21作为促癌基因处于过表达状态[15]。这些miRNA表观遗传修饰不仅有利于肿瘤发展, 而且可能促进肿瘤侵袭和转移。此外, miR-17-92簇在胰腺癌干细胞中受到高表达的DNMT1作用出现显著下调, DNA甲基化抑制剂zebularine可以逆转细胞miR-17-92簇的水平, 减弱肿瘤干细胞的自我更新能力、致瘤性以及药物抗性[16]。这些数据突出了DNA甲基化导致miRNA失调在恶性肿瘤中的重要作用。

miRNA也具有表观遗传功能, 通过向某些启动子募集特定蛋白复合物, 或调节其他表观遗传调控因子, 如DNMT、组蛋白去乙酰化酶(histone deacetylase, HDAC)和多梳抑制复合物(polycomb repressor complex, PRC)的组分, 促进细胞的表观遗传, 在基因组的不同水平发挥作用[6,17]。FABBRI等[18]在肺癌细胞系中发现, miR-29家族可以直接靶向DNMT3A和DNMT3B。miR-29在癌细胞中的再表达通过抑制DNMT的活性可以重新激活由DNA甲基化沉默的肿瘤抑制因子, 从而抑制肿瘤生长[18-19]。受甲基化调节的miR-148a也能够调节DNMT的水平, 这表明, miRNA和DNA甲基化之间存在紧密连接的调节环[20-22]。其他直接控制DNMT活性的miRNA还有miR-152、miR-185、miR-301[17]、miR-708-5p[23], miR-101[24]等。

3 DNA甲基化调控的miRNA与肺癌

3.1 DNA高甲基化miRNA对肺癌的影响

甲基化是最常见的表观遗传调控机制之一, miRNA表达的表观遗传学改变也被发现与肺癌的进展有关。在肺癌中, miR-124a[25]、miR-126[26]、miR-9、miR-34b/c[27]和miR-200c等miRNA的甲基化依赖性沉默参与了肺癌的发生、肿瘤侵袭性表型的形成和转移的发展(图2)。

3.1.1 *迁移、侵袭与转移* 许多肺癌患者在肺切除术后仍发生肿瘤转移和复发, 这是肺癌治疗失败和死亡的主要原因。miRNA参与对靶基因的调控, 在肿瘤转移过程中起着重要作用。花生四烯酸(arochidonic acid oil, AA)可通过环氧化酶-1(cyclooxygenase-1, COX-1)和COX-2或5-脂氧合酶(5-lipoxygenase, 5-LO)的酶促作用转化为前列腺素(prostaglandin, PG)或白三烯(leukotriene, LT)。PG和LT是多种疾病(包括多种癌症)的脂质信号分子。5-脂氧合酶激活蛋白(5-lipoxygenase activating protein, ALOX5AP, FLAP)在LT产生的前两个转化步骤中协同作用。以往的研究表明, LT在肿瘤的发生发展中起着重要作用。miR-146a在肺癌细胞系中高甲基化, 通过靶向*COX-2*和*FLAP*的3′-UTR从而调节PGs和LTs的产生, 直接控制细胞增殖、存活、迁

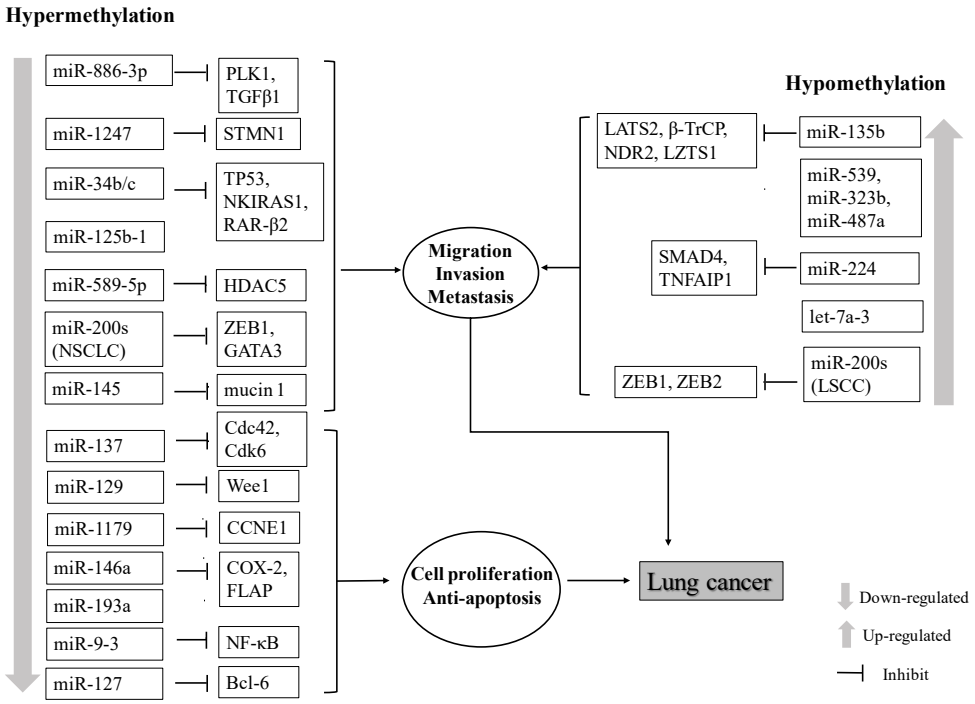


图2 DNA甲基化调控的miRNA对肺癌的影响

Fig.2 Effect of DNA methylation regulated miRNAs on lung cancer

移和侵袭的信号级联的激活, 促进了肺癌的发生发展[28]。miR-34启动子在癌症中普遍甲基化, 低表达的miR-34b/c与LAC细胞的远处转移有关, 重新表达miR-34b/c可以导致LAC细胞的侵袭性降低[27,29]。在NSCLC中, 受甲基化调控表达下降的miR-1247和miR-145分别通过靶向STMN1(stathmin 1)和mucin 1影响NSCLC细胞的迁移和侵袭[30-31], 而且 miR-145的甲基化程度与NSCLC组织的分化程度呈负相关[32]。受甲基化调控表达下调的miR-125b-1和miR-137参与了NSCLC的转移进程, 并且miR-137与NSCLC的淋巴结转移及不良临床预后相关[33-34]。与肺上皮细胞相比, NSCLC细胞的miR-589基因启动子高甲基化更为显著, miR-589-5p可以通过靶向*HDAC5* mRNA的3′-UTR来降低HDAC5的表达, 用5-Aza-dC抑制甲基化可降低HDAC5的表达。体内外研究表明, miR-589-5p/HDAC5通路在NSCLC细胞的迁移、侵袭和致瘤性中起关键作用[35]。在人类SCLC中, 另一个全面参与调节肿瘤进展的miRNA是miR-886-3p, 这种miRNA在66%的SCLC中被甲基化沉默, 其表达减少与生存期缩短相关。重要的是, miR-886-3p的再表达通过抑制其靶基因*PLK1*(polo-like kinase 1)和*TGFβ1*(transforming growth factor在β1)可以强烈抑制H446细胞的增殖、迁移和侵袭[36]。

一些miRNA参与调控肿瘤细胞的EMT过程, 如miR-200家族(miR-200a、miR-200b、miR-200c、miR-141和miR-429)通过靶向包括E盒结合锌指蛋白1(zinc finger E-box-binding protein 1, ZEB1)、GATA3、miR-132和miR-149在内的多种EMT效应器, 后者miRNA靶向ZEB2和叉头盆蛋白质M1(forkhead box protein M1, FOXM1), 并且ZEB2是下调E-钙黏蛋白(E-cadherin, CDH1)的转录抑制因子, 在肿瘤转移中起重要作用[37-38]。在NSCLC中, miR-200c表达的丢失与启动子甲基化相关, 且miR-200c表达下调又与分化不良、淋巴结转移和E-钙黏蛋白表达减弱相关[37]。

3.1.2 *增殖与凋亡* 控制细胞增殖、凋亡和分化的基因的功能异常和表达谱的改变是肿瘤恶性过程的关键特征。大多数癌症发病的关键是细胞周期阻滞的中断。miR-129在4株肺癌细胞中处于高甲基化状态, 脱甲基药物DAC处理恢复miR-129的水平后, 后者在G_2/M期通过Wee1使CDK1失活, 从而抑制肺癌细胞增殖, 并通过控制核因子-κB(nuclear factor-kappaB, NF-κB)和基质金属蛋白酶2(matrix metalloproteinase 2, MMP2)的蛋白水平来减少肺癌细胞迁移和侵袭[39]。miR-1179在原发性NSCLC组织中较非恶性肺组织中甲基化水平高, 并且以*CCNE1*(cyclin E1)为靶基因调控癌细胞的增殖[40]。miR-127在NSCLC中

被甲基化沉默, 并且通过调节Bcl-6发挥肿瘤抑制功能[41]。受甲基化调控下调的miR-137通过靶向细胞周期分裂蛋白42(cell division cycle 42, Cdc42)和周期蛋白依赖性激酶6(cyclin-dependent kinase 6, Cdk6)调控肺癌细胞的周期进程, 影响细胞的增殖[41]。

miR-193a和miR-9-3在NSCLC患者中高甲基化, miR-193a去甲基化有利于通过抑制Mcl-1(myeloid cell leukemia-1)来抑制细胞增殖和诱导凋亡[42-43]。在miR-9-3下调的NSCLC细胞中, miR-9-3启动子受甲基化调控出现高甲基化状态, 5-Aza-dC可逆转miR-9-3水平, 从而下调其靶基因*NF-κB*的表达[43-44]。然而, miR-9在人肺癌中的表达并不相同, 一些研究显示, miR-9上调并促进肿瘤转移[45-46], 另一些研究发现, miR-9在肿瘤细胞中下调, 能够抑制增殖, 促进凋亡[43,47]。虽然很难解释产生这些矛盾结果的确切原因, 但其中一个可能的原因是, miR-9-3在肿瘤发生中具有复杂的双重作用。

3.2 DNA低甲基化miRNA对肺癌的影响

导致肿瘤DNA低甲基化的机制尚未阐明。DNA低甲基化的原因多种多样, 包括饮食中*S*-腺苷蛋氨酸前体或叶酸的缺乏, 或甲基供体代谢途径的遗传异常。另外, DNA低甲基化也可归因于DNMT的缺乏。基因启动子区域的低甲基化可以增加转座子的表达而导致基因组稳定性的降低。生理条件下, 转座子的表达通常被DNA甲基化沉默, 但在病理条件下, 甲基化的降低导致染色体的不稳定和原癌基因活化, 从而促进肿瘤的发生。DNA低甲基化在转移癌中比在肿瘤转化的早期更常见[48]。

肿瘤基因组广泛低甲基化的程度与肿瘤恶性程度密切相关, 其作为生物学指标具有一定的诊断价值。部分促癌miRNA启动子区的异常低甲基化诱导其表达增加, 发挥对靶基因的抑制作用, 促进肿瘤的发展和转移。miR-135b在高侵袭性NSCLC细胞中上调, 通过靶向Hippo途径中的多个关键成分如LATS2(large tumor suppressor, homolog 2)、β-TrCP(beta-transducin repeats-containing protein)、NDR2(nuclear Dbf2-related 2)、LZTS1(leucine zipper, putative tumor suppressor 1), 增强了肿瘤细胞的体外侵袭、原位肺癌生长和迁移能力。miR-135b受DNA去甲基化和NF-κB信号双重调控, 提示miR-135b在肿瘤中的异常表达可能是炎症和表观遗传调控的共同结果[49]。研究发现, 位于染色体14q32上与淋巴结转移相关的miRNA簇(miR-539、miR-323b和miR-487a)的过度表达与各自的基因组低甲基化有关, 促进了肿瘤细胞的迁移和侵袭性, 有助于LAC细胞的转移[50]。

let-7a-3的CpG岛在正常细胞中高度甲基化, 但在LAC细胞中低甲基化, 导致其高表达。在肺癌细胞中, let-7a-3通过作用于参与细胞增殖、黏附和分化的多个基因而发挥促癌作用[51]。CUI等[52]的研究显示, miR-224在NSCLC组织中显著上调, 尤其是在切除的NSCLC转移中, 并发现miR-224启动子低甲基化和激活的ERK信号通路参与了miR-224在NSCLC中的表达调控。上调的miR-224通过改变肿瘤抑制因子SMAD4(mothers against decapentaplegic homolog 4)和TNFAIP1(tumor necrosis factor, alpha-induced protein 1)的部分拮抗功能的平衡, 促进NSCLC的侵袭和生长。SHEN等[53]比较LSCC组织与邻近正常组织, 发现7个miRNA在LSCC组织中甲基化异常(低甲基化与高甲基化), 并且E2F1-Cdc25A、miR29a-RAN、miR326-TBL1XR1可能参与LSCC的发展。另外在体外实验中发现, 与肺上皮细胞BEAS-2B相比, LSCC细胞系SK-MES-1中, miR-200家族的表达水平较高, 而ZEB1的表达水平较低。过表达miR-200c能够显著降低ZEB1和ZEB2的表达, 抑制了SK-MES-1细胞的增殖和迁移, 说明异常甲基化的miR-200家族和ZEB1/ZEB2之间的前馈环也参与了LSCC的发展。这与前文所述miR-200家族在NSCLC中高甲基化表现相反, 说明基于不同的癌症类型、转移过程, miR-200成员发挥不同的作用。

3.3 miRNA甲基化对肺癌放疗与化疗敏感性的影响

化疗是临床治疗癌症的一个重要手段, 但是肿瘤细胞的耐药限制了恶性肿瘤的临床疗效和预后。miR-7高甲基化被认为是肺癌细胞顺铂(Cisplatin, CDDP)耐药的生物标记物。miR-7表达的沉默导致MAFG(musculoaponeurotic fibrosarcoma oncogene family, protein G)水平升高, MAFG的高表达能够强烈增加敏感细胞对CDDP的抵抗力, 说明miR-7对MAFG的直接调控并且参与人肿瘤细胞CDDP耐药性的形成[54-55]。另外, 肺癌标本中miR-7的非甲基化与较好的无进展生存期和总生存期相关, 在早期NSCLC中, miR-7甲基化的存在提示细胞侵袭能力增强, 尤其是对于LAC肺癌患者[56], 这不仅为早期NSCLC的表观遗传学分类奠定了基础, 还为NSCLC

的早期诊断提供了治疗决策。miR-493在CDDP耐药肺癌细胞中由于甲基化异常而沉默, miR-493在肺癌细胞中的重新表达可通过DNA损伤修复和增加体内外细胞凋亡而促进CDDP的化疗敏感性。此外还发现, 舌癌耐药蛋白1(tongue cancer resistance-related protein 1, TCRP1)是miR-493的直接功能靶点[57]。受甲基化调控的miR-503也可能影响NSCLC细胞对CDDP的敏感性, 甲基化使miR-503沉默导致FANCA(Fanconi anemia complementation group A)表达增加, FANCA通过参与DNA交联修复, 促进了癌细胞对CDDP耐药的形成[58]。miR-512和miR-373在肺癌细胞中受表观遗传学调控, 用5-Aza-dC加TSA逆转DNA甲基化和组蛋白去乙酰化, 重新表达这些miRNA可以增强CDDP诱导的细胞凋亡和抑制细胞增殖与迁移。TEAD4(TEA domain family member 4)被证实为miR-512的直接靶点, miR-373也被发现直接靶向RelA、PIK3CA和ITGα11的mRNA[59]。

研究显示, 在获得性EGFR-TKI(tyrosine kinase inhibitor)耐药的具有EMT特征的NSCLC细胞中, miR-200家族通过启动子甲基化沉默。miR-200c沉默与多种致癌途径改变有关, 包括EMT改变和LIN28B(lin-28 homolog B)过度表达。导入miR-200c可以通过PI3K/Akt信号通路和靶向ZEB1显著增强吉非替尼(Gefitinib)耐药细胞的敏感性, 诱导细胞凋亡, 也可使具有EMT特征的获得性EGFR-TKI耐药细胞产生LIN28B抑制。有趣的是, miR-200c的引入和LIN28B的敲除都对获得性EGFR-TKI耐药细胞产生了肿瘤抑制作用, 而对亲代细胞则没有影响[60-61]。这些数据提示, 以受甲基化调控的miRNA作为预防肺癌化疗耐药的潜在治疗靶点, 利用表观遗传干预可能是改善现有治疗方法的一个有希望的途径。

因启动子高甲基化而表达下调的miR-203参与DNMT1-miR-203-Survivin信号轴的调控, 可以增强内抑素和紫杉醇的联合治疗对DNMT1和/或Survivin过表达的NSCLC患者的化疗疗效[62]。

放射治疗与基因治疗相结合对于提高NSCLC的治疗效果至关重要。在NSCLC的研究中, miR-9基因的启动子甲基化状态随着电离辐射的反应而增加, miR-9的激活可以赋予癌细胞电离辐射敏感性, 使肺癌的治疗效果显著改善, 表明miR-9增强了NSCLC的放射敏感性, 并且这种作用受其启动子甲基化状态的高度调控[63]。受甲基化调控下调的miR-200a在NSCLC细胞受到电离辐射后表达上调, 其通过抑制HGF(hepatocyte growth factor)/c-Met途径中的关键因子HGF的表达来调节肿瘤的恶性程度和放射敏感性[64]。

4 结语和展望

在长期对肺癌的研究与治疗过程中了解到, 癌细胞的局部和远处转移是决定肺癌患者生存率的关键, 检测和抑制肿瘤细胞的扩散可以提高肺癌患者的预后, 这促使开发具有诊断和治疗意义的肿瘤生物标志物至关重要。对癌症早的期诊断可以增加治疗的有效性和适当的监测机会, miRNA在组织和生物流体(如血液、血清、尿液)中非常稳定并可被检测, 具有高灵敏度和特异性, 因此, miRNA特异基因的甲基化检测有望成为癌症早期诊断的分子标志物、靶点和判断预后的手段。异常的DNA甲基化发生在癌症发展的早期阶段, 而特定的基因似乎在不同的肿瘤阶段被甲基化, 并且甲基化是可逆的。以DNA甲基化miRNA作为治疗靶点, 寻找针对肿瘤发生发展的特定驱动因素, 将临床化疗药物与之相结合发挥协同作用, 可以为临床治疗提供新的有效途径。

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