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·综述·

miR-206在肿瘤中的作用及机制研究进展

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【摘要】 微小RNA (microRNA,miRNA)是一类由内源基因编码的长度约为22个核苷酸的非编码单链RNA分子,它们在动植物中参与转录后基因表达调控,其在细胞增殖、分化、凋亡等诸多生理过程中发挥着重要作用。MicroRNA-206 (miR-206)定位于人类第6号染色体上,参与人体中一系列的生物学过程例如细胞增殖、组织器官的生长及肿瘤的发生等。miR-206在肺癌、乳腺癌、胃癌、肝癌及其他肿瘤中发挥抑癌或促癌作用,本文就其在不同肿瘤中的生理活性做一综述。

【关键词】 微小RNA;miR-206;肿瘤;增殖;调节基因;
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Research advances of miR-206 in the development and progression of tumors. *WANG Ao, JIAN Shao-qin, REN Ying-meng, XIAO Man, CAI Wang-wei. Department of Biochemistry and Molecular Biology, Hainan Medical University, Haikou 570100, Hainan, CHINA*

【**Abstract**】 MicroRNAs (miRNAs) are a kind of non-coding single stranded RNA molecules about 22 nucleotides in length encoded by endogenous genes. They participate in the regulation of post transcriptional gene expression both in animals and plants, and play an important role in many physiological processes such as cell proliferation, differentiation, and apoptosis. MicroRNA-206 (miR-206) is located on human chromosome 6 and takes part in a series of biological processes in the human body as like as cell proliferation, growth of tissues and organs, and tumorigenesis. miR-206 plays a role in suppressing or promoting cell growth in lung cancer, breast cancer, gastric cancer, liver cancer and other tumors. This article reviews its physiological activity in different tumor.

【**Key words**】 microRNA; miR-206; Tumor; Proliferation; Regulatory gene

微小RNA (microRNA,miRNA)是一类长度为22(19~25)个核苷酸左右,5'端带磷酸基团、3'端带羟基的的非编码调控家族RNA[1]。其通过与特定mRNAs的3'非编码区(3-UTRs)结合来调节基因表达[2],并在个体发育、增殖和分化中发挥重要作用[3-4]。miRNA在个体发育的不同时期及组织中表达模式也不尽相同,约50%已被注释的miRNA在基因组上定位于肿瘤相关的脆性位点,提示miRNA在肿瘤的发生发展中具有重要作用[5]。

miR-206位于人类第6号染色体上,是肌肉特异表达的miR-1家族成员之一,其他成员包括miR-133a-1、miR-133a-2、miR-133b、miR-1-1与miR-1-2[6]。其中,miR-1-2与miR-133a-1、miR-133a-2与miR-1-1、miR-206与miR-133b分别构成作用相反的三个基因簇[7]。研究显示,miR-206可与上百个靶基因相结合(如CORO1C、SMIM14、ARPC3、PTPLAD1及TAGLN2等),且近半数以上的结合靶基因与细胞增殖、分化、凋亡、侵袭、转移等生理过程密切相关,这表明miR-206及其靶基因组成的复杂生物调控网络在肿瘤发生发展中发挥重要作用。

1　miR-206与肺癌

肺癌是全球范围内导致肿瘤死亡的主要原因,死亡人数约为140万[8-11]。非小细胞肺癌(NSCLC),包括包括鳞癌、腺癌、大细胞癌,占肺癌的85%[12-15]。五年来,晚期癌症的总生存率仅为5%~20%[16-20]。尽管目前采用了预防性手术、放疗和药物治疗,肺癌的总体存活率仍然不高[21-23],因此,确定无创、新的预测性生物标记物对于肺癌的治疗靶向性发展非常重要。

许多研究表明miRNA-206的异常表达在肺癌的发生发展过程中扮演着十分重要的角色。MENG等[24]发现在35例肺腺癌样本与及肺腺癌细胞系(A549、SPC-A1、h1299和h23)中,Rmrp2基因表达明显上调;其中Rmrp2基因有促进肺腺癌细胞增殖、形成和侵袭的作用,在H1299细胞中Rmrp2过表达后,miR-206的表达受到抑制,而Kras、Fmnl2和Sox9基因的表达却上调;当miR-206过表达后,逆转了Rmrp2诱导的H1299细胞的增殖和迁移,这就表明在肺腺癌中miR-206的表达与癌细胞增殖与迁移具有负相关性。 最近WATT等[25]在H1299肿瘤异种移植实验中发现,miR-206的稳定表达抑制了小鼠肿瘤的生长和

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转移，同时利用测序技术对肿瘤生长与转移的相关靶基因进行分析，发现miR-206调控TGF-β信号转导的基因网络，其中主要包括TGFB1配体，Smad3基因的直接转录靶点；这些结果表明miR-206可以通过限制TGF-β的自分泌来抑制肿瘤的生长和转移。另外ZHANG等[26]证实miR-206可作为肿瘤抑制因子，其通过p-Smad3调节癌基因TRIB2的活性，从而诱导肺腺癌细胞死亡并抑制癌细胞增殖。WU等[27]证明SNHG14可通过抑制miR-206-3p/abcb1通路，使非小细胞肺癌患者产生吉非替尼耐药性，表明miR-206在获得性耐药中也起一定的作用。

总之，miR-206可以通过调节MET、Smad3、EGFR和TGF-β等相关信号通路，诱导肺癌细胞凋亡，抑制细胞增殖、迁移和侵袭，增强肺癌细胞的耐药性。这些研究结果表明miR-206可通过调节不同基因的相关分子途径，从而在肺癌中起到促进肺癌细胞凋亡、抑制肺癌细胞增殖及肿瘤血管生成、最终达到抑制肿瘤生长的作用，这可能为肺癌患者的预后和生存率的改善提供临床证据。

2 miR-206与乳腺癌

乳腺癌是女性最常见的恶性肿瘤之一，占所有恶性肿瘤的8%~12%[28]。TURNER等[29]、HINDIE等[30]预测在未来50年内，乳腺癌的发病率将超过50%，5年生存率仅为62.4%，将成为仅次于胃癌的第二常见恶性肿瘤。乳腺癌早期通常无明显症状，容易被忽视，导致死亡率高。乳腺癌因其发病率和死亡率高，长期以来一直是临床研究的热点。

最近QUAN等[31]对372例乳腺癌患者的癌标本和癌旁组织进行检测，结果发现miR-206在乳腺癌组织中的表达水平显著高于癌旁组织，因此确定miR-206可作为预测乳腺癌患者重要的临床指标。同样AMIR等[32]检测了miR-206对Tbx3的调节作用，结果证明Tbx3被miR-206直接抑制，并且使乳腺肿瘤细胞增殖受到抑制、侵袭减弱，肿瘤干细胞数量减少。XIANG等[33]发现WDR1可通过RhoA-MRTF-A信号途径促进EMT标记物及迁移标记物的表达，从而增强MRTF-A诱导的乳腺癌细胞迁移。MRTF-A再通过启动子CArG-box促进miR-206的表达，但是miR-206可通过3'-UTR抑制WDR1和MRTF-A的表达，进而使乳腺癌细胞的迁移率下降。LIANG等[34]研究发现，miR-206在三阴性乳腺癌中表达下调；miR-206的降低水平与VEGF的表达水平呈负相关；而将miR-206模拟物转染至三阴性乳腺癌细胞后，使VEGF、MAPK3和SOX9的基因表达水平明显下调，最终证实miR-206可抑制三阴性乳腺癌乳腺细胞的侵袭和血管生成。

简而言之，miR-206的表达与乳腺癌的发生发展有着密切的关系，深入探讨miR-206的表达与PTP1B[35]、TM4SF1[36]、HDAC9[37]、TGF-β[38]、Nrp1[39]、FTH1P3[40]等相关基因的关联对今后乳腺癌的诊断、治疗和预后判断都具有重要意义。

3 miR-206与肝癌

肝细胞癌是全世界癌症相关死亡的第三大原因[41]。肝癌的发病率不断上升、转移复发率和死亡率居高不下，已成为对人类健康的严重威胁[42-43]。研究表明，肝癌的发生与许多因素有关，如基因组和表观遗传学改变、基因表达异常和信号转导功能障碍[44-47]。一般来说，肝癌的发生机制尚不清楚，但近年来对于miRNAs作为肿瘤抑制基因或癌基因，在肝癌细胞的增殖、侵袭、迁移和凋亡中的作用研究越来越多，已然成为一个研究热点。

最近WANG等[48]对27例人肝癌组织和相应的癌旁组织进行对比，发现miR-206在肝癌组织中的表达较癌旁组织明显降低，而cMET在人肝癌组织中表达上调，cMET水平与miR-206表达呈负相关；并且miR-206在三种肝癌细胞系(SMMC-7721、HepG2和Huh7)中表达增强，且抑制了细胞生长、转移和侵袭，促进了细胞凋亡；最终证实在肝癌细胞中miR-206可与cMET基因的3'-UTR为结合，使cMET表达量增加，从而降低了miR-206对肝癌的抑制作用。同样YANG等[49]在人肝癌细胞株hepg2和Huh7中，通过萤光素酶报告基因检测发现miR-206可通过与PTP1B mRNA的3'-UTR结合而抑制了PTP1B的表达；过表达PTP1B后，mir-206对癌细胞的增殖、迁移、侵袭抑制作用减弱；最终证实miR-206通过靶向PTP1B抑制肝癌的发生发展。PANG等[50]发现miR-206在肝癌细胞系中的表达水平明显低于正常肝细胞系(L02)，且CDK9在肝癌细胞株中表达上调；通过萤光素酶报告基因检测miR-206直接结合其mRNA 3′ UTR下调肝癌细胞CDK9，进一步发现miR-206具有抑制细胞增殖，诱导细胞周期阻滞和凋亡的作用，而CDK9具有促进细胞增殖、抑制细胞凋亡的作用；miR-206过表达或抑制CDK9后，细胞增殖受到抑制、细胞周期受到阻滞、细胞凋亡得到增强；最终得出结论：miR-206通过靶向CDK9抑制肝癌细胞的生长，提示miR-206-CDK9通路可能是肝癌治疗的新靶点。另外TU等[51]预测了CDK14可作为miR-206的靶点，并证明了它们之间的相关性，向我们暗示LITC00707/miR-206/CDK14轴参与了肝癌的发生，而miR-206可能是肝癌的生物标志物。

根据上述结论，miR-206对肝癌细胞的增殖、转移和侵袭有较好的抑制作用，但其作用机制目前尚不清楚，有待进一步的研究。

4 miR-206与胃癌

胃癌是人类最常见的恶性肿瘤之一，其发病机制尚不清楚。胃癌的发生与多种因素有关，如生活方

式、幽门螺杆菌感染、息肉、胃溃疡、遗传病和残留胃组织等[52-53]。胃癌早期无特异性症状，当症状变得相当明显时，大多数患者通常以至晚期，有时伴有远处转移，导致较高的死亡率和较低的5年生存率[54]。因此针对胃癌的早期诊断与治疗及分子机制的研究已成为大家非常关注的问题。

最近DENG等[55]通过荧光素酶报告基因检测表明miR-206可能直接与MUC1基因的3'UTR结合，抑制MUC1的表达，并且在胃癌组织中MUC1与miR-206的表达水平呈负相关；当过度表达MUC1后，miR-206表达下调，而癌细胞的增殖、迁移和侵袭力增强、细胞凋亡受到抑制，这些结果表明miR-206可能通过抑制MUC1的表达而发挥抗肿瘤作用，这可能是胃癌治疗的一个有效和潜在的靶点。ZHENG等[56]检测了40例胃癌组织及邻近正常组织，发现在胃癌组织中miR-206表达水平明显降低，与此同时c-Met水平缺显著增高，两者呈反比例关系；进一步研究表明miR-206抑制了细胞增殖与迁移，诱导了细胞周期阻滞，并且c-Met下调抑制了胃癌细胞增殖、迁移和侵袭，最终证实在胃癌中miR-206受到抑制，使c-Met表达增高，从而引起了胃癌细胞的异常增殖和迁移。CHEN等[57]证明miR-206的低表达与胃癌细胞的顺铂抗性有关，增强miR-206的表达可通过靶向抑制MAPK3的表达来减弱耐药性胃癌细胞的增殖，从而促进细胞凋亡并降低顺铂耐药性。ZHANG等[58]发现miR-206在30份胃癌样品和胃癌细胞株中表达明显下降，并且miR-206的过表达抑制了胃癌细胞的生长和克隆的形成能力；之后进一步的研究表明miR-206通过靶向细胞周期蛋白2 (CCND2)进而抑制胃癌细胞的增殖。

总的来说，miR-206的表达量高低与胃癌的发生、发展、转移及预后密切相关，这为临床检测及治疗提供潜在的生物靶点，但具体深入机制还有待进一步阐明。

5 miR-206与其他肿瘤

miR-206除了与上述四种肿瘤的发生、发展密切相关外，还参与肾癌[59]、膀胱癌[60]、胰腺癌[61]、鼻咽癌[62]、喉癌[63]、胆囊癌[64]等多种肿瘤的基因调控。WANG等[65]研究表明miR-206可通过靶向BAG3抑制人宫颈癌细胞的增殖、迁移和侵袭。WANG等[66]发现miR-206通过抑制RAP1B的表达，进而抑制了甲状腺癌细胞的增殖、侵袭和迁移活性。ZHOU等[67]证实miR-206在胶质母细胞瘤的发生发展中起着关键的抑制作用，并通过下调FZD7发挥抑制肿瘤生长的作用。PARK等[68]发现miR-206可通过靶向TM4SF1抑制PGE2诱导的结直肠癌细胞的增殖，迁移和侵袭。DAI等[69]研究表明miR-206可通过直接靶向c-Met抑制c-Met/AKT/mTOR信号通路，从而抑制上皮性卵巢癌细胞的生长。WANG等[70]证实miR-206对前列腺癌细胞增殖和迁移有抑制作用，并可作为前列腺癌的肿瘤抑制因子通过靶向xcl11a来抑制细胞周期。ZHANG等[71]发现miR-206在食管癌中下调，miR-206的过表达可能通过c-Met/AKT/mTOR信号通路抑制食管癌细胞增殖并诱导细胞凋亡。LIU等[72]研究表明miR-206可能通过PTEN/AKT/mTOR途径调控下游靶基因HDAC6，从而促进头颈部鳞状细胞癌细胞的增殖。ZHAN等[73]发现miR-206可通过靶向PAX3和MET的表达在体外降低骨肉瘤细胞增殖，并下调PI3K-AKT和MAPK-ERK的信号通路。

上述结果显示miR-206可通过多种不同信号通路和靶点来调控肿瘤细胞增殖、迁移和侵袭。可见miR-206在肿瘤防治方面有很大的临床应用潜能，并为临床针对不同信号通路进行靶向治疗提供参考。

6 展望

综上所述，miR-206在大部分肿瘤组织呈现低表达状态，但在正常生理状态下miR-206在组织中呈现高表达状态，由此可见miR-206的表达对机体是更为有利的，甚至可以作为一种“抑癌基因”，起到抗肿瘤的作用；但在极少数肿瘤中miR-206却呈高表达状态，堪比“癌基因”，起到促肿瘤作用。从miR-206对基因表达调控的作用也表明miR-206在人类肿瘤的发生发展中起着至关重要的作用。miR-206不管是作为一种抑癌或是促癌因子，在临床肿瘤预防、早期诊断、靶向治疗等方面上显示出巨大的应用价值，但它与肿瘤发生发展的具体关系及分子机制仍有待进一步探究。

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