miR-21在头颈肿瘤中的研究进展

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摘要 微小RNA(microRNA, miRNA)是一类小分子非编码RNA, 可引起靶mRNA的降解或翻译抑制, 从而对基因进行转录后表达调控, 它在细胞生长、发育和衰老等生命过程中扮演着重要角色。miR-21在人类组织和细胞中较早发现, 是广泛存在的miRNA之一, 也是实体肿瘤中最常见的过高表达miRNA之一, 在肿瘤的发生发展中可能发挥癌基因的作用。该文就miR-21在头颈肿瘤中的研究作一综述。

关键词 头颈肿瘤; miRNA-21; 机制

The Research Progress of miR-21 in Head and Neck Cancer

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Abstract MicroRNA (miRNA) is a kind of small non-coding RNA, which can cause degradation or translation inhibition of target miRNA, and thus, it regulates the expression of genes after transcription. It plays an important role in cell growth, development and aging. miR-21 is one of miRNA which was found earlier and exists extensively in human tissues and cells, and is also one of the most common overexpressed miRNA in solid tumors. It may play a role as an oncogene in the development of tumors. This article reviews the research of miR-21 in head and neck tumors.

Keywords head and neck cancer; miRNA-21; mechanism

尽管目前对于癌症的治疗取得了很大进展, 但头颈部鳞状细胞癌(head and neck squamous cell carcinoma, HNSCC)的死亡率仍然很高。许多研究已经证实了miRNA在癌症治疗中的潜在作用, 微小RNA(microRNA, miRNA)主要作为肿瘤抑制基因或致癌基因发挥作用。转移是癌症的一个标志, 被定义为疾病从一个器官或器官的一部分转移到另一个不直接与之相连的部分。颈部淋巴结转移是影响HNSCC患者预后的重要因素[1], 转移后其存活率降低约50%[2-3], 由于缺乏临床症状, HNSCC在疾病的早期阶段通常不被发现[4]。因此, 寻找新的早期诊断策略以及基于miRNA的治疗剂的开发是非常有意义的, 并且这对于癌症的治疗具有重要意义。

1 miRNA及miR-21概述

miRNA是一类由约22个核苷酸组成的高度保

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守的内源性、非编码小RNA分子, 广泛存在于动物、植物等细胞内。最早发现的miRNA是miRNA-lin-4, 由Lee等[5]在线虫中发现的。miRNA的生物合成需要经历两个过程: 首先, 初期miRNA编码基因转录生成初级转录产物即pri-miRNA, 转录产物很快被核糖核酸酶剪切、加工成为含有60~70个核苷酸的前体miRNA(pre-miRNA); 其次, pre-miRNA由胞核转运至胞质中, 在另一种核糖核酸酶以及解旋酶和ATP的共同作用下剪切、加工成含有22个核苷酸左右的成熟miRNA[6]。miRNA可以与靶基因以互补配对原则相结合, 从而抑制或降解目标mRNA转录, 以达到负性调控靶基因的目的。目前已证实miRNA广泛参与细胞的生长、分化、衰老和防御等过程, 并对人类的生命活动起着积极作用[7]。

miR-21是miRNA的一员, 也称为miRNA-21、miR-21, 如果指人类miRNA, 则也称为hsa-miR-21, 人类miR-21基因位于染色体17q23.2上的跨膜蛋白49编码基因(transmembrane protein-49, *TMEM-49*)[8]。研究发现, miR-21在非小细胞肺癌、喉鳞状细胞癌、乳腺癌、胶质母细胞瘤、胃癌、胰腺癌、肝癌、结肠癌、卵巢癌、骨肉瘤和慢性淋巴细胞性白血病等组织中均表达上调, 是实体肿瘤中最常见的过高表达miRNA之一, 在肿瘤的发生发展中可能发挥癌基因的作用[9-11]。

2 miR-21与头颈肿瘤

在全球范围内, 头颈部鳞状细胞癌是第六大常见癌症, 每年发病人数为60万, 总体死亡率为50%~60%。2013年, 美国报告的新病例为53 640例, 占所有癌症的3%[12]。所有头颈部恶性肿瘤都来自各个部位(包括口腔、咽喉和喉部)的表面黏膜。尽管它们有共同的组织学起源, 但是颈部鳞状细胞癌在行为和遗传学上是异质的。总的来说, miR-21在头颈部肿瘤中表达上升, 且可用于评估治疗效果并作为预后判断的标志物[13]。

2.1 miR-21与鼻咽癌

鼻咽癌(nasopharyngeal carcinoma, NPC)每年引起8万例新发病例和5万人死亡, 占头颈部肿瘤发病率首位, 是我国高发肿瘤之一[14]。Heshenq等[15]发现, NPC中miR-21的表达与临床分期、淋巴结转移成正相关, 信号传导与转录激活因子3(signal transducer and activator of transcription 3, STAT3)直接在鼻咽癌细胞株中激活miR-21以及miR-21显著抑制第10号染色体缺失的磷酸酶张力蛋白同源物基因(phosphatase and tensin homology deleted on chromosome ten, *PTEN*), 从而增加蛋白激酶B(protein kinase B, Akt)的活性, 诱导NPC的增殖和抑制凋亡。Yumei等[16]通过52例配对样本证明了miR-21抑制剂下调B淋巴细胞瘤-2(B-cell lymphoma-2, Bcl-2)的表达水平, 且抑制鼻咽癌迁移及增殖并促进其凋亡。Miao等[17]发现, NPC中的miR-21能诱导IL-10(+)B细胞, 后者能够抑制CD8(+)T细胞活性, 认为miR-21可能是NPC治疗的潜在靶点, 还有发现miR-21的下调能增强鼻咽癌细

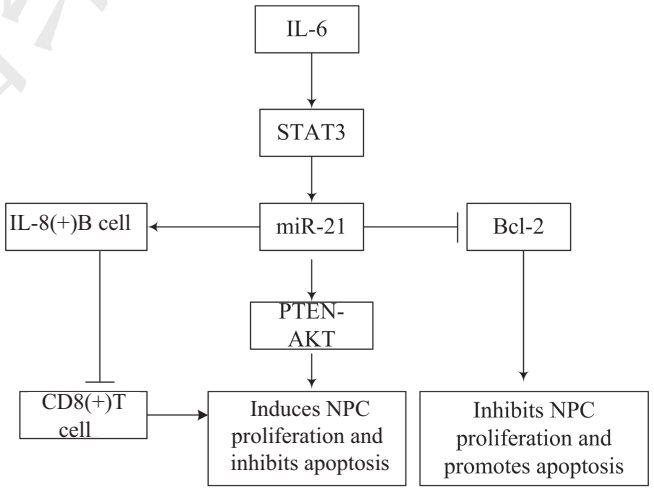

图1 miR-21在鼻咽癌中的主要作用机制(根据参考文献[15-17]修改)

Fig.1 The main mechanism of miR-21 in nasopharyngeal carcinoma (modified from reference [15-17])

胞对放疗的敏感性[18]。综合目前研究, 我们可以得出miR-21在鼻咽癌中的主要作用机制(图1), 日后可根据现有机制来阻断或治疗鼻咽癌。

2.2 miR-21与喉癌、喉咽癌

喉鳞状细胞癌(laryngeal squamous cell carcinoma, LSCC)是仅次于肺癌的常见呼吸系统肿瘤, 超过95%的喉癌为鳞状细胞癌[19]。喉鳞状细胞癌多发于男性, 其发病的主要危险因素包括酗酒和吸烟。研究发现, 喉鳞状细胞癌患者中的miR-21上升, 血清中miR-21的表达与LSCC的临床参数显著相关, miR-21和HOTAIR血清表达的联合可能是用来筛选LSCC的有效标志物[20]。Zhou等[21]通过Meta分析的总结也再次证实了喉癌组织中miR-21表达高于非肿瘤组织。其次, Wei等[22]发现, 喉癌前病变和LSCC患者的组织和血浆中的miR-21水平均增高, 认为miR-21参与从正常到喉癌前病变和从喉癌前病变到LSCC的疾病进展。Sasaki等[23]研究发现, 在小鼠体内miRNA-21失调使核因子-κB(nuclear factor κB, NF-κB)激活胃十二指肠液, 从而导致喉黏膜早期的癌前病变。此外, 还有研究发现, miR-21抑制剂通过第10号染色体缺失的磷酸酶张力蛋白同源物基因(phosphatase and tensin homology deleted on chromosome ten, PTEN), 即PTEN-AKT信号通路抑制人喉鳞癌Hep2细胞增殖和诱导凋亡, 且能调节细胞凋亡相关蛋白的表达[24]。喉咽鳞状细胞癌(hypopharyngeal squamous cell carcinoma, HSCC)约占所有头颈部癌症的5%[25]。国内外对于与喉咽鳞状细胞癌的报道并不多, 研究发现, miR-21在喉咽鳞状细胞癌组织中的表达上升, 癌旁正常组织相对下降[26]。综合目前研究, miR-21在喉咽癌和喉癌中的表达均上升的, 通过现有作用机制(图2)抑制miR-21的表达, 可促进癌细胞的凋亡, 并且我们可考虑把miR-21作为肿瘤标志物应用于喉鳞癌的临床检测、预后判断以及靶向治疗中。

2.3 miR-21与口腔癌

口腔鳞状细胞癌(oral squamous cell carcinoma, OSCC)是恶性的口腔肿瘤, 占全部头颅及颈部癌症的24%[14]。在过去的三十年, OSCC的治疗并不充分, 长期生存率中5年生存率只有27%[27]。对于OSCC患者来说, 更安全的、更有效的治疗以及改善长期生存和生活质量是关键。研究发现, 与对应的正常组织相比, miR-21在肿瘤组织中表达上升[28], 认为口腔癌的预后、神经浸润和miR-21升高也有关系[29-32], 且miR-21能使程序性凋亡因子4(programmed cell death protein 4, PDCD4)在恶性口腔肿瘤中低表达, PDCD4损失可能是肿瘤侵袭及淋巴结转移的关键步骤之一[33]。此外, 实验发现, miR-21介导的伴有Kazal域的富含半胱氨酸的逆转诱导蛋白(reversion inducing cysteine-rich protein with kazal motifs, RECK)的失调有助于增强肿瘤的侵袭性[34], PTEN介导的AKT活化有助于增强OSCC细胞的凋亡[35], AS-miR-21能降低口腔癌细胞中miR-21表达, 抑制细胞增殖, 降低细胞侵袭, 且研究推出miR-21的抑制作用机制为: miR-21的下降导致PTEN上升, 从而p-AKT蛋白表达量及其下游蛋白CyclinD1、Bcl-2、基质金属蛋白酶-2(matrix metalloproteinase-2, MMP-2)表达下降, OSCC细胞产发生G_1期阻滞[36]。Zhou等[37]发现, STAT3通过上调miR-21的表达和下调miR-21下游靶点, 包括PTEN、金属蛋白酶抑制因子3(tissue inhibitor of metalloproteinase 3, TIMP3)和PDCD4, 介导OSCC细

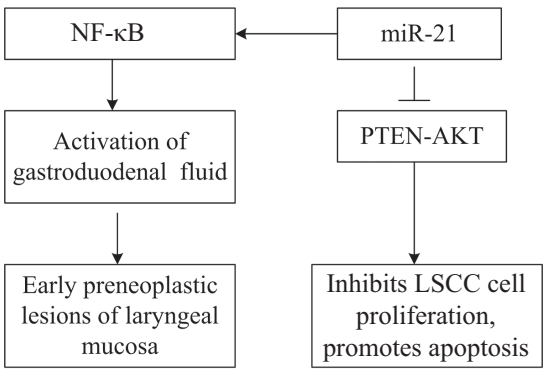

图2 miR-21在喉鳞状细胞癌中的主要作用机制(根据参考文献[23-24]修改)

Fig.2 The main mechanism of miR-21 in laryngeal squamous cell carcinoma (modified from reference [23-24])

胞存活和顺铂(cis-Dichlorodiamineplatinum, DDP)耐受, STAT3抑制剂加DDP处理可通过抑制STAT3磷酸化和miR-21表达来抑制OSCC细胞生长。随后又有研究证明, miR-21通过靶向PTEN和PDCD4, 在口腔鳞状细胞癌中发挥转移DDP抗性的作用, 即从DDP耐药的OSCC细胞释放的miR-21诱导其他OSCC细胞产生的DDP耐药性[38]。近来有研究发现, OSCC中miR-21显著上调, 且上调的miRNA靶基因与细胞蛋白代谢过程, 大分子代谢过程和转化生长因子-β(transforming growth factor-beta, TGF-β)途径有关, 认为miR-21的这些靶基因的潜在功能有利于它成为诊断OSCC的生物标志物和预后预测指标[39]。

舌鳞状细胞癌(tongue squamous cell carcinoma, TSCC)是最常见的一种口腔癌, 在一项小鼠舌癌模型的研究中发现, 表皮生长因子受体(epidermal growth factor receptor, EGFR)或AKT的阻断使人类口腔癌细胞系中的miR-21、miR-31和miR-146a表达逆转, 通过靶向STAT3/miR-21轴, STAT3抑制剂使口腔鳞状细胞癌细胞对DDP敏感[40]。Wang等[41]研究了miR-21和AS-miR-21对舌鳞状细胞癌增殖的抑制作用发现, 在舌鳞状细胞癌中miR-21与之正相关, 肿瘤内注射miR-21的反义寡核苷酸(AS-miR-21)显著抑制TSCC生长, 细胞凋亡指数增加。与此同时, 也有研究发现, miR-21沉默可抑制舌鳞状细胞癌细胞的增殖、迁移和侵袭能力, 阻止细胞周期并诱导舌鳞状细胞癌细胞株(Tca8113及其高转移株)的凋亡[42]。此外, Chen等[43]发现, 微小RNA标志物的特定组合: miR-486-3p、miR-139-5p和miR-21可以区分TSCC与非癌组织。根据目前的主要机制(图3), miR-21可能会为口腔鳞癌的基因治疗开辟一条新的道路。

2.4 miR-21与甲状腺癌

甲状腺乳头状癌(papillary thyroid carcinoma, PTC)为临床上最常见的甲状腺恶性肿瘤, 目前其具体发病机制尚不明确。Sondermann等[44]通过对66例甲状腺乳头状癌患者的研究发现, miR-9和miR-21的表达水平升高, 研究结果支持miR-9和miR-21作为甲状腺乳头状癌复发的预后生物标志物。Zhang等[45]发现, miRNA-21与PDCD4表达的相关性, 发现miRNA-21的过度表达可显着增强甲状腺乳头状癌TPC-1细胞的增殖和侵袭能力, 并抑制TPC-1细胞的凋亡, miR-21和PDCD4的表达在TPC-1细胞中显示出显著的负相关性。综上, miR-21可增强甲状腺乳头状癌细胞的增殖和侵袭能力, 因此它可作为甲状腺乳头状癌复发的预后生物标志物。Pennelli等[46]研究发现, 在甲状腺髓样癌(medullary thyroid carcinoma, MTC)中, miR-21调节PDCD4表达, 并且miR-21/PDCD4途径与临床病理变量和预后相关。此后, Chu等[47]证实了肺癌转移相关转录本1(metastasis-associated lung adenocarcinoma transcript 1, MALAT1)和miR-21的体外致癌作用, miR-21和MALAT1的过度表达可能调节MTC进展。另外, 研究还发现, miR-21和miR-181a-5p在不同类型甲状腺癌患者中的表达不同, 并且它们的比较可以帮助区分不同类型的甲状腺癌, 具有100%的敏感性和77%的特异性[48] 。

2.5 其他

目前, miR-21在头颈肿瘤中的主要研究如下(表

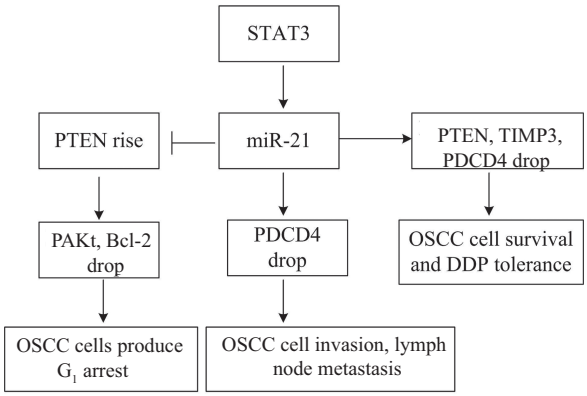

图3 miR-21在口腔鳞状细胞癌中的主要作用机制(根据参考文献[33,35-38]修改)

Fig.3 The main mechanism of miR-21 in oral squamous cell carcinoma (modified from reference [33,35-38])

表1 miR-21在头颈肿瘤中的研究

Table 1 The researches of miR-21 in head and neck cancer

肿瘤种类 Tumor types	主要途径 Pathways	参考文献 References
NPC	PTEN, Bcl-2	[15-16]
LSCC	PTEN, NF	[23-24]
OSCC	PDCD4, PTEN, STAT3	[33,35-38]
PTC, MTC	PDCD4	[44-46]

1), miR-21在头颈其他部位也有研究。Kovarikova等[49]发现, miR-21的表达上调与鼻腔鼻窦癌的发生及不良预后有关。Gui等[50]发现, miR-21抑制剂通过PTEN/PI3K/AKT信号抑制细胞增殖、迁移和侵袭。这些发现揭示了miR-21在视网膜细胞瘤进展中的分子基础, 并为视网膜细胞瘤中的细胞治疗提供了新的手段。此外, 研究还发现, 唾液腺样囊性癌中miR-21的表达水平显著高于正常唾液组织, 其在转移的肿瘤中的表达水平也高于没有转移的肿瘤, 下调miR-21显著降低唾液腺样囊性癌细胞的侵袭和迁移能力, 而pre-miR-21增加唾液腺样囊性癌细胞的侵袭和迁移能力, miR-21的表达水平与PDCD4蛋白的表达正相关, 与唾液腺样囊性癌标本中p-STAT3蛋白的表达水平负相关, 表明STAT3-miR-21-PDCD4通路在肿瘤中的潜在作用[51]。通过靶向PDCD4, miR-21失调对肿瘤生长和侵袭有重要影响[51]。因此, 抑制miR-21可能为治疗晚期唾液腺样囊性癌患者提供一种潜在的方法[51]。

3 展望

目前研究已经证实了miR-21在头颈肿瘤的发生、发展及预后中起重要作用, 也有了不少关于miR-21与头颈肿瘤机制的研究。此外, miR-21也很可能成为临床上头颈部肿瘤诊断及预后的指标。但由于所有研究的样本量不大, 同时不同人之间是否存在miR-21含量的差异, 这些都是我们目前研究的不足。未来我们可以miR-21为靶点, 继续开发新的抗肿瘤药物, 使之成为治疗的一种新方法, 从而减轻手术对生理功能以及心理状态的影响, 改善预后生存率。

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