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• 综 述 •

miR-155-5p在肿瘤中的表达、功能以及调控作用

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miR-155-5p Expression, Function and Regulation in Tumors

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Abstract: MicroRNAs (miRNAs) are a class of small, single-stranded non-coding RNAs that act as important regulators of gene expression and are involved in a number of important processes in life. A large number of studies have suggested that dysregulation of miRNA expression may be an important part of the mechanism of human tumorigenesis and progression. MiR-155-5p is mainly regarded as an oncomiR that acts on multiple target genes to participate in tumor progression, although it has been suggested to possess cancer growth suppressor effects. In this paper, we summarize the effects of miR-155-5p on cancer cell proliferation, invasion, migration, and drug resistance in various tumor types and elucidate its value as a possible potential marker in assisting diagnosis.

Key words: MicroRNA; miR-155-5p; Tumor; Drug resistance; Prognostic markers

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摘 要： MicroRNA（miRNA）是一类小的、单链非编码RNA，作为与基因表达相关的调控因子参与生命过程中的一系列重要进程。目前，已有大量研究表明miRNA的表达失调可能是人类肿瘤产生和发展机制中的重要一环。多数情况下，miR-155-5p作为一种促肿瘤microRNA，可以通过作用于多个靶基因参与肿瘤的发展进程，但也有一些研究指出该miRNA也具有抑癌基因的功能。本文对miR-155-5p在各类型肿瘤中对癌细胞增殖、侵袭、迁移和耐药的影响，以及作为可能的潜在标志物在协助诊断方面的价值作一综述。

关键词： MicroRNA；miR-155-5p；肿瘤；耐药；预后标志物

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0 引言

目前，癌症严重威胁着人类的生命健康，手术与放化疗结合的方法仍然是癌症的首选治疗方案，虽然预后得到一定程度的改善，但是由发病率和死亡率造成的全球癌症负担仍在增长[1]。因此，深入探索肿瘤的发病机制，找寻新的靶向分子来抑制癌细胞繁殖和转移，具有重要的临床意义。

近年来随着研究的深入，越来越多学者发现，基因组的非编码区在肿瘤的发展进程中起着不容小觑的作用。MicroRNA（miRNA）是一类小的、约18~25 nt长、单链、非编码的RNA，被一些酶和蛋白质加工和运输，它们最终与目标mRNA的3’-UTR（非翻译区）结合，导致翻译中断和降解，从而抑制目标基因的表达[2]。该异常表达会影响多种细胞功能和信号通路，导致细胞信号转导过程紊乱，从而促进或抑制疾病进程[3]。几乎在所有的恶性肿瘤中miRNAs的表现形式都发生了改变。作为基因表达的重要调控因子，miRNAs可能为人类癌症的早期诊断、早期医治以及疗效预测提供理论参考。

1 miR-155-5p研究概述

MicroRNA-155染色体定位于21q21.3，长1421 bp，由B细胞整合簇（BIC）基因的241-262核

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苷酸编码加工而成。BIC是鸟类白血病病毒诱导的B细胞淋巴瘤中常见的反转录病毒整合位点[4]，之后的研究证实了人类miR-155是由人类BIC转录本加工而成，现在特指hsa-miR-155-5p（miR-155-5p）[5]。miR-155-5p参与多种生理过程，大量研究已证实其在造血、炎性反应、免疫和细胞系分化中具有调控作用，尤其在促炎、致癌方面发挥关键功能。miR-155-5p在多种造血细胞中表达，Michaela等研究结果显示，miR-155-5p在血小板中高表达，在粒细胞中表达最低[6]，提示其在造血细胞中具有特异性，可用于区分造血细胞谱系。miR-155-5p也参与自身免疫疾病进程，例如，干燥综合征中miR-155-5p水平升高促进了IFN-γ诱导的炎性反应，并且通过NF-κB信号通路加重唾液腺损伤[7]；抑制miR-155-5p/IL-6/STAT3通路可以减少风湿性心脏病的瓣膜损伤[8]。综上，miR-155-5p参与了多种与造血、炎性反应和自身免疫相关的疾病进展。

2　miR-155-5p在肿瘤进展中的作用

miR-155-5p作为一种关键致癌因子起初在淋巴造血组织恶性肿瘤中得以研究[4]。后续发现，miR-155-5p水平在多种实体瘤中都有所上调，在加速肿瘤细胞繁殖、抑制细胞凋亡、促进肿瘤免疫逃避发生、上皮-间质转化（EMT）和肿瘤血管形成等方面起到促进肿瘤进展的microRNA（oncogenic miRNA, oncomiR）的作用。下面就miR-155-5p在常见肿瘤发生发展机制中的作用以及治疗前景展开综述。

2.1　通过调节癌细胞增殖促进肿瘤生长

恶性肿瘤的特征之一为肿瘤细胞增殖失调，这个过程可能通过干扰细胞周期或抑制细胞凋亡实现。研究表明miR-155-5p参与多种与细胞周期和凋亡相关的蛋白及通路的调控。泛素-蛋白酶体系统调控细胞周期过程中重要蛋白质的周转，丝氨酸蛋白酶抑制剂家族E成员1（SerpinE1）可以阻止细胞凋亡促进肿瘤细胞生存。Wang等关注到胶质母细胞瘤中miR-155-5p可以通过抑制泛素E3连接酶RNF123，促进下游靶点SerpinE1表达，增强了胶质母细胞瘤细胞株的增殖能力[9]。E2F家族的E2F转录因子2（E2F2）可以通过调节下游基因增殖细胞核抗原（PCNA）和相关激酶发挥调控细胞增殖的作用，而E2F2与miR-155-5p的表达呈负相关，在透明细胞肾细胞癌中，miR-155-5p的过度表达降低了E2F2的肿瘤抑制作用，并诱导癌细胞增殖[10]。受体相互作用蛋白激酶1（RIPK1）能够通过Caspase-8和适配蛋白Fas相关死亡域蛋白诱导死亡受体介导的细胞死亡，骨肉瘤中miR-155-5p的增多降低了RIPK1水平，抑制了癌细胞的外部凋亡通路[11]，并且miR-155-5p靶向Wnt通路抑制因子HMG-box转录因子1，通过增强Wnt通路来驱动骨肉瘤细胞增殖[12]。在肝细胞癌中，miR-155-5p通过PI3K/Akt途径抑制PTEN的表达，促进G_0/G_1转换，减少G_2期的细胞数量，导致细胞增殖活跃，促进细胞生长和肿瘤扩张[13]。miR-155-5p在乳腺癌中上调，靶向并负调控细胞因子信号转导抑制蛋白1（suppressor of cytokine signaling 1, SOCS1）、FOXO3A等具有促细胞凋亡作用因子，直接或间接调控多种癌症相关途径，抑制癌细胞凋亡，促进肿瘤进展[14]。综上，miR-155-5p一方面通过靶向调控多种细胞周期关键蛋白，干预细胞周期；另一方面发挥类似凋亡途径抑制因子作用，抑制癌细胞的外部凋亡通路，实现肿瘤细胞的无限增殖。

2.2　通过调控免疫细胞功能促进肿瘤进展

肿瘤的发展除癌细胞的特性外，还取决于它们与免疫系统的互动。肿瘤微环境（TME）由肿瘤细胞、基质细胞、浸润的免疫细胞和各种分泌的细胞因子组成，它们帮助肿瘤细胞逃避免疫监视，抵制抗原特异性T细胞的杀伤，在淋巴和血管中浸润生长，并转移到远处。TME中与肿瘤相关的M2巨噬细胞（M2 TAM）在促进肿瘤侵袭和转移方面发挥着重要作用。研究表明，M2 TAM分泌的外泌体miR-155-5p调节RAS相关结构域家族RASSF4促进非小细胞肺癌进展[15]。肾细胞癌中，miR-155-5p参与了IL-6、IL-2和IL-3炎性细胞因子介导的信号转导，可能发挥调控肾细胞癌复发时TME的作用[16]。PD-L1作为介导肿瘤免疫逃逸的关键分子之一，淋巴瘤细胞中发现PD-L1的表达被miR-155-5p上调，通过PD1/PD-L1通路抑制CD8+T细胞功能，增强肿瘤细胞的免疫耐受[17]，此外，miR-155-5p还可参与NF-κB、STAT3等通路发挥肿瘤相关免疫学效应[18]，使肿瘤细胞免疫耐受力增强，导致免疫逃逸发生。因此，以miR-155-5p作为干预靶点可能作为新的抗肿瘤思路，值得深入探究。

2.3　通过调控EMT促进肿瘤进展

EMT是肿瘤早期转移的一个重要步骤。研究表明，miR-155-5p是一种与EMT相关的miRNA，在肾癌细胞中，敲除miR-155-5p可促进癌细胞中的上

皮生物标志物E-钙黏蛋白的表达并抑制间质的生物标志物N-钙黏蛋白的水平，反之miR-155-5p的上调可在体外和体内促进EMT进展[19]。口腔鳞状细胞癌中miR-155-5p通过STAT3信号通路促进EMT转录因子Twist、Snail、Zeb1、Zeb2和Slug的表达[20]。并且有证据证实miR-155-5p在膀胱癌中也上调EMT相关基因发挥促肿瘤作用[21]。这些对EMT标志物的影响表明miR-155-5p通过参与EMT过程，在促进癌细胞迁移过程中发挥重要功能。

2.4 通过调控肿瘤血管生成促进肿瘤进展

实体瘤的重要特质之一是含有大量相互重叠、增生紊乱的不成熟新生血管。miR-155-5p作为癌基因参与促进肿瘤血管生成。三阴性乳腺癌中，缺氧环境下miR-155-5p的表达量增加，高表达的miR-155-5p通过抑制von Hippel-Lindau肿瘤抑制因子（VHL），减少了缺氧诱导因子（HIF）家族主要成员HIF2α和HIF1α的水解，促使HIF主要调节的靶基因，如血管内皮生长因子A（VEGFA）、CD44和M2型丙酮酸激酶等促血管生成因子的表达升高，诱导肿瘤血管生成[22]。Zhou等研究发现，黑色素瘤细胞中的外泌体miR-155-5p诱导肿瘤相关成纤维细胞（CAFs）激活，并通过CAFs促进VEGFA、FGF2和MMP9的表达[23]。M2型巨噬细胞极化后miR-155-5p的表达增加，并迁移到内皮细胞，以靶向E2F2和促进胰腺导管腺癌的血管生成[24]。

2.5 对肿瘤耐药的影响

放化疗是目前治疗恶性肿瘤的有效方法之一，但随着癌细胞抗性的增强，其疗效也在迅速下降。越来越多的证据表明miR-155-5p参与了抗药性，因此，研究它在辐射和药物反应中的作用，并找到化学辐射的有效靶点，探索针对不同肿瘤的个性化治疗方案，有助于新的治疗手段产生。

miR-155-5p的下调增加了耐药细胞对外部药物的敏感度。与亲代骨肉瘤细胞相比，阿霉素耐药细胞系中miR-155-5p、p-AKT和p-mTOR的表达明显增加，抑制miR-155-5p可增加抑癌基因PTEN的表达，降低骨肉瘤细胞的致瘤性，协同促进了阿霉素诱导的自噬和细胞凋亡情况[25]。对西妥昔单抗的耐药性是三阴性乳腺癌治疗中的一个主要障碍，研究发现，miR-155-5p能上调耐药细胞中Bax和活化Caspase-3的表达，负调控凋亡抑制基因BCL-2，增加耐药细胞的抗凋亡作用，而下调miR-155-5p可以通过促进GSDME、Caspase-1、IL-1β和IL-18诱导EGFR过表达的癌细胞焦亡，从而增强西妥昔单抗对EGFR过表达的乳腺癌细胞体内外抗肿瘤作用[26]。一些研究表明，外泌体向肿瘤细胞传递关键分子可能导致化疗耐药性。胃癌紫杉醇耐药细胞可以通过miR-155-5p外泌体转移，在紫杉醇敏感细胞上赋予EMT特征和耐药表型，抑制转录因子GATA3和TP53INP1的表达，增加了紫杉醇敏感细胞的耐药，而下调miR-155-5p逆转了这一现象。因此，靶向miR-155-5p可能是克服胃癌紫杉醇耐药的新策略[27]。此外，癌症患者的放射耐药可能与化疗耐药同时发生，食管癌中miR-155-5p通过激活非同源末端连接修复，上调Ku80修复双链断裂促进DNA损伤修复，诱导食管癌细胞抗辐射能力[28]。

值得注意的是，miR-155-5p在耐药细胞中的功能存在差异。有研究显示，miR-155-5p在肝癌阿霉素耐药细胞中下调，增加了癌细胞对化疗药物的抵抗[29]。出现差异的原因可能与不同类型肿瘤细胞中药物特异性有关。考虑到miR-155-5p在体内RNA调控网络中受多种miRNA相互影响，而不同的miRNA可能靶向相同的基因和信号通路来共同发挥调控功能。为了弄清它在癌症治疗和调节耐药性中的具体作用，还需根据每种药物作用途径和靶点以及肿瘤亚型细胞系的类型，详细分组进行功能研究，理清其机制。

3 miR-155-5p的双重作用

尽管miR-155-5p主要具有促肿瘤microRNA的功能，一些研究表明它也起到了抑制肿瘤的作用。如在卵巢癌和肾母细胞瘤中，miR-155-5p的表达被明显下调，出现了抑制癌细胞增殖、促进细胞凋亡等抑癌基因的特点，但在肺癌、肝癌和宫颈癌中的作用却相反。miR-155-5p受多种上游基因靶向调控，例如，在乳腺癌细胞和组织中，与癌基因相关的长链非编码RNA NORAD的表达减少，而作为NORAD靶点的miR-155-5p则受到竞争性调节，表达增加[14]。而在骨肉瘤、上皮性卵巢癌中NORAD含量显著升高[30]，miR-155-5p表达下降。

另一方面，miR-155-5p在同一类型癌症中出现表达差异可能与不同肿瘤亚型和细胞系有关，如miR-155-5p在肺鳞癌细胞系H2170中高表达并促进其侵袭和迁移[31]，然而在肺腺癌A549细胞中，miR-155-5p低水平表达，上调后显著抑制其增殖、迁移、侵袭等特性[32]。食管鳞状细胞癌的不同细胞株中，miR-155-5p在KYSE-410细胞的表达

量比KYSE-140细胞高55.3倍[28]。HPV⁺宫颈癌组织和细胞中的miR-155-5p表达水平比HPV⁻宫颈癌细胞明显下降，并且与宫颈恶化程度正相关。以上证据表明miR-155-5p在不同肿瘤组织亚型中的表达存在差异[33]。

综上所述，miR-155-5p在癌症中发挥着双重作用。这种现象产生的原因可能与其上下游基因的多功能性有关。根据TarBasev.8数据库，迄今为止受miR-155-5p直接靶向调控的mRNAs已有一百多个，然而这些靶点还可以被其他miRNAs调控。另外，当miR-155-5p发生改变，与其相关联的上游基因如LncRNAs以及circRNAs等表达也可能存在变化。以上这些有可能是造成miR-155-5p在肿瘤中表达出现差异的原因。其机制将是未来的研究方向。

4　miR-155-5p作为癌症诊断和预后生物标志物

在缺乏早期诊断和预后标志的情况下，恶性肿瘤往往在晚期才出现特定的症状。肿瘤标志物的识别可以有效地帮助临床早期检测和干预，减少不良预后和肿瘤复发。研究表明，癌症患者和健康者的体液中miRNA表达的差异可能作为预测和区分癌症类型的分子标志。在早期乳腺癌中检测miR-155-5p比肿瘤标志物更敏感，特别是在高风险组，通过评估敏感度、特异性、阳性预测值（PPV）和阴性预测值（NPV）以及miRNAs和肿瘤标志物的准确性，发现该miRNA的表达水平可能是早期乳腺癌诊断的重要分子标志物[34]。对慢性淋巴细胞白血病（chronic lymphocytic leukemia, CLL）的单变量Cox回归分析显示，CLL患者单个外周血单核细胞中miR-155-5p高表达的患者死亡风险增加4倍，而且这一结果与临床分期或其他预后标志物的表达无关，表明miR-155-5p高表达是CLL预后不良的一个有前途的分子生物标志物[3]。口腔鳞状细胞癌患者的miR-155-5p水平与TNM病理分期和疾病复发正相关。早期（Ⅰ期和Ⅱ期）口腔鳞状细胞癌患者的生存分析显示，miR-155-5p表达的升高是低无病生存率（DFS）的唯一预后影响因素，并且有miR-155-5p参与的EMT可能是口腔鳞状细胞癌复发的一个早期机制[35]。以上结果表明miR-155-5p的异常表达可能与早期诊断、不良预后和肿瘤复发有一定关联，有望成为潜在的肿瘤靶向治疗候选基因，以及辅助临床诊断和预示复发的可靠工具。除此之外，我们总结了miR-155-5p相关靶基因和作用通路在各类肿瘤组织和细胞系中的表达和功能研究，见表1。

5　结论与展望

miR-155-5p被发现在各种类型的人类癌症中失调，其在不同肿瘤类型和细胞系中的功能差异突出了miR-155-5p在肿瘤发生的复杂机制中的高度参与和重要性。因此，作为癌症的关键调节因子，采取有效手段干扰其表达可能是一种有效的抗癌治疗策略。本文总结了miR-155-5p调控参与肿瘤生长、细胞凋亡、血管生成、EMT和耐药性的诸多方面，以及它作为诊断和预后标志物的巨大潜力。由于miR-155-5p在各类肿瘤中的具体机制仍不明确，建议今后的研究在扩大样本量的同时，对样本的癌种亚型进行详细分类，明确癌细胞株的来源和类型；此外，除对miR-155-5p下游靶基因开展特异性研究外，其上游基因如lncRNAs和circRNAs对miR-155-5p的调控网络也应关注。最后，miR-155-5p在多种肿瘤中参与耐药调节的特性提醒我们还应关注与其他药物联合的治疗潜力，以及实现放化疗增敏的可能性，以便更好的发挥miR-155-5p的临床应用价值。

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表1 MiR-155-5p在人类癌症中的表达及其功能概述

Table 1 Summary of miR-155-5p expression and its functions in human cancers

Type of cancer	Expression	Target gene(s)	Pathway	Cell lines	Functions
Hepato-cellular carcinoma	Down	ATG5, BCL-2	/	HepG2	Increased the sensitivity to Adriamycin and promoted autophagy[29]
	Down	PDK1	/	Hep3B, HuH-7	Increased the sensitivity to cisplatin and promoted autophagy[36]
	Up	PTEN	PI3K/Akt	Hep3B, HepG2	Promoted proliferation, migration and invasion and suppressed apoptosis[13]
	Up	H3F3A	/	Hep3B	Promoted proliferation, migration, and invasion[37]
Colorectal cancer	Down	C/EBPβ	/	HT-29, Lovo	Increased sensitivity to chemotherapeutic agents[38]
	Up	SOCS1	JAK2-STAT3/NF-κB	HCT116, SW620	Promoted proliferation, migration, invasion, and EMT[18]
Gastric cancer	Overexpression in drug-resistant cells	GATA3, TP53INP1	/	MGC-803	Promoted proliferation, migration, invasion, and EMT and increased resistance to paclitaxel[27]
	Down	SP1, SMAD2	/	AGS	Suppressed proliferation, invasion, and migration[39]
Lung cancer	Up	RASSF4	/	A549	Promoted proliferation, migration, invasion, and EMT[15]
	Up	PD-L1	/	A549, NCI-H1650	Promoted proliferation, migration, invasion, and tumor immune escape[40]
	Down	PD- L1	/	A549, EBC-1	Suppressed proliferation, invasion, and migration[41]
Breast cancer	Up	SOCS1	/	HCC70, MCF-7	Promoted proliferation, migration, and invasion[14]
	Overexpression in drug-resistant cells	TP53INP1	/	MCF-7	Promoted proliferation, migration, and invasion and increased resistance to paclitaxel[42]
Renal cell carcinoma	Up	HuR	/	786-O, ACHN	Promoted proliferation, migration, invasion, and poor prognosis[43]
Oral cancer	Up	SOCS1	STAT3	HSC-3	Promoted proliferation, migration, invasion, EMT, and poor prognosis[20]
Chronic lympho-cytic leukemia	Up	BTLA	/	/	Promoted proliferation[44]
	Up	FOXO3	PTEN/ PI3K/AKT	/	Promoted proliferation and poor prognosis[3]
Ovarian cancer	Down	PD-L1	/	A2780	Suppressed proliferation, invasion, and migration[45]
Esophageal cancer	Up	MAP3K10	/	KYSE-140, KYSE-410	Promoted proliferation, migration, invasion, EMT, and poor prognosis and increased resistance to chemotherapeutic agents[28]
Cervical cancer	Down	PDK1	/	HeLa, SiHa, C33A	Promoted autophagy[33]
	Up	TP53INP1	/	SiHa, CaSki	Promoted proliferation, migration and invasion[46]
Osteosarcoma	Down	/	/	Saos-2, U-2 OS	Suppressed proliferation, invasion, and migration[30]
	Overexpression in drug-resistant cells	PTEN	PI3K/AKT/ mTOR	MG-63	Promoted proliferation, migration, and invasion and increased resistance to Adriamycin[25]
Thyroid cancer	Down	ETS1	/	8305C, 8505C	Suppressed proliferation, invasion, and migration[47]
	Up	/	/	/	Promoted proliferation and suppressed apoptosis and poor prognosis[48]
Melanoma	Up	SOCS1	JAK2/STAT3	B16(mouse)	Promoted tumor angiogenesis[23]
	Down	/	/	SK-MEL-28	Suppressed proliferation, invasion, and migration[49]
Pancreatic Cancer	Up	EHF	Akt/NF-κB	Capan-1, SW1990	Promoted proliferation, migration, invasion, and EMT[50]
Nephro-blastoma	Down	IGF2	PI3K/AKT/ mTOR	SK-NEP-1	Suppressed proliferation, migration, and invasion and induced apoptosis[51]
Glioma	Up	ACOT12	/	U87	Promoted proliferation and suppressed apoptosis and poor prognosis[52]
Cholangio-carcinoma	Up	SOX1	RAF/MEK/ ERK	TFK-1, HUCCT-1	Promoted proliferation, migration, and invasion[53]
Bladder cancer	Down	WEE1	/	T24	Suppressed proliferation, migration, and invasion and increased the sensitivity to gemcitabine[54]
	Up	/	/	T24, 5637	Promoted proliferation, migration, and invasion[21]
Non-Hodgkin's lymphoma	Down	APC	/	NK-92	Suppressed proliferation, migration, and invasion and induced apoptosis[55]

Note: /: not reported.

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