doi:10.7659/j.issn.1005-6947.2021.04.012
http://dx.doi.org/10.7659/j.issn.1005-6947.2021.04.012
Chinese Journal of General Surgery, 2021, 30(4):471-481.

·文献综述·

非编码 RNA 在胃癌中的作用机制研究进展

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摘　要　胃癌是目前世界上恶性程度最高的肿瘤之一。近年来大量的研究证明非编码 RNA 在胃癌的发生、增殖、转移等生物过程中占据着重要地位，其中小 RNA（miRNA）、环状 RNA（circRNA）和长链非编码 RNA（lncRNA）组成的非编码 RNA 调控网络涉及多种基因调控过程。目前对胃癌的诊断主要依赖于内镜检查，缺乏简单有效的筛查手段，针对晚期胃癌的治疗方法也十分有限。而非编码 RNA 的出现为胃癌的诊断和治疗提供了一个新的角度。miRNA 可通过与 mRNA 结合导致 mRNA 的降解，从转录后水平上调节靶基因的表达。lncRNA、circRNA 可竞争性与 miRNA 结合以拮抗 miRNA 的作用，从而间接调控基因的表达。肿瘤的产生可以认为是肿瘤细胞本身异常的生理特性、肿瘤微环境的形成及外部环境因素影响共同作用的结果。非编码 RNA 与胃癌细胞的增殖、凋亡、侵袭及转移密切相关。此外，非编码 RNA 还可参与细胞自噬调控过程，并影响肿瘤的干细胞特性及耐药性。肿瘤微环境包括肿瘤周围血管、间质细胞、免疫细胞、信号分子、细胞外基质等组成部分。一方面，非编码 RNA 可参与胃癌细胞诱导微环境形成的作用过程，例如诱导周围血管新生、免疫抑制；另一方面，非编码 RNA 可以外泌体形式参与微环境对胃癌细胞的作用，影响胃癌细胞的增殖、转移、耐药等生理过程。外部环境因素对诱导胃癌发生具有重要意义。幽门螺杆菌感染（HP）感染是导致胃癌的重要致病因素之一，非编码 RNA 与 HP 的致癌特性相关。氧化应激状态、EB 病毒感染也可诱导胃癌发生，非编码 RNA 同样也参与这些机制。非编码 RNA 在胃癌中的重要地位使其可成为潜在的胃癌诊断分子标记物或治疗靶点。目前文献多报道的是以 miRNA 转录后调控基因作用为核心，circRNA、lncRNA 为其上游调控分子的基因调控模式。lncRNA、circRNA 均可竞争性结合 miRNA，那么两者的调控关系仍未明确。circRNA 在肿瘤中的作用是近年来才被初步认识的，在胃癌中的具体调控作用机制有待进一步研究。充分认识非编码 RNA 调控网络将有助于加深对肿瘤发生机制的理解，可为胃癌的临床诊疗提供新的思路和方法。非编码 RNA 在未来或可进一步用于细化对不同胃癌特征的描述，如同基因一样成为肿瘤的“身份证”，对精准医疗、个体化医疗的发展也具有重要意义。

关键词　胃肿瘤；RNA，未翻译；微 RNAs；RNA，环状；RNA，长链非编码；综述
中图分类号：R735.2

Roles of noncoding RNAs in gastric cancer: recent advances

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Abstract　Gastric cancer is one of the most malignant tumors in the world. In recent years, a number of studies have proved that noncoding RNAs play an important part in many biological processes in gastric cancer such as initiation, proliferation

收稿日期：2020-05-14；**修订日期**：2021-03-21。
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and metastasis. The regulatory network of nocoding RNAs consisting of the micro-RNAs (miRNAs), circular RNAs (circRNAs) and long noncoding RNAs (lncRNAs) are involved in the processes of regulating a variety of gene expressions. At present, the diagnosis of gastric cancer mainly depends on endoscopy, the simple and effective screening measures are still lacking, and the treatment modalities for advanced gastric cancer are also limited. Fortunately, the appearance of noncoding RNAs offers a new perspective for diagnosis and treatment of gastric cancer. The miRNAs can bind to the mRNAs to induce their degradation, and thereby regulate the expressions their target mRNAs at post-transcriptional level. The lncRNAs and circRNAs are able to antagonize the functions of miRNAs by competitively harboring miRNAs, and thereby indirectly regulate the gene expressions. Tumorigenesis can be regarded as the joint outcome of the abnormal features of tumor cells, the formation of tumor microenvironment and the influences of external environmental factors. The noncoding RNAs are closely related to the proliferation, apoptosis, invasion and metastasis of gastric cancer cells. Furthermore, the noncoding RNAs are associated with the autophagy and have great influence on stemness and drug resistance of gastric cancer cells. Tumor microenvironment is generally consisted of the components such as the tumor peripheral vasculature, mesenchymal cells, immune cells, signaling molecules and extracellular matrix. On the one hand, the noncoding RNAs are involved in the process of the formation of tumor microenvironment such as angiogenesis and immunosuppression induced by gastric cancer cells. On the other hand, the noncoding RNAs can function as exosomes to participate the action of microenvironment on gastric cancer cells, so as to affect the biological processes that include the proliferation, metastasis, drug resistance of gastric cancer cells. External environmental factors have great significance for inducing tumorigenesis of gastric cancer. Helicobacter pylori (HP) infection is one of the important causes for the occurrence of gastric cancer, and the noncoding RNAs considerably contribute to the oncogenic properties of the HP. In addition, oxidative stress and EB virus infection can also lead to tumorigenesis of gastric cancer, which are as well associated with the noncoding RNAs. The noncoding RNAs have potential to serve as diagnostic biomarker or therapeutic targets for gastric cancer owing to their essential roles in gastric cancer. The pattern of gene expression modulation shown by majority of current reports is post-transcriptional gene regulation by miRNAs serving as the central event with the lncRNAs or circRNAs as upstream regulators. Both lncRNAs and circRNAs competitively combine with the mRNAs but their reciprocal relationship is still unidentified. The actions of circRNAs in tumor are roughly recognized in recent years and their specific roles in gastric cancer remain to be further explored. Full understanding of the roles of noncoding RNAs in gastric cancer will not only help gain insights into the mechanism of tumorigenesis but may provide novel avenues for diagnosis and treatment gastric cancer. In the future, the noncoding RNAs may probably be used for description of different characteristics of gastric cancer after specification and subdivision, and become the “tumor identity cards” just as genes, which also has great significance for the development of precision medicine or personalized medicine.

Key words Stomach Neoplasms; RNA, Untranslated; MicroRNAs; RNA, Circular; RNA, Long Noncoding; Review

CLC number: R735.2

胃癌目前是世界上恶性程度最高的肿瘤之一，根据全球癌症数据显示，2018年有超过100万例被确诊为胃癌，超过78万例死于胃癌[1]。胃癌因早期症状的隐匿性，超过60%的患者确诊时往往已失去了手术机会[2]。由于高通量测序技术的出现，近年来越来越多的研究证明非编码RNA在胃癌的发生、增殖、转移等生物过程中占据着不可或缺的地位，特别是小RNA（microRNA，miRNA）、环状RNA（circular RNA，circRNA）、长链非编码RNA（long noncoding RNA，lncRNA）涉及多种基因调控过程。有研究[3]称肿瘤组织中miR-135b的表达上调提示胃癌患者具有较差的预后，与胃癌的肿瘤分期密切相关，可成为预测胃癌患者生存期潜在的分子标记物。一项临床研究[4]表明，血液中外泌体lncRNA GC1水平在胃癌患者及健康对照组中具有明显差异，并可有效区分早期胃癌与肠

上皮化生、慢性萎缩性胃炎，使非编码RNA应用于胃癌筛查成为可能。此外，该研究还指出经过新辅助化疗后的胃癌患者lncRNA GC1水平下降，为胃癌新辅助化疗效果的判断提供了一种新的评估方法。另一方面，日益成熟的RNA干扰技术为研制抑制目标RNA表达的药物提供了可能，据此胃癌相关信号通路中的关键非编码RNA可成为潜在的治疗靶点[5]。肿瘤的发生可以被认为是肿瘤细胞本身异常的生理特性、肿瘤细胞微环境形成以及外部环境因素影响共同作用的结果。本文将从这几个方面重点阐述miRNA、circRNA、lncRNA为主的非编码RNA调控网络在胃癌中的角色，有助于加深对非编码RNA在胃癌中作用机制的理解，希望为今后的研究提供方向。

1　非编码 RNA 在胃癌中的基因调控机制

1.1　miRNA 的基因调控机制

miRNA是一组长度在19~25个核苷酸的非编码RNA，能够通过与mRNA 3’端非翻译区域结合，在RNA诱导沉默复合物（RNA induced silencing complex，RISC）的介导下导致mRNA的降解，在转录后水平上下调靶基因的表达[6]。有报道[7]称腺嘌呤甲基化修饰（N6-methyladenosine，m^6A）能介导miRNA对mRNA的抑制，在胃癌细胞中E2F3 mRNA 3'非转录区域中m^6A相关核苷酸序列“RRACU”的存在对于miR-660调控E2F3 mRNA水平至关重要。miRNA因其对基因表达的直接调控作用已成为基因表达调控网络中的重要一环，涉及多种生物进程，已发现其在肿瘤中的异常表达普遍具有重要意义。

1.2　lncRNA 的基因调控机制

lncRNA是一组长度大于200个核苷酸的非编码RNA，曾经一度被认为是不具有实际功能的基因表达的副产物，目前已发现lncRNA参与多种基因调控过程，具有分子支架、引导蛋白靶向等作用[6]。在胃癌中关于lncRNA的调控机制已有大量报道。lncRNA OLC8能够稳定IL-11蛋白，避免其降解，从而促进IL-11的表达以激活下游通路[8]。lncRNA THOR能够与SOX9 mRNA的3'端非翻译区域结合增强mRNA的稳定性，并参与调控胃癌的干细胞特性[9]。lncRNA UCA1能够与多梳抑制复合物（polycomb repressive complex 2，PRC2）的亚基EZH2结合，促进PRC2对组蛋白3上第27位赖氨酸（lysine residue 27 of histone 3，H3K27）甲基化的催化活性，而H3K27的甲基化水平能够影响抑癌基因p21的表达[10]。lncRNA FEZF1-AS1能够招募组蛋白脱甲基酶1A（lysine-specifc histone demethylase 1A，LSD1）减少组蛋白3上第4位赖氨酸（lysine residue 4 of histone 3，H3K4）的甲基化水平影响下游基因的表达[11]。此外，lncRNA能够与miRNA的靶基因mRNA竞争性结合miRNA，减少miRNA对靶基因转录后水平抑制，从而间接调控基因的表达。例如lncRNA SNHG1能与miR-140结合，减少miR-140对其靶基因ADAM10的沉默作用以影响胃癌细胞的增殖、侵袭性[12]。lncRNA ZFAS1能通过miR-200b介导的下游Wnt信号通路抑制，发挥其促进肿瘤特性的生物学作用[13]。miRNA也可在转录后水平抑制lncRNA的表达，经研究证实miR-140的异常表达能显著调控lncRNA SNHG1的表达，RNA结合蛋白免疫沉淀实验提示miR-140及lncRNA SNHG1能明显富集在同一种RISC中，由此可推测miRNA对lncRNA的调控作用[12]。

1.3　circRNA 的基因调控机制

circRNA是一类新型的非编码RNA，被认为是由mRNA前体经过头尾相接加工形成的环状RNA[14]。circRNA因其结构稳定性、在肿瘤中的表达特异度近年来成为一研究热点，多项研究揭示其在肿瘤的增殖、侵袭、凋亡等生物过程中的意义。hsa_circ_0000467被发现在胃癌组织中表达上调，其高表达的胃癌患者往往具有较差的临床预后[15]。circRNA可以竞争性结合miRNA的方式参与多种基因调控过程，与lncRNA对miRNA的调控类似。circ-ERBB2能竞争性结合miR-503、miR-637分别促进下游基因CACUL1、MMP-19的表达[16]。circ-DCAF6能吸附miR-1231、miR-1256并下调其表达，从而影响细胞进程[17]。circRNA还参与转录激活调控、mRNA前体剪切修饰过程、蛋白分子支架及rRNA的加工、成熟过程[14]，但这些调控机制在胃癌中的作用角色仍未阐明，有待进一步研究。

2　非编码 RNA 介导胃癌细胞生理特性的作用机制

2.1　非编码 RNA 与肿瘤细胞增殖、凋亡

肿瘤细胞无限增殖特性得益于细胞周期调控

异常和细胞凋亡的抑制。有大量报道提示非编码RNA参与胃癌细胞周期调控过程，例如miR-196a能够抑制HOXA5基因表达，HOXA5过表达可显著减少周期蛋白D1的表达介导抑制细胞增殖过程[18]。miR-383能直接靶向结合周期蛋白E2 mRNA抑制肿瘤细胞分裂周期从G_1期向S期转化[19]。miR-454-3p可在转录后水平抑制STAT3的表达，后者可激活下游基因周期蛋白D1调控G_1期，而抑制lncRNA HOTAIR能上调miR-454-3p的表达，间接影响细胞周期[20]。lncRNA UCA1以分子支架的形式调控H3K27的甲基化水平以抑制周期蛋白依赖性激酶抑制物（cyclin-dependent-kinase inhibitor，CKI）p21的表达[10]。circ_001569可通过吸附miR-145介导对NR4A2基因的调控，其过表达可显著减少S期、增加G_2期的胃癌细胞[21]。

非编码RNA也可调控肿瘤细胞凋亡。MCL-1属于抗凋亡Bcl-2基因家族，在胃癌细胞中lncRNA MYOSLID 可通过吸附miR-29c-3p介导促进MCL-1的表达[22]。lncRNA CCAT2可下调Bcl-2的表达，上调胱冬肽酶-8的表达以介导胃癌细胞的凋亡[23]。miR-196a可靶向调控转录因子HOXA5，抑制HOXA5诱导的胃癌细胞凋亡的作用[18]。

2.2 非编码RNA与肿瘤细胞侵袭、转移

上皮间质转化（epithelial mesenchymal transition，EMT）是细胞从上皮细胞表型转分化成间质细胞表型的过程，是肿瘤转移、侵袭性的重要机制。肿瘤细胞通过EMT减少细胞连接，重塑细胞骨架，获得游走、侵袭及转移的能力。EMT的核心机制在于E钙黏蛋白表达的减少，波形蛋白、N钙黏蛋白表达的增加。研究[24]证明ZEB1、ZEB2、Snail、Twist等是调控E钙黏蛋白的重要转录因子，可诱导EMT进程。在胃癌细胞中，非编码RNA广泛涉及EMT的调控过程。miR-574-3p、miR-495可分别靶向ZEB1、Twist1以抑制EMT进程[25-26]。circ-RBMS3可抑制miR-153对转录因子Snail家族之一SNAI1表达的下调作用以诱导EMT[27]。lncRNA PCAT1以吸附miRNA的作用通过miR-128/ZEB1调控轴促进EMT[28]。miR-1275可靶向JAZF1基因抑制胃癌细胞的侵袭和转移，后者可与波形蛋白的启动子结合以促进其表达诱导EMT[29]。转化生长因子β（transforming growth factorβ，TGF-β）信号通路是EMT的重要驱动因素，miR-106a可靶向抑制Smad7（可负调控TGF-β信号通路活性的分子）以促进EMT进程[30]。lncRNA HOTAIR可抑制乙酰转移酶CBP活性从而增加H3K27甲基化水平，后者可外部修饰E钙黏蛋白启动子调控EMT[20]。

除EMT机制外，基质金属蛋白酶（matrix metalloproteinase，MMP）家族蛋白也是促进肿瘤转移的重要因子之一，它可降解细胞外基质以促进转移，有研究[15,31]报道circ-ERBB2、lncRNA ZEB2-AS1可分别调控MMP-19、MMP-9的表达。胞外基质蛋白1（extracellular matrix protein，ECM1）也与肿瘤转移相关，在胃癌组织中表达明显上调，其表达不仅可以诱导EMT，而且可增加胃癌细胞抗失巢凋亡、腹膜种植转移的能力，而miR-92a可靶向ECM1拮抗其作用[32]。

2.3 非编码RNA与肿瘤耐药性

化疗是胃癌必不可少的辅助治疗方法，但由于在化疗过程中胃癌耐药性的产生导致化疗失败率的增加。耐药性机制与多药耐药性（multidrug resistance，MDR）、DNA修复调控、凋亡诱导调控等密切相关，非编码RNA可从多个方面参与胃癌的耐药机制。在耐阿霉素及长春新碱的胃癌细胞中，miR-1的表达可靶向可溶抗药相关性钙结合蛋白Sorcin，继而诱导耐药胃癌细胞凋亡，并促进药物排出泵P-gp和MRP-1转运体蛋白的表达，最终抑制肿瘤的MDR[33]。ATP结合盒（ATP-binding cassette，ABC）转运体蛋白是著名的MDR蛋白，能够泵出细胞毒药物，造成耐药。miR-320a、miR-4496可分别在转录水平及转录后水平上负调控ABCG2转运体蛋白的表达[34]。切除修复复合物（excision repair cross-complementing，ERCC）蛋白家族是核切除修复（nuclear excision repair，NER）信号通路的关键因子，是肿瘤对顺铂药物耐药的始动因素。ERCC1可以与ERCC4形成异聚体切除损伤DNA的5’端，而增强肿瘤对顺铂的耐药性，miR-138-5p则可实现对ERCC1、ERCC4的调控以介导胃癌细胞对顺铂的敏感度[35]。顺铂也可诱导线粒体分裂上游调控因子动力蛋白相关蛋白1（dynamin-related protein 1，DRP1）的去磷酸化，以激活DRP1促进线粒体分裂介导的细胞凋亡。A激酶锚定蛋白1（A-kinase anchoring protein 1，AKAP1）可诱导DRP1的磷酸化和失活，而miR-148a-3p可下调AKAP1水平以增强顺铂对胃癌细胞的毒性[36]。circ-AKT3可吸附miR-198促进PI3K调节亚基PIK3R1表达，继而激活PI3K/AKT信号通路，后者可上调DNA修复分子BRCA1的表

达以增强DNA损伤修复，并抑制顺铂诱导凋亡从而导致胃癌细胞对顺铂的耐药性[37]。

2.4 非编码 RNA 与细胞自噬

细胞自噬也是肿瘤耐药性产生的重要机制之一。细胞自噬是细胞内自我降解、自我消化的代谢过程。在某些因素的诱导下，部分细胞质、受损细胞器、蛋白质、病原体等成分可被双层膜胞质小泡包裹形成自噬小体，与溶酶体结合形成自噬溶酶体，最后被自噬溶酶体内的水解酶分解为满足细胞的代谢需求提供原料。细胞自噬的分子机制十分复杂，自噬相关基因家族（autophagy-related genes，ATGs）蛋白是参与自噬过程中必不可少的组成部分，蛋白激酶mTOR（mammalian target of rapamycin）也是调控自噬的重要因子。mTOR可通过磷酸化灭活自噬驱动主要蛋白激酶ULK1继而抑制自噬过程，研究[38]证实可通过激活AMPK/mTOR信号通路及PI3K/Akt/mTOR信号通路调控细胞自噬。在自噬代谢活跃的细胞中，Beclin1、LC3I/II明显上调，P62明显下调，均被作为常用的细胞自噬分子标记物。近年来大量报道揭示了细胞自噬参与调控肿瘤的增殖、凋亡、EMT、耐药性等，起着促癌或抑癌的作用。

非编码RNA也参与胃癌中细胞自噬的调控。在耐药胃癌细胞中，miR-495-3p、miR-148a-3p可分别靶向GRP78、RAB12基因以激活mTOR抑制细胞自噬，减少胃癌细胞的耐药性[36,39]。FoxM1表达可明显增加IC3II、beclin1的水平，提示其促进细胞自噬的作用，而lncRNA HULC可通过结合FoxM1蛋白阻碍其泛素化降解，以促进其在顺铂耐药的胃癌细胞中的表达，最终诱导自噬相关的耐药性产生[40]。lncRNA MALAT1可分别抑制miR-30b、miR-23b-3p对ATG5、ATG12的下调作用，继而导致自噬相关的耐药[41-42]。miR-1265则可通过下调腺苷酸活化蛋白激酶（AMP-activated protein kinase，AMPK）上游调控相关蛋白CAB39灭活AMPK/mTOR通路抑制自噬，不利于肿瘤的生长[43]。miR-133a-3p可直接靶向ATG13及GABARAPL1（可招募ULK1、Beclin1至自噬小体成核位点）阻碍胃癌细胞中的自噬过程，且饥饿环境下的胃癌细胞中miR-133a-3p的水平更低，自噬代谢更活跃。该报道还称自噬可促进谷氨酰胺分解代谢，其代谢产物一方面能促进NADPH的产生减少活性氧ROS的形成，另一方面可进入三羧酸循环产生ATP为细胞提供能量，由此增强肿瘤细胞对恶劣环境的适应程度[44]。相反地，细胞自噬也可诱导肿瘤细胞凋亡表现出抑癌的特性。miR-183可通过促进细胞自噬诱导细胞凋亡、抑制细胞增殖，可负调控自噬调控关键因子SIRT1的表达，而后者可能激活PI3K/AKT/mTOR信号通路介导自噬抑制。值得一提的是，lncRNA MALAT1也可削弱miR-183对自噬的促进作用，与其在耐药胃癌细胞中对自噬的调控角色相反[45]。

2.5 非编码 RNA 与肿瘤干细胞

目前肿瘤普遍被认为是一种干细胞疾病，即肿瘤中存在一组具有类似干细胞样的细胞亚群，被称为肿瘤干细胞（cancer stem cells，CSCs），具有自我更新及多分化潜能，能够维持肿瘤经久不衰的能力，并可增加肿瘤对化疗药物的耐药性[46]。lncRNA MALAT1、lncRNA THOR分别可结合并增强SOX2、SOX9 mRNA的稳定性而促进胃癌细胞的干细胞特性[9,47]。miR-19b/20a/92a可促进胃癌CSCs的自我更新和增殖能力，并随着胃癌CSCs的分化表达逐渐减少[48]。Lgr5是公认的胃癌CSCs的分子标记物。Lgr5阳性胃癌CSCs中miR-132较Lgr5阴性胃癌CSCs及其分化后代细胞表达明显增加，可直接靶向调控去乙酰酶SIRT1的表达。SIRT1可通过去乙酰化灭活转录因子CREB，后者可与ABCG2的启动子结合诱导Lgr5阳性胃癌CSCs的耐药性[49]。在胃癌CSCs中miR-25可转录后抑制蛋白激酶Gsk3β的表达，继而减少β连环蛋白在细胞核内的积累，β连环蛋白可激活并与T细胞因子形成转录复合物促进多种CSCs分子标记物如CD44、EpCAM的表达[50]。

2.6 非编码 RNA 与信号通路

众所周知，肿瘤细胞内的多种信号通路异常激活有助于肿瘤的发生、发展，同前文所提到的，非编码RNA也可通过调控靶基因的表达以改变多种信号通路的活性，如wnt/β-catenin[13, 51-52]、PI3K-AKT/mTOR[53-54]、JAK/STAT[55]、NF-κB[56]、Notch[57-58]、Hippo[59]、FGF[60]、Hedgehog[61]等信号通路，由此发挥对肿瘤细胞活性的促进或抑制作用。

3 非编码 RNA 介导胃癌微环境形成的作用机制

如果将肿瘤细胞比作“种子”，那肿瘤微环境（tumor microenvironment，TME）便是肿瘤发

生的“土壤”，肿瘤微环境包括周围血管、间质细胞、免疫细胞、信号分子、细胞外基质等组成部分，日益增多的证据证明肿瘤微环境的形成对肿瘤的生长、侵袭、转移至关重要。

3.1 非编码 RNA 与肿瘤内血管新生

肿瘤内异常的血管新生便是肿瘤微环境的重要因素之一，临床上已证实抗血管形成药物可起到一定的抑制肿瘤的作用。miR-632在胃癌患者血清及胃癌组织中表达上调，可通过负调控三叶因子肽家族之一TFF1基因表达而促进招募内皮细胞形成血管的能力[62]。miR-130a可以外泌体的形式被胃癌细胞分泌，作用于内皮细胞内c-MYB转录因子，后者可促进内皮细胞的增殖、迁移、形成血管[63]。血管内皮生长因子（vascular endothelial growth factor，VEGF）是促进肿瘤新生血管的重要因子，miR-377可转录后抑制VEGFA的表达[64]。miR-574-5p则可通过抑制蛋白酪氨酸磷酸化酶PTPN3以促进蛋白激酶MAPK的磷酸化水平，最终激活MAPK通路诱导VEGFA的表达[65]。circ-RanGAP1可通过抑制miR-877-3p的调控作用，继而促进后者靶基因VEGFA的表达[66]。

3.2 非编码 RNA 与肿瘤相关细胞

肿瘤相关巨噬细胞（tumor-associated macrophages，TAMs）、间质干细胞（mesenchymal stem cells，MSCs）、骨髓间质干细胞（bone marrow-derived mesenchymal stem cells，BM-MSCs）、肿瘤相关成纤维细胞（cancer-associated fibroblasts，CAFs）等细胞是肿瘤微环境的重要组成部分，均可从不同方面刺激肿瘤的生长，侵袭及转移，非编码RNA也介导这些细胞对肿瘤的促进作用。TAMs在肿瘤中的比重可达50%，是肿瘤微环境中主要的免疫细胞群体，TAMs与M2型巨噬细胞十分相似，可在Th2、IL-4、IL-10等细胞因子的作用下分化而来，其在肿瘤组织的密度增加预示着较差的临床预后[67]。TAMs可分泌miR-21进入胃癌细胞激活PTEN/PI3K/AKT信号通路，由此增强胃癌细胞的抗凋亡能力和耐药性[68]。miR-30c可抑制胃癌肿瘤组织中TAMs内REDD-1（DNA damage responses 1）的表达，而REDD-1一方面可抑制诱导向M1型巨噬细胞分化相关细胞因子的分泌，从而增加M2型巨噬细胞即TAMs的比例，另一方面可灭活mTOR信号通路。mTOR信号通路高度激活的TAMs可通过增加对葡萄糖的利用率而减少对血管内皮细胞的激活[67]。MSCs也是肿瘤微环境中一重要角色。有研究[69]称MSCs可分泌转化生长因子TGF-β1作用于胃癌细胞，后者可促进lncRNA MACC1-AS1的表达。lncRNA MACC1-AS1可通过吸附miR-145-5p促进脂肪酸氧化代谢过程，从而进一步增加胃癌细胞的干细胞特性和化疗耐药性。积累的证据表明BM-MSCs可移动进入肿瘤组织内，并分化成肿瘤相关的间质细胞如CAFs，成为肿瘤微环境的一部分。一项研究称小鼠胃癌细胞培养基可以促进小鼠BM-MSCs获得肿瘤间质细胞样表型及作用，例如增加肿瘤促进生长因子IL-6、CXCL15、VEGF的基因表达，而miR-155-5p可通过抑制NF-κB信号通路而部分削弱肿瘤细胞基质对BM-MSCs的驯化作用[70]。CAFs是肿瘤组织中最丰富的间质细胞，miR-214可通过抑制成纤维细胞生长因子FGF9的表达，削弱CAFs对胃癌细胞侵袭及转移性的促进作用[71]。

3.3 非编码 RNA 与外泌体

外泌体是指由细胞分泌的直径在40-100 nm的细胞外小泡，细胞可通过分泌外泌体促进细胞间交流，或影响周围的环境。近年来发现非编码RNA可以外泌体的形式被肿瘤细胞分泌作用于间质细胞或本身，以影响肿瘤微环境的形成，如前文提到的胃癌细胞可分泌miR-130a影响血管内皮细胞。miR-423-5p可以外泌体形式介导促进胃癌细胞及胃黏膜内皮细胞增殖和侵袭性[72]。miR-155-5p可被分泌诱导胃癌细胞的EMT进程并使其获得对紫杉醇的耐药性[73]。circ-NRIP1也可被分泌作用于胃癌细胞，通过吸附miR-149-5p上调蛋白激酶AKT1的表达，继而激活mTOR信号通路影响胃癌细胞[53]。外泌体的脂质双层膜结构可以保护其内含物不被降解，为外泌体非编码RNA成为潜在可靠的肿瘤血清诊断分子标记物提供基础。

3.4 非编码 RNA 与免疫抑制微环境

非编码RNA还可介导肿瘤免疫抑制微环境的形成。胃癌细胞可通过下调miR-200b、miR-152水平促进后者的靶点B7-H1的表达。B7-H1是一种跨膜糖蛋白，可作为配体与T细胞膜表面的PD-1（programmed death 1）受体结合，从而诱导T细胞的凋亡抑制T细胞的增殖，有助于肿瘤的免疫逃逸[74-75]。也有研究[76]称胃癌组织内浸润的淋巴细胞可导致肿瘤微环境中的乳酸堆积，乳酸可减少辅助性T细胞TH-1、细胞毒性淋巴细胞比例，而淋巴细胞中减少的miR-34水平可增加乳酸脱氢酶A水平

导致乳酸的堆积，继而促进免疫抑制微环境的形成。

3.5 非编码RNA与缺氧微环境

缺氧也是肿瘤微环境一重要特征，其可诱导缺氧诱导因子1（hypoxia-inducible factor-1，HIF-1）的产生。HIF-1α在不同细胞中的表达可从不同方面起到肿瘤促进作用，如胃癌细胞中HIF-1α的表达可上调miR-574-5p诱导产生VEGFA[65]，下调miR-338-3p激活SOX5/Wnt/β-catenin信号通路；巨噬细胞中HIF-1α的表达可下调miR-30c水平以增加TAMs在肿瘤微环境中的比例[67]。实体肿瘤内往往处于缺氧状态，缺氧条件下的胃癌细胞可产生HIF-1α并促进miR-301a-3p的表达，后者不但能抑制HIF-1α的降解，而且能促进胃癌细胞的生长、转移及EMT进程，形成一正反馈调控环影响肿瘤进程，还可以外泌体形式分泌诱导周围非缺氧环境下的胃癌细胞内HIF-1α的积累[77]。

4 非编码RNA在外部环境因素介导胃癌发生中的作用机制

4.1 非编码RNA与幽门螺杆菌

幽门螺旋杆菌（helicobacter pylori，HP）感染是中的胃癌致病因素之一。目前HP如何诱导胃癌产生的机制尚未明了，但越来越多研究表明非编码RNA参与这一过程。在HP感染的胃癌细胞中发现miR-1915表达下调、miR-222-3p上调，分别靶向RAGE、HIPK2基因起到对肿瘤的抑制或促进作用[78-79]。内毒素相关基因A（cytotoxin-associated gene A，CagA）是HP主要的毒力因子，CagA阳性HP感染的胃癌患者往往有更差的临床预后。CagA可通过调控miR-155/KLF4通路促进胃上皮细胞的恶性转化[80]。HP的其它毒力因子还可诱导miR-150-5p、miR-3163的表达，前者可通过抑制POLD3增加细胞内基因的不稳定性，后者可抑制DNA错配修复蛋白MSH2、MSH3，从而共同导致DNA复制错误的积累形成微卫星不稳定性（microsatellite instability，MSI）现象，有利于肿瘤的发生、发展[81]。Hp的脂多糖（lipopolysaccharide，LPS）也可诱导胃内皮细胞的恶性转化。LPS可与细胞表面TLR4受体结合诱导miRNA前体降解相关酶Dicer的产生，继而减少miR-375、miR-106表达水平而激活JAK/STAT3信号通路[82]。此外miR-375还可通过SP1/MDM2/P63/Dicer通路形成一正反馈调控环。HP还可协助胃癌细胞免疫逃逸，可抑制miR-152、miR-200b以上调B7-H1的表达[74]。

4.2 非编码RNA与其他外部环境因素

长期的氧化应激状态也可诱导肿瘤的产生，有报道称miRNA hsa-let-7g可参与这一机制，它在H_2O_2处理下的胃癌细胞中表达下调，可诱导H_2O_2处理下胃癌细胞的凋亡，并间接减少DNA损伤修复系统相关基因的表达[83]。此外，EB病毒（Epstein-Barr virus，EBV）病毒感染也可影响胃癌发生。EBV病毒可自我编码miRNA，主要分为miR-BHRFs和miR-BARTs两类，均可参与胃癌细胞内基因的调控，例如miR-BART20-5p可转录后抑制诱导凋亡基因BAD的表达以促进胃癌细胞的抗凋亡作用[84]。

5 小　结

非编码RNA不仅涉及胃癌细胞增殖、凋亡、自噬、转移等生理过程，还可参与肿瘤微环境的形成以及外部环境因素介导胃癌发生机制，甚至在多种信号通路中作为关键调控分子，由此可见其在胃癌中的重要地位，可成为潜在的早期诊断标志物或治疗靶点。目前文献多报道的是以miRNA转录后调控基因作用为核心，circRNA、lncRNA为其上游调控分子的基因调控模式。lncRNA、circRNA均可竞争性结合miRNA，那么两者的调控关系仍未明确。circRNA在肿瘤中的作用是近年来才被初步认识的，在胃癌中的具体调控作用机制有待进一步研究。充分认识非编码RNA调控网络将有助于加深对肿瘤发生机制的理解，可为肿瘤的临床诊疗提供新的思路和方法。非编码RNA在未来或可进一步用于细化对不同胃癌特征的描述，如同基因一样成为肿瘤的“身份证”，对精准医疗、个体化医疗的发展也具有重要意义。

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（本文编辑　宋涛）

本文引用格式：郑晋, 苏婷婷, 李永盛, 等. 非编码RNA在胃癌中的作用机制研究进展[J]. 中国普通外科杂志, 2021, 30(4):471–481. doi:10.7659/j.issn.1005–6947.2021.04.012

Cite this article as: Zheng J, Su TT, Li YS, et al. Roles of noncoding RNAs in gastric cancer: recent advances[J]. Chin J Gen Surg, 2021, 30(4):471–481. doi:10.7659/j.issn.1005–6947.2021.04.012