doi:10.3971/j.issn.1000-8578.2024.24.0433

• 综 述 •

miR-21在乳腺癌中的作用机制及研究进展

王锐[1]，王玉凤[1,2]，关泉林[1,3]

Mechanism and Research Progress of miR-21 in Breast Cancer

WANG Rui[1], WANG Yufeng[1,2], GUAN Quanlin[1,3]

1. The First Clinical Medical College of Lanzhou University, Lanzhou 730000, China; 2. Department of Breast Disease, Gansu Provincial Cancer Hospital, Lanzhou 730000, China; 3. Department of Oncology Surgery, First Hospital of Lanzhou University, Lanzhou 730000, China

Corresponding Author: GUAN Quanlin, E-mail: guanql@lzu.edu.cn

Abstract: As a highly heterogeneous disease, breast cancer ranks first in new cases and deaths of female malignant tumors. In recent years, the incidence of breast cancer increases and tends to be younger. Early-onset breast cancer (<40 years old) is mostly associated with adverse biological characteristics and poor prognosis. Although immunotherapy and targeted therapy have advances in the treatment of breast cancer, a major challenge of neoplastic resistance to systemic therapy remains. Therefore, early diagnostic markers and potential therapeutic targets with high specificity and sensitivity must be identified. miR-21 affects the occurrence and development of breast cancer by targeting related genes and regulating related signaling pathways (PTEN/PI3K/Akt and NF-κB/ miR-21-5p/PDCD4 signaling pathways). This paper reviews the mechanism and progress of miR-21 in breast cancer.

Key words: Breast cancer; miR-21; MicroRNAs; Signaling pathway; PTEN; PDCD4

Funding: National Key Research and Development Program of China (No. 2017YFC0908302)

Competing interests: The authors declare that they have no competing interests.

摘 要：乳腺癌作为一种高度异质性疾病，其新发及死亡病例均居女性恶性肿瘤首位，近年来，乳腺癌发病率呈上升趋势并趋于年轻化，且年龄轻（<40岁）多与乳腺癌不良生物学特征及较差的预后相关。尽管免疫治疗及靶向治疗在乳腺癌治疗中取得了一系列进展，但目前乳腺癌治疗仍面临着肿瘤对全身治疗新生耐药这一重大挑战，迫切需要寻找特异度及敏感度高的早期诊断标志物和潜在的治疗靶点。miR-21通过靶向相关基因、调节相关信号通路（PTEN/PI3K/Akt和NF-κB/miR-21-5p/PDCD4信号通路）来影响乳腺癌的发生发展，本文就此进行综述。

关键词：乳腺癌；miR-21；MicroRNAs；信号通路；PTEN；PDCD4

中图分类号：R73；R737.9 **开放科学(资源服务)标识码(OSID):**

0 引言

乳腺癌（breast cancer, BC）作为世界上最常见的女性癌症[1]，其新发病例及死亡病例均居女性恶性肿瘤首位，发病率呈上升趋势并趋于年轻化。作为一种高度异质性疾病，尽管免疫治疗及靶向治疗在乳腺癌治疗中取得了一系列进展，但目前乳腺癌治疗仍面临着肿瘤对全身治疗新生耐药性这一重大挑战[2]。而对比其他年龄段乳腺癌患者，年轻乳腺癌（<40岁）患者多具有不良生物学特征及较差的预后，但也有更高的生育及美观需求[3]，因此，急需开发新的诊断标志物和治疗靶点来改善目前的困境。

MicroRNAs是一类由内源基因编码的长度约20~23个核苷酸的非编码单链RNA，约占人类基因组总数的1%~4%，对转录后基因表达至关重要[4-5]。miRNAs生物合成过程会产生两个有潜在活性的分子miRNA-5p与miRNA-3p[6]，单个miRNA即可调节多种mRNA分子的表达进而影响各种生理病理过程。在癌症发展中起关键作用的miRNAs也称为oncomiRs[5]，失调的miRNA可以作为癌基因（oncomiRs）或肿瘤抑制因子，从而调控肿瘤的发生。位于染色体17q23.2的miR-21，已被确定为致癌miRNA，通过靶向多种肿瘤抑制基因，包括磷酸酶和

收稿日期：2024-05-13；**修回日期**：2024-07-03

基金项目：国家重点研发计划（2017YFC0908302）

作者单位：1. 730000 兰州，兰州大学第一临床医学院；2. 730000 兰州，甘肃省肿瘤医院乳腺内科；3. 730000 兰州，兰州大学第一医院肿瘤外科

通信作者：关泉林（1968-），男，教授，主任医师，主要从事消化道及甲状腺肿瘤的基础与临床研究，E-mail: guanql@lzu.edu.cn，ORCID: 0000-0003-0409-6823

作者简介：王锐（1998-），女，硕士在读，主要从事乳腺癌的基础与临床研究，ORCID: 0009-0007-8376-6552

张力蛋白同源物（PTEN）、程序性细胞死亡因子4（PDCD4）和T细胞免疫球蛋白和黏蛋白结构域-3（TIMP3）等促进肿瘤发生[7-8]，在乳腺癌、结直肠癌、肺癌、前列腺癌、胰腺癌和胃癌中高表达，并且可以抑制肿瘤细胞凋亡[9]，但其机制尚不清楚。相较于其他miRNA（如miR-221/222、miR-9、miR-29a、 miR-96、 miR-146a、 miR-181、 miR-375和miR-589等），miR-21作为BC特异性oncomiR可以激活乳腺癌发生的转录因子[10]、降低化疗药物抗肿瘤敏感性[11]及增加BC细胞中的抗凋亡蛋白BCL-2的表达和化疗耐药性[10]。此外，Wang等研究发现血清miR-21-5p可作为胃癌诊断和预后标志物[12]。因此，本文主要对miR-21在乳腺癌中的研究进展及临床意义作一总结，以此为乳腺癌的精准治疗及分子标志提供新的策略。

1　miR-21与乳腺癌发生发展紧密相关

越来越多的研究证实，与正常乳腺组织相比，miR-21在乳腺肿瘤中过表达，且该过表达与乳腺癌的增殖、分化、转移及化疗敏感性相关[13]。MCC-Spain病例对照研究通过对比分析乳腺癌与非乳腺癌患者的血液样本，发现miR-21-3p 在乳腺癌患者中显著上调[14]。miR-21通过直接靶向抑癌基因促进乳腺癌的发生[15]。已有研究证明miR-21通过靶向抗血管生成因子（如PTEN）的表达来促进肿瘤相关血管生成，从而增强HIF-1α和VEGF的表达，而抗miR-21通过下调抗凋亡因子Bcl-2的表达，可在体外抑制乳腺癌的细胞生长[16]。此外，miR-21与乳腺癌治疗过程中产生耐药性有关，Amirfallah等的研究表明，miR-21的过表达可能有助于TNBC细胞通过MSH2对DNA损伤化疗药物产生耐药性[16]。不同亚型乳腺癌中miR-21也存在差异性表达，如Luminal A和TNBC亚型中，miR-21表达显著下调。miR-21与乳腺癌的转移和侵袭性显著相关，有研究发现[17]侵袭性乳腺癌细胞中miR-21较普通乳腺癌细胞表达显著增加，敲除侵袭性乳腺癌中的miR-21后癌细胞的转移能力受到明显抑制。

2　miR-21调控乳腺癌发生发展的分子机制

miR-21作为miRNA的一员，在乳腺癌的发展过程中通过以下三个方面调控乳腺癌细胞增殖、侵袭、凋亡等:（1）miR-21通过靶向相关基因调控不同亚型乳腺癌的发生发展；（2）miR-21激活或抑制相关信号通路（Wnt/β-catenin 和 PI3K/AKT信号通路）影响乳腺癌的进展；（3）miR-21还可以通过影响TME调控乳腺癌的发生发展。

2.1　miR-21通过相关基因调控乳腺癌发生发展

miR-21被认为通过控制肿瘤抑制基因的表达，如PDCD4、原肌球蛋白α1链-1（TPM1）、PTEN、乳腺丝氨酸蛋白酶抑制剂（MASPIN），参与肿瘤增殖和转移。在乳腺癌中，目前已鉴定出miR-21调节凋亡的靶点有PTEN和PDCD4[5,10,15]。PTEN基因是一个经典的抑癌基因，大量研究发现其在多种类型的癌症中存在突变或缺失，PTEN蛋白的异常表达与癌细胞的生长、凋亡、黏附、迁移、浸润等过程密切相关[18]。Liao等[19]通过构建携带抗miR-21的RNA纳米颗粒治疗TNBC小鼠模型，发现miR-21基因表达降低，肿瘤生长受到抑制，并诱导细胞凋亡，同时PTEN和PDCD4蛋白表达上调。另一项研究表明miR-21在Smad7和PTEN的调控介导下，能诱导肌成纤维细胞分化，并加速乳腺叶状肿瘤的恶性进展及转移[20]。这表明治疗性抗miR-21可通过上调PTEN和PDCD4蛋白抑制肿瘤进展，有望成为潜在的新型TNBC疗法。

诸多研究表明PDCD4作为miR-21的另一靶点在乳腺癌细胞的生长抑制及介导乳腺癌细胞凋亡中发挥重要作用[21-22]。有研究表明PDCD4在PI3K-AKT-mTOR通路下游发挥作用，其表达水平与miR-21在乳腺癌细胞中呈负相关[23]，这与Zhu等[24]的发现一致。同时Zhu等的研究还发现抑制miR-21可显著降低转移性乳腺癌MDA-MB-231细胞侵袭和肺转移能力，提示miR-21在转移性乳腺癌中的潜在作用。Li等[25]证明NF-κB在管腔样乳腺癌中可促进miR-21表达，然后进一步抑制PDCD4的表达。上述研究均显示miR-21通过调控PDCD4基因表达在乳腺癌中发挥重要作用。

但是关于miR-21在乳腺癌中的作用目前尚有争议，有研究表明miR-21-3p 是乳腺癌的致癌因子[26]，也有研究[27-28]表明miR-21-3p 作为肿瘤抑制因子可减少癌细胞生长。因此，需要更多的临床研究来论证miR-21，特别是miR-21-3p在乳腺癌中的作用。

2.2　miR-21通过相关信号通路调控乳腺癌发生发展

miR-21是STAT3和Wnt等多种致癌通路的调节因子，PTEN/PI3K/Akt轴是重要的下游靶点。miR-21通过PTEN下调诱导PI3K/Akt信号转导，从而促进肿瘤进展[29]。大量研究证实PI3K/AKT信号通路在乳腺癌、卵巢癌和肺癌等多种恶性肿瘤中过表达，该信号通路的异常激活在抑制细胞增殖、诱导细胞凋亡、改善肿瘤微环境和逆转乳腺癌耐药性方

面发挥着重要作用[30-32]。miR-21靶向乳腺癌细胞中的PDCD4，通过PI3K/Akt通路激活诱导PD-L1表达，从而诱导T细胞耗竭和抑制效应T细胞功能使肿瘤细胞从宿主免疫反应中逃逸[33]。癌细胞可以激活自噬途径，在细胞应激下存活，这可能与癌症治疗耐药性有关，miR-21抑制剂通过抑制PI3K-AKT-mTOR通路来增强自噬细胞死亡[34]，从而增强他莫昔芬（TAM）和氟维司群（FUL）在雌激素受体α阳性（ER+）乳腺癌患者的治疗敏感性。

此外，miR-21还通过NF-κB/miR-21-5p/PDCD4信号转导促进管腔样乳腺癌的生长和转移[26]。转录因子核因子-κB（NF-κB）[35]在多种癌症中起重要作用，参与细胞存活、侵袭、增殖、转移、血管生成和化疗耐药。一项研究[36]证实了miR-21通过触发IL-6/STAT3/NF-κB介导的信号转导通路并影响HER2阳性乳腺癌患者对曲妥珠单抗的治疗反应，提示可以通过灭活miR-21来干扰NF-κB 信号转导进而拮抗癌症治疗耐药性和转移。针对miR-21调控乳腺癌发生发展的相关信号通路，主要是PTEN/PI3K/Akt和NF-κB/miR-21-5p/PDCD4信号通路，有望开辟新的乳腺癌治疗策略。

3 miR-21在不同亚型乳腺癌的差异性表达

乳腺癌根据 ER、PR 和 HER2 的表达分为Luminal A型、Luminal B型、HER2型及三阴型，这些亚型在预后和治疗靶点方面存在显著差异。研究表明，miRNAs在不同乳腺癌亚型中存在差异性表达[15]。导致这种差异的具体机制目前尚不清楚，仍需进一步探索。Amorim等[37]发现miR-30c-5p、miR-30b-5p、miR-182-5p和miR-200b-3p在Luminal型乳腺癌中表达水平显著高于正常乳腺组织，而其余miRNA的水平没有差异，且这4种miRNA可作为管腔型乳腺癌内分泌治疗临床获益的独立预测因子。另一项研究[38]通过反转录酶定量聚合酶链反应（RT-qPCR）分析得出miR-16、miR-145、miR-155、miR-451a、miR-21和miR-486在Luminal A型乳腺癌患者中表达上调。此外，Thakur等[39]首次报告了在TNBC中miR-21、miR-221和miR-210显著过表达，而miR-195和miR-145下调。Wu等[40]的研究发现miR-21-3p作为保护因子在TNBC中显著表达并利用α9-烟碱乙酰胆碱受体（nAChR）在TNBC中大量表达的特性，通过构建携带抗miR-21的RNA纳米颗粒治疗TNBC小鼠模型发现，miR-21基因表达降低能显著抑制TNBC肿瘤生长并诱导细胞凋亡，这表明治疗性抗miR-21可被RNA纳米颗粒有效递送，并有望成为潜在的新型TNBC疗法。

4 miR-21在年轻乳腺癌中的差异性表达

基于乳腺癌发病率逐年升高及年轻化的发展趋势，且相对于老年患者，年轻乳腺癌患者具有更差的预后，急需新的治疗靶点用于年轻乳腺癌的诊治。而研究[41]发现miRNA确实存在重要的年龄相关差异，其中miR-21更是显示出基于年龄分组的精准治疗的潜力。

有研究通过对比老年与年轻乳腺癌患者血清中的miRNA发现miR-21、miR-210、miR-320b、miR-378和miR-423-5p相对于老年患者，年轻乳腺癌患者血清中的丰度减少[41]。Wu等[42]通过使用miRNA芯片对45例年轻乳腺癌患者RNA进行分析，发现无论是单独还是联合监测miR-183-5p、miR-194-5p和miR-1285-5p的表达水平，都与OS相关，提示miRNA可以作为年轻乳腺癌患者的预后生物标志物。另一项研究通过实时逆转录聚合酶链反应分析年轻乳腺癌患者中miRNA的表达，发现年轻女性乳腺癌患者的高恶性程度与肿瘤组织中miR-182、miR-21、miR-29b和miR-34a表达升高以及miR-27a水平降低相关，这表明它们具有预测年轻乳腺癌侵袭性的应用前景。

5 miR-21在乳腺癌治疗中的临床应用

乳腺癌现有的筛查方法，如乳腺钼靶检查，不能在早期阶段识别疾病，此外肿瘤组织活检和细针抽吸细胞学检查作为有创性操作往往与高昂的费用相关，因此，迫切需要特异性及敏感度高的诊断生物标志物和有效性高的治疗靶点。而已有的研究表明miR-21作为肿瘤标志物在乳腺癌的早期诊断和预后判断中具有潜在作用。

5.1 miR-21作为肿瘤标志物用于乳腺癌的早期诊断和预后判断

通过使用miRNA作为具有合理敏感性和特异性的生物标志物，可以区分正常乳腺组织和乳腺癌。有研究纳入43名健康患者和50名临床证实的乳腺癌患者，使用qPCR研究了两组人群血清中miRNA-21和miRNA-195的表达水平，发现在早期乳腺癌患者中，miRNA-21的表达高于健康对照组，miRNA-195的表达低于健康对照组，且同时监测这两种miRNA更具有特异性。MCC-Spain研究[14]通过对比分析乳腺癌与非乳腺癌患者的血液样本，发现miR-21-3p在乳腺癌患者中显著上调。另一项研究显示，miR-21、miR-20b、IGF1R和E2F2高表达以及miR-

125a、PDCD4和PTEN低表达的乳腺癌患者总生存期较短[43]。Gong等[44]的研究表明与良性乳腺叶状肿瘤相比，miR-21是恶性乳腺叶状肿瘤中上调最显著的microRNA之一，其表达增加主要局限于α-SMA阳性肌成纤维细胞，α-SMA和miR-21是复发和转移的独立预测因子，其复发预测价值优于组织学分级。一项前瞻性、多中心试验[45]通过分析120名接受新辅助治疗（Neoadjuvant chemotherapy, NAC）的乳腺癌患者全血中的miRNA表达，发现miR-21具有预测NAC pCR的潜力，其他临床试验也得出类似的结论[46-49]，见表1。

5.2　miR-21作为乳腺癌的潜在治疗靶点

不断明确miR-21调控乳腺癌的作用机制, 可能为乳腺癌诊治提供新策略。miR-21作为乳腺癌潜在治疗靶点基于2种方法：（1）使用miR-21作为药物分子，基于特定寡核苷酸的合成和递送，能够增加或降低BC中的miR-21水平；（2）miR-21与非基于miRNA的疗法相结合，以提高常规治疗的疗效。例如，为了证明miR-21可能通过调节细胞自噬来改变乳腺癌细胞对他莫昔芬（TAM）和氟维司群（FUL）的敏感性，Yu等[50]通过敲低ER（+）乳腺癌细胞的miR-21，将细胞暴露于TAM或FUL中，并测定细胞凋亡和自噬的百分比，发现敲低miR-21显著增加了TAM或FUL诱导的ER（+）乳腺癌细胞凋亡，表明靶向自噬相关的miRNA是克服内分泌对TAM和FLU耐药的潜在策略。另有研究[51]表明芳香族-新霉素衍生物通过靶向miR-21前体阻止其进一步加工为miR-21，从而拮抗其致瘤作用并抑制上皮间充质转化（EMT），这为乳腺癌的治疗提供了较为乐观的前景。Shang等[52]设计了一种纳米递送系统高效共递送抗miR-21和抗miR-155，结合光动力疗法治疗TNBC，显示了抗miR-21与光动力疗法相结合在癌症治疗中的前景。

6　总结与展望

综上所述，miR-21在乳腺癌的发生发展过程中起着至关重要的作用，下调miR-21的表达水平可以抑制乳腺癌细胞的增殖和侵袭，并促进乳腺癌细胞凋亡；目前的研究表明，miR-21主要通过靶向PTEN、PDCD4基因、调节相关信号通路（PI3K/AKT和NF-κB信号通路）来影响乳腺癌的发生发展。此外，由于miR-21受遗传、生活习惯等影响较小，且其在不同亚型及年轻乳腺癌中差异性表达，有望成为乳腺癌的重要诊断标志物，且具有乳腺癌靶向药物研究的潜力。鉴于目前 miRNA与乳腺癌相关性的研究相对缺乏，因此需要更多的研究来阐明miR-21在乳腺癌及年轻乳腺癌中的作用机制。总之，miR-21在乳腺癌发生发展过程中起着重要的调控作用，或可为乳腺癌的诊断、精准治疗和预后带来新靶点和新疗法并改善患者生活质量。

表 1　miR-21在BC患者中的部分临床试验汇总

Table 1　Summary of some clinical trials of miR-21 in breast cancer patients

Study type	Study population	Primary endpoint	Conclusions	Reference
Prospective, multicenter trial	Undergo standard-of-care NAC for breast cancer	Miller-Payne classification	MiRNAs may personalize therapeutic decision-making for patients indicated to receive standard-of-care NAC	[46]
Prospective, multicenter trial	Patients treated with standard of care NACT	Pathological complete response (pCR)	The prognostic power of miR-21 as circulating biomarkers to stratify breast cancer patients by NACT response	[47]
Prospective, multicentre translational research trial	Patients treated with NAC for breast cancer	Patient-specific toxicities to NAC	These results support the ideology that circulatory miRNAs are biomarkers with utility in predicting chemotherapy toxicity as well as treatment response	[48]
The prospectively randomized GeparQuin to trial	Patients received chemotherapy combined with either trastuzumab or lapatinib	Pathological response (pCR)	A specific influence of neoadjuvant therapy on the serum levels of miR-21 in breast cancer patients together with a prognostic value of miR-21	[49]

利益冲突声明：

所有作者均声明不存在利益冲突。

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[编辑：安凤；校对：刘红武]

作者贡献：

王　锐：文献查阅、论文撰写

王玉凤：思路设计、归类总结

关泉林：论文修改及审阅