World Journal of Cancer Research 世界肿瘤研究, 2022, 12(2), 52-60
Published Online April 2022 in Hans. http://www.hanspub.org/journal/wjcr
https://doi.org/10.12677/wjcr.2022.122007

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长链非编码RNA在乳腺癌中的研究进展

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收稿日期：2022年3月14日；录用日期：2022年4月4日；发布日期：2022年4月14日

摘　要

乳腺癌是异质性的恶性肿瘤，发病率位居全球女性恶性肿瘤之首，传统的治疗手段如手术切除和放化疗的作用较为有限，而分子靶向治疗作为乳腺癌的新型治疗手段，具有效率高、特异性强和副作用小等优点。长链非编码RNA (long noncoding RNA, lncRNA)是一类长度大于200 nt且无蛋白编码功能的转录本，其参与细胞的多个生物学进程，进而在多种生理病理活动中起到关键调控的作用。随着高通量测序技术的发展，现已发现多种lncRNA在乳腺癌中异常表达，其与乳腺癌的发生、发展、转移以及耐药均密切相关，有望作为乳腺癌诊断、预后和治疗的分子靶标。

关键词

乳腺癌，诊断，长链非编码RNA，竞争性内源RNA，耐药，分子靶标

Research Progress of Long Noncoding RNA in Breast Cancer

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Received: Mar. 14th, 2022; accepted: Apr. 4th, 2022; published: Apr. 14th, 2022

Abstract

As a heterogeneous malignant tumor, female breast cancer has become the most commonly diagnosed cancer worldwide. Conventional treatments such as surgical resection, radiotherapy and chemotherapy are not that useful. Molecular targeted therapy is a new way for breast cancer treatment, with high efficiency, high specificity and less side effects. LncRNA (long noncoding RNA)

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文章引用: 郑欣, 刘杰, 宋鹏霞, 姚水洪, 罗烨. 长链非编码 RNA 在乳腺癌中的研究进展[J]. 世界肿瘤研究, 2022, 12(2): 52-60. DOI: 10.12677/wjcr.2022.122007

is a noncoding transcript with lengths over 200 nt. LncRNA modulates various biological functions and participates in a variety of physiological and pathological processes. With the development of transcriptome high-throughput sequencing, it has been found that abnormally expressed LncRNA is associated with occurrence, development, metastasis and drug resistancein breast cancer. lncRNA is expected to act as a molecular target for diagnosis, prognosis and treatment of breast cancer.

Keywords

Breast Cancer, Diagnosis, Long Noncoding RNA (lncRNA), Competing Endogenous RNA (ceRNA), Drug Resistance, Molecular Target

1. 引言

GLOBOCAN 提供的最新数据显示，2020 年全球新增癌症病例数量达到 1930 万，有近 1000 万人死于癌症。乳腺癌的发病率已赶超肺癌，位居全球第一，死亡率仅次于肺癌、肝癌和胃癌，位居全球第四[1]。在我国，乳腺癌病例数量从 2015 年的 30 万增加到 2020 年的 42 万，发病率居女性恶性肿瘤之首，死亡人数约占全球乳腺癌死亡人数的 18%，死亡率位居全国肿瘤第七[2]。乳腺癌是异质性的恶性肿瘤，根据肿瘤细胞三种表面受体：雌激素受体(ER)、孕激素受体(PR)和表皮生长因子受体 2 (HER-2)表达情况的不同分为：管腔 A 型 (ER/PR-阳性、HER-2-阴性)、管腔 B 型(ER/PR-阳性、HER-2-阳性)、HER2 过表达型 (ER/PR-阴性、HER-2-阳性)和基底细胞样型(ER-、PR-、HER-2-均阴性)，其中基底细胞样乳腺癌即三阴性乳腺癌(triple negative breast cancer, TNBC) [3]。三阴性乳腺癌患者约占乳腺癌患者的 15%~20%，其远处复发率和转移风险更高，往往预后不佳[4]。近年来，随着科学家们对癌症发生发展机制的深入研究，鉴定出一系列乳腺癌诊治的分子靶标，分子靶向治疗逐渐成为乳腺癌治疗的新手段。LncRNA 作为一种新型分子靶标，为乳腺癌的早期诊断、治疗和预后提供了新思路。本文通过对近年来相关文献的查阅和总结，综述了一些致癌 lncRNA 在乳腺癌中的研究进展。

2. LncRNA 概述

癌症从根本上来说是一种基因疾病。然而，只有不到 2%的基因组编码蛋白质，却有至少 75%的基因组转录成非编码 RNA (non-coding RNA, ncRNA) [5]。其中，长链非编码 RNA (long non-coding RNA, lncRNA)是 ncRNA 家族中十分重要的一员，其长度大于 200 nt [6]。尽管科学家们在很早以前就发现了 lncRNA，但“lncRNA”一词的诞生并不是一个简单的过程，1990 年，Brannan 等将 lncRNA H19 定义为“非经典 mRNA”[7]，直到 21 世纪初，Maeda 等在对小鼠全长 cDNA 文库进行大规模测序时，才首次定义 lncRNA [8]。如今，随着二代测序技术的发展，我们能从多个数据库中，如非编码数据库(http://www.noncode.org)和 LNCipedia (http://www.lncipedia.org)获取各种 lncRNA 的相关信息[9]。

LncRNA 大量表达并广泛参与多种癌症进程，其异常表达与肿瘤发生、发展、转移以及 TNM 分期密切相关。例如，MALAT1 可通过激活 Wnt/β-连环蛋白通路、PI3K/AKT 通路、ERK/MAPK 通路和促进血管生成进而促进多种肿瘤发生[10]；AK023948 在乳腺癌中上调，并促进乳腺癌细胞生长[11]；HOTAIR

在乳腺癌中上调，其表达与乳腺癌转移和患者生存密切相关[12]。此外，lncRNA 在癌症中特异表达，并且可在血液或尿液中检测到。因此，lncRNA 是肿瘤治疗的潜在靶点，也是癌症诊断及预后的潜在指标。

3. LncRNA 在乳腺癌中的作用

LncRNA 在乳腺癌的发生、发展、转移和耐药等多个进程中起到关键作用，探究其在乳腺癌中的作用机制，将对乳腺癌的早期诊断、临床治疗和预后监测提供十分重要的帮助。LncRNA 在乳腺癌中的功能及作用机制如表 1 所示。

Table 1. The function and mechanism of lncRNA in breast cancer
表 1. LncRNA 在乳腺癌中的功能及作用机制

lncRNA	Expression	Mechanism	Biological function
BCAR4	Up	ERBB2/3 signaling	Promotes breast cancer tamoxifen resistance [13]
		Hedgehog/GLI2 signaling	Promotes breast cancer metastasis [14]
		Hippo and Hedgehog signaling	Promotes YAP-dependent glycolysis [15]
LUCAT1	Up	miR-5582-3p, TCF7L2 and Wnt/*β*-catenin signaling	Increases stem-like properties of breast cancer cells [16]
		miR-5702	Increases cell proliferation, metastasis and cell cycle progression, and suppresses cell apoptosis [17]
SPRY4-IT1	Up	ZNF703	Promotes cell proliferation and inhibites cell apoptosis [18]
		miR-6882-3p, TCF7L2	Promotes cell proliferation and stemness [19]
LINC 00511	Up	miR-185-3p, E2F1	Promotes cell proliferation, sphere-formation ability, stem factors expression and tumor growth [20]
		miR-150, MMP13	Promotes cell proliferation, migration and invasion [21]
		miR-185, STXBP4	LINC00511 knockdown restricted cell proliferation, promoted cell apoptosis, and enhanced radiosensitivity [22]
		miR-29c, CDK6	LINC00511 knockdown enhanced paclitaxel cytotoxicity [23]
TINCR	Up	miR-7, KLF4	Stimulates cell proliferation, anchorage-independent growth and suppresses cell apoptosis [24]
		miR-589-3p, IGF1R-AKT pathway	Promotes cell proliferation, migration and invasion, and inhibites cell apoptosis. [25]
		miR-503-5p, EGFR, JAK2-STAT3 signaling	Promotes cell proliferation,invasion, colony formation,and tumor growth [26]
		miR-125b	Promotes trastuzumab resistance [27]

3.1. LncRNA BCAR4

LncRNA BCAR4 在多种肿瘤组织中高表达，如乳腺癌[28]、宫颈癌[29]、结肠癌[30]、胃癌[31]、非小细胞肺癌[32]、前列腺癌[33]等。BCAR4 高表达的患者往往生存率降低、转移风险增高。2006 年，Meijer 等在筛选乳腺癌内分泌抵抗相关基因时首次鉴定出了 lncRNA BCAR4 [34]。研究发现约 29%的乳腺癌患

者表达 BCAR4，BCAR4 高表达的患者其无进展生存期、无远处转移生存期和总生存期均较短[13]。BCAR4 的表达水平与抗雌激素抵抗呈正相关，其能够通过诱导 ERBB2/3 的磷酸化激活 ERBB2/3 信号通路，进而促进乳腺癌的抗雌激素抵抗[13]。应用 EGFR/ERBB2 抑制剂拉帕替尼和抗雌激素对 BCAR4 高表达患者进行联合治疗是一种潜在的有效治疗方法[35]。另一项研究表明，BCAR4 对于乳腺癌侵袭和转移具有促进作用。在趋化因子 CCL21 的诱导下，BCAR4 能够与两种转录因子 SNIP1 和 PNUT 结合，经过下游一系列蛋白的信号放大作用，最终激活 Hedgehog/GLI2 通路进而促进乳腺癌转移。在小鼠模型中，使用靶向 BCAR4 的锁核酸(LNA)能明显抑制小鼠乳腺癌的肺转移[14]。亦有研究表明，BCAR4 能够促进乳腺癌的糖酵解。BCAR4 能够调节 Hippo 和 Hedgehog 通路以促进糖酵解中两个关键酶：己糖激酶和果糖-2,6-二磷酸酶 3 的转录，在小鼠模型中，使用靶向 BCAR4 的锁核酸能够明显抑制肿瘤生长和糖酵解[15]。由此，以 BCAR4 为靶标的分子靶向治疗有望成为乳腺癌治疗的有效途径。

3.2. LncRNA LUCAT1

LncRNA LUCAT1 是在吸烟相关肺癌中首次发现的，且与非小细胞肺癌的不良预后密切相关[36]。目前，越来越多的证据表明 LUCAT1 参与多种肿瘤的发生发展。在乳腺癌中，LUCAT1 的高表达与肿瘤大小(P = 0.015)、淋巴结转移(P = 0.002)和 TNM 分期(P < 0.001)显著相关，且 LUCAT1 高表达的患者总生存期(P = 0.006)和无病生存期(P = 0.011)较短，可作为评估乳腺癌患者预后的重要生物标志物[16]。研究表明，LUCAT1 能通过竞争性地与 miR-5582-3p 和 TCF7L2 结合来激活 Wnt/β-连环蛋白信号通路，进而增强乳腺癌细胞的干细胞特性，LUCAT1/miR-5582-3p/TCF7L2 轴为寻找乳腺癌新型诊断标志物和治疗靶点提供了理论支持[16]。另一项研究表明，LUCAT1 的高表达与三阴性乳腺癌的不良预后密切相关，LUCAT1 能与 miR-5702 结合并抑制 miR-5702 的表达，进而促进三阴性乳腺癌的发生和转移[17]。LUCAT1 有望成为乳腺癌潜在的治疗靶点和预后指标。

3.3. LncRNA SPRY4-IT1

SPRY4-IT1 在黑色素瘤中首次发现，其在黑色素瘤中表达上调，并在缺失时诱导细胞凋亡[37]。随着研究的深入，科学家们发现 SPRY4-IT1 在乳腺癌的发生发展中具有重要作用。研究指出，SPRY4-IT1 能够通过上调 ZNF703 的表达发挥其致癌作用，促进乳腺癌细胞的增殖，抑制乳腺癌细胞凋亡[18]。亦有研究发现，SPRY4-IT1 能够通过靶向 miR-6882 调节 Wnt/β-catenin 信号通路的活性，促进乳腺癌细胞的干性[19]。Wu 等研究发现，SPRY4-IT1 可促进乳腺癌细胞的增殖、迁移和侵袭，抑制细胞凋亡，而 NT21MP 可以通过 SDF-1α/CXCR4 途径抑制 lncRNA SPRY4-IT1 的表达，从而发挥其抗肿瘤作用[38]。SPRY4-IT1 在乳腺癌中高表达，并且其表达水平与肿瘤大小(P = 0.009)、TNM 分期(P = 0.0008)和淋巴结转移(P = 0.01)显著相关。一项 Kaplan-Meier 法分析得出，SPRY4-IT1 高表达的患者总生存率(P = 0.0056)和无病生存率(P = 0.0001)均显著降低[39]。SPRY4-IT1 还与乳腺癌的化疗耐药有关，SPRY4-IT1 的过度表达能促进 MCF-7 和 MDA-MB-231 细胞对表阿霉素的耐药性[40]。SPRY4-IT1 可成为预测乳腺癌患者新辅助化疗疗效和预后的生物标志物。

3.4. LncRNA LINC00511

LINC00511 在乳腺癌中表达显著升高，且其高表达水平与乳腺癌患者的总生存期降低和淋巴结转移显著相关[41]。研究表明，LINC00511 能够促进乳腺癌细胞的增殖和侵袭。LINC00511 作为 miR-185-3p 的 ceRNA 促进 E2F1 的表达，进而促进乳腺癌细胞的球体形成能力以及干细胞因子 Oct4、Nanog、SOX2 的表达，有助于维持乳腺癌干细胞特性，促进肿瘤生长[20]。另一项研究表明，LINC00511 能够与 miR-150

竞争性结合 MMP13 蛋白，从而促进乳腺癌细胞的增殖、迁移和侵袭[21]。LINC00511 还与保乳术后放疗的复发和低生存率相关，敲除 LINC00511 可在体外抑制乳腺癌细胞增殖，促进细胞凋亡，增强放射敏感性，并通过增加体内对辐射的反应抑制肿瘤生长。进一步研究发现，LINC00511 与 miR-185 竞争性结合，促进了 STXBP4 的表达，而沉默 LINC00511 则降低了 STXBP4 的表达并增强了乳腺癌细胞的放射敏感性。LINC00511/miR-185/STXBP4 轴可作为改善乳腺癌预后的潜在治疗靶点[22]。LINC00511 还与乳腺癌耐药有关，LINC00511 可作为 miR-29c 的 ceRNA 正向调节 CDK6 的表达，敲除 LINC00511 能够通过调节 miR-29c/CDK6 轴增强乳腺癌细胞中紫杉醇的细胞毒性[23]。负载 LINC00511 siRNA 的新型治疗剂能有效降低三阴性乳腺癌对于顺铂的耐药性，为三阴性乳腺癌耐药提供了一种潜在的临床治疗策略[42]。探究 LINC00511 的致癌机制对于乳腺癌的治疗有重要意义。

3.5. LncRNA TINCR

LncRNA TINCR 是从分化良好的人体组织中分离出来的，为正常表皮分化所必需[43]。随着研究的深入，研究者们发现 TINCR 参与多种癌症进程，如乳腺癌[24]、肝细胞癌[44]和宫颈鳞状细胞癌[45]。TINCR 在乳腺癌中高表达，沉默 TINCR 能显著抑制乳腺癌细胞的生长和增殖，降低迁移和侵袭能力，促进凋亡。进一步研究发现，TINCR 可作为 miR-7 的 ceRNA 促进 KLF4 的表达，进而发挥其致癌作用[24]。另一项研究表明，TINCR 可通过抑制 miR-589-3p 的表达促进 IGF1R-AKT 通路的激活，从而促进乳腺癌细胞的增殖、迁移和侵袭能力，并抑制癌细胞凋亡[25]。Wang 等发现 TINCR 能将 DNMT1 招募至 miR-503-5p 基因座启动子，增加 miR-503-5p 甲基化并抑制其转录表达，此外，TINCR 还作为 miR-503-5p 的 ceRNA 上调 EGFR 的表达。TINCR 刺激 EGFR 下游的 JAK2–STAT3 通路，STAT3 又反过来增强 TINCR 的转录。该研究揭示了 STAT3-TINCR-EGFR 反馈环在肿瘤发生中的重要作用，是乳腺癌的潜在治疗靶点[26]。亦有研究表明，乳腺癌患者，尤其是三阴性乳腺癌患者的血清 TINCR 水平显著增高，并且血清高 TINCR 水平与三阴性乳腺癌患者的不良临床病理特征和生存率密切相关，血清 TINCR 是三阴性乳腺癌的独立预后因素[46]。Dong 等发现 TINCR 能够通过靶向 miR-125b，从而释放 HER-2 并诱导曲妥珠单抗耐药。临床上，TINCR 高表达水平的 HER-2-阳性乳腺癌患者对曲妥珠单抗治疗反应差，生存时间短[27]。TINCR 是提高曲妥珠单抗治疗临床疗效的治疗靶点，也是乳腺癌患者的预后指标。

4. LncRNA 与乳腺癌诊断

癌症的早期诊断是取得有效治疗的关键，如今，已有越来越多的研究集中于寻找癌症检测的生物标志物。乳腺癌组织中存在多种差异表达的 lncRNA，对患者的诊断及预后有较大的帮助。研究发现 lncRNA ANRIL、HIF1A-AS2 和 UCA1 在三阴性乳腺癌患者血浆中的表达水显著平升高，研究人员基于这三个 lncRNA 构建了 TNBC SigLnc-3 模型，其曲线下面积(area under curve, AUC)值为 0.934，敏感性为 76.0%，特异性为 97.1%。因而，这三种 lncRNA 可作为三阴性乳腺癌的特异性诊断标记物，且联合诊断效果更佳[47]。亦有研究发现 lncRNA H19 在乳腺癌患者血浆中异常上调，进一步分析发现，H19 的 AUC 值为 0.81，敏感性为 56.7%，特异性为 86.7%，表明 H19 可作为乳腺癌早期筛查和预后监测的潜在生物标志物[48]。Zhang 等研究表明，lncRNA HOTAIR 的诊断能力高于 CEA 和 CA15-3，其 AUC 值为 0.80；敏感性为 69.2%；特异性为 93.3%。此外，HOTAIR 与 CEA 和 CA15-3 联合检测可提高诊断能力，这三项血浆指标的 AUC 值为 0.82；敏感性为 73.1%；特异性为 90.0% [49]。

Fan 等对 TCGA 数据库中 1097 例乳腺癌样本的 lncRNA 表达谱和临床数据进行了全面分析，最终确定了 lncRNA AC091043.1、AP000924.1 和 FOXCUT 对 TNBC 具有很强的诊断价值。另外，lncRNA AC010343.3、AL354793.1 和 FGF10-AS1 的表达水平与三阴性乳腺癌患者的临床预后相关[50]。最近的一

项 Meta 分析总结了 27 篇文献的 2803 例 TNBC 患者的数据，最终汇总出 24 个 lncRNAs 的预后价值，该 Meta 分析证明 lncRNA SNHG12、MALAT1、HOTAIR、HIF1A-AS2、HULC、LINC00096、ZEB2-AS1、LUCAT1 和 LINC000173 与淋巴转移阳性显著相关，另外，lncRNA MALAT1、HIF1A-AS2、HULC、LINC00096、ADPGK-AS1、ZEB2-AS1、LUCAT1 的表达水平与远处转移呈正相关，而 lncRNA MIR503HG 高表达水平的患者远处转移率较低[51]。Bermejo 等进行的表观基因组关联研究发现，LINC00299 在三阴性乳腺癌患者的外周血中高度甲基化，高度甲基化的 LINC00299 可成为三阴性乳腺癌患者诊断的循环生物标记物[52]。以上研究表明，lncRNA 是一种新型无创的诊断及预后的生物标志物，但也有待于大规模的临床试验来加以证实。LncRNA 在乳腺癌诊断中的作用如表 2 所示。

Table 2. The role of lncRNA in breast cancer diagnosis
表 2. LncRNA 在乳腺癌诊断中的作用

Index	AUC	Sensitivity	Specificity	References
ANRIL, HIF1A-AS2, UCA1	0.934	0.760	0.971	[47]
H19	0.810	0.567	0.867	[48]
HOTAIR	0.80	0.692	0.933	[49]
HOTAIR, CA15-3, CEA	0.820	0.731	0.900	[49]

5. 总结与展望

乳腺癌是全世界女性最常见的癌症之一，尽管随着医疗技术的不断进步，乳腺癌患者的诊断、治疗及预后有了很大改善，但它仍是一种高发病率和高死亡率的疾病，尤其是缺乏治疗靶点的三阴性乳腺癌，其治疗药物缺乏和化疗耐药性的问题仍有待解决。因此，为患者开发新型诊断工具、研究新的治疗方案至关重要。LncRNA 参与维持乳腺癌的多种恶性生物学行为，目前仅有少部分 lncRNA 功能被阐明，继续深入探究 lncRNA 在乳腺癌发生、发展以及耐药中的作用机制，不仅有助于乳腺癌的诊断及预后分析，更有助于确定潜在的治疗靶标并制定更有效的治疗策略。未来，lncRNA 功能的揭示可能进一步加深我们对乳腺癌发生发展机制的理解，并为高效、快速、特异的诊断和治疗提供新的应用。

基金项目

衢州市科技竞争性项目 2020K42，衢州职业技术学院重点项目(QZYZ1903)。

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