Advances in Clinical Medicine 临床医学进展, 2024, 14(3), 928-935
Published Online March 2024 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2024.143793

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长链非编码核苷酸膀胱癌相关转录因子1在咽部鳞状细胞癌中的研究进展

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收稿日期：2024年2月21日；录用日期：2024年3月15日；发布日期：2024年3月21日

摘　要

长链非编码核苷酸(long noncoding RNA, lncRNAs)是由200多个核苷酸组成的转录本，由于缺乏开放性阅读框架从而无法编码蛋白质。然而，lncRNAs以多种方式参与基因转录及转录后的多个层面，从而调控肿瘤的发生与发展。其中，长链非编码核苷酸膀胱癌相关转录因子1 (lncRNA BLACAT1)被证实通过与miRNAs竞争性结合、参与Wnt/β-catenin信号通路和STAT3信号通路以及作用于相关蛋白和分子，从而在恶性肿瘤的发生发展过程中起重要的作用。本文中，我们将概括lncRNA BLACAT1在咽部鳞状细胞癌中的作用机制，并预测其将来有望成为咽部鳞状细胞癌的新型生物标志物和治疗靶点。

关键词

长链非编码核苷酸(lncRNAs)，长链非编码核苷酸膀胱癌相关转录因子1 (lncRNA BLACAT1)，咽部鳞状细胞癌，生物标志物，治疗靶点

Research Progress on lncRNA BLACAT1 in Pharyngeal Squamous Cell Carcinoma

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Received: Feb. 21st, 2024; accepted: Mar. 15th, 2024; published: Mar. 21st, 2024

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文章引用: 开日麦·艾尼瓦尔, 赵辉. 长链非编码核苷酸膀胱癌相关转录因子 1 在咽部鳞状细胞癌中的研究进展[J]. 临床医学进展, 2024, 14(3): 928-935. DOI: 10.12677/acm.2024.143793

Abstract

Long noncoding RNAs (lncRNAs) are a class of transcripts that are longer than 200 nucleotides, and since they lack an open reading frame, they do not encode proteins. However, lncRNAs are involved in multiple aspects of gene transcription and post-transcriptional regulation, thereby influencing the oncogenesis and progression of tumors. The long non-coding RNA Bladder Cancer-Associated Transcript 1 (lncRNA BLACAT1) has been confirmed to play a crucial role in the occurrence and development of malignant tumors by competitively binding with miRNAs, participating in the Wnt/*β*-catenin signaling pathway and STAT3 signaling pathway, and interacting with relevant proteins and molecules. In this paper, we will summarize the mechanism of action of lncRNA BLACAT1 in pharyngeal squamous cell carcinoma and predict that it is expected to become a novel biomarker and therapeutic target for pharyngeal squamous cell carcinoma in the future.

Keywords

Long Noncoding RNA, Long Noncoding RNA Bladder Canner Associated Transcript 1, Pharyngeal Squamous Cell Carcinoma, Biomarker, Therapeutic Target

1. 引言

根据最新癌症数据统计，尽管肿瘤的诊断技术和治疗方法在不断的进步，但肿瘤患者的预后仍比较差，使肿瘤成为全世界人们关注的公共卫生问题[1] [2]。在近数十年里，越来越多的人对肿瘤发生的机制进行了广泛的研究和探讨。其中 IncRNAs 更是成为了近几年的研究热点。IncRNAs 通过基因转录和转录后修饰在肿瘤发生和转移中起特定作用[3] [4]。例如，IncRNAs 可以与基因启动子区域结合来调节宿主基因的表达[5]。同时，IncRNAs 也通过参与组蛋白修饰、染色质和 miRNA 相互作用、介导 mRNA 降解等过程从而在恶性肿瘤的发生发展中起作用[6] [7] [8] [9]。此外，IncRNAs 可以改变特定蛋白质的活性和细胞定位，从而调节癌症的发展[10]。S. Ghafouri-Fard 等人[11] [12]提出 IncRNAs 还参与了增殖、侵袭、迁移、细胞周期、细胞凋亡、细胞焦亡和自噬等多种细胞活动。目前位于人类染色体 1q32.1 上的 lncRNA BLACAT1 被检测为多种恶性肿瘤的致癌基因[13] [14]。这篇综述中，我们将概括 lncRNA BLACAT1 在咽部鳞状细胞癌中的异常表达及其在恶性肿瘤中的作用机制。

2. 咽部鳞状细胞癌

咽部鳞状细胞癌(Pharyngeal squamous cell carcinoma, PSCC)主要涵盖鼻咽部、口咽部及下咽部鳞状细胞癌。鼻咽部鳞状细胞癌(Nasopharyngeal squamous cell carcinoma, NSCC)是来自鼻咽部上皮组织的恶性肿瘤。按照世界卫生组织(World Health Organization, WHO)的分类，鼻咽癌(Nasopharyngeal Carcinoma)分为角化型鳞状细胞癌和非角化型(分化或未分化)鳞状细胞癌。鼻咽癌与其他头颈部恶性肿瘤不同，其发病具有明显的种族和地域特异性。在中国南方地区、东南亚各国以及非洲东北部属于鼻咽癌高发地区[15]。据统计，全球范围内鼻咽癌的发病率不足 1/100,000，然而在我国广东和香港地区，鼻咽癌的发病率却高达 15~30/100,000 人，其中 95%以上属于非角化型鳞状细胞癌[15]。随着诊断技术与肿瘤综合治疗的进步，

鼻咽癌患者的生活质量、预后越来越好。然而，其仍是严重威胁人们健康的问题。因此，进一步研究鼻咽癌的发病机制对鼻咽癌的早期诊断、疗效以及预后等方面具有重大意义。

口咽部鳞状细胞癌(Oropharyngeal squamous cell carcinoma, OSCC)发病率较高，主要发病年龄在50至60岁之间，男性患者较为常见，男女比例约为1.7:1。OSCC主要包括上皮或腺上皮来源的癌、中胚层来源的肉瘤和淋巴瘤。其中以上皮来源的癌和中胚层来源的淋巴瘤为多见。按发病部位，扁桃体区恶性肿瘤占比约为60%，舌根占25%，软腭部约占15%。早期口咽部鳞状细胞癌患者主要采用手术或放射治疗，晚期则以放化疗综合治疗为主。目前，口咽部鳞状细胞癌的病因尚不明确。多数文献指出，吸烟、饮酒、维生素缺乏、口腔卫生不良、营养不良等因素可能参与口腔癌的发生。因此，研究口咽部鳞状细胞癌的发病机制有助于提高诊断准确性、发现新的治疗靶点以及改善患者预后。

下咽鳞状细胞癌(Hypopharyngeal squamous cell carcinoma, HSCC)是一种源自上呼吸消化道的恶性疾病，被视为头颈部最具侵略性的肿瘤[16]。近年来，得益于诊断技术和治疗方法的不断进步，HSCC的手术切除、放射治疗以及新辅助化疗等技术得以优化，患者生存率有所提升。然而，鉴于下咽组织结构的特殊性以及发病部位的隐匿性，多数患者在确诊时已进入晚期，并伴有肿瘤远处转移，因此HSCC患者的五年生存率仍在25%~40%之间[17] [18]。为此，深入探索并发现下咽部鳞状细胞癌的高敏感性和特异性肿瘤标志物，以及寻找新的治疗靶点，已成为一项亟待解决的任务。

3. 长链非编码核苷酸(lncRNA)

人类基因组计划揭示，大约75%的人类基因可以转录，但只有约1.2%的转录RNA具有蛋白质编码能力[16]。其余大部分基因属于非编码RNA(ncRNA)，例如microRNA (miRNA)、小干扰RNA (siRNA)和长非编码RNA (lncRNA)等。ncRNA在细胞增殖[19]、细胞凋亡[20]、上皮间质转化(EMT) [21]、细胞分化[22]和免疫反应[23]等过程中起着重要的作用。其中，lncRNAs被定义为大于200个核苷酸组成的缺乏蛋白质编码能力的转录本。众多研究发现，IncRNAs在多种恶性肿瘤中异常表达从而调控肿瘤的发生发展。此外，IncRNAs通过参与调节宿主基因的表达、组蛋白修饰、染色质和miRNA相互作用、介导mRNA降解以及改变特定蛋白质的活性和细胞定位等过程，从而在恶性肿瘤的发生发展中起重要作用。

4. 长链非编码核苷酸膀胱癌相关转录因子1 (lncRNA BLACAT1)

长链非编码核苷酸膀胱癌相关转录因子1 (lncRNA BLACAT1)又叫linc-UBC1，是一种位于染色体1q32.1上的线性lncRNA。BLACAT1是常见的lncRNAs之一，长度为2616 bp [24]。BLACAT1不能编码蛋白质，但被证实可作为“分子海绵”与miRNAs竞争性结合，从而作用于其下游靶基因。同时，BLACAT1通过作用于多梳抑制复合体(Polycomb repressive complex, PRC)到特定位点进行基因甲基化。此外，，BLACAT1参与Wnt/β-catenin信号通路和STAT3信号通路以及作用于相关蛋白和分子，从而在恶性肿瘤的发生发展过程中起重要的作用。

BLACAT1于2013年首次在膀胱癌被检测到[24]。众多研究发现，BLACAT1在神经胶质瘤[25] [26]、乳腺癌[27]、肺癌[28]、肝细胞癌[29]、胃癌[30]、结直肠癌[31]、卵巢癌[32]、宫颈癌[33]和骨肉瘤[34]等恶性肿瘤中具有致癌作用。同时，BLACAT1在恶性肿瘤中的表达水平与肿瘤体积、淋巴结转移及远处转移呈正相关，导致总体生存期及无进展生存期(PFS)缩短。但廖登辉等人[35]发现，BLACAT1在甲状腺乳头状癌(Papillary thyroid carcinoma, PTC)患者的血清中低表达并可能发挥抑癌作用。

综上所述，BLACAT1在恶性肿瘤中的作用机制极其复杂，了解其在咽部鳞状细胞癌中机制，需要进一步的研究。

5. lncRNA BLACAT1 在癌症中的生物学机制

5.1. lncRNA BLACAT1 与 miRNAs

越来越多的证据表明，lncRNA 作为竞争内源性 RNA (ceRNA)与 miRNAs 结合，从而影响其同源基因和不相关基因，从而在各种人类癌症的发生和进展中发挥着重要作用[36]。因此，据报道 miR-142-5p [37]、miR-144 [38]、miR-485-5p [39]、miR-424 和 miR-143 [40]参与 BLACAT1 的致癌活性，这仍然是需要进一步研究其下游靶标以及与信号通路或生物分子的相互作用。值得注意的是，BLACAT1 通过 miR-605-3p/VASP [27]、miR-503/Bcl-2 [41]、miR-150-5p/CCR2 [32]、miR-17/ATG7 [42]发挥致癌作用、miR-361/ABCB1 [43]和 miR-519d-3p/RPS15A [44]轴，可被确定为临床干预的潜在靶标。

5.2. lncRNA BLACAT1 有关信号通路

众所周知，Wnt/β-catenin 信号通路及 STAT3 信号通路在众多人类癌症中通常被激活，从而加剧其恶性表型[45] [46]。此外，在 BLACAT1 功能过程中，同样观察到了此类现象。在 Wnt/β-catenin 信号传导过程中，敲低 mRNA 和蛋白水平的 BLACAT1，关键调节蛋白 β-catenin 的表达也受到显著抑制[47] [48] [49] [50]。杨华等人[44]证实，降低 BLACAT1 的表达量细胞核 β-catenin 的表达明显降低，细胞质 β-catenin 水平没有明显影响。因此，抑制 BLACAT1 可有效下调核 β-catenin 的表达，但未引起细胞质 β-catenin 表达的明显变化。此外，研究显示 c-myc 与细胞周期蛋白 D1 在 BLACAT1 活性中与 β-catenin 呈平行关系[48]。有趣的是，王等人[50]研究发现 Wnt/β-catenin 信号传导途径的主要目标基因 MMP-7 [51]，通过 BLACAT1 的过度表达而上升，进而诱导细胞迁移和侵袭能力的增强。在 STAT3 信号传导过程中，BLACAT1 被证实具有致癌活性，其主要通过 STAT3 Tyr705 的磷酸化发挥作用[52] [53]。

5.3. lncRNA BLACAT1 与蛋白质和分子

BLACAT1 在细胞核中的表达明显高于细胞质，这表 BLACAT1 可能在转录水平上具有主要的调节功能[54]。最近，其他生物蛋白或分子也检测到了 BLACAT1 的活性。PSEN1 是一种与放疗敏感性相关的蛋白质[55]介导 BLACAT1 的致癌活性[17]。苏军等人[56]发现敲低 BLACAT1 能够抑制 p15 启动子上 EZH2 与 H3K27me3 水平的协同作用，从而推测 BLACAT1 可能需要靶向 EZH2 并对其进行表观遗传调控以影响 p15 的表达。

5.4. lncRNA BLACAT1 与咽部鳞状细胞癌

苟彩霞等[17]发现 BLACAT1 在鼻鳞状细胞癌及其 5 个细胞系中均高表达。进一步分析鼻鳞癌的临床特征，发现 BLACAT1 在鼻鳞癌中高表达与临床分期($p = 0.015$)、肿瘤分期($p = 0.001$)和淋巴结分期($p = 0.004$)显著相关。BLACAT1 高表达的鼻鳞癌患者放射敏感性降低，总生存期较低，这也具有重要的临床意义。随后的力学研究表明，BLACAT1 通过调节早衰蛋白 1 (PSEN1)，一种处理淀粉样前体蛋白(APP) [55]的酶，使鼻鳞癌的不良预后和放射抵抗性增加。

戴冬秋等[37]证实 BLACAT1 在口腔鳞癌及其 5 个细胞系(SCC9、HSC3、CAL-27、FaDu 和 OECM-1 等)中呈高表达。功能丧失实验表明，通过下调 BLACAT1 可抑制了口腔鳞癌细胞的活力、迁移和侵袭。Western blot 检测细胞周期相关蛋白(cyclin D1, p21, p27) [30]，结果显示下调 BLACAT1 导致口腔鳞癌细胞中 cyclin D1 明显降低，p21，p27 明显升高，证实 BLACAT1 通过促进细胞周期进展而起致癌作用。有趣的是，功能研究表明 BLACAT1 在口腔鳞癌细胞中负向调控 miR-142-5p 的表达，而 miR-142-5p 过表达可以逆转 BLACAT1 的功能作用。然而，BLACAT1 在口腔鳞癌中的临床意义及其对鼻鳞癌和口腔鳞癌异种移植模型的影响尚不明确，有待进一步研究。综上所述，BLACAT1 可能是一种致癌因子，可为

鼻鳞癌和口腔鳞癌提供新的治疗靶点。

6. 总结及展望

咽部恶性肿瘤因咽部解剖结构复杂且周围临近重要器官，而难以进行手术治疗。咽部恶性肿瘤对电离辐射比较敏感，因此放射治疗是目前咽部恶性肿瘤的首选治疗之一，但因放抗性等原因患者的总生存期仍较短、预后较差。因此，研究出有效的治疗靶点显得尤为重要。lncRNA BLACAT1 近年来更是受到了广泛关注，综上所述 BLACAT1 通过与 miRNAs 结合，参与 Wnt/β-catenin 信号通路、STAT3 信号通路及与其他蛋白质和分子相互作用，从而在多种恶性肿瘤的发生发展中起作用。众多研究表明，BLACAT1 在鼻咽鳞癌、口咽鳞癌等多种癌症中呈高表达并促进肿瘤的发生发展，其表达量与肿瘤的分化程度、淋巴结转移、总生存期及无进展生存期(PFS)密切相关。这使得 BLACAT1 成为了癌症治疗中的重要生物标志物和治疗靶点。但 BLACAT1 在甲状腺乳头状癌(Papillary thyroid carcinoma, PTC)患者的血清中低表达并可能发挥抑癌作用。并且，BLACATI 在肿瘤发生发展过程中的调控机制收肿瘤类型、微环境、上下游调节因子等各种因素的影响。BLACATI 在肿瘤细胞增殖、细胞周期、肿瘤细胞侵袭转移等环节中的作用，使其成为一个潜在的治疗靶点和生物标志物。然而，目前对于 BLACATI 的上下游分子调控机制仍不明确，因此需要更深入的研究来揭示其在肿瘤发展中的具体作用机制。同时，研究也表明 BLACATI 的表达失调与肿瘤患者的临床特征及预后相关，这进一步突显了其作为生物标志物的潜在价值。然而，要将 BLACATI 应用到实际的临床诊断和治疗中，还需要更多的深入研究来验证其临床应用的准确性和有效性。

总之，lncRNA BLACAT1 在人类癌症治疗中具有巨大的潜力。通过对 BLACAT1 的功能、作用机制和应用前景进行总结，我们将为癌症治疗提供新的研究方向。未来，BLACAT1 有望为癌症患者带来更为有效的治疗方法，提高生存率和生活质量。

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