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在线全文

肿瘤微环境中lncRNA的研究进展*

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【摘要】 肿瘤微环境包括肿瘤相关的各种细胞和非细胞组分，其在肿瘤发生、生长和转移的过程中起着非常重要的作用。长链非编码RNA（long noncoding RNA，lncRNA）是一类长度超过200 nt的非编码RNA，参与多种生理和病理进程。研究表明，lncRNA在肿瘤与其微环境相互作用中起重要作用，进而影响肿瘤进展。本文将近年来关于肿瘤微环境中lncRNA的研究进展进行了总结，并探讨其在肿瘤早期诊断和治疗中的应用前景，提出开发有效特异性敲除lncRNA的策略和选择合适的体内运载工具特异性靶向目的细胞等方面是未来深入探索的方向。

【关键词】 肿瘤微环境 长链非编码RNA 肿瘤进展 肿瘤治疗

Latest Findings on Long Noncoding RNA in Tumor Microenvironment

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【**Abstract**】 Tumor microenvironment incorporates various tumor-related cellular and non-cellular components, playing a crucial role in the process of the pathogenesis, growth, and metastasis of tumors. Long noncoding RNA (lncRNA), a kind of noncoding RNA with a length of more than 200 nt, participates in a variety of physiological and pathological processes. Recent studies have shown that lncRNA plays a vital role in the interaction between tumors and the tumor microenvironment, thereby affecting tumor progression. Herein, we reviewed the research progress on the lncRNA in tumor microenvironment, discussed the potential application of lncRNA in early diagnosis and treatment of tumors, and suggested that some issues should be further explored in future research, including developing effective strategies for knocking out specific lncRNA and selecting appropriate *in vivo* delivery vehicles targeting specific cells.

【**Key words**】 Tumor microenvironment Long noncoding RNA Tumor progress Tumor treatment

肿瘤微环境主要是由肿瘤细胞、肿瘤相关成纤维细胞、肿瘤相关免疫细胞、血管内皮细胞、各种信号分子及细胞外基质等组成[1]。在肿瘤微环境中，肿瘤细胞与非肿瘤细胞或非细胞组分相互作用，不断适应其所处的内外环境，维持肿瘤的生长、进展和转移[2-3]。

长链非编码RNA（long noncoding RNA，lncRNA）一般是指长度大于200 nt、没有蛋白编码功能的RNA分子。按照lncRNA在基因组上的位置和方向，其一般分为5类：正义、反义、双向、内含子和基因间lncRNA，目前已发现上万种lncRNA的存在[4-7]。相比于蛋白编码基因，lncRNA基因种类更多，且其表达分布在细胞、组织或肿瘤中具有特异性[8-10]。

近年来研究发现，lncRNA通过转录、转录后或翻译水平在转录激活、转录抑制、基因印迹、染色质修饰及X染色体失活等过程中发挥重要作用，进而影响肿瘤的发生或进展[11-13]。与miRNA相比，lncRNA可通过多种调控方式发挥作用[14-15]。lncRNA可通过结合或移除转录因子来激活或抑制基因的表达[16]。一些lncRNA可介导招募染色质重塑复合物，或者作为染色质重塑复合物的支架[17-18]。一些反义lncRNA还可特异性结合互补的mRNA在转录后水平调控基因的剪切、翻译或降解[19]。还有一些lncRNA可以改变蛋白的定位，调控蛋白活性或者作为蛋白复合物的组成成分[20-21]。也有一些lncRNA可以剪切产生小RNA的前体或者作为内源竞争性RNA（competitive endogenous RNA，ceRNA）充当miRNA的“海绵”[22-24]。

近年来研究表明，lncRNA在肿瘤与肿瘤微环境相互作用中起重要作用。在肿瘤微环境中，肿瘤细胞、非肿瘤细胞或其他非细胞组分通过lncRNA相互作用，进而促进肿瘤生长、转移、血管新生、耐药、细胞代谢重编程和诱导免疫抑制等进程，且肿瘤微环境中的lncRNA具有作为肿瘤检测的分子标记物或者肿瘤治疗的靶标的潜在可能性[25-31]。本文将对近年来肿瘤微环境中lncRNA的研究进展进行综述，探讨lncRNA在肿瘤临床诊断和治疗中的应用前景。

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1 lncRNA与肿瘤微环境

在肿瘤发生发展的进程中,肿瘤细胞不断与其周围环境相互作用,肿瘤细胞可通过释放包括lncRNA在内的信号分子影响其所处的微环境,促进周围非肿瘤细胞的增殖、迁移,血管新生和诱导免疫抑制等。肿瘤微环境中的其他组分也可通过lncRNA影响肿瘤或其他非肿瘤细胞的增殖和迁移、耐药等过程,进而影响肿瘤进展。

1.1 lncRNA与肿瘤相关成纤维细胞

肿瘤相关成纤维细胞是肿瘤微环境中最丰富的基质细胞,在肿瘤微环境中促进肿瘤进展,而lncRNA被发现在肿瘤相关成纤维细胞与肿瘤细胞相互作用中起重要作用[32-37]。研究发现,lncRNA LOC100506114在口腔鳞状细胞癌肿瘤相关成纤维细胞中显著上调,且其可通过与转录因子RUNX家族相关转录因子2(RUNX2)结合上调生长分化因子10(GDF10)的表达和分泌,诱导正常成纤维细胞转化为肿瘤相关成纤维细胞,进而促进肿瘤细胞的增殖和迁移[34]。lncRNA MALAT1在包括卵巢上皮癌的多种实体瘤中表达上调,在肿瘤相关成纤维细胞中过表达MALAT1可促进卵巢上皮细胞的迁移[35]。

此外,肿瘤成纤维细胞可促进肿瘤细胞中某些长链非编码RNA异常表达,进而影响肿瘤进展。在食管癌中,肿瘤相关成纤维细胞以PDGFβ/PDGFRβ/FOXO1信号通路依赖的方式促进食管癌细胞中lncRNA DNM3OS的高表达,而lncRNA DNM3OS通过调节DNA损伤反应促进食管癌细胞对放疗的抵抗性[36]。而且,肿瘤微环境中肿瘤相关成纤维细胞的异质性与化疗耐药密切相关。对铂耐药的胰腺癌患者的肿瘤相关成纤维细胞可促进肿瘤细胞过量表达lncRNA UPK1A-AS1,以促进非同源末端连接(NHEJ),从而增强DNA双链断裂(DSB)修复,影响胰腺癌细胞对奥沙利铂的耐药性;而阻断UPK1A-AS1的表达,增加了体内肿瘤细胞对奥沙利铂的敏感性[37]。这些研究结果提示,lncRNA可以作为肿瘤治疗的潜在靶点。

1.2 lncRNA与血管内皮细胞

在肿瘤微环境中,血管内皮细胞被激活进而增殖和迁移,从而形成血管,促进肿瘤发生发展、浸润和转移。研究发现,lncRNA可促进血管内皮细胞的激活[38-42]。在乳腺癌中,lncRNA NR2F1-AS1与内皮细胞标记物CD31和CD34表达呈正相关,NR2F1-AS1通过与miRNA-338-3p结合而增加乳腺癌细胞中胰岛素样生长因子-1(IGF-1)的表达,然后激活血管内皮细胞HUVEC中的IGF-1受体(IGF-1R)和细胞外信号调节激酶(ERK)通路,从而促进HUVEC的增殖、管形成和迁移能力[40]。lncRNA PVT1在胃癌中表达上调,其可通过激活STAT3/VEGFA信号轴促进肿瘤血管生成[41]。LINC00173.v1在肺鳞癌组织中特异性上调,过表达LINC00173.v1通过海绵化miR-511-5p上调血管内皮生长因子A(VEGFA)表达促进血管内皮细胞的增殖和迁移,进而促进肿瘤进展。而通过反义寡核苷酸(antisense oligonucleotide, ASO)策略抑制LINC00173.v1可降低肺鳞癌肿瘤生长,并提高肺鳞癌细胞对顺铂的治疗敏感性[42]。

1.3 lncRNA与肿瘤相关免疫细胞

在肿瘤微环境中,肿瘤相关巨噬细胞是最丰富的炎性细胞,与多种类型肿瘤患者的不良预后相关[43]。研究发现,巨噬细胞可通过影响肿瘤细胞中lncRNA的表达,增强肿瘤细胞的恶性程度,包括增殖、运动、侵袭性和化疗耐药性,进而肿瘤进展[44-46]。研究发现,肿瘤相关巨噬细胞通过细胞外囊泡传递lncRNA HISLA,阻断PHD2和HIF-1α的相互作用,以抑制HIF-1β的羟基化和降解,增强乳腺癌细胞的有氧糖酵解和抗凋亡能力。而糖酵解过程中肿瘤细胞释放的乳酸上调巨噬细胞中的HISLA,从而构成肿瘤相关巨噬细胞和肿瘤细胞之间的正反馈回路。阻断细胞外囊泡传递的HISLA可抑制乳腺癌细胞的糖酵解和化疗耐药性[45]。

肿瘤相关巨噬细胞在功能上可分为M1和M2巨噬细胞两个亚群,通常M1巨噬细胞与抗肿瘤活性相关,而M2巨噬细胞与促肿瘤活性相关。肿瘤细胞可通过lncRNA影响肿瘤相关巨噬细胞的分化。研究发现,lncRNA RPPH1在结直肠癌组织中显著上调,RPPH1通过与β-微管蛋白Ⅲ(TUBB3)相互作用来诱导结直肠癌细胞的上皮-间质转化(EMT)。结直肠癌细胞衍生的外泌体将RPPH1运输到巨噬细胞中,参与M2巨噬细胞的极化调控,从而促进结直肠癌细胞的增殖和转移[46]。

1.4 lncRNA与缺氧肿瘤微环境

缺氧是肿瘤微环境的一个重要特征[47]。在包括乳腺癌、胃癌等在内的多种肿瘤中,肿瘤细胞高消耗,而肿瘤微环境中的血管异常导致供氧不足。在缺氧环境中,多种基因包括lncRNA异常表达,并促进肿瘤进展和转移[48-50]。研究发现,缺氧诱导胃癌细胞高表达lncRNA CBSLR,CBSLR可以与YTHDF2相互作用,形成CBSLR/YTHDF2/CBS信号轴,通过增强YTHDF2与CBS mRNA的m^6A修饰,降低CBS mRNA的稳定性,引起ACSL4的降解,从而避免胃癌细胞发生铁死亡[49]。在缺氧环境中,缺氧诱导因子(HIF)可诱导肿瘤细胞lncRNA的异常表达,从而影响肿

瘤进展。在乳腺癌中, HIF2可以诱导乳腺癌细胞过表达lncRNA RAB11B-AS1, RAB11B-AS1通过增加RNA聚合酶Ⅱ。的募集来增强缺氧性乳腺癌细胞中血管生成因子(包括VEGFA和ANGPTL4)的表达, 从而促进血管形成, 进而促进乳腺癌远端转移[50]。

1.5　lncRNA与外泌体

外泌体是一类直径在40 ~ 150 nm的脂质双分子层囊泡, 其组分包括蛋白、DNA、mRNA、lncRNA及miRNA等, 几乎所有类型的真核细胞都可分泌外泌体, 其在作为疾病诊断的分子标记物和药物载体方面具有巨大的潜在应用价值[51-52]。在肿瘤微环境中, lncRNA可以被包装进外泌体内, 参与肿瘤微环境中细胞之间的交流, 从而调控肿瘤血管新生、肿瘤生长、转移及耐药等[53-55]。lncRNA CRNDE在胃癌患者的肿瘤组织和肿瘤相关巨噬细胞中表达上调, CRNDE可通过M2极化巨噬细胞衍生的外泌体(M2-exo), 从M2转移到胃癌细胞中。而CRNDE可促进神经前体细胞表达发育下调蛋白4-1(NEDD4-1)介导的磷酸酶和紧张素同源物(PTEN)泛素化, 沉默M2-exo中CRNDE的表达可逆转M2-exo对顺铂处理的胃癌细胞的细胞增殖和顺铂处理裸鼠的同种移植瘤生长的促进作用[54]。在肺腺癌中, 肿瘤相关成纤维细胞通过外泌体将lncRNA LINC01614传递至肺癌细胞中, LINC01614可直接与AXNA2和p65相互作用, 激活NF-κB信号通路, 上调谷氨酰胺转运体SLC38A2和SLC7A5的表达, 增强肺癌细胞的谷氨酸代谢, 从而促进肺癌进展[55]。在肿瘤微环境中, 由于外泌体脂质双分子层的保护, lncRNA可稳定地在不同细胞中进行传递, 从而影响肿瘤进展。

2　肿瘤微环境中lncRNA的临床应用价值

肿瘤微环境中的长链非编RNA异常表达, 影响肿瘤生长和进展。随着肿瘤微环境中lncRNA的研究不断深入, lncRNA被发现作为肿瘤早期诊断的分子标记物和肿瘤治疗的潜在靶点[56-59]。

2.1　lncRNA在肿瘤诊断中的作用

由于早期肿瘤症状具有隐匿性, 目前传统的肿瘤标记物(如CA153、CA125和CEA等)用于临床肿瘤诊断的特异性和敏感性较差, 大多数肿瘤患者出现症状就诊时就已处于晚期, 导致患者预后较差[60]。近年来研究表明, 肿瘤微环境中异常表达的lncRNA可随外泌体或其他方式进入并稳定存在于体液(包括血液和尿液等)中, 其在体液中异常表达, 与肿瘤的发生、进展及患者预后密切相关, 单个、多个lncRNA或与其他分子标记物联合应用具有作为肿瘤早期诊断的分子标记物的潜在临床价值[61-62]。

目前, 研究较多的lncRNA PCA3已被美国食品和药品监督管理局批准用于前列腺癌的早期临床诊断。与健康人相比, lncRNA HOTAIR在胶质母细胞瘤患者的肿瘤组织和血液中均高表达, 且二者呈正相关, HOTAIR的高表达与高级别脑肿瘤显著相关, 提示血液中HOTAIR可用于胶质母细胞瘤早期诊断的潜在可能性[63]。相较于传统的肿瘤标记物CEA, 5种lncRNA(TINCR、CCAT2、AOC4P、BANCR和LINC00857)联用能较好地区分胃癌患者与健康人, 其曲线下面积值为0.91(95%置信区间: 0.88 ~ 0.95)[64]。此外, lncRNA ZFAS1、SNHG11、LINC00909和LINC00654的组合被发现可以作为早期结直肠癌诊断的分子标记物[65]。

2.2　lncRNA在肿瘤治疗中的临床应用

基于肿瘤微环境的复杂性, 越来越多的研究表明, 仅靶向肿瘤细胞并不能有效治疗肿瘤, lncRNA肿瘤微环境中的lncRNA可作为肿瘤预后的分子标记物和治疗的潜在靶点[66-67]。已有研究者利用siRNA、ASO、CRISPR和锁核酸(locked nucleic acid, LNA)等技术靶向肿瘤微环境中的lncRNA, 继而开发治疗肿瘤的新策略[68-69]。

研究发现, 靶向lncRNA逆转化疗耐药, 增强药物的敏感性。在舒尼替尼耐药的晚期肾细胞癌中, lncRNA lncARSR通过竞争性结合miR-34/miR-449促进肿瘤细胞中AXL和c-MET的表达, 促进舒尼替尼的耐药性, 且lncARSR可以被整合到外泌体中并传递到敏感细胞, 从而增强舒尼替尼的耐药性。而利用LNA策略靶向小鼠体内的lncARSR可有效延缓舒尼替尼耐药的肾细胞癌进展, 且恢复了肿瘤对舒尼替尼的敏感性[70]。lncRNA FLANC在结直肠癌组织中高表达, 并促进胃癌的转移, 其高表达与患者的预后呈正相关, 利用纳米囊泡递送靶向FLANC的siRNA可有效抑制小鼠肿瘤生长和转移[71]。此外, lncRNA PKMYT1AR被发现在非小细胞肺癌中高表达, PKMYT1AR/miR-485-5p/PKMYT1轴通过抑制β-TrCP1介导的β-连环蛋白泛素降解促进肿瘤干细胞的维持, 利用ASO靶向PKMYT1AR可显著抑制小鼠肿瘤生长[72]。

3　总结和展望

综上所述, 在肿瘤微环境中, 异常表达的lncRNA在肿瘤生长、进展、转移和耐药等方面发挥重要作用。继续深入研究肿瘤微环境中lncRNA中的功能和作用机制将为我们理解肿瘤的发病和进展机制提供新的思路, 并为肿瘤的治疗提供新的工具。lncRNA在临床应用中的研究还属于起步阶段, 其应用于肿瘤治疗仍面临巨大挑

战，探索更多lncRNA的作用机制、开发有效特异性敲除lncRNA的策略和选择合适的体内运载工具特异性靶向目的细胞等方面仍需要进行深入探索。

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利益冲突 所有作者均声明不存在利益冲突

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