长链非编码RNA在鼻咽癌转移机制中的研究进展

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摘要 鼻咽癌是头颈肿瘤中较常见且侵袭性较强的肿瘤。随着放化疗及分子靶向等综合治疗的发展, 鼻咽癌死亡率明显下降。早期患者预后较好, 但中晚期及复发转移的患者预后仍较差。因此, 全面了解鼻咽癌转移机制至关重要。目前长链非编码RNA(long noncoding RNA, LncRNA)在肿瘤中的研究较为热门, 且越来越多的研究发现, LncRNA在鼻咽癌转移机制中起到重要作用, 如细胞上皮间质转化、细胞外基质降解及微血管形成等。该文就LncRNA在鼻咽癌转移机制研究作一综述。

关键词 鼻咽癌; 长链非编码RNA; 转移机制

Progress of Long Noncoding RNA in the Metastasis Mechanism of Human Nasopharyngeal Carcinoma

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Abstract Nasopharyngeal carcinoma is the more common and aggressive head and neck tumor. With the development of comprehensive therapies such as chemoradiotherapy and molecular targeting therapy, the mortality rate of nasopharyngeal carcinoma has decreased significantly. The prognosis of patients in early stage is favourable, while the prognosis of patients in middle and late stage or with recurrence and metastasis is still poor. Therefore, it is important to understand the molecular mechanism of nasopharyngeal carcinoma metastasis fully. At present, LncRNA (long noncoding RNA) is popular in tumor researches. More and more studies have found that LncRNAs play an important role in the metastasis mechanism of nasopharyngeal carcinoma, including EMT (epithelial mesenchymal transformation), degradation of ECM (extracellular matrix) and microvascular formation. This article reviews the metastasis mechanism of LncRNAs in nasopharyngeal carcinoma.

Keywords nasopharyngeal carcinoma; LncRNA; metastasis mechanism

鼻咽癌是一种在头颈中较常见且侵袭性较强的肿瘤。其常见于男性, 且在我国南方及东南亚地区高发[1-2]。据统计, 鼻咽癌发病率及死亡率正在逐年下降, 这归功于生活质量的提高、EB病毒(Epstein-Barr virus, EBV)的筛查、内镜技术的发展及放化疗的综合治疗。但与早期鼻咽癌患者5年生存率87%~96%相比, 晚期鼻咽癌患者5年生存率为67%~77%[3]。晚期鼻咽癌患者病情较差, 容易复发及转移, 而远处转移是治疗失败的主要原因[4]。手术区范围过大及放化疗剂量过高严重影响患者的生

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存质量, 包括耳聋、上消化道损伤、骨髓抑制, 严重时会出现鼻咽癌部位大出血。流行病学研究发现, 遗传易感性、表观遗传变异、种族、化学致癌物质暴露史、EBV感染等因素在该类恶性肿瘤中发挥着重要作用[5]。肿瘤转移是恶性肿瘤进展的一个重要特征[6]。其包括多方面, 如细胞上皮间质转化(epithelial-mesenchymal transition, EMT)促进癌细胞“游离”, 癌细胞微环境的改变包括细胞外基质(extracellular matrix, ECM)改变促进癌细胞转移, 新生血管生成促进癌细胞增殖转移等。其中EMT是肿瘤转移的关键。EMT即为上皮细胞失去极性, 失去与基底膜连接, 减少细胞间黏附。更多的“游离”癌细胞进入血液循环, 在继发部位增殖, 扩散癌细胞。近几年越来越多研究发现长链非编码RNA(long noncoding RNA, LncRNA)在肿瘤中发挥重要作用。除有肿瘤诊断价值外, LncRNA在肿瘤中的机制越来越多的被学者们所发现。研究表明, LncRNA作为内源性竞争RNA及反义RNA, 在多种肿瘤中起抑制或促进作用。面对目前鼻咽癌晚期转移患者预后差的现状, 全面了解鼻咽癌转移机制具有一定的重要性。本文对近几年国内外LncRNA在鼻咽癌中的转移机制研究作一分析总结, 为今后LncRNA在鼻咽癌转移机制的研究提供新方向, 为抑制鼻咽癌转移、改善患者预后提供新思路。

1 LncRNA概述

LncRNA是长度大于200个核苷酸的RNA分子, 不具有编码蛋白的功能, 以前一度被认为是无功能RNA。LncRNA作用最初于2002年在大规模测序小鼠全基因组cDNA文库过程中被发现[7]。目前, LncRNA的起源并不明确, 可能的来源包括蛋白质编码基因的突变、染色体重排、相邻LncRNA序列重复及可转座元件插入[8]。LncRNA有多种基因组起源, 根据它们与蛋白质编码基因的关系[9], 可分为以下5种。(1)正义LncRNA: 其与蛋白质编码基因的有义链转录本一个或多个重叠。(2)反义LncRNA: 其与蛋白质编码基因的反义链转录本一个或多个重叠; (3)双向LncRNA: 其在转录起始位点下游小于1 000碱基对开始, 同时位于蛋白编码基因的互补链上。(4)内含子LncRNA: 其可在任何方向内含子内启动, 与外显子序列无重叠。(5)基因间LncRNA: 其位于两个蛋白质编码基因之间的基因组区间内, 同时距离最近的编码基因超过1 000个碱基对。近十多年研究发现, 众多有功能的LncRNA。LncRNA可通过与DNA、RNA及蛋白质相互作用在相关基因的表观遗传、转录及转录后水平上的表达起着重要的作用, 进而调节细胞生长, 如基因印记、染色体重组、剪接调控和转录RNA衰退、转录及翻译调控等[10-11]。

2 LncRNA在鼻咽癌转移机制的研究进展

鼻咽癌转移机制的研究对鼻咽癌治疗及预后有重要意义。鼻咽癌转移机制与其他癌有相同之处, 包括EMT相关转录因子和传导通路、ECM改变相关分子、微血管形成相关分子等。目前研究中, EBV感染是公认的鼻咽癌致病因素之一[12]。EBV产物, 如潜伏膜蛋白1(latent membrane protein 1, LMP1)[13-15]、潜伏膜蛋白2A(latent membrane protein 2A, LMP2A)[16-17]、EBV核抗原1(Epstein-Barr virus nuclear antigen 1, EBNA1)[18-19]等通过影响肿瘤细胞EMT转录因子如Snail等、ECM降解酶如基质金属蛋白酶(matrix metallproteinases, MMPs)等及微血管因子如血管内皮生成因子A(vascular endothelial growth factor A, VEGFA)等的表达影响肿瘤转移。而EBV感染仅是鼻咽癌研究的冰山一角。自从发现LncRNA以来, 越来越多的研究表明, LncRNA在鼻咽癌转移机制也起一定作用。研究发现, LncRNA主要以微小RNA(microRNA, miRNA)为靶点来介导其功能, 且大多数LncRNA在鼻咽癌中起抑制转移的作用。我们主要从LncRNA对鼻咽癌EMT、ECM的降解及微血管形成等三方面的影响进行讨论。

2.1 LncRNA影响鼻咽癌EMT

EMT以上皮细胞表型的缺失和间充质细胞表型出现为特征, 使癌细胞“游离”, 促进癌细胞转移。目前相关转录因子包括: Snail、Twist(twist-related protein)、E-钙黏蛋白(E-cadherin)及ZEB(zinc finger E-box-binding homeobox)等[20]。相关通路包括: 转化生长因子β/Sma和Mad相关蛋白(transforming growth factor β/Smad, TGF-β/SMAD)、Wnt/β-联蛋白(β-catenin)、磷脂酰肌醇-3-激酶/蛋白激酶(phosphoinositide-3-kinase/threonine kinase, PI3K/Akt)、白细胞介素6/信号转导与转录激活因子3(interleukin 6/signal transducers and activators of transcription 3, IL-6/STAT3)等[21]。其中E-cadherin属上皮细胞标记物, 而N-钙黏蛋白(N-cadherin)和波形蛋白(vimentin)

属间充质细胞标记物。

2.1.1 LncRNA内源性竞争miRNA诱导EMT 研究发现, LncRNA大部分通过内源性竞争miRNA影响miRNA靶基因的表达, 诱导癌细胞EMT。

LncRNA肺腺癌转移相关转录本-1(metastasis-associated in lung adenocarcinoma transcript-1, MALAT1), 全长超过8 700 nt, 位于11q13号染色体上, 在多种肿瘤(如肺癌、胰腺癌、结肠癌等)中高表达[22]。MALAT1生物学功能较多样, 如涉及丝氨酸/精氨酸富集蛋白(serine/arginie riched protein, SR protein)的招募和磷酸化、mRNA前体加工、基因表达调控等过程[22]。研究发现, MALAT1在高转移性鼻咽癌细胞系和癌组织中高表达。过表达MALAT1可通过下调miR-124从而上调钙蛋白酶4(calpain small subunit 1, Capn4)的表达, 加速鼻咽癌EMT进程[23]。另有一篇研究报道, 在鼻咽癌细胞CNE-1细胞株中MALAT1过表达可抑制E-cadherin的表达, 诱导细胞EMT的进程, 进而增强细胞侵袭及转移能力[24], 同时MALAT1也可直接抑制E-cadherin的表达。

LncRNA H19在人体正常组织中低表达或不表达, 而在多种肿瘤中却高表达, 并参与肿瘤的发展和转移[25]。LI等[26]报道, H19可通过miR-630/Zeste同源序2的增强子(enhancer of zeste homolog 2, EZH2)通路抑制E-cadherin表达, 诱导EMT, 明显促进鼻咽癌细胞的侵袭能力[26]。同样, 之前也有报道, 膀胱癌细胞内H19高表达, 促使EZH2表达, 下调E-cadherin, 进而增强细胞的转移性[27]。而H19在胶质母细胞瘤中, 不仅与EZH2相互作用, 还可招募多梳蛋白抑制复合体2(polycomb repressive complex 2, PRC2)到*E-cadherin*基因启动子区域, 引起组蛋白3甲基化(H3K27me3)使*E-cadherin*基因表达受到抑制。此外, 裸角质蛋白1(naked cuticle 1, *NKD1*)基因的表达也受到抑制, 而NKD1可通过Wnt/β-catenin信号通路, 促进EMT[28]。

LncRNA牛磺酸上调基因1(taurine upregulation gene 1, TUG1)在新生小鼠视网膜细胞中被发现, 因随牛磺酸加入上调故得名[29]。在鼻咽癌中, TUG1抑制miR-384表达, 促进vimentin、N-cadherin、TGF-β1表达, 而这3个蛋白是EMT的关键因子[30]。此外, TUG1在其他肿瘤中如膀胱癌(miR-145)[31]、胆囊癌(miR-300)[32]等肿瘤中也可通过miRNA影响肿瘤EMT。

研究较少的LncRNA, 如LncRNA尿路上皮癌相关蛋白1(urothelial carcinoma-associated 1, UCA1)通过吸附miR-145, 抑制miR-145的表达, 进而提高miR-145靶向基因解聚素–金属蛋白酶17(a disintegrin and metalloproteinase-17, ADAM17)的表达, 增强了鼻咽癌细胞侵袭能力[33]。而ADAM17可激活TGF-β/SMAD通道, 诱导EMT, 促进癌细胞侵袭[34]。此外, LncRNA细胞重组调节因子(regulator of reprogramming, ROR)通过诱导EMT促进鼻咽癌的侵袭和转移[35]。其机制可能与乳腺癌相同, ROR可作为一种内源性竞争miR205的RNA, 阻止miR205靶基因的降解, 其中miR205靶基因包括了EMT诱导物*ZEB1*和*ZEB2*[36]。LncRNA核仁小分子RNA宿主基因1(small nucleolar RNA host gene 1, SNHG1)可通过抑制miR-145-5p的表达, 导致miR-145-5p抑制新型(nua)激酶1[novel (nua) kinase family1, NUAK1)表达的作用减弱, 促进NUAK1表达, 而NUAK1可通过Akt信号通路诱导EMT, 增强鼻咽癌细胞的侵袭性[37]。LncRNA核富含丰富的转录本1(nuclear paraspeckle assembly transcript 1, NEAT1)则可通过靶向抑制miR-34a-5p, 促进Wnt/β-catenin信号通路, 进而促进EMT[38]。

2.1.2 其他LncRNA诱导EMT LncRNA FOXC1基因启动子上游转录体(FOXC1 promoter upstream transcript, FOXCUT)可诱导EMT, 其表达与叉头框蛋白C1(forkhead box Fox C1, FOXC1)表达呈正相关, 在鼻咽癌组织中高表达。下调FOXCUT可导致β-catenin表达下调, 可显著抑制鼻咽癌细胞株的增殖和迁移[39]。作为鼻咽癌的致癌基因, FOXCUT还可通过与STAT3相互作用并增强Janus激酶1(janus kinase, JAK1)与STAT3结合, 进而增强IL-6/JAK1/STAT3信号转导, 增强鼻咽癌侵袭能力[40]。GAO等[41]研究表明, 沉默LncRNA HOXC13反义RNA (HOXC13 antisense RNA, HOXC13-AS)可使E-cadherin蛋白质含量增加, 而N-cadherin和vimentin蛋白质含量减少。这些蛋白改变说明, HOXC13-AS可诱导EMT, 促进癌细胞迁移。LncRNA分化拮抗非蛋白编码RNA(differentiation antagonizing non-protein coding RNA, DANCR)可通过与核因子90/核因子45复合体(nuclear factor 90/nuclear factor 45, NF90/NF45)相互作用, 增加低氧诱导因子1α(hypoxia inducible factor 1α, *HIF1α*) mRNA稳定性, 诱导EMT[42]。此外, 还有LncRNA如SNHG12(Notch-1)[43]、SNHG20(TGF-β1)[44]

可直接通过信号通路诱导EMT(图1)。

2.2 LncRNA调节微血管形成

肿瘤微环境中的新生血管不但提供肿瘤生长所需的养分, 而且促进肿瘤转移。与成熟血管相比, 新生毛细血管的基底膜不完整的特点使肿瘤细胞更易进入血管。肿瘤血管生成调节主要取决于血管生成促进因子和抑制因子的改变。其中血管内皮生成因子(vascular endothelial growth factor, VEGF)是目前已知的直接刺激血管内皮细胞增殖作用最强且特异高的因子, 其高表达预示着肿瘤生长及新生血管的形成[45]。其促进因子除了VEGF, 还有促血管生成素、成纤维细胞生长因子、生长转化因子等; 抑制因子包括内皮抑素、血管抑素等。

LncRNA同源框基因转录反义RNA(HOX transcript antisense intergenic RNA, HOTAIR)是第一个发现与肿瘤发生相关的LncRNA[46]。研究发现, 其在鼻咽癌细胞和癌组织样本中高表达[47]。在体内外试验中, 下调HOTAIR能显著减弱肿瘤细胞的生长及血管生成。此外, HOTAIR可通过直接激活血管内皮生成因子A(vascular endothelial growth factor A, VEGFA)的转录或通过葡萄糖调节蛋白78(glucose regulated protein 78 kDa, grp78)介导间接使VEGFA和促血管生存素2(angiopoietin 2, Ang2)表达上调促进鼻咽癌血管生成[48]。FOXCUT作为经典的LncRNA之一, 也可促进VEGFA表达来实现鼻咽癌转移[39]。NEAT1在微血管形成中也起重要作用, 其可抑制miR-101-3p表达, 而促进上皮膜蛋白2(epithelial membrane protein-2, EMP2) mRNA及蛋白水平的表达[49]。而EMP2是细胞间隙链接的主要构成元素, 细胞间隙链接的缺失可导致癌细胞侵袭及转移。

2.3 LncRNA影响ECM的降解

ECM是癌细胞转移和侵袭的天然屏障。ECM连接紧密抑制癌细胞扩散, 而ECM交联结构降解可促进癌细胞转移。能溶解ECM的蛋白主要是蛋白水解酶, 包括基质金属蛋白酶(matrix metallproteinases, MMPs)、丝氨酸蛋白酶、半胱氨酸蛋白酶及天门冬氨酸蛋白酶。MMPs几乎能降解ECM中的各种蛋白成分, 破坏肿瘤细胞侵袭的组织学屏障, 在肿瘤侵袭转移中起关键性作用, 被认为是该过程中主要的蛋白水解酶[50]。

FOXCUT促进鼻咽癌迁移, 除了可诱导EMT, 促进微血管形成外, 还可促进ECM的降解。其主要影响MMP7和MMP9的表达[39]。MMP7主要降解明胶及纤维蛋白, 而MMP9可降解多种胶原蛋白、明

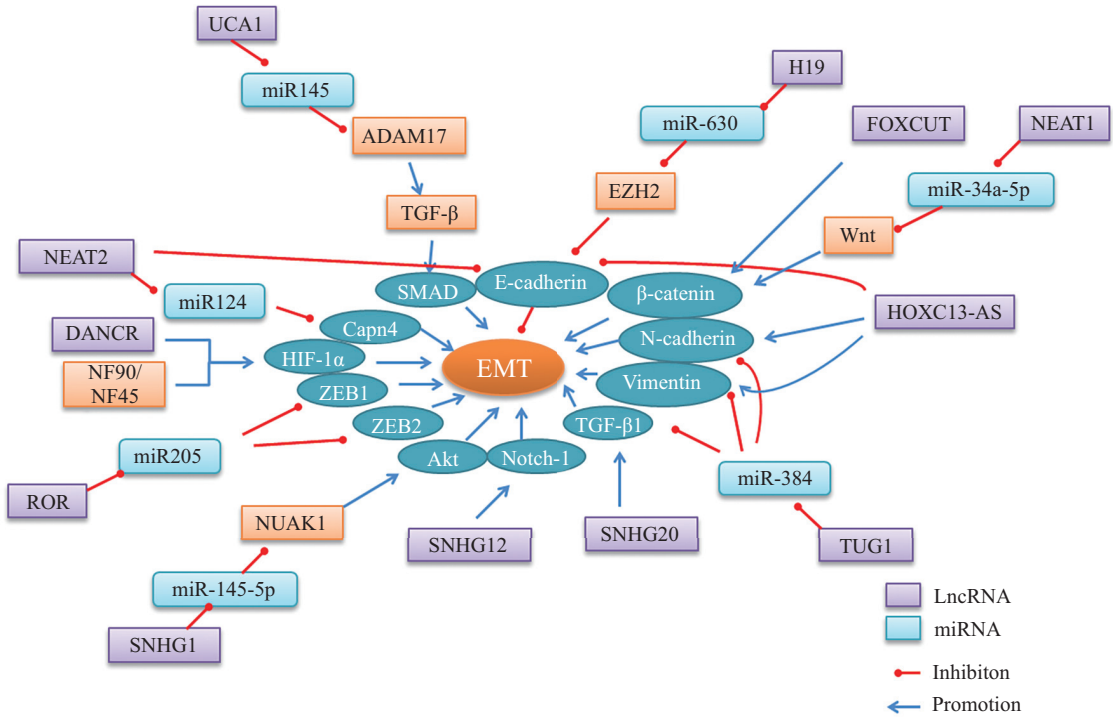

图1 LncRNA在鼻咽癌上皮间质转化中的分子机制(根据参考文献[24-25,27,31,34-45]修改)

Fig.1 Molecular mechanism of LncRNA in epithelial mesenchyma transformation of nasopharyngeal carcinoma (modified from reference ([24-25,27,31,34-45])

胶、纤维黏连蛋白、层黏连蛋白、弹性蛋白等。LncRNA n326322的过表达促进了鼻咽癌细胞的增殖和侵袭, 而其低表达抑制了鼻咽癌细胞的增殖和侵袭, 机制研究表明, n326322通过胞外调节激酶/丝裂原活化蛋白激酶(extracellular signal-regulated kinase/mitogen-activated protein kinase, ERK/MAPK)通路促进癌细胞侵袭[51]。而MMPs是ERK/MAPK通路的重要下游信号元件, 尤其是MMP2和MMP9[52]。此外, SNHG1的下游基因*NUAK1*除了可抑制E-cadherin表达诱导EMT外, 还可促进MMP2、MMP-9和内膜1型基质金属蛋白酶(membrane-type-1 matrix metalloproteinase, MT1-MMP)等ECM酶的表达, 促进鼻咽癌转移[37]。

3 展望

目前已有多种LncRNA在鼻咽癌转移分子机制研究中较为全面, 如SNHG1、FOXCUT、NEAT1、MALAT1等。而部分LncRNA如lncRNA ENST00000438550[4]、LINC00312[53]、LncRNA结肠癌相关转录本1(colon cancer associated transcript 1, CCAT1)[54]、LncRNA ZNF674-1(OTTHUMG00000021416)[55]及LncRNA肌动蛋白丝相关蛋白1反义RNA1(actin filament associated protein 1 antisense RNA1, AFAP1-AS1)[56]等仅局限于鼻咽癌转移表观研究, 其深层次的转移机制有待进一步去发现。此外, LncRNA在鼻咽癌转移EMT机制中研究较为深入, 而在ECM改变及微血管形成中研究较少, 以及在其他肿瘤中LncRNA的作用机制仍需在鼻咽癌中进行研究。本综述为今后鼻咽癌转移分子机制提供新方向, 为抑制鼻咽癌转移、改善患者预后提供新思路。

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