·综　述·

长链非编码RNA MALAT1在恶性肿瘤中的作用及机制研究进展

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[摘　要]　长链非编码RNA(long noncoding RNA,lncRNA)近几年成为研究热点,已证实某些lncRNA的异常表达与肿瘤的发生、发展关系密切。其中,肺腺癌转移相关转录本1(metastasis associated lung adenocarcinoma transcript 1,MALAT1)在转移性肿瘤细胞中表达上调。MALAT1广泛表达于正常组织,而在多种人类肿瘤组织、细胞及外周血中的表达均存在显著差异性,提示其可能在肿瘤的发生发展及侵袭转移等过程中起重要作用。文章就MALAT1的分子特点、功能以及在肿瘤分子病理学中的研究进展作一综述。

[关键词]　MALAT1;非编码RNA;恶性肿瘤

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Progress on the studies of functions and mechanisms of long non-coding RNA MALAT1 in tumors

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[**Abstract**]　Long non-coding RNA(lncRNA) has become a research hotspot in recent years, and it has been proved that abnormal expressions of some certain lncRNAs are closely related to the occurrence and progression of tumors. Among many kinds of lncRNAs, the metastasis associated lung adenocarcinoma transcript 1 (MALAT1) is upregulated in metastatic carcinoma cells. MALAT1 was widely expressed in normal tissues, and the expressions displayed significant differences in a variety of human tumor tissues, cells and peripheral blood, which suggests that MALAT1 may play an important role in the process of tumorigenesis, progression, invasion and metastasis. Herein we document the molecular characteristics and functions of MALAT1 with a reference to their implications in the molecular pathology of various cancers.

[**Key words**]　MALAT1; non-coding RNA; tumor

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1　概　述

人类基因组序列资料显示超过90%的DNA有转录活性,但其中仅有2%转录为编码蛋白质的RNA,绝大部分被称为非编码RNA(non-coding RNA,ncRNA)[1-2]。根据长度ncRNA分为两大类,短小非编码RNA(< 200 nt)和长链非编码RNA(long noncoding RNA,lncRNA)(> 200 nt)。最近的研究发现,lncRNA在机体生理及病理过程中均具有广泛的功能,尤其与恶性肿瘤发生发展关系密切[3]。lncRNA的遗传多态性可以改变基因结构从而产生广泛的基因多态性,有望成为新型肿瘤标志物和肿瘤治疗的靶点[4]。lncRNA在肿瘤细胞增殖、侵袭和转移中起重要作用,且可通过调控肿瘤耐药相关基因及信号通路从而介导多种肿瘤细胞耐药的发生[5-7]。lncRNA发挥功能的机制多样,其中一个机制是ln-

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cRNA可与小干扰RNA(microRNA，miRNA)相互作用参与靶基因的表达调控[8-9]。肺腺癌转移相关转录本1(metastasis associated lung adenocarcinoma transcript 1，MALAT1)最初在转移性非小细胞肺癌细胞中被发现[10]，目前已经有大量文献研究其在恶性肿瘤包括肺癌发生发展中的作用机制[11]。

2 MALAT1的分子特征

1997年，在一项鉴定编码多发性内分泌腺瘤病Ⅰ型的基因位点产生的多个转录本研究中，被称为α转录本的MALAT1基因第一次被描述[12]。2003年，在研究早期非小细胞肺癌患者远处转移时发现了MALAT1转录本，MALAT1是细胞内表达量最高且最保守的lncRNA[10]。除了在肿瘤细胞中异常表达外，MALAT1还广泛表达于正常组织。Spector等[13]发现MALAT1转录本定位于富含pre-mRNA加工因子的核散斑体，且在这一区域有非常丰富的表达，提示MALAT1可能参与了RNA代谢。MALAT1缺乏开放读码框，不编码蛋白质。其3′末端缺乏poly(A)尾巴，2种内源性的核糖核酸酶(RNase P和RNase Z)参与了MALAT1 3′末端的加工过程。此过程产生了定位于胞核的MALAT1与定位于胞浆的小tRNA样的ncRNA——mascRNA[14]。人类细胞中MALAT1的半衰期较其他非编码RNA长，为9~12 h，可能与3′末端的三级螺旋结构有助于MALAT1的稳定有关[15-17]。

3 MALAT1的调节机制

3.1 MALAT1的功能和相互作用因子

哺乳动物细胞核通常由数个亚核区域组成，包括核仁、核散斑、核旁斑、Cajal小体与早幼粒细胞(promyelocytic leukemia，PML)小体等。核散斑是1个富含pre-mRNA剪切与加工因子的亚核区域，由于MALAT1定位于核散斑，这一区域富含涉及pre-mRNA剪切的多种因子，而SR剪切因子蛋白家族和SR蛋白特异性激酶是在剪切调控中起着重要作用的因子。因此，MALAT1与一系列的SR蛋白相互作用，包括SRSF1(SF2/ASF)、SRSF2(SC35)和SRSF3(SRp20)，以及其他的剪切体蛋白，如U2AF65、IBP160和RNPS1[18-21]。通过紫外交联免疫沉淀结合高通量测序(HITS-CLIP)法进行RNA-蛋白质之间作用的研究证明SRSF4(SRp75)、TDP-43、DGCR8和AGO2蛋白可与MALAT1形成复合物[22-27]。RNA pull-down实验证实不均一核糖核蛋白C1/C2和E2F转录辅激活因子如LSD1和SETD2可特异性结合MALAT1[28-29]，显示MALAT1可与多种蛋白质结合发挥其生物学功能。

3.2 MALAT1的转录调节

MALAT1在多种肿瘤细胞中呈现不同形式的调节。在人SK-N-SH神经母细胞瘤细胞中，垂体后叶素、催产素通过结合到MALAT1基因启动子上的cAMP反应元件，上调MALAT1的表达[30]。组蛋白去甲基化酶JMJD1A可以与MALAT1基因启动子区结合从而促使JMJD1A脱甲基，导致MALAT1表达升高[31]。在膀胱癌中，转化生长因子β(TGF-β)可诱导MALAT1的转录从而促进上皮-间充质转变(EMT)[32]。子宫内膜癌中，抑癌基因PCDH10启动子甲基化激活Wnt/β-catenin通路，导致MALAT1转录增加[33]。在表达雌激素受体α的乳腺癌细胞中，17β-雌二醇可下调MALAT1的转录水平，从而抑制肿瘤细胞的增殖、转移和侵袭[34-35]。在食管癌中，SOX17可抑制MALAT1的表达[36]。张道奇等[37]研究发现在A549细胞中，干扰素调节因子3(interferon regulation factor 3，IRF3)是MALAT1的靶基因，MALAT1通过调控IRF3启动子区来影响IRF3的转录与表达。

人血管内皮细胞中，低氧促进MALAT1转录从而导致血管增生[38]。肌肉生长抑制素(myostatin)可负性调节MALAT1的转录，从而在一定程度上调节骨骼肌的生长与发育[39]。

3.3 MALAT1的转录后调控和修饰

转录后调控在基因功能调控中亦具有重要作用。MALAT1的转录后调控表现在剪切、蛋白激活和内源性竞争RNA方面[40]。核糖核酸酶Drosha的减少可以增加MALAT1的转录，相关蛋白DGCR8[25]和TDP-43可调节MALAT1的转录，敲减DGCR8可增加MALAT1的转录[41]，通过HITS-CLIP分析证实TDP-43与MALAT1密切相关，小鼠脑组织中TDP-43的减少可降低MALAT1的表达[23]。

近年来的研究发现，lncRNA与miRNA及其下游靶基因之间的相互调控与肿瘤的发生发展密切相关，已成为肿瘤研究领域的热点之一。miRNA作为一个转录后调控的重要因子，其活性可被lncRNA通过“海绵”吸附的方式调控，这类lncRNA又被称为竞争性内源RNA(competing endogenous RNA，ceRNA)。lncRNA除了可以直接参与调控基因的表达，也可以通过吸附miRNA，影响靶基因mRNA的丰度从而影响其蛋白质水平[42]。Leucci等[43]研究发

现，miR-9通过直接绑定2个MALAT1的mRNA序列位点调控MALAT1的表达并导致其在核内降解；沉默Ago2或抑制miR-9表达将显著提升MALAT1在人体内的稳定水平。Chou等[44]发现MALAT1可以作为细胞分裂周期蛋白cdc42 3′UTR的ceRNA，通过与miR-1作用来诱导乳腺癌细胞迁移和侵袭，并降低cdc42的水平，从而证实MALAT1的作用是通过与cdc42竞争性结合miR-1实现。宫颈癌研究中，MALAT1可以通过竞争性结合miR-124调节靶基因GRB2的表达，GRB2基因敲除后可以减少细胞生长和侵袭，促进细胞凋亡[45]。MALAT1和miR-140在间质瘤内皮细胞中[46]和肌肉形成过程中[47]也表现出类似的相互作用。此外，MALAT1可作为ceRNA解除miRNA对靶基因的抑制作用，如miR-22-3p[48]、miR-125b[49]等，增加靶基因的表达。MiR-101和miR-217转录后调节MALAT1能抑制食管鳞癌细胞的增殖、迁移和侵袭[50]。肾透明细胞癌中，MALAT1可作为ceRNA竞争结合miR-200从而调节肾透明细胞癌细胞的增殖和转移[51]。目前MALAT1和miRNA相互作用的研究进一步揭示了MALAT1在恶性肿瘤的调节功能和通路机制。

3.4　其他调节机制

除了前述的调节机制外，MALAT1的作用机制还包括调节EMT，如MALAT1可以通过调节Snail进而调节EMT进程[52]。在乳腺癌中抑制MALAT1后可通过PI3K/Akt途径调节EMT，抑制肿瘤细胞的迁移和侵袭[53]。TGF-β可诱导膀胱癌细胞中MALAT1的表达以及EMT，抑制MALAT1后可以抑制TGF-β诱导的EMT[54]。

作为哺乳动物中高度保守的lncRNA，MALAT1大量存在于细胞核内，但是在G2/M期细胞，MALAT1会转移进入细胞质。Tripathi等[55]研究发现MALAT1能对细胞周期进行调控；降低MALAT1水平后，调节细胞周期的相关蛋白也随之变化，G0/G1期的细胞数增多，而复制能力在S期降低；该研究还发现在MALAT1缺乏的人类正常的二倍体肺成纤维细胞中，P53能减弱E2F1转录因子的活性和细胞增殖，抑制细胞周期。Guo等[56]在宫颈癌的研究发现降低MALAT1可导致诱导细胞凋亡基因Caspase-3和Caspase-8激活；抑制Bcl-2和Bcl-xl凋亡基因表达。

4　MALAT1在恶性肿瘤中的作用及机制研究进展

MALAT1最初是在肺癌转移标本中被发现显著升高。以后随着研究的深入，发现除了肺癌外，其在多种恶性肿瘤患者中均有异常表达。Schmidt等[57]研究发现MALAT1在非小细胞肺癌（NSCLC）特别是在腺癌和大细胞癌中的表达显著升高，且MALAT1的表达水平与鳞癌患者的预后呈负相关。Weber等[58]在NSCLC患者外周血中检测到MALAT1表达下降，但由于其敏感性相对较低，所以血液中MALAT1不适合作为NSCLC独立的诊断和判断预后标志物。

Xia等[59]研究发现，MALAT1在胃癌组织中显著高表达，表达程度与胃癌远处转移相关，并且发现胃癌患者外周血中MALAT1水平的升高与患者预后呈负相关，可以作为判断预后的一个独立因子。

在乳腺癌的临床研究中，Huang等[60]发现在雌激素受体（ER）阳性的患者中MALAT1的表达显著升高，提示MALAT1与ER的表达密切相关，且MALAT1的表达水平与他莫昔芬治疗效果呈负相关。Miao等[61]的研究提示MALAT1在乳腺癌中的表达上调，血清MALAT1水平可作为乳腺癌早期诊断的潜在标志物。

研究者在肝细胞癌（hepatocellular carcinoma，HCC）组织中也发现了MALAT1表达升高[62-63]，其表达水平与miR-146b-5p呈反比，MALAT1可作为ceRNA与mRNA竞争结合miR-146b-5p调控HCC的增殖与转移。而Konishi等[64]的研究发现HCC患者非癌肝组织中MALAT1的表达水平与结直肠癌肝转移患者的非癌肝组织比较显著升高。HCC患者外周血MALAT1水平显著升高，亚组分析显示丙型肝炎病毒感染的HCC患者MALAT1表达水平较乙型肝炎患者高，肝硬化的HCC患者外周血MALAT1水平升高更显著。提示外周血MALAT1可预测HCC的进展。

在膀胱癌的研究中，有学者发现MALAT1除了在肿瘤组织中表达增加外，在转移性膀胱癌中的表达较原位癌更明显[65-66]。Duan等[67]通过筛选13个候选lncRNA，最后鉴定出在膀胱癌患者外周血中显著升高的3个lncRNA，包括MEG3、SNHG16和MALAT1，可以作为膀胱癌的诊断和复发的指标。

5　小结与展望

自从2003年鉴定出MALAT1以来，其在多种疾病包括恶性肿瘤中的研究逐渐深入。MALAT1在多种肿瘤组织中表达增高，并且可以调控多种下游基因的表达，特别是2011年提出了ceRNA以后，lncRNA与miRNA之间互相作用并调控下游基因，从

而影响肿瘤生物学行为,展现了非编码RNA更复杂的机制。MALAT1作为ceRNA与多种miRNA之间的调控机制也逐渐有研究报道,体现了这一复杂的调控网络之间的精细调节,而且这个调控网络也有更多的信号通路参与其中。但是MALAT1在肿瘤的发生发展中的作用途径、作用靶点、具体的调节机制及网络通路等方面仍有大量工作需要深入进行,从而为MALAT1成为一个潜在的肿瘤标志物以及治疗靶点做提供分扎实的理论基础及实验依据。

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