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长链非编码 RNA 在肿瘤发生和天然免疫中的功能与调控机制

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摘要:长链非编码 RNA(Long non-coding RNA,lncRNA)是长度大于 200 个核苷酸的不具有编码蛋白质能力的 RNA 分子。长链非编码 RNA 一度被认为是转录"噪音"。然而,近年来大量的实验证据表明长链非编码 RNA 通过表观遗传修饰与转录调控、转录后加工、翻译调控等多种机制,在细胞生命活动中发挥重要作用。lncRNA 的异常表达和调控往往与肿瘤发生、宿主抗病原微生物感染的天然免疫应答密切相关,本文就这些方面研究进展进行综述。

关键词:长链非编码 RNA,肿瘤发生,天然免疫,转录调控

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随着 ENCODE(Encyclopedia of DNA Elements)项目的开展,人们发现人类基因组中超过 90% 的 DNA 均能被转录为 RNA,而其中不到 2% 的基因转录产物被翻译为蛋白质,其余 98% 的 DNA 转录产物为编码能力极低或无编码功能的非编码 RNA(non-coding RNA, ncRNA)[1]。在 ncRNA 中,除 tRNA、rRNA 等为人熟知外,其余大量 ncRNA 一直被视作转录过程的"暗物质"而未受重视。近来研究证实,ncRNA 可形成复杂的二级或者三级结构,通过与 DNA、RNA 或者蛋白质相互结合,在细胞分化和代谢等生命活动中发挥举足轻重的作用[2]。根据 ncRNA 的长度,将 ncRNA 分为小非编码 RNA 和长链非编码 RNA(long non-coding RNA, lncRNA),后者碱基长度在 200 nt 到 100000 nt 之间。lncRNA 由 RNA 聚合酶Ⅱ(RNA polⅡ)或者 RNA 聚合酶Ⅲ(RNA polⅢ)转录产生,可定位在细胞质或者细胞核,其表达具有组织特异性或发育阶段特异性等特征[3]。lncRNA 既参与表观遗传、可变剪接、入核转运等过程,也能作为小 RNA 前体发挥功能,其转录和功能失调往往伴随着疾病的发生[4]。

1 长链非编码 RNA 的分类

目前 lncRNA 还没有一个规范的分类方法,只是研究者根据其作用特点、结构特点、作用形式等进行分类。根据它们不同的特性可分为不同的类别:依据 lncRNA 作用特点分为转录调节 lncRNA 和转录后调节 lncRNA;依据 lncRNA 的基因组定位可分为基因间 lncRNA 和内含子 lncRNA、正义 lncRNA 和反义 lncRNA;依据 lncRNA 的作用形式分为顺式 lncRNA 和反式 lncRNA[5-6]。

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2 长链非编码 RNA 的作用机制

长链非编码 RNA 可以在表观遗传修饰水平、转录水平、转录后加工以及翻译水平等多个层面上(图 1),参与调控基因的表达[7]。

2.1 表观遗传修饰调控

表观遗传指在基因组 DNA 序列不发生改变的情况下,基因表达发生改变,该现象普遍存在于动植物中,例如 DNA 甲基化、基因组印迹和基因沉默等。lncRNA 主要通过对目的基因的表观遗传修饰来完成表观遗传调控。lncRNA 参与的表观遗传修饰调控过程中,与 lncRNA 互作的组蛋白修饰复合体主要为 PRC1 和 PRC2 复合体。例如 lncRNA ANRIL 可以招募 PRC1 复合体到 INK4A/ARF 基因簇,从而抑制基因的转录[8]。lncRNA Xist 通过和 lncRNA HOTAIR 相似的机制,招募并结合 PRC2 复合体,介导基因沉默[9]。除了 PRC 复合体之外,lncRNA 还与其他的组蛋白修饰复合体相互作用,调控基因的转录。例如 lncRNA AIR 能够与 H3K9 组蛋白甲基转移酶 G9a 相互作用,通过影响组蛋白甲基化,抑制基因的转录[10]。此外,有些 lncRNA 可以与一种以上的组蛋白修饰复合体相互作用,例如 lncRNA HOTAIR(HOX transcript antisense RNA)5′末端有 PRC2 结合区,3′末端有 LSD1/CoREST1 结合区,HOTAIR 能作为支架招募并结合相应复合体,参与基因的表观遗传调控[11]。

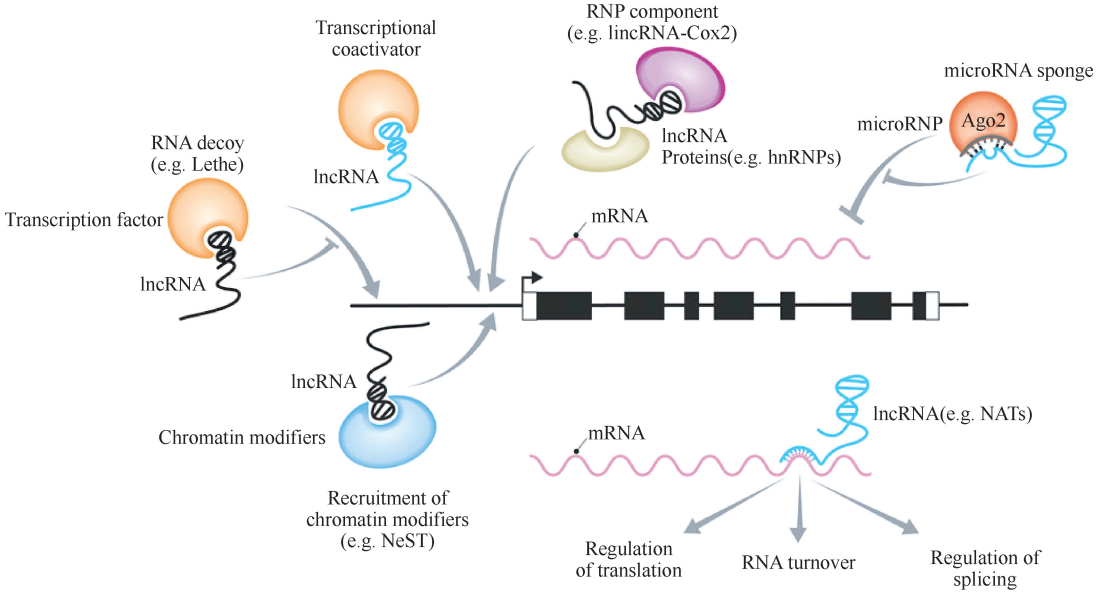

图 1. lncRNA 作用模式图[12]

Figure 1. Paradigms for how lncRNAs function[12].

2.2 转录调控

在已知作用机制的 lncRNA 中,大部分通过调控转录水平而发挥其功能。lncRNA 可以占据转录因子的结合位点,抑制基因转录和表达,也可以招募转录因子到启动子或增强子上,促进基因的转录和表达。例如 lncRNA DHFR 上游转录产物(DHFR upstream transcripts)与二氢叶酸还原酶(dihydrofolate reductase,DHFR)基因启动子通过互补序列结合阻碍转录因子 IIB 结合 DHFR 启动子并抑制转录[13]。在小鼠细胞内,lncRNA Evf2 由启动子区域转录而来,它可以招募转录因子 DLX2 结合到增强子上,从而诱导邻近蛋白编码基因的转录。除此之外,lncRNA 还可以通过与转录因子或转录复合物基本组分相互作用影响基因的转录。例如在静息细胞中,位于细胞质中的 lncRNA NRON 与 KPNB1、CSE1L、IQGAP1、CK1、GSK3、DYRK 几个蛋白互作形成 RNA-蛋白复合物,干扰 NFAT1 转录因子的活化以及入核,从而抑制转录[14]。热激(heat shock)产生的 Alu 元件能够与 RNA 聚合酶Ⅱ结合,抑制转录起始复合体的形成[15]。

2.3 转录后加工

lncRNA 对转录后 mRNA 剪接和加工过程的调控有多种模式。第一种，lncRNA 通过与正义链 mRNA 碱基配对形成 RNA-RNA 双链，改变 mRNA 的剪接模式。例如 MYC 反义 lncRNA 与神经母细胞瘤 MYC 的 mRNA 形成双链，抑制剪接[16]。第二种，通过调节剪接因子的活性来调控 mRNA 剪接模式。例如 lncRNA MALAT1 与 SR 蛋白相互作用，进而调控 SR 及其他剪接因子在核斑点区域中的分布，并通过调节 SR 磷酸化水平影响 mRNA 前体的选择性剪接[17]。第三种，除了调节 mRNA 剪接模式，还有一类反义 lncRNA，能够指导与其重叠的 mRNA 的编辑。这类 lncRNA 与 mRNA 形成双链 RNA，在 ADAR 酶的催化下，将腺苷酸变为次黄苷酸，这种转变能影响 RNA 结构、编码潜能和 microRNA 的靶定。例如在黑腹果蝇中，lncRNA Sas10 能够影响与之部分重叠的 Rnp4F (RNA-binding protein 4F) mRNA 的编辑[18]。

2.4 翻译调控

除了转录后加工，lncRNA 还以多种模式参与蛋白质的翻译调控。第一种模式，lncRNA 能直接调控翻译过程。例如酵母中肌醇磷酸合成酶 KCS1 的反义 lncRNA 调控同一基因位点的 KCS1 mRNA 的翻译，合成截短的活性缺失蛋白[19]。第二种，lncRNA 能调节 mRNA 的稳定性。例如 BACE1AS 是来源于 BACE1 (beta-site APP-cleaving enzyme Ⅰ) 基因位点的反义 lncRNA。BACE1AS 与 BACE1 mRNA 形成 RNA 双链增加了 mRNA 的稳定性，进而解除了 miRNA 的降解作用[20]。第三种，属于内源竞争性 RNA (competing endogenous RNAs, ceRNA) 的 lncRNA 竞争性地与 miRNA 互补配对结合，从而阻止 miRNA 介导的降解作用，保护靶 mRNA。例如在 Bcr-Abl 诱导细胞转化的过程中，由于 lncRNA-BGL3 (Beta Globin Locus 3) 和 PTEN 具有相同的 miRNA 反应元件 (miRNA response elements, MREs)，lncRNA-BGL3 竞争性结合这些 miRNA，降低了这些 miRNA 对 PTEN 的抑制作用，从而调控 PTEN 的水平[21]。

3 lncRNA 与肿瘤发生

从分子层面来说，肿瘤是抑癌基因或致癌基因异常作用的基因疾病。越来越多的研究证明，lncRNA 的异常表达和调控与肿瘤发生、发展密切相关。

3.1 致癌 lncRNAs

PCAT-1：在前列腺癌组织中 lncRNA PCAT-1 (prostate cancer associated transcript 1) 特异性地高表达，而且其高表达能够显著促进肿瘤细胞的生长和增殖[22]。PCAT-1 的表达受 PRC2 复合体的负调控，其中的组蛋白甲基转移酶 EZH2 和 SUZ12 均起着重要作用。目前研究已证实，PCAT-1 主要作为转录抑制因子而发挥促癌作用，可调控一系列肿瘤相关基因的表达，如 CENPF，BRCA2 和 CENPE 等[23]。

UCA1：在静息细胞里，hnRNP I 与 p27 (Kip1) mRNAs 的 5′-UTR 相互作用来增强其蛋白翻译水平，进而抑制细胞增殖，阻断细胞生长于 G1 期。而在乳腺癌细胞中，lncRNA UCA1 (urothelial cancer associated 1) 与 hnRNP I 形成一个稳定的功能性 lncRNA-蛋白(核糖核蛋白)复合物，进而竞争性地抑制了 p27 蛋白的表达，解除了细胞增殖的抑制，导致其促癌作用[24]。

3.2 抑癌 lncRNAs

linc-p21：p53 是重要的肿瘤抑制基因，其作用机制多样，不仅能够作为转录因子诱导基因转录，还能够作为转录抑制因子调控肿瘤相关基因的表达。Huarte 等发现，p53 作为转录因子直接诱导基因间长链非编码 RNA p21 (Long intergenic ncRNA p21, lincRNA-p21) 的转录表达。而后者通过结合核不均一核糖核蛋白-K (Heterogeneous nuclear ribonucleoprotein-K, hnRNP-K)，进一步协助 p53 的转录抑制因子功能，促进肿瘤细胞的凋亡，发挥抑癌作用[25]。

lncRNA CCND1：细胞周期蛋白 D1 是一个促进细胞增殖的细胞周期调节蛋白。lncRNA CCND1 的编码基因位于细胞周期蛋白 D1 基因的启动子区。CCND1 招募并结合与 DNA 损伤相关的 RNA 结合蛋白 TLS，引起 TLS 的变构和活化。随后 TLS 结合并抑制 CREB 结合蛋白质(CBP)和 p300 的组蛋白乙酰化转移酶活性，导致细胞周期蛋白 D1 基因的表达降低，进而抑制肿瘤的发生[26]。

3.3 兼有致癌和抑癌性质的 lncRNAs

H19：H19 基因是最早鉴定的印迹基因之一。在许多实体瘤中，包括肝癌和膀胱癌等，都发现了

lncRNA H19 的异常表达。H19 作为癌基因或者抑癌基因影响肿瘤的发生发展,可能与特定的肿瘤类型以及它所处的肿瘤微环境密切相关[27-28]。在 Wilms 肾母细胞瘤细胞中, H19 在双等位基因上的 DMR 区域均发生超甲基化,表达显著降低,这导致与其相邻的 IGF2 基因的印迹缺失(Loss of imprint, LOI)得以大量表达,并促进了肿瘤细胞的生长。H19 基因很可能通过调控 IGF2 的印迹而抑制肿瘤的发生[29]。然而在 Bcr-Abl 诱导细胞转化的研究中发现,干扰 lncRNA H19 的表达能够促进 K562 细胞凋亡,并抑制细胞在裸鼠体内诱导的肿瘤生长,这显示了 lncRNA H19 的促癌作用[30]。

与肿瘤发生、发展密切相关的 lncRNAs 见表 1 和表 2。

表 1. 致癌 lncRNA

Table 1. Oncogenic lncRNAs

lncRNAs	Genomic location	Expression	Function	Cancer types	Length/kb	References
H19	11p15.5	up	Enhance carcinogenesis and metastasis of gastric cancer.	Breast, Stomach, Bladder, Ovary, Colon etc.	2.3	[31-35]
HOTAIR	12q13.13	up	Increase cancer invasiveness and metastasis in a manner dependent on PRC2.	Breast, Ovary, Lung, Liver.	2.2	[36-40]
MALAT1	11q13.1	up	Bind to SFPQ and release PTBP2 from the SFPQ/PTBP2 complex.	Lung, Prostate, Breast, Colon.	8.7	[41-44]
PCGEM1	2q32	up	Act as a coactivator for c-Myc and AR. Reprogram the androgen network and the central metabolism.	Prostate.	1.6	[45]
PCAT-1	8q24.21	up	Regulate BRCA2 and control homologous recombination. Regulate c-Myc with miR-3667-3p.	Prostate, Esophageal squamous cell.	1.9	[23,46-47]
PTENP1	9p13.3	down	Act as a ceRNA to titrate the miRNAs targeting PTEN.	Endometrium.	3.9	[48-49]
UCA1	19p13.12	up	Repress p27 (Kip1).	Esophageal squamous cell, Bladder, Breast, Tongue.	2.3	[24,50-51]
LncRNA-HEIH	5q35.3	up	Interact with EZH2.	Liver.	1.6	[52]
ANRIL	9q21.3	up	Repress p15(INK4b) locus and silence miR-99a/miR-449a.	Stomach, Esophageal squamous cell.	3.8	[53]
CCAT2	8q24.21	up	Regulate MYC and WNT.	Stomach, Esophageal squamous cell, Breast, Colon.	1.7	[54-56]
PVT-1	8q24	up	Downregulate caspase3 and smad4 expression.	Colon.	3.0	[57]
linc-p21	6p21.2	up	linc-p21 induced by p53 mediates global gene repression in the p53 response.	Colon.	3.1	[58-59]

4 lncRNA 与天然免疫

lncRNAs 在天然免疫中的作用最初于 2009 年被 Guttman 等证实。他们用 LPS 刺激小鼠骨髓树突状细胞后,发现有 20 条 lncRNA 表达异常。随后的基因芯片和 RNA 测序结果也证实了 lncRNAs 表达异常与小鼠肺部的病毒感染、单核细胞和巨噬细胞的激活密切相关[78]。

THRIL:THRIL 基因位于编码 BRI3 结合蛋白(Bri3 bp)基因的下游,与 Bri3 bp3'末端有部分重复序列。在细菌脂多糖 LPS 类似物 Pam3CSK4 的刺激下,THP1 巨噬细胞中 THRIL 表达水平显著降低。Li 等发现 lncRNA THRIL 与 hnRNP L 相互作用形成 RNA-蛋白复合物,将结合到 TNF-α 和 IL8、CXCL10、CCL1 和 CSF1 的启动子上,起始转录。但当细胞外的 TNFα 增加到一定浓度时,则负反馈调控 THRIL 的转录[79]。

表 2. 抑癌 lncRNA

Table 2. lncRNAs that act as tumor suppressors

lncRNAs	Genomic location	Expression	Function	Cancer types	Length/kb	References
H19	11p15.5	down	Imprinted at the lgf2 locus; control igf2 expression in cis; lncRNA H19/miR-675 axis represses prostate cancer metastasis by targeting TGFBI.	Prostate, Renal.	2.3	[60,29]
ncCCND1	11q13	up	Induce TLS allosteric change and silencing cyclin D1 gene expression.	DNA damage.	0.2	[61]
Loc285194	3q13.31	down	Act as a p53-regulated tumor suppressor. Repress miR211.	Bone.	2.1	[62-63]
Loc554202	9p21.3	down	Produce miR31.	Breast.	2.2	[64]
MEG3	14q32	down	Mediate the effect of p53, and inhibit angiogenesis.	Ovary, Bladder, Stomach.	1.5 – 9.7	[65-68]
linc-p21	6p21.2	down	Mediate p53-dependent transcriptional repression. Inhibit JunB and CTNNB1.	Liver.	3.1	[69]
PTCSC3	14q13.3	down	Act as a ceRNA of miR574 – 5p.	Thyroid.	1.1	[70]
RERT-lncRNA	19q	up	RERT-lncRNA upregulated EGLN2 to affect tumorigenesis.	Liver.	2.8	[71]
lncRNA-MVIH	10q22	up	Inhibite phosphoglycerate kinase 1 (PGK1).	Liver.	2.1	[72]
GAS5	1q25.1	down	Bind with and titrate away GR.	Breast, Cervix.	0.6	[73-75]
ncRuPAR	5q13.3	down	Downregulate protease-activated receptor-1.	Colon, Stomach.	0.4	[76-77]

NEAT1：lncRNA NEAT1 (Nuclear Enriched Abundant Transcript 1)又被称为病毒诱导的非编码 RNA VINC (Virus Inducible NonCoding RNA)。NEAT1 可被多种病毒感染所诱导表达,包括人类免疫缺陷病毒(HIV-1)、流感病毒、日本脑炎病毒、狂犬病毒和单纯疱疹病毒(HSV)。NEAT1 能与蛋白 NONO 相互作用,促进了核内旁斑的形成。而且 NEAT1 能结合剪接因子 SFPQ (splicing factor proline/glutamine-rich),将 SFPQ 从 IL8 的启动子区移至旁斑中,解除了 SFPQ 对转录的抑制作用,从而开启抗病毒基因 IL8 的表达。而在 HIV-1 感染的细胞,lncRNA NEAT1 通过促进 HIV-1 mRNA 从细胞核运输到细胞质,影响 HIV-1 的复制[80]。

lincRNA-Cox2：lincRNA-Cox2 基因位于 Cox2 (Ptgs2)基因下游 50 kb 处。当树突状细胞受到细菌脂多糖 LPS 刺激后,lincRNA-Cox2 被诱导表达。在静息的 BMDM(bone marrow-derived macrophages)细胞中,lincRNA-Cox2 抑制了 787 个基因的表达,然而在 Pam3CSK4 刺激后,lincRNA-Cox2 诱导了 713 个基因的表达,其中包含大量免疫基因,例如 Ccl5 和 IL6。虽然具体机制仍然不清楚,但 lincRNA-Cox2 的抑制作用依赖于其与 hnRNP-A/B 和 hnRNP-A2/B1 的结合。这些 hnRNPs 是多功能 RNA 结合蛋白家族的成员,它们在 mRNA 前体的加工和基因表达的调节中发挥重要作用[15]。

Lethe：Rapicavoli 等发现,在小鼠胚胎成纤维细胞(MEF)中,伴随着各种病原微生物感染诱导激活 TNF-α,Rps15a-ps4 假基因的表达也大量增加,这个假基因叫做 Lethe。促炎细胞因子选择性地诱导 lncRNA Lethe 的产生。而 lncRNA Lethe 能作为 NF-κB 的负反馈调节信号,通过与 NF-κB RelA 亚基相互作用,抑制 RelA DNA 结合和靶基因的激活,进而抑制由 TNF-α 引起的炎症反应[81]。

lnc-DC：lnc-DC 只在受到病原微生物刺激后,由单核细胞分化的传统树突状细胞(conventional dendritic cells,cDCs)中特异性表达。Pin W 等认为细胞质中的 lnc-DC 能直接结合转录因子 STAT3,促进 STAT3 TYR705 位点的磷酸化和入核。避免了 STAT3 与磷酸酶 SHP1 结合后,STAT3 的去磷酸化。持续活化的 STAT3 最终促进了树突状细胞分化基因的表达,进而影响着天然免疫反应[82]。

PACER：Krawczyk M 等发现,在人乳腺上皮细胞和单核细胞/巨噬细胞受到细菌脂多糖 LPS 刺激后,CTCF(the chromatin boundary/insulator factor)打开了 Cox2 区域的染色质结构,导致 Cox2 转录起始位点上游的 lncRNA PACER 表达增多。lncRNA

PACER 和 p50 – p50(NF-κB 的抑制形式)相互作用,进而减少了 Cox2 启动子区 p50 – p50 的结合,增加了 Cox2 启动子区 p50 – p65(NF-κB 的活化形式)的结合。Cox2 启动子区 p50 – p65 的结合促进 p300 组蛋白乙酰转移酶的招募以及 RNA 聚合酶 II 起始复合物的组装,促进 Cox2 的表达,进而参与炎症反应[83]。

NRAV:人源 lncRNA NRAV(Negative Regulator of Anti-Viral response,又称为 DYNLL1-AS1)位于染色体 12q24.31。在未感染甲型流感病毒的细胞中,lncRNA NRAV 通过影响一些关键干扰素刺激基因(ISGs)的组蛋白修饰(H3K4me3 和 H3K27me3)从而抑制这些基因的初始转录,包括重要的抗病毒效应蛋白 MxA 和 IFITM3。而当病毒感染细胞后,宿主为了保护自身,调控 lncRNA NRAV 丰度下降,解除对 ISG 转录的抑制作用,从而促进多种 ISG 抗病毒蛋白的快速、大量表达。宿主通过调控 NRAV 而发挥的抗病毒作用,不仅仅局限于抵御甲型流感病毒感染,还被普遍应用于抵御多种其它病毒的感染,如其它 RNA 病毒,包括仙台病毒和呼肠孤病毒,以及 DNA 病毒,如单纯疱疹病毒[84]。

5 总结和展望

lncRNA 通过其特殊的基序或立体结构与 DNA、RNA 或蛋白质分子相互作用,在细胞生命活动的调控网络中发挥着重要作用。但是与小分子 RNA 调控功能相关的大量研究成果相比,目前针对 lncRNA 的研究还仅仅处于起步阶段。ENCODE 的数据表明,迄今为止,该项目所收录的 9640 多个人类 lncRNA 基因位点中,人们仅对大约一百多条 lncRNA 进行了深入的功能研究[85-86],所用技术包括过表达、干扰表达、及动物模型等。因此,目前已知的关于 lncRNA 在肿瘤发生和天然免疫中的功能与调控机制,仅仅是 lncRNA 重要功能的冰山一角。此外,不断增加的转录组学研究数据表明,lncRNA 表达和调控的异常还与阿尔兹海默症、自闭症、银屑病、脊髓小脑共济失调等众多疾病相关。然而,lncRNA 如何参与并调控这些疾病尚不清楚。面对 lncRNA 复杂的作用机制,我们尚未找到可以广泛适用的规律,因而无法有效地预测 lncRNA 的结构与功能。

当前在进行 lncRNA 的研究中,人们不仅应用了传统技术,如基因组预测、cDNA 文库构建、过表达、以及 siRNA 介导的基因沉默等,还广泛利用了许多现代高通量、高灵敏度的检测技术,如 Microarray 芯片分析技术和新一代高通量测序等技术。但是针对 lncRNA 的功能预测方面,还缺乏有效的生物信息学工具。由于 lncRNA 主要通过其高级结构发挥生物学作用,现有的技术方法难以对 lncRNA 二级结构和靶标进行有效的预测。

此外,肿瘤相关 lncRNA 可作为肿瘤标志物,辅助疾病的诊断和预后。异常表达的 lncRNA 与细胞凋亡、信号通路的激活、肿瘤转移及浸润等密切相关,从而影响肿瘤的发生与发展过程,也在一定程度上反映肿瘤的恶性发展情况。目前已发现了一些能够反映肿瘤病程的 lncRNA,如 lncRNA HOTAIR 在乳腺癌中呈现高水平表达,可以作为肿瘤诊断的一个重要指标[87]。再如 lncRNA MALAT-1 是肺癌转移的标志物,并且在结肠癌、胰腺癌、乳腺癌、肝癌和前列腺癌等癌组织也发现其异常性地高表达,说明 MALAT-1 作为肿瘤标志物可能具有广谱性[88]。然而,相对于其它生物大分子而言,lncRNA 极易被降解,所以血液中的 lncRNA 是否可以视为肿瘤标记物,仍值得我们进一步探讨。

近年来 lncRNA 已经成为国际生物与医学领域的研究热点,我们相信随着研究的广泛开展与深入,冰山之下的部分会逐渐浮出水面,人们将会发现越来越多的 lncRNA 参与肿瘤发生和病原微生物的致病过程,了解其在疾病发展过程中的重要作用。总之,深入了解 lncRNA 的功能及其分子调控机制,将有助于阐明有关疾病的发病机制。lncRNA 可能作为一些疾病的分子标记物或治疗靶点,为疾病的诊断和治疗提供新契机。

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Function and regulation of long non-coding RNAs in tumorigenesis and host innate immunity-A review

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Abstract: Long non-coding RNA(lncRNA) is a class of RNA transcripts with length over 200 nucleotides and absence of the ability to encode a functional protein. Although long non-coding RNAs were previously thought as transcriptional noises, increasing evidences have recently shown that they play important roles in a variety of cellular processes through regulating epigenetic modifications and thereby affecting gene transcription, post-transcriptional processing, and protein translation. Importantly, it has been found that abnormal expression or dysregulation of lncRNAs are closely associated with tumorigenesis and host innate immune response to various infections with pathogens. In this review, we will discuss the progresses in understanding the function of lncRNAs in these processes.

Keywords: long non-coding RNA, tumorigenesis, innate immunity, transcriptional regulation

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