



长链非编码 RNA 在神经系统疾病中的研究进展

Research progress on long non - coding RNA in nervous system diseases

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摘要: 神经系统疾病的病因复杂,严重影响人类的健康。近年来,长链非编码 RNA(lncRNAs)已成为神经系统的研究热点。lncRNAs 广泛参与人类神经系统疾病的病理生理进程。本文主要讨论 lncRNAs 在神经系统疾病中的研究进展,重点阐述 lncRNAs 在神经退行性疾病、神经胶质瘤、中风和精神分裂症中的研究进展。

关键词: 长链非编码 RNA; 神经退行性疾病; 神经胶质瘤; 中风; 精神分裂症

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Abstract: The etiologies of neurological diseases are complex, which seriously affect human health. Recently, long non - coding RNAs (lncRNAs) have become a hot research topic in the nervous system. Many research results show that lncRNAs are involved in the pathophysiological processes of human neurological diseases. In this review, we discuss the research progress on lncRNAs in neurological diseases and mainly illustrate the research progress of lncRNAs in neurodegenerative disease, gliomas, stroke and schizophrenia.

Key words: long non - coding RNAs; neurodegenerative diseases; gliomas; stroke; schizophrenia

长链非编码 RNA (Long non - coding RNA, lncRNA) 是一类长度大于 200 个核苷酸、缺乏显著开放阅读框架的非编码 RNA, 主要存在于细胞核内, 参与基因调控、蛋白质剪接调控、与其他 RNA 相互作用等多种重要功能调控^[1]。lncRNAs 广泛参与人类神经系统疾病的病理生理进程, 其相关研究可以阐明神经系统疾病一些潜在的发病机制。本文就 lncRNAs 在神经退行性疾病、神经胶质瘤、中风和精神分裂症中的研究进展做重点阐述。

1 LncRNA 与神经退行性疾病的的相关性

神经退行性疾病是一种大脑和脊髓的神经元丧失的疾病状态, 主要由神经元或其髓鞘的丧失所致^[2]。

1.1 LncRNA 与阿尔茨海默病

阿尔茨海默病 (Alzheimer's disease, AD) 是引起痴呆最常见的原因。lncRNAs 能与氧化应激、丝氨酸 - 苏氨酸激酶及蛋白激酶等 AD 易感基因相关, 通过分子调节机制改变神经系统功能。 β 分泌酶 (β -site of APP cleaving enzyme 1, BACE1) 基因的反义转录物 lncRNA BACE1-AS (BACE1-antisense, BACE1-AS) 在各种细胞应激的诱导

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下表达上调,通过增加BACE1 mRNA的稳定性造成BACE1蛋白表达上调,导致有毒性的 β -淀粉样蛋白(β -amyloid,A β)不断累积,使AD患者病情进行性加重^[3]。lncRNA 51A是分拣蛋白相关受体1(sorting protein-related receptor 1,SORL1)基因内含子1的反义转录产物,通过改变SORL1 mRNA的剪接形式,导致A β 42聚积^[4]。

lncRNA HAR1A和HAR1B是第一号人类加速区(human accelerated region 1,HAR1)基因的反义转录产物,在成熟大脑中与神经传递、记忆结构和突触可塑性有关,它们的异常表达也与AD存在相关性^[5]。Roberts等^[6]通过实验发现,AD患者脑组织中lncRNA BC200表达显著上调,BC200选择性调节突触后树突结构的变化,导致突触树突损伤退化,进而导致AD形成。lncRNA CRNDE是结直肠癌差异表达基因(colorectal neoplasia differentially expressed,CRNDE)的转录产物,在AD患者的大脑皮质中表达异常,导致AD早期的脑海马细胞变性^[7]。

1.2 lncRNA与亨廷顿病

亨廷顿病(Huntington's disease,HD)是一种具有进行性运动障碍、智力衰退等临床特征的神经退行性疾病。在HD中,毒性亨廷顿蛋白(Huntingtin,Htt)会造成纹状体和皮质神经细胞的进行性死亡。lncRNA HttAS-v1是Htt基因的反义转录产物,在HD患者的额叶皮质中的低表达,导致Htt mRNA高表达,推动了HD的发病过程^[8]。

lncRNA BDNF-AS是脑源性神经营养因子(brain-derived neurotrophic factor,BDNF)保守的反义转录产物,在HD中表达上调,负性调节BDNF的转录和BDNF-mRNA的翻译。有实验证明,通过siRNA技术处理BDNF-AS,可以诱导神经元的生长,对神经元有保护作用,改善HD的表型^[9]。这对HD的预防、治疗有一定的积极意义。lncRNA GDNFOS是胶质细胞源性神经营养因子相反链(Glia cell line-derived neurotrophic factor opposite strand,GDNFOS)的转录产物,在HD中也可以负性调节BDNF的表达^[10]。

lncRNA HAR1(HAR1F and HAR1R)的表达被抑制,元素1沉默转录因子(repressor element-1-silencing transcription factor,REST)抑制,HD患者纹状体中出现异常的REST核浆交换,HAR1F明显下降,大脑功能异常^[11]。lncRNA DGCR5是迪乔治临界区5(DiGeorge critical region 5,DGCR5)的转录物,也存在着REST的基因组结合位点,在HD中起到重要的转录调节作用。母系表达基因3(maternally expressed genes,

MEG3)编码的lncRNA MEG3在HD脑组织中表达明显下调,其表达下调同样也受到了REST的抑制^[12]。

Liu等^[13]研究表明,Paraspeckles结构是一种RNA依赖的亚核结构。核富含丰富的转录本1(nuclear enriched abundant transcript 1,NEAT1)的转录对于新生paraspeckles的组装至关重要。lncRNA NEAT1和paraspeckles介导的3'非翻译区含有IRAlus元件(是灵长类动物所特有的序列)的mRNA核滞留广泛存在于人源细胞中,而且NEAT1在HD患者中表达量上调^[14]。

在HD的鼠模型中,lncRNA Abhd11os(在人体内为ABHD11-AS1)过表达可防止Htt mRNA毒性。研究表明,在HD鼠模型中敲除Abhd11os会产生毒性,而过表达的Abhd11os会产生神经保护作用^[15]。牛磺酸上调基因1(taurine-upregulated gene 1,TUG1)编码的lncRNA TUG1在HD中表达上调,通过polycomb抑制性复合物2(polycomb repressive complex 2,PRC2)介导的染色质修饰,影响细胞周期调控^[16]。lncRNA TUNA(Tel1上游神经元相关,Tel1 upstream neuron-associated,TUNA)在脊椎动物中是高度保守的,在神经系统的发育过程中起调节作用,且与HD的预后有关^[17]。

1.3 lncRNA与帕金森病

帕金森病(Parkinson's disease,PD)是中老年人中常见的神经退行性疾病,表现为禁止性震颤、肌张力不稳、姿势不稳等。lncRNA PINK-AS是同源性磷酸酶张力蛋白诱导的激酶1(phosphatase and tensin homologue induced kinase 1,PINK1)基因的反义转录物,可通过加强其靶基因的正义转录产物svPINK1的稳定性,干扰正常线粒体呼吸链功能,提高神经细胞对凋亡信号的敏感性,从而参与PD的发病进程^[18]。

2 lncRNA与中风的相关性

中风是以脑部缺血及出血性损伤症状为主要临床表现的疾病,以缺血性脑中风最为常见,是世界上最重要的致死性疾病之一。在缺血性脑中风患者的脑组织中发现了多种lncRNA的异常表达。lncRNA ANRIL是INK4基因座中反义非编码RNA(antisense noncoding RNA in the INK4 locus,ANRIL),可能通过胱天蛋白酶募集结构域的含蛋白8(caspase recruitment domain-containing protein 8,CARD8)调节通路增加缺血性中风的风险^[19]。研究结果表明,lncRNA piRNA(Piwi-interactingRNA,piRNA)在中风后会发生改变,而一些以piRNA为靶点的反转录转座

子可有效防止 piRNA 在中风后的突变,这为中风的预防和治疗提供了新的策略^[20]。

LncRNA AF030089 和 MRAK135044 分别由 Doublecortin 样激酶 1 (Doublecortin – like kinase 1, Dclk1) 基因的外显子和内含子转录而来,在缺血性中风患者大脑皮层中,这两个 lncRNA 可能通过成对两亲性螺旋蛋白 Sin3A (Paired amphipathic helix protein Sin3A, Sin3A) 控制 Dclk1 功能^[21]。LncRNA MRAK159688 在缺血性脑中风患者的脑组织中表达显著改变,可能与 Sin3A、阻遏元件 -1 沉默转录因子辅阻遏物 (corepressor for repressor element -1 silencing transcription factor, CoREST) 相互作用有关^[22]。

3 LncRNA 与神经胶质瘤的相关性

神经胶质瘤 (glioma) 是最常见的原发性中枢神经系统肿瘤,约占所有颅内原发肿瘤的一半。LncRNAs 具有抑癌或致癌的作用,为开发癌症新疗法打下基础。LncRNA MEG3 在神经胶质瘤细胞中表达水平降低。有实验证明,MEG3 的过度表达会抑制神经胶质瘤细胞的体外增殖,可能的机制是和 p53 抑癌基因相互作用^[23]。肺腺癌转移相关转录子 1 (Metastasis associated lung adenocarcinoma transcript 1, MALAT1) 是 lncRNA 家族重要成员,在神经胶质瘤细胞中高表达,癌细胞中 MALAT1 表达量与癌转移恶化的机率成正相关^[24]。Lnc-POU3F3 可能会通过改变 POU3F3 基因 (POU 同源域蛋白基因家族一员) 的表达水平,影响神经胶质瘤的发展^[25]。LncRNA XIST (X 染色体失活特异录本, X chromosome inactivation specific transcription) 通过 lncRNA-miRNA 的功能性网络在神经胶质瘤中起作用^[26]。最新研究发现了 lncRNA ATB 在神经胶质瘤组织中高表达,它可以被转化生长因子 β (transforming growth factor - β, TGF - β) 活化,促进神经胶质瘤细胞的侵袭和转移^[27]。LncRNA CRNDE 通过哺乳动物雷帕霉素靶点 (mammalian target of rapamycin, mTOR) 信号通路,促进神经胶质瘤细胞的生长和侵袭^[28]。

4 LncRNA 与精神分裂症的相关性

精神分裂症 (schizophrenia) 是一种多因素的疾病,个体之间症状差异很大,目前发病机制并不是很清楚。有研究揭示,lncRNA DAOA - AS1 调控精神分裂症的相关基因——D - 氨基酸氧化酶激动子基因 (D - amino acid oxidase gene promoter, DAOA 或 G72/G30) 的表达^[29]。人类染色体 1q42 上精神分裂症断裂基因 1 (disrupted in schizophrenia 1, DISC1) 被认为是精神分裂症的易感位点,DISC1 受它的 lncRNA

DISC2 调控。DISC2 与精神分裂症密切相关,但具体机制不清楚^[30]。另外,TRAF3IP2 - AS1、Linc00271、BDNF - AS 及 DISC2 等 lncRNAs 也参与到精神分裂症的发展历程中。

5 讨论

目前 lncRNA 在神经系统疾病中的研究已取得一些成果,提示其可以作为相关疾病的 RNA 分子标记物,进行疾病诊断和新药设计。但 lncRNAs 与神经系统疾病相关性的证据主要来源于其表达上的差异,仅有少数 lncRNAs 的功能是清楚的,而且解析其在体内的动态变化还受相关分析技术的牵制。因此 lncRNAs 在神经系统疾病中的研究还有待探寻。

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