

Effects of circRNA in Notch Pathway on Differentiation and Maturation of Oligodendrocyte Progenitor Cells in Cerebral Palsy

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ABSTRACT

CircRNAs are ubiquitous non-coding RNAs, which are richly expressed in brain tissues and participate in the development and signaling of the nervous system and regulate complex functions and various neural activities of the brain. The Notch pathways can regulate multiple processes of cell morphology by regulating cell damage and apoptosis, inflammation, nerve repair and angiogenesis, and other processes involved in the occurrence and development of diseases. The Notch pathway critically regulates the differentiation and maturation of oligodendrocyte progenitor cells (OPCs), and the abnormal expression of circRNA can regulate the differentiation and maturation of OPCs through many pathways, including the Notch pathway, thus participating in the occurrence and development of cerebral palsy. This paper systematically reviewed the effects of circRNA on the differentiation and maturation of OPCs in cerebral palsy by regulating the Notch pathway to provide new ideas for the diagnosis, treatment, and research of cerebral palsy.

Keywords: *CircRNA; Notch; Cerebral palsy; OPCs differentiate and mature*

Introduction

脑性瘫痪 (Cerebral Palsy, CP), 简称脑瘫, 是一组持续存在的中枢性运动和姿势发育障碍、活动受限症候群。其运动障碍常伴有感觉、知觉、认知、交流和行为障碍, 以及癫痫和继发性肌肉、骨骼问题 [1]。据文献报道, 中国0~6岁儿童脑瘫患病率约为0.248%, 其中男童脑瘫患病率为0.22%, 女童脑瘫患病率为0.12% [2,3], 发达国家脑瘫的发病率在2.11‰ [4]。CircRNA分子呈封闭环状结构, 不受RNA外切酶影响, 表达更稳定, 不易降解 [5]。CircRNA在脑组织中表达丰富, 参与神经系统发育和信号传递, 调控大脑复杂的功能和多种神经活 [6]。而Notch通路是决定细胞命运的关键通路, CircRNA与Notch通路可能在CP的发生与发展中起到重要的调控作用。

CircRNA的作用及在神经系统中的应用

1. CircRNA简介及作用

人类基因组在转录水平上极为活跃, 约1.9%的基因序列被转录为蛋白质, 其他则被转录为非编码RNA [7]。CircRNA是一类参与多种生物学过程的非编码RNA, 没有5'帽和3'尾, 是mRNA反向剪接产生的共价闭合RNA分子, 根据基因组的起源和产生方式, CircRNA大致可以分为三种类型: 内含子环状CircRNA、外显子环状CircRNA和外显子内含子环状CircRNA [8]。CircRNA是真核生物中共价封闭的内源性生物分子, 且具有丰富的miRNA结合位点, 可充当miRNA或蛋白质“海绵”; 与蛋白结合, 调控蛋白活性; 参与蛋白翻译 [9-11], 以及miRNA对其靶基因的调控作用 [12]。

2. CircRNA在神经系统中的应用

2.1 CircRNA参与神经系统的发育。

在大鼠发育时间点包括幼年(2周)、青春期(6周)、成年(21周)和老年期(104周)对大脑、心脏、肺、肝脏、肾脏、肌肉、睾丸和胸腺的circRNA进行检测,发现在大脑中有更高的丰度和多样性,其次是肺和胸腺。幼年大鼠产生的CircRNA水平最低,随后在发育过程中呈上升趋势,脑CircRNA宿主基因在神经递质分泌、突触活动和神经元成熟中富集[13]。且在突触、突触前活性区、突触前膜等与突触功能相关的功能群明显富集,通过定量PCR技术明确了CircRNA的表达水平受神经可塑性的调节[14]。

2.2 CircRNA参与调控神经系统疾病

circRNA在人类大脑和视网膜中高度代表的一种是ciRS-7 (CDR1as),低CDR1as水平可导致miR-7表达增加,从而下调阿尔茨海默病 (Alzheimer's disease, AD) 的重要靶点UBE2A的活性,其功能参与清除AD脑中的毒性淀粉样肽,进而影响疾病的进程[15]。Ma N [16]发现AD小鼠模型中CircRNA相关的ceRNA网络主要参与树突发育与记忆 (Sorbs2) 和小鼠神经发育 (ALS2)。急性缺血性脑卒中患者血浆中CircSCMH1水平明显降低, CircSCMH1增强了神经元可塑性,抑制了神经胶质激活和外周免疫细胞浸润,可促进小鼠和猴子中风后的功能恢复[17]。Chen W [18]通过上调CircUCK2水平可显著减少缺血性脑中风的梗死体积,减轻神经元损伤,改善神经功能缺损,且发现CircUCK2作为内源性miR-125b-5p海绵抑制miR-125b-5p活性,导致生长分化因子11 (GDF11)表达增加,进而改善神经元损伤。mmu-CircRNA-015947参与脑缺血再灌注损伤也说明Circ RNA参与神经系统发育和信号传导[19]。

CP作为儿童神经系统中常见的病症之一,也是儿童严重神经残疾最常见的原因,CP的高致残性和防治困难的特点,取决于其病因及病理生理机制的多样性和复杂性。CP的主要生理病理病机是少突胶质细胞 (oligodendrocytes,OLs) 发育不良、脱髓鞘、损伤和变性引起的脑室周围白质损伤。CircRNA在CP中的异常表达为阐明CP发生发展机制和探明早期干预靶点提供了条件。本文重点探讨CircRNA通过CircRNA-miRNA-mRNA轴在Notch通路中对CP的少突胶质前体细胞 (oligodendrocyte precursor cells, OPCs) 分化和成熟的影响。

Notch通路及其与CP的联系

1. Notch通路及其信号因子的作用机制

Notch通路是通过细胞与细胞之间的通信实现的,即一个细胞上的跨膜配体激活相邻细胞上的跨膜受体。首次研究来源于约翰·德克斯特和托马斯·亨特·摩根观察到翅膀有凹槽的突变果[20]。迄

今为止,已经确定了信号转导级联的主要组成部分和步骤,明确了Notch通路能够在大量的细胞类型中决定细胞命运。哺乳动物表达四种高度同源受体 (Notch 1、2、3和4) 和五种典型配体 (Delta-like 1、3、4和Jagged 1、2),受体和配体都是跨膜蛋白。经典的Notch通路,即信号从Jagged/Delta like配体与Notch受体相互作用到受体切割[21],3次蛋白水解步骤产生一个活化的Notch片段[22]。第1次蛋白裂解步骤 (S1裂解) 由Furin介导,第2次裂解 (S2裂解) 由 γ -分泌酶介导的, γ -分泌酶在表达Notch的细胞中第3次裂解靠近膜内小叶 (S3裂解) 的栓系受体,产生具有转录活性的NICD, NICD进入细胞核,与转录因子相互作用形成转录激活复合物,激活下游靶基因转录[23, 24]。

Hes1、Hes5、Hey1、Hey2和HeyL是Notch信号通路的靶基因[25]。Hes基因属于抑制型碱性螺旋-环-螺旋 (basic helix-loop-helix, bHLH) 家族,不仅能够调节中枢神经系统的功能,而且对胶质细胞的形成至关重要[26]。Ohtsuka等[27]通过逆转录病毒错误表达Notch (caNotch) 在野生型、Hes1缺失、Hes5缺失和Hes1-Hes5双缺失的小鼠胚胎,发现诱导内源性Hes1和Hes5表达的caNotch在野生型、Hes1缺失和Hes5缺失背景下抑制了神经元分化,而在Hes1-Hes5双缺失背景下则没有,说明Hes1和Hes5是调控哺乳动物神经元分化的重要Notch效应因子。

1.1 Notch通路在神经系统疾病中的作用

在斑马鱼中发现Notch通路与其中枢神经胚胎髓鞘缺陷的相关性[28]。多发性硬化症中以配体依赖性Notch信号通路促进再髓鞘化[29]。蛋白激酶R活化因子与C启动子结合因子1 (CBF1) 相互作用,并显著增强CBF1与Notch胞内区域 (NICD) 之间的关联,证明Notch通路的相关转录因子,在哺乳动物大脑发育过程中发挥着关键作用[30]。中枢神经系统感染小鼠中,下调miR-25可能通过激活Notch通路提高中枢神经系统感染小鼠的记忆能力[31]。人类特异性Notch2NL的三个平行序列在神经胶质细胞中高度表达,功能分析表明Notch2N异位表达推迟了神经元祖细胞的分化,而其缺失则加速了皮层神经元的分化[32]。Notch通路广泛参与神经系统疾病,低氧/缺血状态激活Notch通路,可通过低氧/缺血预处理的方式调控Notch通路从而起到神经保护的作用。

2. Notch通路与CP的联系

2.1 CP的病因及发病机制

CP的病因和发生机制复杂,可概括为宫内、围产期因素及新生儿脑室内出血、脑室周围白质软化、脓毒症和新生儿中风等[33]。CP的脑部病理改变主要是脑白质损伤、脑部发育异常、颅内出血、脑部缺氧引起的脑损伤。根据临床表现,CP又可分为痉挛型、不随意运动型、强直型、共济失调型

、肌张力低下型、混合型共6种分型[1]，其中以痉挛型多见，占85%-91% [34]。脑室周围白质损伤是痉挛型CP的常见原因，磁共振成像可显示脑室周围白质区异常信号和/或体积损失、侧脑室增大、胼胝体变薄 [35]，而CP患者常伴有白质结构连接异常 [36]。白质是皮层下的重要组成部分，是分布式神经网络中信息传递的提供者。白质束约占整个脑容量的一半，贯穿整个大脑，其补充了大脑皮层的信息处理，提供了大脑内部的信息传递，使神经系统具有快速、有效的整合能力 [37]。

正常的脑白质主要由大量的神经元轴突和被少突胶质细胞OLs包绕形成的髓鞘组成 [38]。OLs在中枢神经系统轴突周围生成多层髓鞘膜，以实现快速有效的神经传导，OLs既可形成髓鞘，又可为轴突提供代谢支持 [39,40]，但极易受到氧化损伤 [41]。缺血缺氧等因素会阻止OLs及髓鞘发育 [42]。脑室周围白质软化 (periventricular leukomalacia, PVL) 被定义为脑深部白质损伤，是脑室周围白质损伤的经典病理表现，以侧脑室旁白质深部坏死灶为特征，严重的情况下，可延伸至半卵圆中心，甚至皮质下白质。PVL的主要特征是一种慢性髓鞘形成障碍，提示OLs谱系进展被缺血损伤所破坏 [43]。OLs谱系是从OPCs分化到Pre-OLs，再到成熟OLs，最后到完全成熟OLs的过程，在小白鼠中大多数OLs产生于出生后的前4周，新的OLs的产生持续到整个成年期，尽管这一过程随着年龄的增长而下降，但还受到诸如日光或体育锻炼等环境因素的影响 [44]。研究发现PVL与OLs谱系密切相关，脑室周围顶叶白质是脑室周围白质软化的高易感区域，主要在妊娠24-32周，此阶段是PVL的高发时期 [42]。可见在发育过程中，OPCs最终分化和成熟为构成髓鞘的OLs，在促进神经元信号传导中发挥重要作用 [44,45]。

2.2 OPCs的分化和成熟是CP脑白质修复的关键

OPCs起源于胚胎脑和脊髓的脑室区，从这些区域OPCs通过中枢神经系统广泛迁移，实现均匀分布 [46]。成人中OPCs约占中枢神经系统胶质细胞总数的5-8%，在脱髓鞘反应中，OPCs分裂和分化成新生OLs取代已丢失的OLs。OPCs在中枢神经系统中含量丰富，可分化为OLs直至其成熟，以适应髓鞘形成和损伤或疾病后髓鞘再生的能力[47]。Kirby [48]发现 OPCs可在多发性硬化症中经免疫系统维持以维持自身的免疫反应，这提示可通过抑制OPCs的免疫激活从而促进髓鞘再生。Huang W [49]研究发现OPCs可在相同时间内对称分裂，数量上以指数方式产生子代细胞以扩增祖细胞池，其子代细胞互相远离，呈放射状向相反方向迁移以确保可广泛分布于脑皮层，这表明OPCs的增殖和分散特性对白质扩张和髓鞘形成非常重要。

脑室周围白质损伤扰乱了正常的OPCs分化进程和白质发展中的髓鞘化 [43]。许多创伤、损伤和感染

都可触发OLs死亡，造成脱髓鞘从而导致功能紊乱。脱髓鞘诱导轴突缺陷，如节点复杂改变、传导阻滞和/或不可逆的轴突丢失，明显破坏远程连通性，这些障碍共同导致运动、感觉和认知功能障碍 [50]。Hesp等 [51]发现在脊髓损伤后1-2天分裂的OPCs产生的OLs主要分布在胶质瘢痕或病变边缘和病变周围的剩余组织中，相比之下，4周分裂的OPCs产生的新OLs分布更为广泛，主要位于靠近脑顶边缘的远端备用白质中，以重新形成未受损的轴突。斑马鱼身上使用活体成像显示OLs在体内非常短的时间窗 (约5小时) 内可生成新的髓鞘 [52]。Keirstead研究 [53]提示髓鞘再形成的失败可能是由于OPCs的减少和耗尽。OPCs向OLs的分化和髓鞘形成不仅受时间和空间的调控 [41]细胞内的转录因子、表观遗传调节因子、DNA甲基化、非编码RNA和信号通路都参与调节其分化和成熟 [45]。

2.3 Notch通路可调控OPCs的分化和成熟

Zhou H [54]通过脑瘫幼鼠测序发现Notch通路与脑瘫密切相关。而脑白质变性的患者，磁共振成像在T2加权图像中显示多个高强度的白质病变，甚至在临床症状出现前10-15年，基因检测发现其Notch3基因发生突变。多年后其女儿基因检测也发现Notch3基因出现异常 [55]。Gao L [56]发现在新生儿缺血缺氧性脑损伤模型中，与假手术组相比，实验组中Hes1蛋白和mRNA的表达增加，且通过TWS119调控Notch通路在缺血缺血性脑损伤后7天实现神经保护作用。体外试验 [57]表明细胞缺血缺氧可上调Notch信号通路中Notch1、Hes1和Hes5的表达。此外，有研究发现使用Notch抑制剂DAPT后抑制了OPCs的增殖和分化 [58]。Fbxw7通过调控Notch通路限制斑马鱼OPCs的数量 [59]。内皮素-1以自分泌的方式通过调控Notch通路促进星形胶质细胞的维持和增殖 [60]。

CircRNA 通过CircRNA-miRNA-mRNA轴在Notch通路中对CP的作用

1. CircRNA/miRNA对CP的影响

CP中异常的CircRNA可能参与了其发病机制。Liu CY [61]对60例新生儿缺氧缺血性脑病患者检测血清中miRNA-373、缺氧诱导因子 (HIF-1 α)、基质金属蛋白酶9 (MMP-9) 和血管内皮生长因子 (VEGF) 的表达，结果显示miRNA-373与三者都存在很强的关系，且实验组中miRNA-373、HIF-1 α 、MMP-9、VEGF表达水平明显高于对照组。在CP模型中，过表达miR-146b-5p可显著抑制缺血缺氧诱导的PC12细胞损伤、炎症反应和氧化应激从而减轻缺血缺氧诱导的神经元损伤 [62]。细胞在髓鞘培养基培养14天发现，miR-219/miR-338处理后的培养基中成熟OLs的数量变多、髓鞘长度增加和髓鞘结构更完整，表明miR-219/miR-338增加了OLs的分化率和分化程度，参与髓鞘化过程 [63]。

2. CircRNA/miRNA与Notch通路的联系

Zhao X等[31]通过转染具有miR-219和/或miR-338模拟物的原代少突胶质细胞前体细胞培养物4天,发现Hes5的mRNA表达显著降低,同时在成年海马源性神经祖细胞中Hes5表达同样大幅降低;相反,通过miRNA抑制剂敲低miR-219和/或miR-338,导致原代少突胶质细胞前体培养中Hes5表达上调,这些观察结果表明,Hes5的表达受到miR-219和miR-338的负调控。Circ_0111277在滋养层细胞中吸附hsa-miR-494-3p,通过调控HTRA1/Notch-1上调hsa-miR-494-3p的表达水平[64]。与正常脑组织相比,Notch信号在肿瘤组织中显著上调,CircNFIX充当了miR34a-5p的海绵,这是一种靶向Notch1的miRNA。下调CircNFIX和上调miR34a-5p均可抑制细胞增殖和迁移。此外,miR34a-5p抑制剂可中和CircNFIX对胶质瘤细胞的抑制作用。在体内实验中,CircNFIX通过调控miR34a-5p和Notch1抑制胶质瘤的生长[65]。精神活性大麻素和非精神活性大麻二酚可以通过降低脂多糖上调的Notch配体Dll1的表达,被调控的miRNA及其靶基因受到Notch等交叉信号控制,参与免疫应答、细胞周期调控以及细胞应激和氧化还原稳态[66]。

CircRNA在神经系统中作用机制的研究发展迅速,随着测序技术和生物学技术迅速发展,CircRNA的功能将越来越多的被揭示出来。大鼠胚胎中分离出的皮质神经干细胞经培养后发现,CircRNA 9-cis-RA可显著降低Notch通路转录因子Hes5的表达从而促进OPCs的分化[67]等研究,可证明Notch通路在CP的发生发展过程中确实发挥着不可或缺的作用,通过CircRNA-miRNA-mRNA轴探索CircRNA与Notch通路参与调控CP的作用机制值得深入。

Conclusion

脑瘫的病因病机复杂,是临床及基础研究的重点及难点。近年来对Notch信号通路的研究中已经发现了其对中枢神经系统中的重要作用,主要是通过调控细胞形态的多个发生过程所造成神经系统的损伤。因此通过调控Notch通路抑制细胞损伤及凋亡、炎症、神经修复和血管再生等过程,成为临床防治脑瘫疾病的重要途径。CircRNA通过CircRNA-miRNA-mRNA轴影响脑瘫的发生发展过程的报道也备受关注,尽管愈来愈多的证据表明CircRNA在神经系统中重要作用,但CircRNA相互之间复杂的分子机制及相关通路尚未完全了解。将CircRNA作为靶点进行深入的实验研究,分析其上、下游的分子调节机制,可为阐明脑瘫的发生机制提供理论依据,并且为脑瘫的诊断和治疗方法提供新思路。

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