

重视孤独症谱系障碍发生的神经生物学机制

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摘要: 孤独症谱系障碍(ASD)是一种常见的儿童神经发育性疾病,其特征为社交沟通障碍和重复刻板行为,全球患病率持续上升。其病因复杂,涉及遗传和环境因素。本文系统总结了关于 ASD 神经病理机制的研究进展,包括突触功能、神经递质失衡、神经环路异常、神经解剖学变化以及神经炎症等。深入理解 ASD 的病理机制可为相关临床治疗策略的开发提供科学依据和指导。

关键词: 儿童神经发育; 孤独症谱系障碍; 神经突触; 神经环路

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Emphasizing the neurobiological mechanisms of autism spectrum disorder

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Abstract: Autism spectrum disorder (ASD) is a common neurodevelopmental disorder in children characterized by impairments in social interactions and repetitive, stereotyped behaviors, with a globally increasing incidence rate. Its etiology is complex, involving both genetic and environmental factors. This article systematically summarizes the research progress on the neuropathological mechanisms of ASD, encompassing synaptic function, neurotransmitter imbalance, neural circuit abnormalities, neuroanatomical changes, and neuroinflammation. A deep understanding of the pathological mechanisms of ASD can provide scientific evidence and guidance for the development of related clinical treatment strategies.

Keywords: neurodevelopment; autism spectrum disorder; synapse; neural circuit

孤独症谱系障碍(autism spectrum disorder, ASD)已逐渐成为一种影响全球儿童的常见神经发育障碍性疾病,其主要表现为社交沟通障碍、重复性和刻板行为^[1]。一项发表于 JAMA 的文章显示,美国 ASD 的患病率一直在上升,从 2008 年的 1.1% 上升到 2018 年的 2.3%^[2]。另一项 2024 年的美国横断面研究调查了 2011—2022 年 ASD 的诊断率,其中 5~8 岁儿童的 ASD 诊断率最高^[3]。我国一项对 6~12 岁儿童的横断面流行病学调查研究显示,ASD 患病率约为 0.7%^[4]。随着诊断标准的变化、筛查和诊断工具性能的提高以及公众意识的提高,ASD 已成为重大的公共卫生问题。ASD 的病因复杂,被认为是多种因素导致,包括遗传因素、环境因素以及遗传与环境交互作用等,其中遗传因素占了主要位置^[5-6]。近年来,随着科学技术的发展,尤其是基因组学、神经科学和神经影像学的进步,对 ASD 的神经生物学基础有了更深入的了解,逐步揭

示出其复杂的发病机制。本文就 ASD 的神经生物学机制进行阐述。

1 孤独症谱系障碍发病的遗传因素

ASD 的遗传基础是一个重要的研究领域。大量研究表明,ASD 具有明显的遗传倾向。双胞胎研究结果显示,同卵双胞胎中 ASD 的共病率可高达 70%,而异卵双胞胎的共病率则在 10%~20% 之间,这一现象突显了 ASD 的高度遗传性^[7-8]。

随着全基因组及外显子组测序技术的应用,研究已经鉴定出 1 000 多个 ASD 风险基因,它们中的大多数还与其他神经系统疾病有关,其中只有少数被确认为 ASD 的致病基因^[9-10]。鉴于 ASD 病因复杂,许多研究工作都集中在致病原因明确的单基因遗传综合征上,例如 Phelan-McDermid 综合征、结节性硬化综合征、Rett 综合征和脆性 X 综合征等,这是因为很大一部分综合征患者符合 ASD 的诊断标

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准,而且这些综合征可以根据变异基因进行分类,并可在模型动物中制造相同的基因突变^[10]。ASD 的风险基因可以根据其所编码蛋白质的功能分为突触功能相关蛋白、作用于翻译调控的相关蛋白和染色质修饰的蛋白。

1.1 与突触功能相关蛋白 大部分 ASD 风险基因编码的蛋白在突触功能中发挥重要作用,如 *NRXN1*、*NLGN3* 和 *SHANK3* 等^[6]。例如, *NRXN1* 基因编码突触黏附分子,编码突触前神经连接蛋白,在突触的粘附、分化和成熟中发挥重要作用^[11],其突变也被发现与 ASD 的发生密切相关^[12-13],可能是 *NRXN1* 突变导致谷氨酸能突触和 γ -氨基丁酸(γ -aminobutyric acid, GABA)能突触不能正常分化,从而影响突触传递功能^[14]。*NLGN3* 编码突触后神经连接蛋白,与 *NRXN1* 编码的突触前神经连接蛋白形成跨突触复合体,被认为是介导突触稳定的关键因子^[15]。*NLGN3* 突变小鼠表现出一系列 ASD 行为改变,可能与 *NLGN3* 缺失导致大脑兴奋性突触传递减少相关^[16-17]。*SHANK3* 编码突触后致密蛋白,可与谷氨酸受体相互作用,并将它们与肌动蛋白细胞骨架连接起来^[18],其突变可能会影响突触成熟,导致突触传递受损以及社交行为相关的神经元活动降低,继而出现 ASD 样症状^[12,19]。综上所述,这些 ASD 风险基因在大脑中均与突触功能相关,它们的异常表达会影响突触的形成、发育、可塑性和成熟等,进而导致 ASD 相关的神经病理改变。

1.2 作用于翻译调控的相关蛋白 与蛋白质合成失稳态相关的 ASD 风险基因包括 *TSC1/2*、*CYFIP1*、*NLGN3* 和 *FMR1* 等^[20-21]。例如,在脆性 X 综合征中, RNA 结合蛋白 FMRP 突变可导致真核细胞翻译起始因子 eIF4E 失去 FMRP 和 CYFIP1 对它的抑制, mRNAs 翻译被启动,突触蛋白被过度表达^[22]。此外多项研究表明磷脂酰肌醇 3 激酶/蛋白激酶 B/哺乳动物雷帕霉素靶蛋白 (PI3K/AKT/Mtor) 信号通路的过度表达会导致下游突触蛋白的翻译障碍,从而导致 ASD 的发生^[23-24]。例如, *TSC1* 和 *TSC2* 等可通过 mTOR 信号通路解除 eIF4EBP1 对 eIF4E 的抑制,从而引起蛋白质翻译失衡^[25]。

1.3 染色质修饰的蛋白 编码染色质重塑和基因转录关键调节因子如 *MEF2C*、*HDAC4* 和 *CHD8* 等的基因突变在 ASD 患者中曾有过报道^[10]。其中, *CHD8* 是一种编码蛋白质染色质解旋酶 DNA 结合蛋白的基因,这是一种染色质调节酶,其表达降低可导致神经发育相关信号网络(如 WNT 信号传

导)被破坏,从而引起 ASD 有关的神经病理变化^[26]。还有研究认为 *CHD8* 单倍体不足导致 GABA 能神经元和深层兴奋性神经元的异常发育从而导致 ASD 的发生^[27]。

2 孤独症谱系障碍发病的神经递质与神经环路机制

越来越多的证据表明神经递质的失衡以及神经元的兴奋性/抑制性的不平衡可能导致 ASD 的发生^[10,28]。部分 ASD 患者可表现出多巴胺、血清素和谷氨酸、甘氨酸等神经递质的水平异常^[29-30]。此外,谷氨酸和/或 GABA 信号传递失衡,可能导致 ASD 中的病理性突触传递^[12,30]。国内一项临床试验使用磁共振波谱测量 ASD 儿童后岛叶皮质中的神经递质浓度,发现 ASD 儿童的 GABA 水平降低^[31]。在 ASD 小鼠模型中也发现了 GABA 神经传递受损及 GABA 释放减少^[32]。这些神经递质的失衡可能是 ASD 患者情绪调节、学习和社交行为异常的分子基础。

近年来对神经环路的深入研究已成为探索 ASD 发病机制的一个热点。有研究显示 ASD 患者表现出基底外侧杏仁核(basolateral amygdala, BLA)-伏隔核(accumbens nucleus, NAc)神经环路,前扣带皮质(anterior cingulate cortex, ACC)-BLA 神经环路以及皮质纹状体环路等与奖赏共情相关环路异常^[33-34]。BLA-NAc 是调节社交能力的神经环路,有研究发现在小鼠脑内激活 BLA-NAc 环路,小鼠表现出社会交往降低以及增加社交回避等模拟 ASD 核心症状的行为^[35]。此外,在 ASD 小鼠模型中,边缘皮质到纹状体尾部异常神经信号传导可能引发出排斥新奇事物行为,从而模拟出 ASD 的病理状态^[36]。综上,ASD 核心症状相关的神经环路异常可能是导致 ASD 发生发展的重要神经病理机制之一。

3 孤独病谱系障碍发病的神经解剖学变化

ASD 患者常常表现出特定的脑结构变化^[37]。多项研究通过磁共振成像(MRI)技术发现,ASD 儿童的大脑体积通常大于同龄人,尤其是在幼儿时期^[37-39]。这种大脑体积的增加可能与神经元的过度生长和突触形成过多有关^[40-43]。其中,额叶和扣带皮层的发育异常被认为与 ASD 的核心症状有关^[44]。额叶负责决策、社交互动和情绪调节^[45],而 ACC 参与认知和情感功能,也与社交行为密切相关^[46]。有研究表明,2~5 岁左右的 ASD 儿童的额叶皮质存在异常生长^[39,47]。额叶的功能异常,也可

能与其社会认知障碍密切相关^[48-49]。此外,ASD 的 ACC 神经元分层性较差,且多个脑区的神经连接降低^[50-51]。ASD 患者的脑白质连接模式也常常出现异常^[49]。比如,ASD 儿童的前额叶和后部脑区之间的白质纤维束连接较差^[49,52]。这种连接模式的改变可能导致信息处理的效率降低,从而影响社交交往和沟通能力。

4 其 他

近年来,线粒体功能障碍、氧化和炎症等代谢异常被证明与 ASD 有关^[53-55]。线粒体在大脑发育中扮演着核心角色,它们不仅促进神经细胞的生成和突触的形成,还支持神经胶质细胞的成熟,并参与调节细胞凋亡、坏死、自噬等多个生命过程^[56]。有研究表明 ASD 产前多个风险因素,例如接触包括香烟烟雾、邻苯二甲酸酯、空气污染和农药等环境毒物,都与线粒体功能障碍相关^[53]。在母体免疫活化的小鼠大脑中线粒体的形态、密度发生了变化,氧化应激水平也有所升高,并表现出类似 ASD 的社会行为缺陷以及感觉运动协调障碍^[57]。

此外,神经炎症在 ASD 中的作用也引起了广泛关注。研究表明,ASD 患者的脑组织中可能存在神经炎症的迹象,包括小胶质细胞和星形胶质细胞的活化^[58-59]。小胶质细胞是大脑中的免疫细胞,其功能包括清除细胞垃圾和维护神经元的健康。然而,当神经发育过程中出现异常时,小胶质细胞可能会过度活化,释放促炎症因子,导致神经细胞损伤^[60-61]。有研究显示小胶质细胞通过释放细胞因子(例如 IL-6、TNF- α 等)来影响突触修剪,从而导致突触传递功能障碍和 ASD 的发生^[62-63]。星形胶质细胞是中枢神经系统中最丰富的神经胶质细胞,具有参与神经发生、突触发育、突触传递和可塑性调控等重要功能^[64]。在 ASD 患者和动物模型的大脑中发现,星形胶质细胞所分泌的突触蛋白量改变,这可能影响星形胶质细胞对突触功能的支持和神经可塑性^[65-68]。此外,有研究表明星形胶质细胞钙信号传导功能障碍可导致小鼠出现类似 ASD 的行为,这可能也是 ASD 病理生理改变的潜在分子机制之一^[69]。

ASD 是一种多因素疾病,其病因错综复杂,涉及遗传、环境等多种因素的相互作用,这种疾病的异质性给研究其潜在的发病机制带来了挑战。本文从遗传背景、神经突触和环路机制、炎症改变等多个角度探讨了 ASD 的发病机制,并寻找这些因素背后的生物学基础,而进一步深入理解 ASD 的神经生物学

机制将有助于开发更有效的治疗方法。

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