

SMPD1基因与帕金森病研究进展

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摘 要

帕金森病是一种常见的神经退行性疾病, 主要的运动症状包括运动迟缓、震颤、肌肉强直、姿势不稳, 非运动症状包括睡眠障碍、嗅觉减退、自主神经功能障碍和焦虑抑郁等, 其病因和发病机制尚不明确, 涉及多个方面。近年来, 尼曼匹克病的主要致病基因——SMPD1基因, 该基因编码酸性鞘磷脂酶, 在维持脂质代谢方面发挥重要作用, 被证明与PD的发病密切相关, 本综述着重阐述SMPD1基因结构及基本功能、流行病学、导致PD发生发展的作用机制等。

关键词

帕金森病, SMPD1, 酸性鞘磷脂酶, 基本功能, 发病机制

Research Progress on the SMPD1 Gene and Parkinson's Disease

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Abstract

Parkinson's disease (PD) is a common neurodegenerative disorder. Its major motor symptoms include bradykinesia, tremor, muscular rigidity, and postural instability, while non-motor symptoms include sleep disturbances, hyposmia, autonomic dysfunction, and anxiety or depression. The etiology and pathogenesis of PD remain unclear and involve multiple factors. In recent years, the primary pathogenic gene of Niemann-Pick disease—SMPD1, which encodes acid sphingomyelinase and plays an important role in lipid metabolism—has been shown to be closely associated with the onset of PD. This review focuses on the structure and basic functions of the SMPD1 gene,

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epidemiological findings, and its mechanisms contributing to the development and progression of PD.

Keywords

Parkinson's Disease, SMPD1, Acid Sphingomyelinase, Basic Function, Pathogenesis

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1. 引言

帕金森病(Parkinson's disease, PD)是一种常见的慢性神经退行性疾病,主要表现为运动症状、非运动症状以及认知损害。其典型的运动症状包括运动迟缓、震颤、肌肉强直、姿势不稳,非运动症状包括睡眠障碍、嗅觉减退、自主神经功能障碍,其典型病理特征是黑质纹状体多巴胺能神经元的退化和丢失以及出现路易小体[1]。帕金森病发病机制与多种因素的相互作用密切相关,包括遗传易感性、环境毒素暴露以及正常衰老过程中的神经退行性改变[2]。在PD相关遗传因素中,SMPD1基因是新发现的与PD发生密切相关的风险基因。该基因编码酸性鞘磷脂酶(Acid Sphingomyelinase, ASMase),在脂质代谢、细胞稳态维持方面发挥着重要作用。是尼曼-匹克病(一种常染色体隐性遗传的糖脂代谢性疾病)的主要致病基因,但近年来诸多研究表明,SMPD1基因变异与帕金森病发生有密切关系[3]。

2. SMPD1 基因及蛋白的结构及生理功能

SMPD1基因(OMIM:*607608)位于染色体11p15.1~p15.4区域,全长约4.6kb,包含6个外显子,该基因编码ASMase,其蛋白产物由631个氨基酸组成,由N端结构域和C端催化结构域组成,N端结构域多见于溶酶体蛋白,通过与膜结合或从膜中提取脂质,后被水解酶分解而发挥作用,ASMase蛋白包括6个N-连接糖基化位点、8个二硫键和2个锌离子,在蛋白质折叠和稳定性中起关键作用[4]。作为一种关键的磷酸二酯酶[5],ASMase在几乎所有细胞类型中都广泛表达[6],尤其富集于内溶酶体区室[7]。

鞘磷脂(Sphingomyelin, SM)是细胞膜的主要鞘脂类成分,广泛分布于质膜、溶酶体及高尔基体等多种膜结构[8],参与调节细胞凋亡、自噬等多个生物学过程[9]。SMPD1基因编码的ASMase是主要的SM降解脂肪酶[4],ASMase催化SM分解为神经酰胺(ceramide, Cer)和磷胆碱(phosphocholine, PCho)[10],防止SM及其溶血衍生物鞘氨醇磷酸胆碱(Sphingosylphosphorylcholine, SPC)异常积累,维持细胞稳态和溶酶体膜的脂质组成平衡与结构稳定性[11]。此外,ASMase还能降低晚期内体和溶酶体内腔囊泡(intraluminal vesicles, ILVs)中的SM水平,促进鞘糖脂(Glycosphingolipid, GSL)代谢、胆固醇分泌及ILV的成熟,保障溶酶体正常功能[5]。

Cer作为ASMase催化反应的主要产物,在鞘脂代谢及多种细胞活动中发挥核心作用,其胞内水平受ASMase活性直接调控。Cer是细胞膜结构的重要调节因子,还广泛参与细胞信号转导、膜蛋白功能维持[12]、自噬启动[13]、细胞增殖、分化与凋亡[14]等多个过程。其浓度变化可显著影响膜流动性、膜蛋白排列及信号识别效率。因此,ASMase通过调节Cer的生成,在维持膜功能完整性、物质转运、信号传导及应激反应中发挥关键作用[6]。

ASMase的正常功能是维持细胞稳态和生理活动的基础,当SMPD1突变或ASMase活性异常时,可引发多种疾病。研究表明,病理性分泌型ASMase与重度抑郁症、肌萎缩侧索硬化症(Amyotrophic Lateral

Sclerosis, ALS)、帕金森病(PD)和阿尔茨海默病(Alzheimer's disease, AD)等神经系统疾病密切相关。其在血液及脑组织中异常表达或活性改变,会诱导细胞凋亡、增加膜通透性、导致异常自噬、促进神经炎症及免疫细胞功能紊乱,最终加速疾病进展[15]。因此,阐明 SMPD1 的作用机制,对于相关疾病的早期诊断、治疗和预防具有重要意义。

3. SMPD1 基因与 PD 关联

SMPD1 基因突变通过影响 ASMase 的功能,与多种疾病的发生密切相关,其中,最明确的致病关系是尼曼匹克病(Niemann-Pick Disease, NPD) A 型和 B 型。作为典型的溶酶体贮积病,其核心机制是鞘磷脂代谢异常,导致脂质在溶酶体内积聚引起细胞损伤[16]。

近年来, SMPD1 被确定为 PD 的常见风险基因。流行病学研究发现,该基因与 PD 的关联存在显著的人种差异:在德系犹太裔人群中,三种创始突变(p.R496L、p.L302P 和 c.996delC, fsP330)占 NPD A 型致病等位基因的 95%以上,其中 p.L302P 被认为是 PD 的强风险因素,而在其他种群中未被证实[17]。罕见突变 p.R591C 在部分中国人群的 PD 患者中被发现与 PD 易感性增加相关[18]。以上发现在动物实验中也得到进一步验证,如敲除 SMPD1 的小鼠表现出明显的神经退行性改变,如神经元数量减少、小胶质细胞过度活化以及行为学异常[19]。

4. SMPD1 基因与 PD 发病机制

4.1. 酸性鞘磷脂酶与 α -突触核蛋白(α -Synuclein, α -Syn)聚集及释放

PD 主要病理特点 α -syn 是聚集形成的路易小体[1], α -syn 由单体逐步形成寡聚体和原纤维并最终构成路易小体的过程受膜脂质组成调控[20]。ASMase 活性下降可促进 α -syn 的病理聚集过程。一方面, ASMase 活性下降导致鞘磷脂在细胞膜上异常聚集,改变脂筏结构和表面电荷,影响 α -syn 的膜结合与构象转化能力,诱导其寡聚化和原纤维形成,产生具有神经毒性的聚集体[21]。另一方面, α -syn 的清除主要依赖溶酶体途径[22], ASMase 活性下降导致溶酶体功能受损时, α -syn 降解受阻,胞质内 α -syn 毒性负荷增加[23]。

此外,外泌体在 α -syn 的清除与胞间转运中也发挥关键作用[24]。外泌体是由多种细胞(包括神经元)分泌的直径约 40~100 nm 的小囊泡[25],其通过运输蛋白质、脂质、Messenger RNA (mRNA)、MicroRNA (miRNA)、Long Non-Coding RNA (lncRNA)和 Deoxyribonucleic Acid (DNA),能够执行维持细胞稳态、清除细胞碎片、促进细胞间和器官间通讯等重要功能[26]。已有研究表明, Cer 可通过改变内体膜性质促进外泌体形成与分泌[24]。SMPD1 突变导致 Cer 生成减少,外泌体生成受抑, α -syn 的胞外分泌减少、胞内聚集风险增加[27]。

综上, SMPD1 突变导致 ASMase 活性降低可影响 α -syn 的异常折叠、降解受限和分泌障碍,最终加剧神经元损伤并推动 PD 的发生发展。

4.2. 酸性鞘磷脂酶与溶酶体自噬

在真核细胞中,蛋白质降解主要依赖于泛素-蛋白酶体系统(Ubiquitin-proteasome system, UPS)和内溶酶体-自噬途径(Autophagy-lysosome pathway, ALP) [28]。其中, ALP 是神经元清除 α -突触核蛋白的核心机制,其功能障碍不仅破坏神经元稳态,还显著增加蛋白质聚集的风险[29]。ASMase 在维持 ALP 正常功能中起关键作用[3]。该酶通过水解 SM 生成神经酰胺和磷胆碱,维持溶酶体膜脂组成和膜蛋白稳定性,并参与多种信号转导过程[30]。当 SMPD1 基因突变导致 ASMase 活性下降时, SM 在溶酶体膜内层异常积聚,从而破坏溶酶体结构与功能,最终影响自噬效率[31]。

转录因子 EB (Transcription Factor EB, TFEB)是调控溶酶体、自噬功能及能量代谢的主要调节因子[32]。ASMase 活性降低导致 SM 在溶酶体内积累,造成溶酶体损伤和未消化底物的堆积,触发应激反应,并激活以 TFEB 为核心的溶酶体-质膜轴。TFEB 转位至细胞核,促进溶酶体生物发生以及溶酶体与质膜的融合[33]。在溶酶体膜与质膜融合过程中,溶酶体胞吐作用增强,导致水解酶释放至胞外环境,并改变其结构。胞吐作用释放的水解酶可扰乱膜脂质稳态,诱导鞘磷脂异常代谢与细胞损伤。ASMase 缺失小鼠中观察到的 SM 积聚、TFEB 激活、自噬通量障碍以及鞘脂类二次储存现象,进一步提示 SM 介导的溶酶体损伤通过异常激活溶酶体-质膜轴,驱动细胞周期停滞与神经毒性过程[34]。

综上, SMPD1 突变导致的 ASMase 活性下降通过影响溶酶体功能,诱发自噬障碍,从而促进病理性 α -突触核蛋白的聚集,可能是 SMPD1 基因变异导致 PD 的主要致病机制。

4.3. 酸性鞘磷脂酶与神经炎症

神经炎症是帕金森病的重要病理过程之一,主要由中枢神经系统内小胶质细胞和星形胶质细胞的活化以及外周免疫反应共同驱动。在炎症状态下,胶质细胞过度活化并分泌多种促炎因子如白细胞介素-1 β (Interleukin-1 β , IL-1 β)、肿瘤坏死因子- α (Tumor Necrosis Factor- α , TNF- α)、干扰素- γ (Interferon-gamma, IFN- γ),导致神经元损伤并加剧炎症反应[35]。研究发现,神经炎症的发生可能早于神经元退行性变,提示其在帕金森病早期阶段发挥关键作用[36]。

脂质代谢异常与炎症调控密切相关。已有研究表明,当通过抑制 ASMase 或 SMPD1 基因沉默降低神经酰胺水平时,巨噬细胞对脂多糖(Lipopolysaccharide, LPS)刺激的炎症反应增强,并伴随 TNF- α 和巨噬细胞炎性蛋白-2 (macrophage inflammatory protein-2, MIP-2)分泌增加[37],提示神经酰胺具有一定的抗炎功能[38]。当 SMPD1 突变导致 ASMase 活性下降时,鞘磷脂在溶酶体内异常积聚、神经酰胺水平下降,破坏了脂质信号稳态,并向邻近胶质细胞传递应激信号[39],小胶质细胞由静息状态转变为促炎表型,分泌 TNF- α 、IL-1 β 等炎症因子以清除异常脂质或受损细胞。然而,过度激活则可能放大神经炎症反应,进而加重神经元损伤[40]。

因此, SMPD1 突变导致的脂质代谢异常通过鞘磷脂及神经酰胺生成减少放大神经炎症反应,进一步加重神经元损伤,并可能在帕金森病的发生与进展中发挥关键作用。

4.4. 酸性鞘磷脂酶与氧化应激

SMPD1 突变可导致 ASMase 活性下降,引起溶酶体内鞘磷脂异常积聚及神经酰胺生成减少,破坏细胞脂质稳态。脂质稳态紊乱被认为是帕金森病的早期启动因素之一[41]。氧化应激是脂质代谢异常与神经退行性病变的关键环节[42]。氧化应激促使 α -突触核蛋白聚集,形成有毒蛋白质聚集体,加剧神经毒性,并激活小胶质细胞和星形胶质细胞,诱导炎症因子释放,触发神经炎症反应并恶化神经元损伤[43]。ASMase 活性下降导致鞘磷脂在细胞膜及细胞器膜中过度积聚,破坏其结构稳定性,影响膜的流动性和通透性,从而干扰线粒体等细胞器的功能。线粒体损伤导致呼吸链功能紊乱和活性氧过度生成,进一步诱导氧化应激破坏细胞膜及细胞器膜的结构稳定性,影响膜流动性和通透性,干扰线粒体等细胞器的正常功能。线粒体损伤引发呼吸链紊乱和活性氧生成增加,诱导氧化应激[44]。此外,过量活性氧还可促进脂质过氧化,形成恶性循环,进一步损害神经元[45]。ASMase 活性下降通过鞘磷脂蓄积和神经酰胺减少,破坏脂质稳态并诱导氧化应激,导致 α -突触核蛋白聚集、神经炎症和线粒体功能障碍。这一系列病理变化共同构成帕金森病发生与进展的重要分子基础。SMPD1 基因突变与帕金森病的发生发展存在潜在关联,其作用机制可能涉及溶酶体功能障碍、鞘磷脂代谢紊乱及 α -突触核蛋白聚集等。SMPD1 突变致酸性鞘磷脂酶(ASMase)活性下降是帕金森病(PD)发生发展的核心始动因素,引发溶酶体自噬障碍,破坏 α -突触核

蛋白(α -syn)清除的核心途径, 为 α -syn 异常聚集奠定基础; 且导致 α -syn 降解受阻、胞外分泌障碍, 形成恶性循环; 脂质代谢紊乱与 α -syn 聚集进一步激活小胶质细胞, 诱发神经炎症(损伤放大通路), 加剧溶酶体功能异常与 α -syn 聚集; 同时 SM 蓄积破坏膜稳定性, 干扰线粒体功能引发氧化应激(全程协同因素), 促进 α -syn 聚集并放大炎症反应, 多途径破坏神经元稳态, 推动 PD 进展。现有研究提示其为 PD 的潜在遗传易感基因, 但其具体致病机制仍不明确。未来需进一步揭示 SMPD1 的致病作用, 有望为 PD 的早期诊断与治疗干预提供新的思路与靶点。

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