

VDAC1在中枢神经系统疾病中的作用 及机制研究进展

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摘要 中枢神经系统疾病包括神经退行性疾病、脑血管疾病等, 线粒体功能障碍在其中发挥重要作用。电压依赖性阴离子通道1(voltage-dependent anion channel 1, VDAC1)是线粒体外膜上的通道蛋白, 其参与细胞质和线粒体之间代谢产物和离子的交换、细胞能量代谢、 Ca^{2+} 稳态, 介导线粒体途径的细胞凋亡。越来越多研究表明, VDAC1参与阿尔茨海默病、帕金森病、肌萎缩侧索硬化和脑卒中等多种中枢神经系统疾病的病理生理过程。该综述总结了目前VDAC1在中枢神经系统疾病中的作用, 重点介绍了VDAC1与疾病特异性蛋白(如 β -淀粉样蛋白、磷酸化tau蛋白、 α -突触核蛋白)之间的相互作用, 并探讨了以VDAC1为作用靶点的潜在治疗策略。

关键词 VDAC1; 线粒体; 阿尔茨海默病; 帕金森病; 肌萎缩侧索硬化; 亨廷顿舞蹈症; 脑卒中

Progress of Effects of VDAC1 in Central Nervous System Diseases and Its Mechanism

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Abstract Central nervous system diseases include neurodegenerative diseases, cerebrovascular diseases, etc., in which mitochondrial dysfunction plays an important role. VDAC1 (voltage-dependent anion channel 1) is a channel protein on the outer membrane of mitochondria that is involved in the exchange of metabolic products and ions between the cytoplasm and mitochondria, cellular energy metabolism, Ca^{2+} homeostasis, and mediating apoptosis through the mitochondrial pathway. More and more studies have shown that VDAC1 is involved in the pathophysiological processes of multiple central nervous system diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and stroke. This review summarizes the current role of VDAC1 in central nervous system diseases, focusing on the interaction between VDAC1 and disease-specific proteins (such as β -amyloid, phosphorylated tau, and α -synuclein), and explores potential treatment strategies targeting VDAC1.

Keywords VDAC1; mitochondria; Alzheimer's disease; Parkinson's disease; amyotrophic lateral sclerosis; Huntington's disease; stroke

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中枢神经系统疾病,包括阿尔茨海默病(Alzheimer's disease, AD)、帕金森病(Parkinson's disease, PD)、脑卒中和其他疾病,已成为严重危害人类健康的重大公共卫生问题^[1]。线粒体功能障碍,包括线粒体能量代谢和电子传递链紊乱、线粒体动力学障碍、活性氧(reactive oxygen species, ROS)的大量产生、细胞内钙稳态失衡以及细胞凋亡增加,在疾病的发生、发展过程中具有重要作用。因此,有效地改善线粒体功能是治疗中枢神经系统疾病的重要环节^[2]。

电压依赖性阴离子通道(voltage-dependent anion channel, VDAC)是真核细胞线粒体外膜上最丰富的蛋白质,目前在哺乳动物中共发现3个亚型,分别为VDAC1、VDAC2和VDAC3,这三种亚型在大多数组织中均有表达,其中,VDAC1表达量最多,其结构和功能已被广泛研究。VDAC1的功能多样参与了细胞质和线粒体之间代谢产物和离子的交换,介导了线粒体途径的细胞凋亡等。近年来,VDAC1在中枢神经系统疾病中的作用越来越受到关注,这篇综述旨在阐述VDAC1在中枢神经系统疾病中的作用及其机制,为中枢神经系统疾病的精准治疗提供新思路。

1 概述

1.1 VDAC的分型及结构

VDAC是线粒体外膜上分子量约30 kDa的通道蛋白,具有离子选择性和电压依赖性。研究数据表明,VDAC在低电压(± 10 mV)下显示出完全开放状态,其中更倾向于阴离子交换;而其在高电压($\pm 10 \sim 30$ mV)下处于闭合状态时具有阳离子选择性,并且对小离子具有渗透性^[3]。在哺乳动物中,核DNA编码三种不同的亚型,即VDAC1、VDAC2和VDAC3,其序列同源性高达70%,三种同工型几乎是普遍存在的,其中VDAC1表达最丰富,VDAC1和VDAC2具有非常强的造孔特性,而VDAC3形成较小的电导通道^[4],从而调节其他蛋白质的生理功能。

VDAC具有约12~19个跨膜 β 折叠和一个位于分子N端的 α 螺旋,但其精确结构仍存在争议。研究发现VDAC1是由19个 β 折叠形成的桶状结构,其具有25个氨基酸残基的N末端结构域,以 α 螺旋结构组成的N末端结构域处于动态平衡状态,位于孔内部或暴露于 β 桶外部,从而参与通道门控特性以及

VDAC1二聚体的形成,此外,与Bcl-2家族蛋白(Bax、Bak、Bcl-2)和己糖激酶(hexokinase, HK)相互作用介导细胞凋亡发生^[5]。

1.2 VDAC1的功能

VDAC1在细胞中执行多项重要功能(图1),VDAC1的基本功能是在细胞质和线粒体之间进行代谢产物和离子的交换。通过VDAC1,新合成的ATP/ADP和 NAD^+/NADH 在胞质和线粒体之间不断交换,并通过与HK的结合调节糖酵解进而介导细胞能量的产生。VDAC1通过葡萄糖调节蛋白75(glucose-regulated protein 75, GRP75),与内质网上控制 Ca^{2+} 释放的1,4,5-三磷酸肌醇受体(inositol 1,4,5-triphosphate receptor, IP3R)关联并形成线粒体相关内质网膜(mitochondria-associated endoplasmic reticulum membrane, MAM),调节 Ca^{2+} 信号转导。此外,VDAC1也是导致ROS释放到细胞质的通道,参与细胞内氧化还原状态的调节^[6]。线粒体自噬是通过自噬对受损和功能失调的线粒体进行选择降解,是线粒体质量控制的重要机制,也是线粒体降解的主要途径。线粒体自噬主要受PTEN诱导激酶1(PTEN induced putative kinase 1, PINK1)和E3泛素连接酶Parkin信号通路的调节。近年来研究发现,VDAC1参与PINK1/Parkin介导的线粒体自噬, Parkin从细胞质募集到线粒体,对线粒体蛋白(如VDAC1、Mfn等)进行泛素化,导致线粒体自噬,而VDAC1基因沉默可以抑制Parkin从细胞质到受损线粒体的易位,并抑制线粒体的降解^[7-8]。

VDAC1作为细胞凋亡的调节剂,介导细胞色素c、细胞凋亡诱导因子(apoptosis-inducing factor, AIF)、线粒体核酸内切酶G(endonuclease G, EndoG)等凋亡因子的释放,其可能的机制有:(1) VDAC1处于关闭状态导致线粒体肿胀和线粒体外膜(outer mitochondrial membrane, OMM)破裂^[9];(2) VDAC1通过与线粒体内膜中的腺嘌呤核苷酸转位酶(adenine nucleotide translocase, ANT)和线粒体基质中的亲环蛋白D(cyclophilin D, CypD)形成复合物,从而成为线粒体通透性转换孔(mitochondrial permeability transition pore, mPTP)的关键成分, Ca^{2+} 和氧化应激诱导mPTP开放,导致细胞色素c释放^[10];(3) 各种凋亡刺激诱导VDAC1过表达,从而使VDAC1从单体聚集成寡聚体(包括二聚体、三聚体和四聚体),寡聚化的VDAC1形成了能够释放促凋亡因子的大通

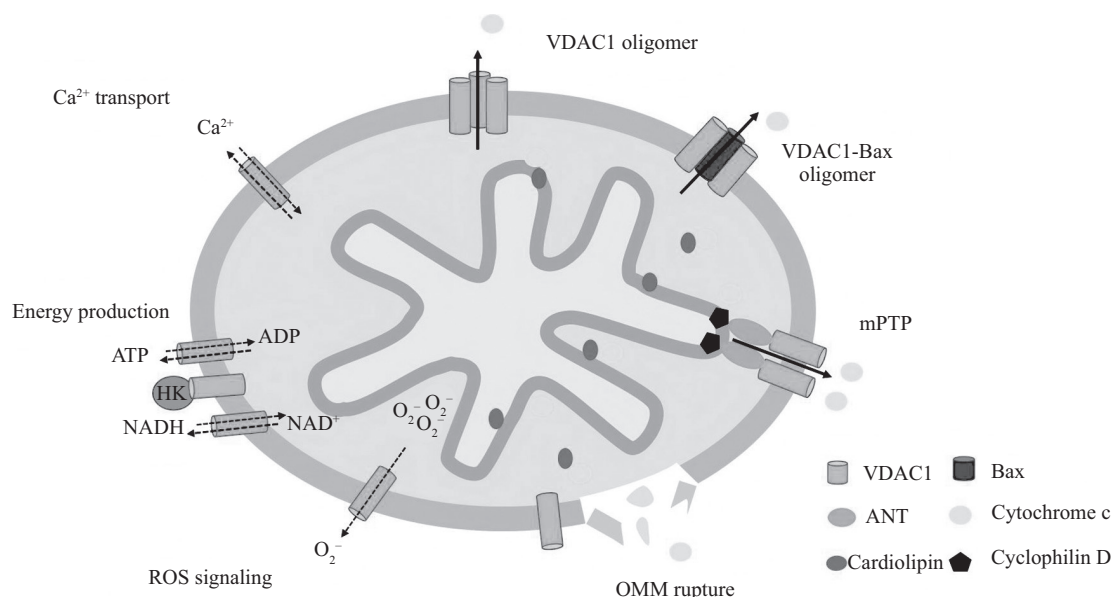


图1 VDAC1的功能
Fig.1 Functions of VDAC1

道,参与了线粒体介导的细胞凋亡,而VDAC1寡聚化抑制剂(例如DIDS、VBIT-4、VBIT-12)通过抑制该寡聚体的形成,减少促凋亡蛋白的释放,改善线粒体功能^[11-12]。有趣的是,最新研究发现,VDAC1寡聚化在介导谷氨酸诱导的HT22细胞线粒体片段化过程中发挥着重要作用^[13]。氧化应激条件下,VDAC1寡聚化形成释放线粒体DNA(mitochondrial DNA, mtDNA)片段的通道;(4) VDAC1通过与促凋亡蛋白(Bax、Bak)和抗凋亡蛋白(Bcl-2、Bcl-xL)相互作用,参与线粒体介导的细胞凋亡。例如在凋亡刺激下,VDAC1与Bax相互作用形成一个大通道促进细胞色素c释放激活细胞凋亡,从而发生寡聚化^[14-15];(5) 一些激酶,例如糖原合酶激酶3 β (glycogen synthase kinase 3 β , GSK3 β)和HK,通过与VDAC1相互作用,调节VDAC1的活性,进而影响细胞凋亡^[16]。

VDAC1的活性受翻译后修饰的影响,例如磷酸化、氧化、泛素化和乙酰化^[17]。磷酸化发生在丝氨酸、酪氨酸或苏氨酸残基中,影响VDAC1的通道活性和调节细胞凋亡。例如,SINGH等^[18]发现TLK1/Nek1通路通过调节VDAC1的磷酸化,从而调节线粒体功能和细胞凋亡。

2 VDAC1与神经退行性疾病

神经退行性疾病包括阿尔茨海默病(AD)、帕金森病(PD)、亨廷顿舞蹈症(Huntington's disease,

HD)和肌萎缩侧索硬化(amyotrophic lateral sclerosis, ALS)等,是一类以神经元缺失为主要特征的退行性疾病,具有不可逆性和进行性加重的特点。线粒体功能障碍被认为是导致多种神经退行性疾病的重要因素,VDAC1在线粒体功能障碍中发挥重要作用。研究表明,VDAC1与多种神经退行性疾病特异性蛋白之间存在相互作用,参与疾病的发生、发展过程(图2)。

2.1 VDAC1与AD

AD是最常见的神经退行性疾病,其主要特征是含有 β -淀粉样蛋白(amyloid beta, A β)的细胞外老年斑和由过度磷酸化的tau蛋白组成的细胞内神经原纤维缠结(neurofibrillary tangle, NFT)的沉积。早老素1(presenilin 1, PS1)、早老素2(presenilin 2, PS2)和淀粉样蛋白前体蛋白(amyloid precursor protein, APP)的突变是家族性AD的发病机制。线粒体功能障碍与AD的发生和发展密切相关,如mtDNA的变化、线粒体酶活性降低、线粒体基因表达异常、线粒体片段化增加、线粒体融合减少、Ca²⁺稳态失衡、ROS产生增加和细胞凋亡^[19]。

2.1.1 VDAC1在AD中表达水平升高 VDAC1作为线粒体功能的关键调节因子,在AD转基因小鼠和死亡AD患者的脑组织中过表达^[20]。在经A β ₁₋₄₂处理的PC12细胞中,VDAC1的表达水平升高^[21]。研究表明降低VDAC1的表达水平可以改善突触功能,增

导激酶1(PTEN-induced putative kinase 1, *PINK1*)和帕金森病相关去糖化酶(parkinsonism associated deglycase, *DJ-1*)基因突变时可引起单基因相关帕金森病^[31]。

2.2.1 VDAC1在PD中表达水平差异 VDAC1蛋白水平在多种神经退行性疾病中均有改变, CHU等^[32]发现VDAC1在PD患者的黑质神经元和过表达 α -Syn的大鼠模型的黑质和纹状体中表达水平显著降低, 且这种降低与 α -Syn聚集有关。另一项研究报道, 在多巴胺处理的人神经母细胞瘤细胞(SH-SY5Y)中, VDAC1和VDAC2水平显著降低^[33]。不同的是, 在6-羟基多巴胺(6-OHDA)处理的SH-SY5Y细胞中观察到VDAC1表达水平升高^[34]。VDAC1水平信息的差异可能由多种因素导致, 包括PD模型的类型、疾病表型的异质性以及疾病进展阶段的差异。

miRNA(microRNA)是一组短的非编码RNA, 其是细胞过程(如细胞凋亡、应激反应和衰老)的转录后基因表达的新型调节剂, 研究发现miRNA是神经元功能的重要调节剂, 而VDAC1已经成为miRNA调控的作用靶点。有趣的是, α -Syn和VDAC1的表达均受到miR-7(microRNA-7)的调控。miR-7的下调导致 α -Syn的表达水平的增加、多巴胺能神经元的缺失和纹状体多巴胺的丢失^[35]。研究发现, miR-7可以通过下调VDAC1表达, 调节mPTP的开放, 抑制1-甲基-4-苯基吡啶(1-methyl-4-phenyl-pyridinium, MPP+)诱导的细胞色素c的释放, 从而发挥细胞保护作用^[36]。

2.2.2 VDAC1与 α -Syn相互作用 在神经元中, α -Syn已被证明与所有三种VDAC亚型结合, 与VDAC1的亲和力最高^[37], 之前的研究已经证明了VDAC1和 α -Syn之间相互作用, 导致mPTP激活, 细胞凋亡, 进而导致多巴胺能神经元变性^[38]。这种相互作用还使 α -Syn转位到线粒体, 而在线粒体中聚集的 α -Syn导致ROS产生和线粒体自噬增加^[39]。最近研究发现, 由于VDAC1与 α -Syn结合, VDAC1对 Ca^{2+} 的选择性增加, 因此 α -Syn可以调节VDAC1对 Ca^{2+} 的通透性^[40]。

在过表达 α -Syn的SH-SY5Y细胞中, 神经保护性胆固醇化合物奥利索西通过靶向VDAC1, 抑制 α -Syn的易位, 防止线粒体内 α -Syn积累及ROS产生从而发挥保护作用^[41]。在 α -Syn转基因小鼠中, 白藜芦醇改善了运动和认知功能, 同时降低了VDAC1的

表达水平及其与 α -Syn的相互作用, 从而保护了多巴胺能神经元^[42]。

2.2.3 VDAC1与PINK1/parkin相互作用 帕金森病家族基因*PINK1*和*Parkin*介导线粒体自噬。VDAC的三种亚型与*Parkin*之间均存在相互作用, *Parkin*可以诱导VDAC1两种不同的泛素化模式: 其中单泛素化途径可以抑制细胞凋亡; 而多泛素化可以促进线粒体自噬, 将自噬衔接因子p62/SQSTM1和LC3B募集到线粒体中, 导致受损线粒体降解^[43]。在PD患者中观察到的*Parkin*结构域T415N突变时不能诱导VDAC1单泛素化^[43]。ZHAO研究团队^[44]最新发现在正常条件下, E3泛素连接酶TRIM31与VDAC1结合, 并促进VDAC1的K48链接多聚泛素化。在帕金森病病理状态下, TRIM31的下调抑制VDAC1的泛素化降解, 导致VDAC1蛋白水平升高, 促进mPTP的开放, 导致多巴胺能神经元死亡, 最终促进帕金森病的进展。

最近的研究表明, 维生素D通过降低VDAC1的表达水平, 对6-OHDA诱导的大鼠PD模型具有神经保护作用, 可能的保护机制是通过泛素化诱导自噬并抑制细胞凋亡, 从而保护神经元^[45]。在1-甲基-4-苯基-1,2,3,6-四氢吡啶(1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, MPTP)诱导PD模型小鼠中, 艾地苯醌可以通过调节VDAC1的表达来激活PINK1/parkin介导的线粒体自噬, 促进受损线粒体的降解, 减轻多巴胺能神经元损伤, 改善帕金森病小鼠的行为障碍^[46]。在SH-SY5Y细胞模型中, 鼠尾草酸通过激活PINK1/parkin途径参与VDAC1的泛素化从而清除受损的线粒体发挥神经保护作用^[47]。而4-苯基丁酸钠通过靶向VDAC1介导的线粒体功能和星型胶质细胞的激活, 从而缓解帕金森大鼠模型的运动障碍和多巴胺能神经元变性^[48]。

2.2.4 VDAC1与DJ-1 细胞内DJ-1主要分布于细胞质、细胞核和线粒体, DJ-1根据其在亚细胞不同部位而发挥不同作用。研究证实, DJ-1是一种MAM蛋白, 而VDAC1是MAM中IP3R3-Grp75-VDAC1复合物的的重要组成部分, DJ-1的缺失导致MAM形成障碍。因此DJ-1突变可引起线粒体钙稳态受损, 导致线粒体功能障碍^[49]。

2.3 VDAC1与ALS

ALS是一种致命的无法治愈的神经退行性疾病, 其以上、下运动神经元丢失为主要特征, 导致肌

肉无力、萎缩、瘫痪,最终导致患者在发病后2~5年内死于呼吸衰竭。约90% ALS病例被归类为散发性,没有明显的家族病史,而剩下的10%被归类为家族性,归因于40多种不同基因的突变;其中包括超氧化物歧化酶1(superoxide dismutase 1, SOD1)、TAR DNA结合蛋白43(TAR DNA-binding protein 43, TDP-43)和9号染色体开放阅读框72(chromosome 9 open reading frame 72, C9orf72)。散发性和家族性ALS的病理机制复杂,包括氧化应激水平增加、兴奋性毒性和神经炎症。此外,与ALS发病相关的异常蛋白与线粒体相互作用,导致线粒体功能障碍。

2.3.1 VDAC1与突变型SOD1相互作用 研究发现,在转基因SOD1大鼠模型中,错误折叠的突变型SOD1和VDAC1直接结合并抑制了VDAC1的活性,导致了ATP的合成减少及线粒体膜电位的降低^[50],另外,ANDREA等^[51]发现突变体SOD1 G93A与VDAC1相互作用,同时,己糖激酶I(hexokinase I, HKI) N-端结构域可抑制VDAC1与SOD1 G93A相互作用,改善ALS的线粒体功能障碍,恢复细胞活力。NHK1是一种相当于人类HK1的前11个氨基酸的合成肽,通过减弱VDAC1-SOD1 G93A相互作用,从而减少突变体SOD1 G93A线粒体聚集体的积累,增加VDAC1蛋白水平,恢复细胞活力^[52]。研究发现从突变体SOD1G93A小鼠和大鼠分离的脊髓线粒体中,VDAC1寡聚化水平升高,VBIT-12通过抑制VDAC1寡聚化,挽救突变体SOD1诱导的细胞死亡,显著提高了突变型SOD1G93A小鼠的肌肉耐力^[53]。此外,突变型SOD1通过与Bcl-2的相互作用靶向VDAC1,影响其门控特性^[54]。

2.3.2 VDAC1与TDP-43相互作用 TDP-43是一种核DNA/RNA结合蛋白,在4%的家族性ALS患者中发生突变,研究表明在ALS发病机制中,TDP-43错误定位到线粒体中,与VDAC1相互作用,并导致mtDNA在胞质内累积^[55]。

TDP-43进入线粒体后将mtDNA通过mPTP释放到胞质中引发炎症反应,这种炎症是由细胞质DNA传感器环鸟苷酸(GMP)-AMP合酶[cytoplasmic DNA sensor cyclic guanosine monophosphate (GMP)-AMP synthase, cGAS]驱动的,通过药物抑制cGAS及其下游分子STING可阻止TDP-43诱导炎症反应。VDAC寡聚化抑制剂VBIT-4或VDAC1基因缺失通过降低ALS患者和运动神经元的mtDNA水平,抑制炎症反

应,因此阻断cGAS/STING通路可改善ALS小鼠的神经变性^[56]。其他研究表明氧化的mtDNA,通过mPTP和VDAC1依赖通道转移出线粒体,从而激活细胞质中NLRP3炎性小体,诱发炎症反应^[57]。

2.4 VDAC1与HD

HD是一种进行性认知退化、精神障碍和运动障碍的遗传性神经退行性疾病,由亨廷顿蛋白(Huntingtin, Htt)中的多聚谷氨酰胺(polyglutamine, polyQ)扩增突变引起。在HD诱导型PC12细胞模型中,Htt的表达导致VDAC功能改变,尤其是VDAC1,影响了线粒体代谢及细胞活力^[58]。在HD动物模型的纹状体中发现VDAC1被氧化,降低的VDAC1水平影响线粒体能量代谢^[59]。桑黄素通过抑制mTOR/IRE1- α 信号通路、IP3R/VDAC1通路、PINK1/泛素/Mfn2和细胞色素c/caspase-3轴,抑制HD模型内质网应激、线粒体自噬和细胞凋亡,从而发挥神经保护作用^[60]。

3 VDAC1与脑卒中

脑卒中中以高发病率、致残率和致死率为主要特点,是严重危害人类健康的主要疾病之一。脑卒中分为缺血性和出血性,其中,缺血性脑卒中更常见,约占患者的87%;而出血性脑卒中包括脑出血(intracerebral hemorrhage, ICH)和蛛网膜下腔出血(Subarachnoid hemorrhage, SAH),危险性远高于缺血性脑卒中。

3.1 VDAC1与缺血性脑卒中

缺血性脑卒中的病理机制复杂多样,包括炎症反应、钙超载、线粒体功能障碍和细胞凋亡等,各种因素可能存在交互作用。由于血栓的形成或栓塞导致局部脑组织的正常血流供应不足,引起脑组织缺血、缺氧的发生,导致能量供应障碍和细胞内 Ca^{2+} 超载,导致线粒体功能障碍和ROS的产生,进一步导致神经元细胞坏死或凋亡。因此,线粒体功能障碍是其中的重要环节,而VDAC1介导的生物学功能与缺血性脑卒中的发病机制存在高度重叠。

研究发现,通过干预MAM的复合物IP3R-GRP75-VDAC1对 Ca^{2+} 的转运,抑制 Ca^{2+} 超载,抑制mPTP的开放和细胞色素c的释放,进而减少缺血性半暗带神经细胞的凋亡^[61]。胡黄连苷II可以通过下调VDAC1的表达并降低mPTP的通透性来减轻脑缺血再灌注损伤,从而抑制线粒体凋亡蛋白Endo G释放^[62]。

miRs可能是缺血性卒中的潜在治疗靶标。缺血

后海马CA1区域中VDAC1的表达下调,导致细胞内 Ca^{2+} 超载。VDAC1下调归因于miR-7表达水平增加,抑制miR-7可以减轻局部缺血后神经元的丢失和ATP的下降,改善神经功能从而发挥神经保护作用^[63]。另外,研究发现敲低miR-29导致小鼠海马和小脑区域中VDAC1表达水平升高和细胞凋亡^[64]。在短暂性脑缺血再灌注损伤后,miR-29a的表达水平在海马齿状回中显著增加,而在海马的CA1区中降低,miR-29a的过表达导致CA1神经元免受缺血后应激的影响^[65]。STARY等^[66]研究发现miR-29a通过抑制VDAC1表达对缺血性损伤发挥保护作用。急性缺血性卒中后,转录因子p53在皮质神经元内蓄积,并通过转录依赖和非转录依赖途径促进神经元凋亡。XIA等^[67]研究发现p53通过转录调控miR-183和miR-9,进而靶向线粒体功能蛋白VDAC,最终阻断三羧酸循环和氧化磷酸化过程。研究者也证实了CDK9/p53/miR-183/VDAC信号级联是急性缺血性脑卒中后进行性神经功能损伤和长期不良预后的基础,而CDK9抑制剂千层纸素A提升卒中后小鼠的远期感觉运动能力和空间记忆,并减轻抑郁样行为,从而对卒中后认知障碍和卒中后抑郁具有治疗潜力。

3.2 VDAC1与出血性脑卒中

ICH指一种由脑实质内出血引起的出血性卒中,SAH指各种病因导致脑血管破裂后,血液流入蛛网膜下腔引起的病理过程,其发病率和死亡率均很高。

研究发现,在ICH后观察到cAMP活化交换蛋白-1(cAMP-activated exchange protein-1, EPAC-1)与VDAC1存在相互作用,诱导线粒体损伤,而雷公藤红素结合cNMP(EPAC-1的一个结构域),抑制其与VDAC1的相互作用,并抑制mPTP的开放,改善神经元的线粒体功能障碍,从而可能减轻脑出血引起的继发性脑组织损伤^[68]。早期研究发现大鼠SAH后大脑皮质中VDAC1表达水平变化与皮质神经元凋亡水平呈正相关,表明VDAC1可能是通过线粒体途径引起神经元凋亡的发生^[69]。LI等^[70]发现SAH损伤后VDAC1诱导的线粒体自噬可能在神经保护中发挥重要作用。

4 VDAC1与其他神经系统疾病

4.1 VDAC1与脊髓小脑性共济失调

脊髓小脑性共济失调3型(spinocerebellar ataxia type 3, SCA3),是全球最常见的显性遗传性共济失

调,最近研究认为该疾病与线粒体功能障碍和线粒体自噬受损相关。SCA3是由于MJD1基因的CAG重复扩增导致编码的共济失调蛋白3(ataxin-3)中polyQ序列扩增引起的,使SCA3成为polyQ病家族的一员。ataxin-3可以使VDAC1去泛素化,导致VDAC1的多泛素化减少,从而阻碍线粒体自噬;其还可以引起线粒体肿胀和Bax/VDAC1的寡聚化,导致细胞色素c释放,启动细胞凋亡^[71]。

4.2 VDAC1与癫痫

研究发现,难治性癫痫患者海马VDAC1表达水平升高,同时VDAC2水平降低,导致线粒体功能障碍^[72],VDAC2在毛果芸香碱诱发的颞叶癫痫(temporal lobe epilepsy, TLE)模型中显示出上调,提示VDAC2是癫痫的生物标志物^[73]。

5 总结与展望

随着对VDAC的结构组成、生物学功能的深入研究,VDAC1在多种中枢神经系统疾病中的作用机制以及作为药物治疗靶点已受到越来越多的关注。VDAC1与特异性蛋白(如A β 、 α -Syn、突变型SOD1和TDP-43)的相互作用,影响了线粒体正常功能和细胞能量平衡,其参与了疾病的发生和发展过程。此外,在病理条件下,VDAC1表达水平改变、VDAC1寡聚化增加和翻译后修饰,导致线粒体功能障碍、ROS生成增加和细胞凋亡。几种靶向VDAC1的化合物(如VBIT-4、VBIT-12、白藜芦醇和奥利索西)通过恢复线粒体功能、减少ROS生成和抑制致病性蛋白相互作用发挥了神经保护作用。未来以VDAC1为靶点的治疗策略可能为缓解线粒体功能障碍提供有前景的治疗方案,通过小分子抑制剂、基于肽的疗法等将进一步拓展治疗方法,此外,应用纳米颗粒等先进的药物递送系统可以提高VDAC1靶向治疗的生物利用度和疗效。通过单细胞测序技术,分析VDAC1在不同神经细胞中作用,深入研究VDAC1与疾病特异性蛋白相互作用,以及其在内质网-线粒体关联中的调控作用,将有助于阐明疾病发生发展的分子基础,有望为中枢神经系统疾病的精准治疗提供理论依据。

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