综述

SARM1在神经系统中的作用及机制研究进展

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摘要 无菌α和Toll白介素受体基序蛋白1(sterile alpha and toll interleukin receptor motif-containing protein 1, SARM1)是最新发现的一个在Toll样受体(Toll-like receptor, TLR)通路中起作用的衔接子。SARM1主要在哺乳动物的神经系统中表达, 在神经炎症、神经系统的发育中都发挥重要作用。它可以介导神经元的死亡和形态改变, 调控神经纤维的瓦勒变性, 并且对神经胶质细胞的发生也有影响。与此同时, 在面对损伤(感染、外伤、低氧等)时, SARM1作为神经元损伤和先天免疫之间的联系点, 为神经退行性疾病和精神疾病等的发病机制研究和治疗方案提供新思路。该文对SARM1在神经系统中作用及机制研究进行综述。

关键词 SARM1; 先天免疫; 瓦勒变性; 神经炎症; 神经退行性疾病

The Role and Mechanism of SARM1 in the Nervous System

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Abstract SARM1 (sterile alpha and toll interleukin receptor motif-containing protein 1) is the latest adaptor that plays a role in TLR (Toll-like receptor) signal transmission. SARM1 is mainly expressed in the nervous system of mammals, which plays an essential role in the occurrence of neuroinflammation and neurodevelopment. SARM1 not only mediates the morphology and apoptosis of neurons, but also regulates the Waller degeneration of nerve fibers. What's more, it also has an effect on the development of glial cells. Meanwhile, in the face of risk (infection, trauma, hypoxia, etc), SARM1, as the connection point between neuronal injury and innate immunity, provides a new starting point for the pathogenesis and treatment of neurodegenerative and psychiatric diseases. This article reviews the role and mechanism of SARM1 in the nervous system.

Keywords SARM1; innate immunity; Wallerian degeneration; neuroinflammation; neurodegenerative disease

*SARM1*基因包括TIR、ARM(armadillo like helical)和SAM(sterile alpha motif)三个结构域。SARM1是病理性轴突变性的主要执行者, 通过负调节TRIF的TLR通路, 促进瓦勒变性, 轴突变性常常被认为是神经退行性变的开始[1-2]。SARM1也促进神经元因缺氧、葡萄糖缺乏和病毒感染而死亡的

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进程[3-4]。SARM1的缺失可抑制损伤后小鼠神经元的退化[5]。另外, SARM1与先天免疫相关, 它在神经胶质细胞中表达并调节其活性, 也可触发细胞的应激或死亡[1]。因此, 对SARM1在神经系统中的研究能为神经退行性疾病和精神疾病的发病机制研究和治疗方案提供新思路。

1 SARM1在不同脑区的分布

有研究表明, 人类*SARM1*的mRNA在脑中各类细胞如初级神经元和星形胶质细胞都有较高水平的表达量。同时, 在肝、肾和胎盘内也有较高的表达量, 而在其他组织中其表达量相对较低[6-7]。然而小鼠*SARM1*的mRNA只表达在脑和脾脏中[8]。这表明, SARM1的表达情况在人与小鼠中不同。

成年C57BL/6小鼠(8周龄)的免疫组织化学染色显示, SARM1蛋白广泛分布在不同的脑区, 包括大脑皮层的感觉皮层、运动皮层和压后皮层[9]; 海马的齿状回、CA1区、CA2区和CA3区。SARM1在小脑中主要表达在浦肯野细胞, 但在颗粒细胞层和分子层的中间神经元中也有弱信号表达。在中脑, SARM1表达在腹侧被盖区的多巴胺能神经元中(表1)。LIN等[9]还发现, SARM1在神经元的表达高于星形胶质细胞和小胶质细胞。而在外周组织中, SARM1可与其他物质共存于视网膜组织的感光细胞和双极细胞中[10-11]。

2 SARM1在神经系统中的作用

2.1 SARM1对神经元存活的作用

在氧和葡萄糖剥夺(oxygen-glucose deprivation, OGD)模型中, 秀丽隐杆线虫神经元中*SARM1*的直系同源基因*TIR-1*通过钙/钙调素依赖性蛋白激酶II(Ca^{2+}/calmodulin dependent protein kinase II, CaMKII)接收Ca^{2+}信号后, 激活ASK1-MKK4/7-JNK通路, 调节了基因表达。TIR-1在接收到Ca^{2+}信号后, 易位至神经元的线粒体作为支架, 同时招募c-Jun氨基端激酶(c-Jun N-terminal kinases, JNK)至线粒体与SARM1相互作用, 引起线粒体功能障碍和活性氧的积累, 导致神经元死亡(图1)[3,12]。

病毒诱导神经元死亡的研究也支持SARM1能促进神经元死亡的进程。在拉克罗斯病毒感染神经元期间, 线粒体抗病毒信号蛋白(mitochondrial antiviral signaling, MAVS)被激活, 并导致SARM1蛋白表达量增加, SARM1易位至线粒体并诱导氧化应激, 线粒体损害, 最终导致神经元死亡[4]。SARM1也能促进细胞毒性T细胞死亡, T细胞免疫激活后, SARM1易位于线粒体并产生活性氧, 触发T细胞内源性凋亡[13]。

然而, 还有研究表明, *SARM1*基因缺失会加速神经元死亡。*SARM1*敲除小鼠感染朊病毒后, 神经元中促凋亡基因*XAF1*(X-linked inhibitor of apoptosis-associated factor 1)过表达, 加速神经元死亡[14]。这可能是由于小鼠*XAF1*和*SARM1*基因座位距离近导致的, 敲除*SARM1*基因可能通过影响邻近基因的染色体结构来改变XAF1的表达[14]。

2.2 SARM1对神经元发育的影响

在健康神经元中, SARM1能促进其树突、轴突和突触的发育。SARM1是重组人黏结蛋白聚糖2(syndecan-2, Sdc2)下游的效应物之一, 与Sdc2的胞质结构域(分为C1、V和C2区)有直接作用, 其中与V区的作用最为关键, 并通过MKK4-JNK通路调节神经元树突分支化, 从而影响树突棘的数量和形态[15]。SARM1也调节轴突的生长和分化, 同样通过MKK4-JNK通路增强微管稳定性, 促进轴突生长[15]。SARM1的缺乏会引起树突棘密度降低与轴突长度的缩短[9,15]。

表1 SARM1在神经系统的分布情况

Table 1 Distribution of SARM1 in the nervous system

相关位置 Relative position	相关区域 Relative area	相关神经元 Relative neurons
Cerebral cortex	Sensory cortex, motor cortex and retrosplenial agranular cortex	Projection and inhibitory neurons
Hippocampus	Dentate gyrus, CA3, CA2 and CA1	Projection and inhibitory neurons
Cerebellum	Granulosa layer, purkinje cell layer, molecular layer	Purkinje cells, interneurons
Midbrain	Ventral tegmental area	Dopaminergic neurons

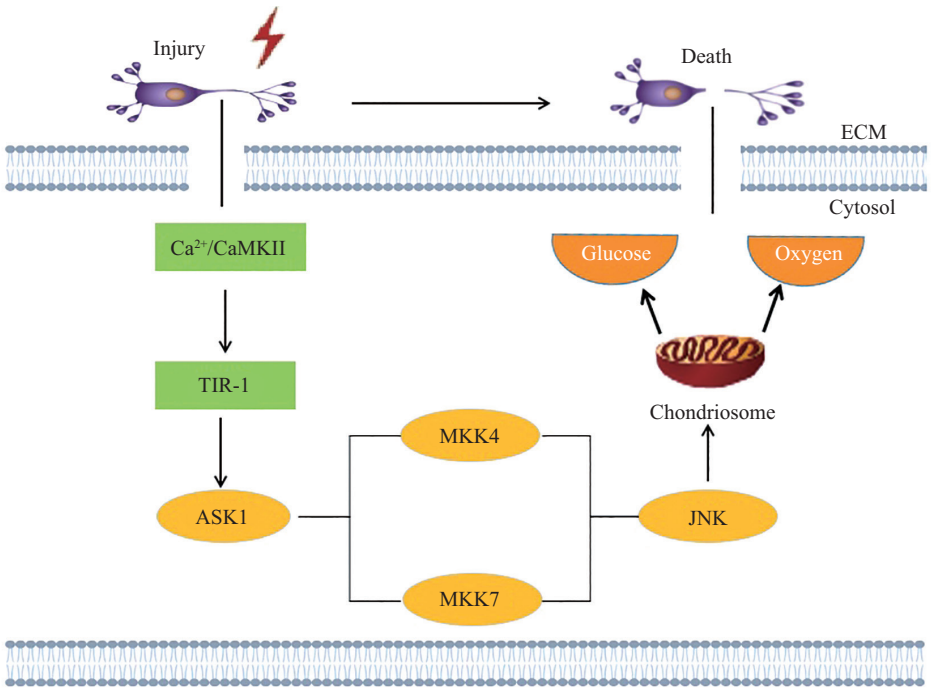


图1 SARM1促进神经元死亡的分子机制

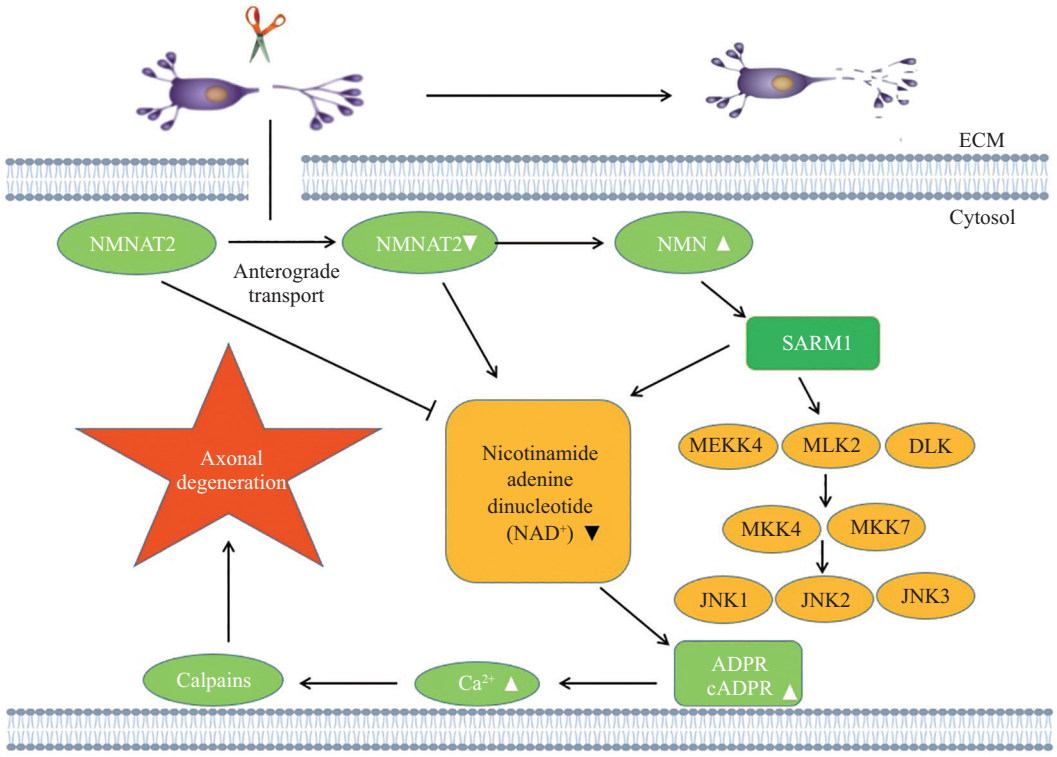
Fig.1 The molecular mechanisms of promoting neuronal death by SARM1

SARM1能抑制轴突分支, 是轴突细胞骨架动力学的负调节因子, *SARM1*敲除的轴突高表达肌动蛋白调节蛋白和线粒体, 预示着轴突产生新的分支[16]。SARM1还能调节突触可塑性, 通过TLR通路促进神经肌肉接头的生长, 抑制驱动蛋白的表达并引起微管的不稳定, 从而形成新的突触小体。这在果蝇中表现为促进其运动神经元发育, 使果蝇的运动能力增强[17]。TIR-1是SARM1在秀丽隐杆线虫神经元中的同源物, 是突触向细胞核传递信号的关键。TIR-1在突触发育中通过钙信号通路来影响神经元命运。TIR-1与CaMKII结合后组装成一个调节气味受体表达的突触信号复合体, 通过ASK1-MKK-JNK通路来调节嗅觉受体的表达, 使一侧嗅觉神经元上气味受体的表达被抑制, 进而导致气味受体表达的左右不对称性[18]。

SARM1对神经元形态的影响与多种神经退行性疾病的发生有关。在肌萎缩性侧索硬化症(amyotrophic lateral sclerosis, ALS)模型中, *SARM1*敲除可以显著抑制运动神经元胞体、轴突和神经肌肉接头的变性, 同时也减轻了其树突棘的缺损[19]。在探究自闭症行为异常的可能原因中, 发现*SARM1*敲除增加小鼠CA1神经元NMDAR(*N*-methyl-*D*-aspartate receptor)依赖性长时程增强(long-term potentiation, LTP)的产生, 但损害mGluR(metabotropic glutamate receptor)依赖性长时程降低(long-term depression, LTD)的产生, 导致了突触功能障碍。用mGluR正向变构调节剂治疗可有效改善*SARM1*敲除引起的自闭症样行为。LIN等[20]的数据表明, SARM1表达的降低还会导致NR1、NR2a和Shank蛋白等突触后蛋白质组成的变化来抑制突触反应, 这都与自闭症的病因密切相关。

2.3 SARM1对瓦勒变性的影响

在神经被切断、压碎时, 损伤部位远端节段的轴突发生一种被称为瓦勒变性的分裂, 表现为神经纤维从细胞体中分离出来, 并在几天内迅速分解成离散的碎片[21]。SARM1介导的瓦勒变性是各种神经退行性疾病的一个公认特征, 靶向抑制SARM1介导的瓦勒变性代表了一种新颖的治疗方法, 具有治疗神经退行性疾病的潜力[22]。抑制SARM1可以通过防止轴突变性和恢复受损的亚稳态轴突, 从而治疗中枢和外周神经系统的轴突病[23]。SARM1也是加速狂犬病引起的瓦勒变性所必需的, SARM1的缺失可延迟狂犬病毒感染神经元的瓦勒变性, 也为治疗感染嗜神经性病毒提供了新途径[24]。由此可见SARM1是一个十分重要的轴突变性因子, 在轴突退化级联中起到关键性作用。



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△: up-regulation; ▽: down-regulation; ▼: down-regulation.

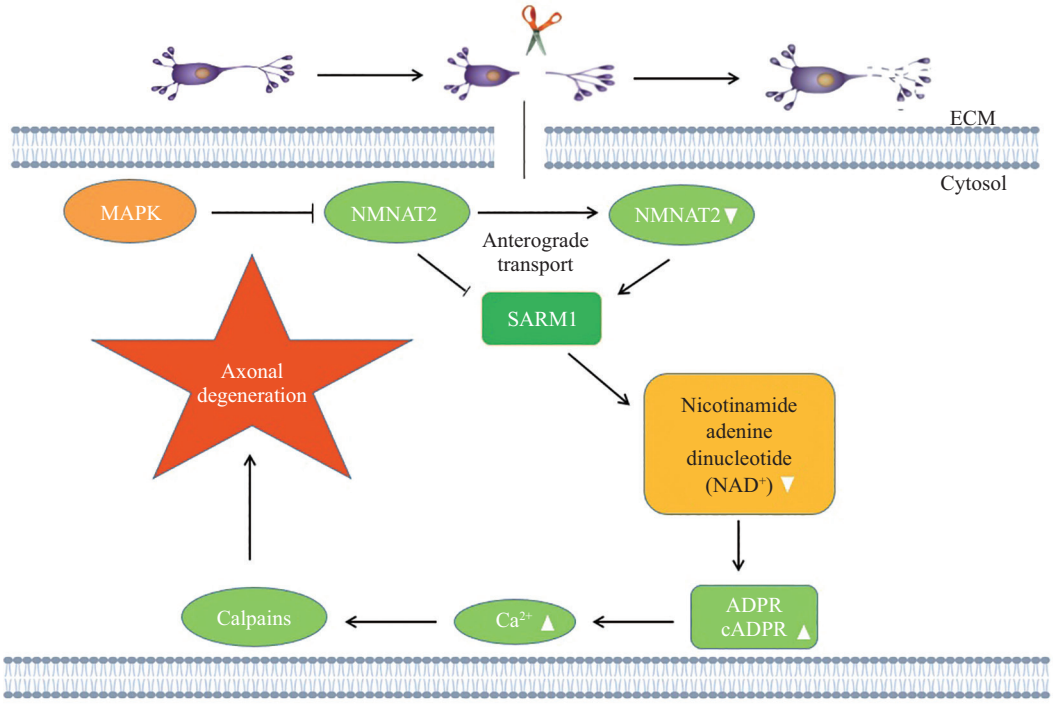
图2　瓦勒变性的分子机制

Fig.2　The molecular mechanism of Wallerian degeneration

SARM1在健康神经元中处于自抑制状态[25]。此外, 烟酰胺腺嘌呤单核苷酸腺苷酰转移酶2(nicotinamide nucleotide adenylyltransferase 2, NMNAT2)是沿轴突向下运输的存活因子, 能将烟酰胺单核苷酸(nicotinamide mononucleotide, NMN)合成为烟酰胺腺嘌呤二核苷酸(nicotinamide adenine dinucleotide, NAD^+)。在健康的轴突中, SARM1活性受到NMNAT2持续传递的限制[26]。切断轴突后, NMNAT2耗竭, 使NMN大量积累, SARM1被激活[27-28], 这是激活丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)通路所必需的。SARM1作用于MAPKKK家族的DLK、MEKK4和MLK2和下游MAPKK家族的MKK4和MKK7, 进而聚合到MAPK家族的JNK(JNK1~3)上, 促进轴突变性[29]。另外, SARM1的TIR结构域本身具有天然的NAD^+酶活性, 可将NAD^+切割成腺苷二磷酸核糖(adenosine diphosphate ribose, ADPR)和环腺苷二磷酸核糖(cADPR)[2]。ADPR与cADPR均可提高钙库膜上ryanodine受体的活性, 引起钙释放机制, 导致胞内钙离子增多, 造成轴突坏死, 引起瓦勒变性[30](图2)。

SARM1也可能在MAPK通路的下游发挥作用。因为在*SARM1*基因敲除的正常神经元中NMNAT2仍在降解[31-32]。同时, 虽然MAPK通路对于损伤依赖性NAD^+耗竭和轴突变性是必需的, 而对于激活的SARM1诱导的NAD耗竭或轴突变性, MAPK通路不是必需的, 这均表明MAPK通路可以在SARM1的上游发挥作用, 以促进SARM1的损伤依赖性激活[33]。WALKER等[32]提出过一个模型: MAPK通路限制了NMNAT2的水平, NMNAT2抑制了SARM1的激活。神经损伤后, NMNAT2的顺行转运被阻断, 导致NMNAT2局部减少。当NMNAT2水平低于临界阈值时, SARM1被激活, 从而降解NAD^+, 增加钙内流来促进轴突变性[32](图3)。

靶向抑制SARM1介导的瓦勒变性为治疗神经退行性疾病提供了广阔的前景。例如, *SARM1*敲除小鼠可以减轻创伤性脑损伤(traumatic brain injury, TBI)[22]和ALS[19]病理模型下轴突脱髓鞘, 阻止瓦勒变性的发生, 并通过逆行营养产生保护作用。GILLEY等[34]发现, ALS患者中富集编码高活性NAD^+酶的*SARM1*等位基因, 这些等位基因无法维持自抑制状态, 当这种*SARM1*等位基因在小鼠神经系统中表达时, 会诱发神经退行性变[35]。在光感受器退化的



△: 上调; ▽: 下调。

△: up-regulation; ▽: down-regulation.

图3 瓦勒变性的模型

Fig.3 The model of Wallerian degeneration

模型中, *SARM1*基因缺失抑制了NMNAT1依赖性视杆和视锥细胞的死亡, 说明SARM1参与了感光细胞的死亡途径, 这为视杆和视锥营养不良患者提供了一个新的药物抑制靶点[11,36]。

3 SARM1对神经炎症的影响

SARM1不仅具有改变轴突退行性的能力, 也能影响先天免疫应答[14]。诱导细胞因子表达是TLR激活后诱导先天免疫的关键步骤。SARM1作为TLR通路的负调节剂, 不仅能抑制TLR3和TLR4通路依赖性促炎因子的释放[37], 还能直接抑制NLRP3炎症小体, 减少caspase-1的激活和IL-1β的产生[38], 抑制先天性免疫应答。*SARM1*基因敲除后会使IL-1β、IL-6、IL-12β和CCL5等细胞因子表达上调[9], 而IL-1β对自闭症患者中mGluR依赖性LTD的形成发挥重要作用[39], 表明SARM1通过影响神经炎症对行为认知产生影响。另外, *SARM1*敲除小鼠的IL-6表达量增加[9], 可调节TBI后的脑炎症反应, 减轻了TBI诱发的神经功能缺陷[40]。

然而, SARM1在一些病理模型下能促进炎症因子的表达。例如在脊髓损伤疾病模型下, 条件性敲除*SARM1*可能会减少神经炎症, 从而促进神经再生[41]。在创伤性轴突损伤模型下, SARM1通过激活下游的JNK通路, 介导CCL2、CCL7、CCL12和CSF1的表达, 阻断JNK通路能有效阻止免疫细胞向受损神经部位募集[42]。在ALS模型中小胶质细胞活化是其标志之一[43], *SARM1*基因敲除可抑制小胶质细胞的活化和细胞因子介导的炎症的产生[44], 由此改善ALS小鼠的认知状态。另外, 濒临死亡的神经元在发育过程中利用SARM1调节先天免疫应答来启动胶质细胞的吞噬作用[42]。总之, SARM1可以通过调节神经炎症的发生和抗病毒细胞因子的表达量来调节先天免疫应答[9]。

4 SARM1的展望

SARM1在哺乳动物的神经系统中广泛表达, 参与神经系统发育、神经元死亡和轴突变性等多种生理和病理过程, 并在其中发挥重要作用。目前仍有一些问题亟待解决, 如: SARM1自抑制的结构基础尚待研究[22]; SARM1抑制剂类药物多为不可逆抑制剂, 无法用于临床治疗, 有效的可逆小分子SARM1抑制剂仍待研究[45]; 抑制SARM1导致的轴突发芽是

否会对神经系统损伤后的可塑性产生不利影响仍待研究[16]。

SARM1在临床上有着巨大的应用前景。*SARM1*基因敲除不仅能够抑制急性损伤, 如外伤性脑损伤等所造成的轴突变性、脱髓鞘和白质萎缩[44], 还能够抑制长春新碱、紫杉醇等化疗药物所引起的亚急性/慢性轴突丧失[45-46]。此外, TNF-α能触发SARM1依赖性轴突变性, 这将神经炎症与轴突变性联系起来[47]。这些发现说明可通过抑制SARM1或者上游分子来治疗那些受到轴突缺失威胁的病人。

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