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MAMs在缺血性脑卒中对NLRP3炎症小体调控作用的研究进展

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摘要 缺血性卒中(ischemic stroke, IS)是导致人类死亡的主要疾病之一, 具有高发病率、死亡率和复发率的特点。IS发生后, NLRP3炎症小体的激活和白细胞介素-1β(interleukin-1β, IL-1β)、IL-18的释放介导了IS后炎症反应。线粒体相关内质网膜(mitochondria-associated endoplasmic reticulum membranes, MAMs)是线粒体与内质网相互物理接触形成的特殊结构, MAMs广泛参与活性氧(reactive oxygen species, ROS)生成、内质网应激(endoplasmic reticulum stress, ERS)、线粒体自噬以及Ca^{2+}稳态等过程, 这些过程与NLRP3介导的炎症反应密切相关。该文以NLRP3炎症小体为枢纽, 重点阐述MAMs在IS中的作用。NLRP3炎症小体和MAMs可能是治疗IS有潜力的靶点, 这为治疗缺血性脑损伤提供了新的研究思路。

关键词 缺血性卒中; 线粒体相关内质网膜; NLRP3炎症小体; 氧化应激; 内质网应激; 线粒体自噬; 钙稳态

Research on the Regulatory Role of MAMs in NLRP3 Inflammasome in Ischemic Stroke

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Abstract IS (ischemic stroke) is one of the leading causes of death in humans, characterized by high incidence, mortality, and recurrence rates. Following IS, the activation of the NLRP3 inflammasome and the release of IL-1β (interleukin-1β) and IL-18 mediate the inflammatory response following the stroke. MAMs (mitochondria-associated endoplasmic reticulum membranes) are specialized structures formed by the physical contact between

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mitochondria and the endoplasmic reticulum, and they are widely involved in processes such as the generation of ROS (reactive oxygen species), ERS (endoplasmic reticulum stress), mitophagy, and Ca^{2+} homeostasis. These processes are closely related to the NLRP3-mediated inflammatory response. This article focuses on the role of MAMs in IS, with the NLRP3 inflammasome as the central theme. The NLRP3 inflammasome and MAMs may represent potential therapeutic targets for treating IS, offering new research insights for the treatment of ischemic brain injury.

Keywords ischemic stroke; mitochondrial-associated endoplasmic reticulum membranes; NLRP3 inflammasome; oxidative stress; endoplasmic reticulum stress; mitophagy; calcium homeostasis

缺血性卒中(ischemic stroke, IS)是因血栓形成导致大脑特定区域血液供应急剧减少甚至中断，从而造成神经元损伤及神经功能障碍的疾病[1]。该病是全球死亡和残疾的主要原因之一，给个人、家庭及社会带来了沉重的经济负担[2]。随着人口老龄化加剧，其疾病负担还将进一步加重[3]。目前，美国食品药品监督管理局(Food And Drug Administration, FDA)批准的唯一治疗IS的方法是重组组织纤溶酶原激活剂(recombinant tissue plasminogen activator, r-tPA)，但需在IS发病后4.5小时内给药。此外，血管内血栓切除术(endovascular thrombectomy, EVT)通过机械清除闭塞血栓以恢复脑血流灌注，也是一种重要的治疗手段[4]。然而，上述治疗方法均存在早期颅内出血风险，且受狭窄治疗时间窗限制，仅有少数患者能从中获益[5-6]。因此，亟待探索新的治疗方案以改善IS的预后。

IS的病理过程涉及多种复杂的机制，包括炎症反应、Ca^{2+}超载、NO过量合成、兴奋性氨基酸(excitatory amino acid, EAA)中毒、氧化应激以及细胞凋亡等[7]。其中，炎症反应在IS的病理生理学中占据关键地位，会进一步加重IS损伤[8]。炎症小体是介导炎症反应的重要细胞内复合体，目前已知的炎症小体包括NOD样受体家族(NOD-like receptors, NLRs)的NLRP1、NLRP2、NLRP3，黑色素瘤2缺乏双链DNA传感器(double-stranded DNA sensors absent in melanoma 2, AIM2)，以及NLR家族含有半胱天冬酶募集结构域蛋白4(nlr family caspase recruitment domain-containing protein 4, NLRC4)。其中，NLRP3炎症小体是NLRs家族中最具代表性和研究最广泛的炎症小体[9]。NLRP3炎症小体参与多种疾病的发病机制，包括阿尔茨海默病(Alzheimer's disease, AD)、II型糖尿病(type 2 diabetes mellitus, T2DM)、痛风(gout)、炎症性肠病(inflammatory bowel disease, IBD)和IS，在固有免疫系统防御中发挥关键作用[9-11]。当IS发生后，核转录因子-κB(nuclear factor kappa-B, NF-κB)和丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)信号通路被激活，促进NLRP3炎症小体表达和激活，导致促炎细胞因子如白细胞介素-1β(interleukin-1β, IL-1β)和IL-18的释放，从而引发炎症反应和神经元损伤，进一步加重IS损伤[12-13]。因此，调节NLRP3炎症小体的激活并减轻炎症损伤，有望成为减轻IS损伤的重要治疗策略。

线粒体相关内质网膜(mitochondria-associated endoplasmic reticulum membranes, MAMs)是线粒体与内质网(endoplasmic reticulum, ER)之间的膜接触位点，参与调控Ca^{2+}稳态、自噬、内质网应激(endoplasmic reticulum stress, ERS)、炎症反应和细胞凋亡等多种细胞生理功能[14]。其中，MAMs参与炎症反应的激活[15]，炎症反应可诱发MAMs功能障碍，而MAMs功能异常亦可加剧炎症反应，这种双向作用可能形成恶性循环，推动心脑血管疾病的病理进展[16]。MAMs还参与炎症小体的形成与调节，在NLRP3炎症小体激活过程中，含有热蛋白结构域(pyrin domain, PYD)的NLRP3、凋亡相关斑点样蛋白(apoptosis-associated speck-like protein containing a caspase-recruitment domain, ASC)等组分可共定位于MAMs[15]。

基于此，本文综合国内外关于NLRP3和MAMs在IS领域的研究进展，简要介绍NLRP3和MAMs的结构及作用，并重点阐述MAMs在NLRP3炎症小体介导的IS炎症中的作用。

1 NLRP3与MAMs

1.1 NLRP3炎症小体的结构

NLRP3炎症小体由NLRP3、ASC和半胱天冬氨酸蛋白水解酶1前体(pro-cysteinyl aspartate specific proteinase 1, pro-Caspase-1)组成[17]。NLRP3由PYD的N-端、含亮氨酸重复序列(leucine-rich repeat,

LRR)的C-端和调节NLRP3活性的核苷酸寡聚化结构域(nucleotide-binding and oligomerization domain, NACHT)组成[18]。NLRP3作为一种胞内模式识别受体(pattern recognition receptors, PRRs), 能够识别病原微生物的病原相关分子模式(pathogen-associated molecular patterns, PAMPs)和损伤相关分子模式(damage-associated molecular patterns, DAMPs)。ASC是一种接头分子, 含有C-端的PYD和半胱天冬酶募集结构域(caspase activation and recruitment domain, CARD), 其CARD与pro-Caspase-1中的CARD通过同型相互作用结合[19-20]。pro-Caspase-1是Caspase-1的非活性前体形式, 是一种半胱氨酸蛋白酶, 其结构包括N-端的CARD、包含大催化亚基(活性位点)的p20结构域和包含小催化亚基的C-端p10结构域[21]。当NLRP3的LRR结构域被激活后, NLRP3通过同型NACHT结构域的寡聚化形成多聚体[22], 随后, NLRP3的N-端PYD与ASC的PYD通过同型相互作用结合, 形成ASC寡聚体, ASC寡聚体进一步通过CARD-CARD相互作用招募pro-Caspase-1, 最终组装成NLRP3炎症小体[19-20](图1)。

1.2 NLRP3炎症小体的活化

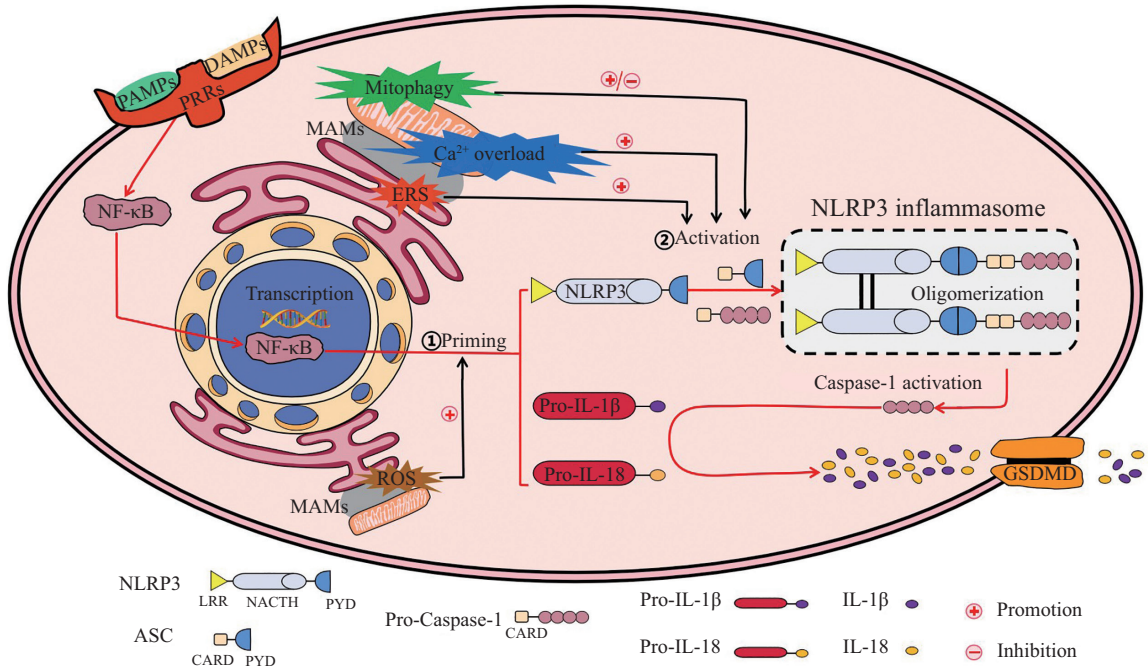
当细胞处于静息状态下, NLRP3炎症小体核心组分蛋白表达水平均处于基础阈值以下[23]。NLRP3炎症小体的活化分为启动与激活两个阶段(图1), 启动阶段需要大量的蛋白质伴侣分子参与, 并且涉及转录与翻译等过程[24-25]。在此阶段, PRRs识别各种PAMPs或DAMPs, 从而诱导NLRP3、Caspase-1和pro-IL-1β的转录上调[25]。在激活阶段, 细胞外毒性物质或者不良应激通过PAMPs和DAMPs信号触发NLRP3寡聚化, 并促进ASC与pro-Caspase-1组装以形成NLRP3炎症小体[25-28]。活化的NLRP3炎症小体会诱导细胞焦亡, 即一种促炎性程序性细胞死亡[29]。

1.3 NLRP3炎症小体的作用

NLRP3炎症小体是细胞内重要的PRRs, 与炎症反应和细胞焦亡密切相关。NLRP3炎症小体主要表达于免疫器官和免疫细胞, 近年来研究发现, 其在中枢神经系统及心血管系统中也有表达, 广泛参与创伤性脑损伤(traumatic brain injury, TBI)、脑出血(intracerebral hemorrhage, ICH)、心肌缺血再灌注损伤(myocardial ischemia-reperfusion injury, MIRI)等疾病的发生和进展[30]。抑制NLRP3炎症小体的活化, 可抑制星形胶质细胞和小胶质细胞的激活, 降低促炎因子表达水平, 从而减轻炎症反应[31]。NLRP3炎症小体在AD、帕金森病(Parkinson's disease, PD)、多发性硬化(multiple sclerosis, MS)等神经退行性疾病中驱动神经炎症[32]。NLRP3炎症小体也与IS有联系, 在IS发生后, NLRP3炎症小体在小胶质细胞和神经元中表达上调, 该过程与线粒体功能障碍有关[33]。同时, NLRP3炎症小体的组装和活化促进了pro-Caspase-1剪切以形成活性Caspase-1, 导致IL-1β和IL-18等促炎细胞因子的成熟和释放, 引起强烈的炎症反应和神经细胞死亡, 加剧IS的损伤[34]。在小鼠大脑中动脉闭塞后再灌注(middle cerebral artery occlusion/reperfusion, MCAO/R)模型中, 缺血侧脑组织中NLRP3的mRNA和蛋白表达量显著上调, 进一步加重脑缺血损伤, 通过药物抑制NLRP3活化可减轻IS损伤[35]。此外, NLRP3炎症小体介导了IS的血脑屏障(blood-brain barrier, BBB)损伤, 通过抑制NLRP3炎症小体激活能减轻IS后BBB损伤[36]。另有研究表明, 抑制NLRP3炎症小体的活化, 可减轻缺氧缺糖诱导细胞模型损伤、脑缺血动物模型的脑损伤以及减少神经血管性并发症的发生[22]。目前, 许多抑制NLRP3炎症小体激活的药物正在被开发用于IS治疗[37]。

1.4 MAMs的结构和功能

线粒体和内质网是细胞中两种重要的细胞器, 它们在功能和结构上紧密相连[38]。自1950年起, 大量研究者通过透射电子显微镜对肝脏细胞进行研究, 在肝细胞中首次观察到内质网−线粒体膜接触结构[39], 从大鼠肝脏中分离出这种结构, 将其命名为MAMs[40]。MAMs是指线粒体外膜(outer mitochondrial membrane, OMM)和内质网的特殊膜接触区域, OMM与ER膜间距离为10~40 nm, 该区域包括系链蛋白、Ca^{2+}转运蛋白和脂质[41]。线粒体和内质网之间的物理相互作用不涉及膜融合, 而是由蛋白质桥接复合物介导的[42]。MAMs结构的完整性对维持细胞器间正常信号传递至关重要, 其关键系链蛋白包括: IP_3R1-GRP75-VDAC1复合物(介导Ca^{2+}转运)、MFN1-MFN2复合物(调控膜动态), 这些复合物为MAMs结构提供稳定性支持, 它们的缺失会破坏MAMs结构的完整性[43]。MAMs在氧化应激、内质网应激、线粒体自噬、Ca^{2+}稳态、炎症反应、细胞凋亡等过程中发挥重要作用[43-45]。在IS中, MAMs功



NLRP3炎症小体的活化。在不良应激刺激条件下, MAMs介导的过量ROS生成会促进NLRP3炎症小体启动阶段的形成, MAMs介导的异常内质网应激(endoplasmic reticulum stress)、线粒体自噬以及Ca^{2+}稳态失衡会影响激活阶段, 进而加剧炎症反应。

Activation of the NLRP3 inflammasome. Under adverse stress stimulation conditions, excessive ROS generation mediated by MAMs promotes the formation of the NLRP3 inflammasome initiation stage. Excessive ERS (endoplasmic reticulum stress), mitophagy and Ca^{2+} homeostasis imbalance mediated by MAMs affect the activation stage, thereby exacerbating the inflammatory response.

图1 NLRP3炎症小体与MAMs介导的ROS生成、内质网应激、线粒体自噬以及Ca^{2+}稳态失衡相关机制

Fig.1 Mechanism of NLRP3 inflammasome and MAMs mediated ROS generation, ERS, mitophagy and Ca^{2+} homeostasis imbalance

能异常可通过上述机制加重神经元损伤, 而靶向调控MAMs的功能可能成为新型IS治疗策略[46]。

2 MAMs在IS后通过NLRP3炎症小体发挥神经保护作用

2.1 氧化应激

氧化应激是导致各种疾病和毒性作用的关键因素, 当活性氧(reactive oxygen species, ROS)和活性氮(reactive nitrogen species, RNS)的过量产生, 不足以被内源性抗氧化剂及时中和时, 就会引发氧化应激[47-48]。ROS是正常细胞代谢过程中产生的一组化学物质, 包括超氧阴离子(O_2^-)、过氧化氢(H_2O_2)、羟基自由基(–OH)等[49]。当受到炎性小体激活剂刺激时, 炎症相关蛋白NLRP3和ASC易位到MAMs, 这个过程可能是由ROS所介导的, ROS积累会诱导细胞中产生IL-1β(图1), 表明ROS可以激活NLRP3炎性小体[50]。IS发生后, 星形胶质细胞和小胶质细胞迅速被激活, 它们通过线粒体和NADPH氧化酶途径产生大量ROS, 导致神经细胞氧化应激损伤[51]。

MAMs与ROS的生成之间存在紧密的联系。硫氧还蛋白相互作用蛋白(thioredoxin-interacting protein, TXNIP)是一种关键调控蛋白, 通过结合硫氧还蛋白(thioredoxin, TRX)并抑制其酶活性, 参与细胞氧化还原信号通路调控[52]。在NLRP3炎症小体激活过程中, TXNIP重新定位至MAMs, 与定位于MAMs上的NLRP3共同参与炎症反应的发生[16]。有研究指出, TXNIP和NLRP3通过氧化还原依赖性相互作用直接结合, 从而激活NLRP3炎症小体。促炎信号和过量ROS也会促进NLRP3炎症小体的形成[53]。在静息细胞中, TXNIP与TRX相互作用, 导致TXNIP无法与NLRP3相互作用, 从而参与NLRP3炎症小体的激活[16]。TRX2是TRX家族成员, 在原核生物和真核生物中广泛表达[54]。研究发现, 氧化应激促使TXNIP与TRX2解离, 从而使TXNIP能够直接与NLRP3结合, 导致NLRP3炎症小体激活和线粒体依赖性细胞凋亡[55-56]。WANG等[57]将PC12细胞经过氧糖剥夺/再灌注(oxygen glucose deprivation/reperfusion, OGD/R)处理后, 发现给予10 μmol/L青蒿素处理可以显著下调NLRP3、

ASC-1、Caspase-1、TXNIP等炎症蛋白的表达, 发挥神经保护作用。从以上研究可以发现, 氧化应激过程中, TXNIP会被定位于MAMs上并介导NLRP3炎症小体的激活, 下调TXNIP的表达, 发挥神经保护作用。

Sig-1受体(sigma-1 receptor, Sig-1R)是一种定位于MAMs上的伴侣受体蛋白, 对维持细胞Ca^{2+}稳态、清除ROS以及维持MAMs的结构和功能稳定性具有重要作用。Sig-1R通过调节线粒体活性氧(mitochondria reactive oxygen species, mtROS)的产生和ROS诱导的下游信号通路转导, 从而减轻线粒体功能障碍导致的病理氧化损伤[58]。ROSEN等[59]在脂多糖(lipopolysaccharide, LPS)诱导的骨髓源性巨噬细胞(bone marrow-derived macrophage, BMDM)模型中发现, 特异性敲除*Sig-1r*基因后IL-6和pro-IL-1β的转录水平显著升高, 且NLRP3炎症小体的激活与pro-IL-1β转录上调相关, 这提示Sig-1R缺陷会导致炎症反应增强。另有研究指出, Sig-1R激动剂可通过抑制缺血或炎症诱导的氧化应激促进细胞存活[60]。WANG等[61]在LPS诱导的炎症反应星形胶质细胞中, 发现给予Sig-1R激动剂SA4503可通过上调核因子E2相关因子2(nuclear factor-erythroid 2-related factor 2, Nrf2)和血红素氧合酶-1(heme oxygenase-1, HO-1)的表达, 减少NO和ROS的产生, 从而减轻氧化应激损伤。ZHAO等[62]通过建立双侧颈总动脉闭塞(bilateral common carotid artery occlusion, BCCAO)的*Sig-1r*基因敲除小鼠模型发现, *Sig-1r*基因敲除后加重小鼠大脑皮层神经元凋亡, 而给予Sig-1R激动剂PRE084能显著改善神经功能并减轻IS损伤。以上研究发现, Sig-1R的表达与NLRP3炎症小体介导的炎症反应有关, 并且可能介导了IS后的氧化应激这一过程。

电压依赖性阴离子通道1(voltage-dependent anion channel 1, VDAC1)是一种定位于MAMs的蛋白[63], 参与线粒体氧化应激、Ca^{2+}信号传递和线粒体自噬等过程[64]。当细胞受到应激条件和凋亡诱导剂等因素干扰时, VDAC1的过表达会导致VDAC1寡聚化形成特定蛋白通道, 使促凋亡蛋白释放到细胞质中, 促进细胞凋亡[65]。VDAC1寡聚化也会增加线粒体膜的通透性, 促进ROS的生成和细胞色素c(cytochrome c, Cyt c)的释放[66]。此外, VDAC1寡聚化还允许mtDNA从VDAC1释放, 两者共同参与NLRP3炎症小体激活组装[67]。而XIE等[68]的研究结果与以上相反, 在高葡萄糖条件下处理的人视网膜毛细血管内皮细胞(human retinal capillary endothelial cell , HRCECs)中发现, VDAC1过表达则会抑制NLRP3炎症小体激活。这提示VDAC1过表达会促进/抑制NLRP3炎症小体的激活, 具体分子机制还需更多研究进行阐述。此外, IS发生后, Ca^{2+}通过MAMs上的IP_3R1-GRP75-VDAC1-MCU途径从内质网进入线粒体, 过量的Ca^{2+}增加线粒体通透性, 最终打开线粒体膜通透性转换孔(mitochondrial permeablity transition pore, MPTP), 导致细胞死亡[46]。

衔接蛋白p66Shc是一种位于MAMs、线粒体和细胞质的蛋白质[69]。氧化应激可促使p66Shc从MAMs转移至线粒体, 进而介导ROS生成[50]。ZHAO等[70]在体外培养的原代肝星状细胞(hepatic stellate cells, HSCs)中发现, 通过siRNA干扰抑制p66Shc的表达可减少mtROS的产生并抑制NLRP3炎症小体的激活, 从而减轻炎症损伤。SPESCHA等[71]在小鼠MCAO/R后, 发现沉默*P66shc*基因可以保持BBB的完整性, 同时降低脑梗死程度, 从而减轻IS损伤。

综上可知, IS发生后, 大量生成的ROS会导致神经细胞氧化应激损伤。此外, ROS也会激活NLRP3炎症小体, 进一步加剧炎症损伤。定位于MAMs的TXNIP、Sig-1R、VDAC1及p66Shc不仅参与ROS生成, 还与NLRP3炎症小体激活密切相关, 同时在IS后的病理生理过程中发挥关键作用。目前关于定位于MAMs的TXNIP、Sig-1R、VDAC1和p66Shc这些蛋白质, 通过调控ROS生成以抑制NLRP3炎症小体激活, 从而减轻IS损伤的研究仍有限。因此, 深入研究TXNIP、Sig-1R、VDAC1和p66Shc通过调控ROS生成以抑制NLRP3炎症小体激活, 进而减轻IS损伤的机制, 可能为治疗IS损伤提供新策略。

2.2 内质网应激

内质网是细胞内最大的细胞器, 主要参与蛋白质合成和加工、运输、脂质和类固醇合成、Ca^{2+}储存以及生命所必需的其他活动[72]。当未折叠或错误折叠的蛋白质在内质网腔内过度积累并超出细胞的处理能力时, 可引起内质网应激[73]。内质网应激参与NLRP3炎症小体激活, 能通过激活NF-κB信号通路促进促炎细胞因子基因的表达, 从而诱导炎症反应[74]。当IS发生后, 内质网应激相关蛋白的表达上调可引起过度的内质网应激并诱导细胞凋亡[75]。研究发现, MAMs对于调节内质网应激发挥了重要作

用[76], 定位于MAMs上的B细胞受体相关蛋白31(B cell receptor-associated protein 31, BAP31)和线粒体融合蛋白2(mitofusin 2, MFN2)可以直接或间接影响内质网应激的相关通路, 维持内质网应激的正常细胞生理功能[77]。

内质网氧化还原酶1α(endoplasmic reticulum oxidoreductase 1α, Ero1α)是一种在缺氧条件下被诱导产生的内质网驻留型氧化酶[78]。在生理条件下, 约75%的Ero1α分布于靠近内质网一侧的MAMs上, 而在缺氧条件下Ero1α则完全定位于MAMs上[79]。当细胞处于缺氧、代谢紊乱或氧化应激等病理状态时, 内质网应激被激活, 上调Ero1α的表达并发挥其功能[78]。在内质网应激期间, Ero1α通过氧化1,4,5-三磷酸肌醇1型受体(inositol 1,4,5-trisphosphate receptor type 1, IP_3R1), 促使位于MAMs中的内质网蛋白44(endoplasmic reticulum protein, ERP44)与IP_3R1结合, 阻断Ca^{2+}通过IP_3R1向线粒体的转运, 同时加速Ca^{2+}从蛋白质二硫键异构酶(protein disulfide isomerase, PDI)中释放, 最终导致mtROS产生过多[50]。研究表明, 内质网应激期间Ero1α表达量显著增加, 并诱导生成过量的ROS。ROS可直接或通过NF-κB通路激活NLRP3炎症小体, 促使IL-1β和IL-18等促炎细胞因子释放, 进而引发炎症反应[80]。JHA等[81]在MCAO/R小鼠模型中发现, 特异性敲除*Ero1α*基因或者使用小分子抑制剂B12-5抑制Ero1α活性, 均可显著降低脑梗死程度并改善神经功能, 表明Ero1α可能是治疗IS的潜在药理学靶点。

促凋亡因子C/EBP同源蛋白(C/EBP homologous protein, CHOP)是定位于MAMs上的蛋白质[46], 在内质网应激诱导的细胞凋亡中起核心作用[82]。作为未折叠蛋白质反应(unfolded protein response, UPR)的主要促凋亡因子, CHOP还通过转录激活Ero1α等多种途径诱导氧化应激。在哺乳动物细胞中, CHOP转录激活Ero1α, 使内质网应激期间ROS的产生显著增加[83]。NAZEAM等[84]发现大鼠高脂高碳水化合物饮食(high-fat/high-carbohydrate diet, HFHCD)可上调NF-κB、IL-1β的表达, 并且伴随着*NLRP3*、*CHOP*的mRNA水平显著增加, 进而引发神经炎症和神经元损伤。SRINIVASAN等[85]将糖尿病大鼠经过建立MCAO模型处理后, 发现与对照组细胞相比, 模型组可显著上调脑组织中CHOP、GRP78等内质网应激相关蛋白以及IL-1β、TNF-α炎症因子的表达, 而给予3-溴-7-硝基吲唑(3-bromo-7-nitroindazole, BNI)能够下调CHOP、GRP78以及促炎因IL-1β、TNF-α的表达, 减少内质网应激, 从而减轻炎症反应, 发挥神经保护作用。

肌醇需求酶1α(inositol-requiring enzyme 1α, IRE1α)是在进化过程中不同物种间高度保守的UPR相关蛋白, 该蛋白定位于MAMs[86-87]。IRE1α是最早被发现的内质网应激感受蛋白, 其作为一种I型跨膜蛋白, 具有激酶和核糖核酸内切酶双重活性[88]。作为分子交叉点, IRE1α通过影响IP_3R1在MAMs上的定位来影响内质网与线粒体之间的信息传递, 从而调节细胞生物能量学[87]。CHEN等[89]将10天的SD乳鼠经过脑缺氧缺血(hypoxia-ischemia, HI)处理后, 发现内源性磷酸化IRE1α的蛋白水平在6小时达到顶峰, HI处理可激活UPR信号通路, 并显著上调TXNIP、IL-1β表达, NLRP3与TXNIP的相互作用增强, 从而促使NLRP3炎症小体活化。而给予IRE1α抑制剂后, NLRP3炎症小体的激活减少, Caspase-1、IL-1β表达水平显著下调, 脑梗死体积减小。这一系列研究结果表明, HI过程中, IRE1α通过激活UPR, 促进NLRP3炎症小体活化, 进而加剧炎症损伤。此外, XU等[90]建立体外HT-22OGD/R细胞模型和大鼠MCAO/R模型后发现, IRE1α的磷酸化水平均显著上调, 加重脑缺血损伤。罗氟司特(roflumilast, Roflu)是一种在神经元细胞中高度表达的选择性磷酸二酯酶4(phosphodiesterase 4, PDE4)抑制剂, 而给予Roflu能够降低IRE1α的磷酸化水平, 对IS诱导的神经元损伤具有保护作用。

上述研究表明内质网应激介导并加剧了IS后脑损伤, 这个过程也与NLRP3炎症小体的激活有关。而内质网应激相关蛋白(如Ero1α、CHOP和IRE1α)的表达上调可促进NLRP3炎症小体的激活, 加剧IS损伤。基于上述研究, 在这里提出: CHOP-Ero1α这对蛋白与IRE1α是否能构成信号通路蛋白系链来抗IS损伤的信号通路, 进而发挥神经保护作用？其具体分子机制仍需进一步研究验证。

2.3 线粒体自噬

线粒体自噬是一种针对功能失调的线粒体进行降解的质量控制途径[91]。当线粒体缺氧、膜去极化和电子传递链(electron transport chain, ETC)受损时, 细胞就会诱导线粒体自噬的发生, 这种特异性细胞器自噬有助于清除受损的线粒体, 维持线粒体质

量[92]。适当的线粒体自噬有助于消除功能失调的线粒体, 防止有害物质的释放, 并维持正常的神经元功能[93]。线粒体功能障碍会导致过量mtROS的产生, 进而激活NLRP3炎症小体[15]。线粒体自噬与NLRP3炎症小体的激活有关, 线粒体自噬能够负向调节NLRP3炎症小体的激活[94]。在IS中, 激活转录因子4(activating transcription factor 4, *Atf4*)基因的过表达可增强线粒体自噬并抑制NLRP3炎症小体介导的炎症反应, 这提示线粒体自噬发挥抗炎作用, 在IS中显示出积极作用[95]。有研究提出线粒体自噬体膜起源于MAMs, 当MAMs结构受损, 线粒体自噬将受到抑制, 这提示MAMs的完整性对线粒体自噬的激活至关重要[96]。

FUN 14结构域的蛋白1(FUN 14 domain-containing 1, FUNDC1)是一种定位于MAMs上的蛋白质, 作为一种线粒体自噬相关受体蛋白在缺氧条件下能够调节线粒体自噬[97-98]。缺氧条件下, FUNDC1发生去磷酸化, 随后与微管相关蛋白1轻链3(microtubule-associated protein 1 light chain 3, LC3)结合并诱导线粒体自噬[97,99]。LI等[100]发现, MCAO/R小鼠相比于对照组, FUNDC1水平显著下调, 并伴随NLRP3、IL-1β和IL-18等炎症蛋白水平显著上调, 并在使用siRNA干扰敲低*Fundc1*基因小鼠中, 发现线粒体自噬被抑制, NLRP3、Cleaved-pro-IL-1β、Cleaved-pro-IL-18等炎症蛋白水平显著下调, 表明FUNDC1能够通过抑制线粒体自噬, 从而抑制NLRP3炎症小体介导的炎症反应。此外, CAI等[101]通过使用CRISPR/Cas9技术构建*Tpa*基因敲除的HT22细胞系并建立OGD/R模型, 发现FUNDC1表达显著下调, 细胞活力降低, 而给予tPA治疗后, FUNDC1表达水平增加, 线粒体自噬增加, 细胞凋亡被抑制。以上研究表明FUNDC1在IS发生后体内外蛋白表达水平下调, 这种下调与NLRP3炎症小体介导的炎症反应有关。

磷酸化酸性簇分选蛋白2(phosphofurin acidic cluster sorting protein 2, PACS-2)是一种定位于MAMs的蛋白质, 该蛋白被鉴定为首个调节MAMs功能的关键蛋白[102-103]。在细胞生理过程中, PACS-2通过调控MAMs结构的完整性及其相关转运蛋白功能, 广泛参与线粒体动力学、内质网应激、Ca^{2+}信号传递及自噬等多种细胞功能[102]。研究发现, PACS-2能够促进MAMs的形成并与自噬相关蛋白Beclin-1结合, 促进其在MAMs上的转位, 进而增强线粒体自噬[104]。另有研究发现, 在人巨细胞病毒(human cytomegalovirus, HCMV)感染期间, 病毒蛋白可促使PACS-2向MAMs转位, 导致MAMs的结构和功能改变, 进而影响炎症反应[16]。此外, YANG等[105]通过将人脐静脉内皮细胞和人肺动脉内皮细胞暴露于缺氧环境中, 经过siRNA特异性敲除MAMs定位的*Pacs-2*处理后, 发现这抑制细胞中缺氧诱导的线粒体Ca^{2+}超载, 导致线粒体膜电位和ATP合成增加, 减少ROS生成, 减轻线粒体损伤。我们推测PACS-2在MAMs上的重新定位还可能间接影响NLRP3炎症小体的活化, 但具体机制尚不清楚。

VDAC1蛋白还参与调控线粒体自噬[104,106]。XIE等[68]使用HRCECs进行实验, 并在高糖诱导下过表达VDAC1, 发现其可显著上调TEN诱导假定激酶1(pten-induced putative kinase 1, PINK1)和E3泛素连接酶parkin(e3 ubiquitin ligase parkin, Parkin)蛋白表达, 显著下调NLRP3表达水平, 这提示VDAC1可通过调控PINK1/Parkin通路介导线粒体自噬, 而这一过程与NLRP3炎症小体有关。综上研究表明, VDAC1在维持线粒体功能、调节线粒体自噬和抑制炎症反应中具有关键作用。

动力相关蛋白1(dynamin-related protein 1, DRP1)是一种定位于MAMs上的蛋白质, 通过GTP依赖的收缩作用介导线粒体分裂[107-108]。DRP1通过调节自噬体的形成, 以DRP1依赖性方式调控线粒体自噬的过程[109]。FENG等[110]研究发现在SD大鼠MCAO/R模型中, 随着再灌注时间增加, DRP1从细胞质募集到线粒体, 并伴随着DRP1的表达上调, 激活PINK1/Parkin介导的线粒体自噬, 从而导致细胞损伤。此外, JIANG等[111]研究发现, 对SD大鼠进行MCAO/R模型诱导后, 与对照组相比, 模型组中NLRP3、ASC、Caspase-1、IL-1β和IL-18的mRNA和蛋白水平以及DRP1的mRNA和蛋白水平显著增加, 而在给予8 mg/kg的氯丙嗪和异丙嗪这两种吩噻嗪类药物后, 与模型组相比, 以上这些蛋白水平显著降低, 促进大鼠神经功能恢复并减小梗死体积, 以减轻大鼠脑损伤。有研究提出, 抑制DRP1介导的线粒体裂变通过抑制NLRP3炎症小体组装以减轻脑缺血损伤[112]。以上结果提示, IS发生后, DRP1的表达上调会激活线粒体自噬, 并且伴随着NLRP3、IL-1β和IL-18等炎症因子的释放, 进一步造成神经细胞死

亡。

MFN2是MAMs组分的关键蛋白[113], 不仅能够维持线粒体功能的完整性, 还参与细胞增殖、线粒体自噬和细胞凋亡等细胞生理过程[114]。研究发现, MFN2在心肌细胞细胞质和线粒体中大量表达, 并通过PINK1-MFN2-Parkin信号通路调节线粒体自噬信号转导来调节线粒体稳态[115]。ZOU等[116]通过对SD大鼠进行心脏骤停/心肺复苏处理后, 发现脑组织皮层中MFN2表达显著下调, NLRP3、IL-1β、p-DRP1表达显著上调, 促进星形胶质细胞或小胶质细胞中NLRP3炎症小体的活化。而在一项关于心肌缺血性损伤模型实验中, 抑制MFN2的表达可降低NLRP3炎症小体的激活水平[117]。*Mfn2*基因的敲低显著抑制了NLRP3介导的信号转导。HUANG等[118]发现对SD大鼠进行MCAO/R模型诱导显著下调MFN2、上调DRP1的表达, 同时线粒体自噬经典蛋白Parkin和OMM标记物TOMM20的共定位显著增加, 这提示MCAO/R后线粒体自噬的增加, 进而促进线粒体损伤, 导致细胞呼吸能力下降。以上这些结果表明, MFN2通过调节线粒体自噬和NLRP3炎症小体的表达, 在细胞应激和炎症反应中发挥重要的保护作用。然而, 目前尚未探索当IS发生后, MFN2在NLRP3炎症小体中的作用, 尚不清楚MFN2是如何具体作用以激活NLRP3炎症小体的。

综上可知, 定位于MAMs上的FUNDC1、PACS-2、VDAC1、DRP1通过调节线粒体自噬, 在IS后的NLRP3炎症小体介导的炎症反应过程中发挥了重要作用, 而MFN2介导了其他缺血模型后NLRP3炎症小体的激活。目前已有研究表明, 在禁食诱导的自噬过程中, Atg5、Atg14、Beclin-1等自噬关键因子会重新定位至MAMs[119], 但MAMs通过线粒体自噬进而调控NLRP3炎症小体的激活机制尚不清楚, 线粒体自噬是一把“双刃剑”, 促进或者抑制线粒体自噬都能够促进NLRP3炎症小体的活化(图1), 但是未来还需要更多研究。因此推测当IS发生后, MAMs可能以适应性方式调节线粒体自噬, 进而调控NLRP3炎症小体的激活, 进而减轻IS损伤。

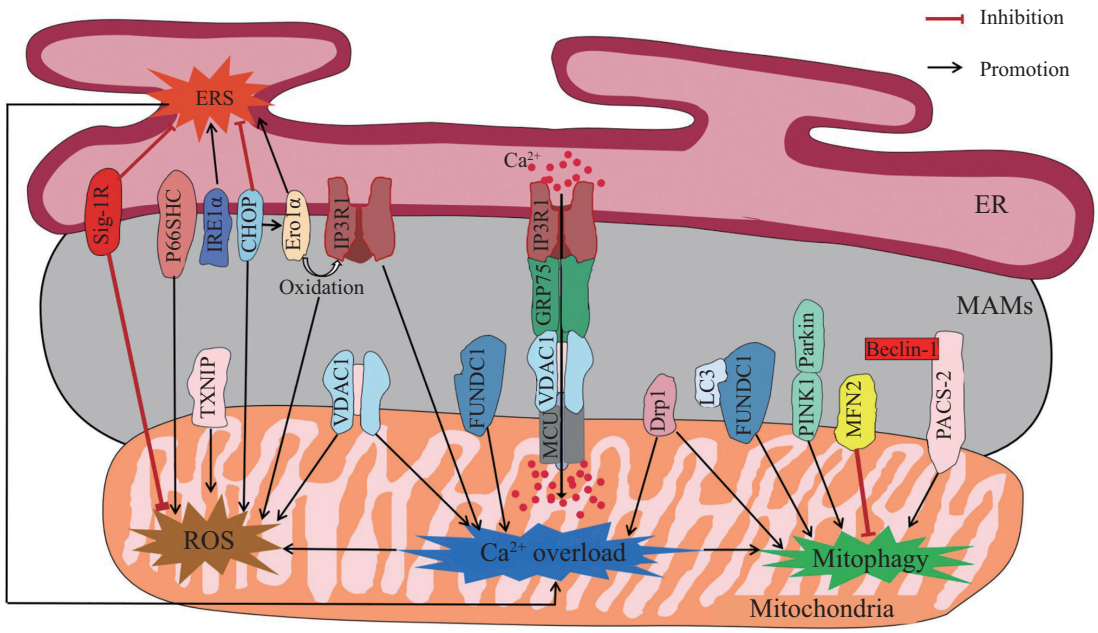
2.4 Ca^{2+}稳态

Ca^{2+}既是细胞信号转导中的关键信使, 也是能量代谢的重要调节因子[120]。线粒体和内质网是关键的Ca^{2+}储存部位, 它们间的物理联系有助于Ca^{2+}从内质网转移到线粒体, 维持细胞正常的Ca^{2+}稳态平衡[121-122]。当细胞处于内质网应激、氧化应激等应激状态时, 线粒体的MPTP过度开放和线粒体膜通透性增加, 导致内质网上的Ca^{2+}异常流向线粒体, 导致内质网上Ca^{2+}耗竭和线粒体Ca^{2+}超载, 最终引起内质网−线粒体之间Ca^{2+}稳态失衡, 破坏线粒体功能[123]。研究发现, Ca^{2+}信号与NLRP3炎症小体存在联系, 胞外Ca^{2+}内流或者胞内内质网释放的Ca^{2+}可以激活NLRP3炎症小体, 引起细胞炎症反应, 导致细胞损伤[124]。此外, Ca^{2+}超载参与了IS病理生理学, 在IS期间, 氧气和葡萄糖缺乏会抑制ATP的产生, 导致膜去极化和电压门控Ca^{2+}通道的激活, 进而引发EAA中毒, 导致细胞损伤[125]。MAMs上的特定蛋白或蛋白复合物可以有效控制线粒体和内质网之间的Ca^{2+}信号传递, 当这些蛋白表达或作用方式发生变化时, 会导致Ca^{2+}转运失衡, Ca^{2+}稳态被破坏。由于MAMs介导的Ca^{2+}信号传递对神经元功能的显著影响, 调控Ca^{2+}稳态已被视为干预神经系统疾病的重要潜在治疗策略[126-127]。

VDAC1可通过控制Ca^{2+}进出线粒体, 影响线粒体内的Ca^{2+}浓度, 从而调节能量代谢和细胞对凋亡刺激的敏感性[66,128]。VDAC1的过表达可促进线粒体与内质网之间的Ca^{2+}转移[43]。IP_3R1、VDAC1和葡萄糖调节蛋白-75(glucose-regulated protein 75, GRP75)这三种蛋白质共同定位于MAMs结构[126]。线粒体Ca^{2+}单向转运蛋白(mitochondrial calcium uniporter, MCU)位于线粒体内膜上, 介导Ca^{2+}从内质网转移到线粒体[46]。研究发现, IP_3R1-GRP75-VDAC1-MCU是介导MAMs上Ca^{2+}从内质网转移到线粒体基质的转运通道[129]。

FUNDC1在调控细胞内Ca^{2+}稳态和MAMs形成中起了关键作用, WU等[130]将小鼠经过心肌细胞特异性*Fudnc1*基因敲除后, 发现MAMs结构被破坏, 这显著降低线粒体和胞质中Ca^{2+}的水平, 增加内质网中的Ca^{2+}水平, 导致线粒体功能障碍。

线粒体分裂主要通过促进DRP1的活化来实现[131], DRP1介导的线粒体分裂影响线粒体内Ca^{2+}信号传递及细胞凋亡敏感性[132]。研究发现, 在MIRI条件下, DRP1和VDAC1之间异常互作导致线粒体功能障碍和心肌细胞死亡, 从而影响线粒体−内质网上的Ca^{2+}信号传递[133]。在亨廷顿病(Huntington’s disease, HD)中, DRP1活性的增加导致线粒体过度碎裂, 从而破坏内质网和线粒体之间的信息传递, 最终破坏MAMs和Ca^{2+}稳态, 引起线粒体功能障碍[134]。MFN2



定位于MAMs上特定蛋白质介导ROS生成、内质网应激(endoplasmic reticulum stress)、线粒体自噬及Ca^{2+}稳态失衡。此外, Ca^{2+}稳态失衡引起的线粒体Ca^{2+}超载与ROS生成、内质网应激和线粒体自噬之间存在串扰。

Some specific proteins located on MAMs mediate ROS (reactive oxygen species) generation, ERS (endoplasmic reticulum stress), mitophagy and Ca^{2+} homeostasis imbalance. In addition, there is crosstalk between Ca^{2+} homeostasis imbalance and ROS generation, ERS and Mitophagy.

图2 MAMs介导的ROS生成、内质网应激、线粒体自噬和Ca^{2+}稳态失衡机制示意图(根据参考文献[107]修改)

Fig.2 The diagram illustrates the mechanisms of ROS generation, ERS, mitophagy and Ca^{2+} homeostasis imbalance mediated by MAMs (modified from reference [107])

通过调节内质网−线粒体接触点, 影响Ca^{2+}从内质网到线粒体的运输[135]。LEAL等[136]将HEK293细胞经过特异性敲低*Mfn2*处理后, 发现线粒体与内质网接触面有所增加, 并且这促进内质网向线粒体的Ca^{2+}转移。

综上可知, Ca^{2+}稳态介导了IS后的病理过程, Ca^{2+}稳态失衡会进一步激活NLPR3炎症小体, 进而引发炎症反应。IP_3R1-GRP75-VDAC1-MCU、FUNDC1、DRP1、VDAC1、MFN2这些蛋白介导了MAMs上的Ca^{2+}信号传递(图2)。

3 结语与展望

IS发生后, 脑组织神经元中NF-κB信号通路转导的激活, 介导了炎症反应中NLRP3炎症小体激活与表达, 此外, MAPK信号通路也参与了这一过程[35]。Toll样受体4(toll like receptor 4, TLR4)与髓样分化因子88(myeloid differentiation factor 88, MyD88)结合, 触发NF-κB的激活, 与NLRP3炎症小体协调神经炎症, 在IS后造成炎症损伤[137]。研究发现, 使用NF-κB、MAPK、TLR4受体抑制剂可抑制神经元NLRP3炎症小体的表达和激活, 进而减轻IS后的炎症反应, 减轻脑损伤[35,138]。NLRP3炎症小体在IS疾病中的作用与临床应用主要体现在其对炎症反应的调控, 通过阻断NLRP3炎症小体的激活或其下游信号通路, 减轻炎症反应, 这是一种治疗IS疾病潜在的治疗策略[139]。有临床研究显示, 入院24 h内的急性IS患者血清炎症生物标志物NLRP3的血清浓度水平与恶性脑水肿风险增加显著相关[140]。现已经成功开发出MCC950和OLT1177等NLRP3炎症小体抑制剂, 并且其在动物模型中表现出显著的神经保护作用, 并已进入临床试验阶段[139]。

研究表明, 在IS发生后, 多种病理生理过程中的信号通路可协同作用, 进而导致细胞损伤。有研究指出, Ca^{2+}信号通过调控ROS生成位点的活性, 进而调节细胞内ROS水平, 从而影响位于质膜、线粒体和内质网中的Ca^{2+}转运蛋白的表达[141]。内质网应激也可能通过诱导Ca^{2+}超负荷, 从而抑制蛋白质合成并促进细胞凋亡[142]。在调节线粒体自噬过程中Ca^{2+}信号也发挥了重要作用, 失调的Ca^{2+}信号传递可以破坏线粒体自噬, 导致有缺陷的线粒体积累, 加剧

了氧化应激并促进了细胞死亡途径的激活[143]。综上可知，Ca^{2+}信号与ROS、内质网应激、线粒体自噬过程都有联系，并且氧化应激、内质网应激和线粒体自噬之间也存在串扰(图2)。此外，MAMs参与NLRP3炎症小体的形成与调节，NLRP3、ASC等炎症蛋白组分定位于MAMs。因此，一方面可以通过调控MAMs上的蛋白质，以上调、下调相关蛋白表达水平或者以蛋白−蛋白间互作的方式影响氧化应激、内质网应激、线粒体自噬以及Ca^{2+}稳态等细胞生理过程来调节NLRP3炎症小体的表达与激活，从而减轻IS损伤。另一方面也可以将ROS生成、内质网应激、线粒体自噬这三个过程共同联系起来，通过MAMs调控Ca^{2+}信号调节NLRP3炎症小体介导的炎症反应激活，进而减轻IS损伤。

现已有研究提出将MAMs上的系链蛋白的超微结构与蛋白质组学特征作为生物标志物，可实现IS的早期识别与病理评估；靶向调节MAMs上相关蛋白，可在IS后期提升神经功能评分，为临床治疗提供新的治疗靶点[144]。因此，深入探索MAMs相关蛋白在IS过程NLRP3炎症小体介导炎症反应中的功能，有助于寻找减轻IS损伤的新方法。然而，由于IS发生机制的复杂性质，通过调控MAMs介导的氧化应激、内质网应激、线粒体自噬以及Ca^{2+}稳态，以降低NLRP3炎症小体的启动水平并减弱其活化程度的具体分子机制尚需深入研究。随着细胞和分子生物学技术的不断发展，MAMs的调控机制将逐步被阐明，通过靶向调控MAMs相关蛋白来调节氧化应激、内质网应激、线粒体自噬以及Ca^{2+}稳态，从而减轻NLRP3炎症小体介导的神经炎症损伤，有望成为治疗IS新的方法。

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