·综述·

类泛素化修饰在缺血性脑卒中的机制及潜在治疗靶点

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摘　要：缺血性脑卒中（IS）是全世界第二大死亡原因，具有高发病率与高致残率的特点。类泛素小分子（SUMO）修饰是一种重要的蛋白质翻译后修饰，在IS的发生发展中至关重要。本文从SUMO化修饰调控神经炎症、线粒体动力学、细胞凋亡、氧化应激和血管生成以及总结靶向SUMO化修饰治疗IS潜在靶点等方面，综述SUMO化修饰与IS的关系，为临床治疗IS提供新的方向。

关键词：缺血性脑卒中；类泛素化修饰；病理机制；治疗靶点；综述
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The Mechanism and Potential Therapeutic Targets of SUMOylation in Ischemic Stroke

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Abstract: Ischemic stroke (IS) is the second leading cause of death worldwide, characterized by high morbidity and disability rates. Small ubiquitin-related modifier (SUMO) modification, a crucial post-translational modification, plays a vital role in the pathogenesis of IS. This review elucidates the relationship between SUMOylation and IS by detailing how SUMOylation regulates key pathological processes, including neuroinflammation, mitochondrial dynamics, apoptosis, oxidative stress, and angiogenesis. Furthermore, it summarizes potential therapeutic targets of SUMOylation for IS treatment, aiming to provide new directions for clinical management.

Key words: ischemic stroke; SUMOylation; pathological mechanism; therapeutic target; review
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缺血性脑卒中（ischemic stroke，IS）又称为脑梗死，是一种动脉闭塞造成脑部血流量减少或中断，导致脑组织损伤的一种脑血管疾病[1]，占所有脑卒中的60%~70%，是全世界第二大死亡原因[2]。据统计[3]，自2015年以来，脑卒中已成为我国居民致死与致残的首要原因，其患病人数居世界首位，给家庭和社会带来了沉重的负担[4]。目前临床上多采用静脉溶栓和血管内取栓的方法治疗IS，但这两种方法均有时间窗的限制[5-6]。除血管再通外，药物如抗血小板药物和神经保护剂，也多用于治疗IS，但是药物治疗会导致出血风险明显增加，并且引起器官的损伤以及过敏反应等并发症[7-8]。因此，迫切需要新的治疗方法来改善IS引起的神经损伤。IS的发病机制较为复杂，早期缺血性损伤造成

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细胞死亡，随后再灌注会诱导氧化应激、炎症反应、线粒体功能障碍、兴奋性毒性以及钙超负荷等一系列病理级联反应，进一步导致大脑组织以及功能的损伤[9]。

类泛素小分子（small ubiquitin-related modifier，SUMO）修饰是一种广泛存在于真核细胞中的翻译后修饰过程。SUMO化修饰由SUMO蛋白通过酶促级联反应共价结合到靶蛋白的赖氨酸残基上，调控靶蛋白的构象、亚细胞定位以及稳定性，进而参与细胞死亡、增殖、分化、代谢和信号转导等一系列重要生物过程[10]。近年来研究发现，SUMO化修饰不仅能调节大脑发育、神经元成熟和突触形成，还可进一步参与IS的病理级联反应，影响IS的发生发展[11]。本篇综述旨在总结SUMO化修饰在IS中的机制以及靶向SUMO化修饰的治疗，为IS寻找新的临床治疗靶点提供依据。

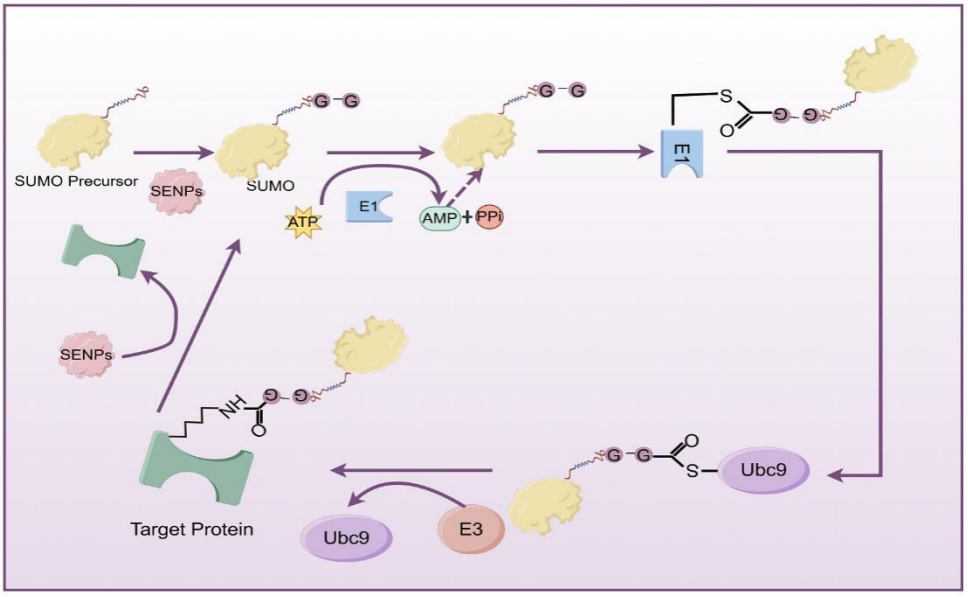
1　SUMO化修饰概述

1.1　SUMO蛋白

SUMO蛋白是一类蛋白翻译后修饰因子，目前在哺乳动物中鉴定出5种类型：SUMO1、SUMO2、SUMO3、SUMO4以及SUMO5，在脑内主要存在SUMO1、SUMO2与SUMO3这三种亚型，而SUMO2和SUMO3序列高度相似，常合称为SUMO2/3[12]。其中，SUMO1经SUMO特异性蛋白酶（sumo-specific proteases，SENPs）水解，暴露C端二甘氨酸基序，进而与目的蛋白结合，影响蛋白质的聚集。SUMO2/3通过SUMO靶向泛素连接酶介导泛素蛋白与目的蛋白结合，促进蛋白质的降解[13]。

1.2　SUMO化修饰的调控机制

SUMO化修饰是一个高度动态且可逆的过程，主要包括激活、结合以及去除3个过程[14]。首先SUMO以非活性前体蛋白的形式存在，其C端有一段较短的延伸肽链，在SENPs的作用下水解切割这段肽链，暴露C端二甘氨酸基序，形成成熟的SUMO蛋白。随后，E1激活酶异二聚体通过水解三磷酸腺苷，生成一磷酸腺苷（adenosine monophosphate，AMP），AMP与SUMO分子C末端的羧基形成高能的混合酸酐键。然后，SUMO分子被激活转移至E1激活酶的半胱氨酸巯基，与其形成一个高能硫酯键。之后SUMO分子转移至E2偶联酶（ubiquitin-conjugating enzyme 9，Ubc9）半胱氨酸残基位点上，最后通过E3连接酶或Ubc9催化在SUMO和靶蛋白上的赖氨酸残基之间形成异肽键，完成SUMO化修饰。修饰结束后，SENPs催化SUMO蛋白从其底物中解偶联，进行去SUMO化[15]（图1）。



SUMO Precursor：small ubiquitin-related modifier Precursor；SENPs：SUMO-specific proteases；ATP：adenosine triphosphate；AMP：adenosine monophosphate；ubc9：ubiquitin-conjugating enzyme 9.

图1　SUMO化修饰的调控机制

Fig. 1　Regulatory mechanisms of SUMOylation

SUMO化修饰过程主要由E1激活酶、E2偶联酶、E3连接酶以及SENPs共同参与。其中哺乳动物只存在一种E1激活酶和一种E2偶联酶参与SUMO化修饰,而存在多种E3连接酶以及SENPs。这提示SUMO化修饰的多样性可能来源于E3连接酶以及SENPs种类的多样性[16]。SUMO E3连接酶主要包含是3个家族Ran结合蛋白2(ran binding protein 2,RanBP2)、活化STAT蛋白抑制剂(protein inhibitor of activated stat,PIAS)和锌指蛋白45(zinc finger protein 45,ZNF45)。不同的SUMO E3连接酶催化SUMO蛋白转移至目的蛋白上的方法不同。RanBP2与Ubc9和SUMO1修饰的RanGAP1结合形成稳定的复合物,进而招募第二个携带SUMO蛋白的Ubc9(Ubc9~SUMO),高效催化SUMO转移到目的蛋白上[17]。PIAS包括N端SAP结构域、Pro-Ile-Asn-Ile-Thr基序(PINIT)基序、SP-PING结构域、SIM和富含丝氨酸/苏氨酸的C端区域。其中SP-RING和SIM结合Ubc9与SUMO,而PINIT基序和C端招募底物蛋白靠近Ubc9~SUMO,进而提高SUMO转移至底物蛋白的效率[18]。ZNF45包括N端的两个SIM以及PxRP基序。其中一个SIM与Ubc9~SUMO结合,将其定位在一个闭合的活性构象里,另一个SIM与Ubc9背面的"支架SUMO"连接,而PxRP基序内ZNF45的Arg40直接与Ubc9的Asp19和His20相互作用,提高其稳定性。以此协助SUMO蛋白转移至目的蛋白上[19]。SENPs家族由SENP1至SENP7等七种蛋白组成,其中SENP1和SENP2不仅能切割激活SUMO蛋白,还能对SUMO1和SUMO2/3进行去修饰,而SENP3、SENP5、SENP6、SENP7只可将SUMO2/3与靶蛋白解离[20]。

2 SUMO化修饰在脑卒中发生发展中的作用

2.1 SUMO化修饰对小胶质细胞介导神经炎症的调控

小胶质细胞是普遍存在于中枢神经系统中的一类疫细胞,并且是响应病理性损伤的第一道防线[21]。在IS发生后,小胶质细胞主要是促炎M1型和抗炎M2型[22]。在IS的不同时期,小胶质细胞的表型也有所不同。在急性期以及亚急性期,小胶质细胞在缺血后被激活,主要表现为促炎M1型,释放促炎细胞因子,如肿瘤坏死因子-α、白细胞介素-1β、白细胞介素-6和趋化因子。这些介质会加剧神经炎症并造成神经元损伤;在慢性期,小胶质细胞向M2表型极化,分泌抗炎细胞因子,促进神经发生、血管生成和组织修复[9]。

NOD样受体蛋白3(NLRP3)炎性小体活化,是IS中触发小胶质细胞介导炎症的关键步骤。有研究表明,小胶质细胞中瞬时受体电位通道1(transient receptor potential channel1,TRPC1) SUMO化水平明显增高,增强了TRPC1与β-抑制蛋白2(arrestin-β 2,ARRB2)的结合。这一过程导致NLRP3/ARRB2复合物的解离,引起NLRP3炎性小体活化。而NLRP3活化能够促进趋化因子表达,增加白细胞的浸润,最后加剧IS的炎症反应[23](表1)。膜联蛋白A1(annexin A1,ANXA1)是一种重要的糖皮质激素调节蛋白,通过限制中性粒细胞募集和促炎介质的产生,进而发挥抗炎的作用[24]。近年来有研究发现,ANXA1 SUMO化修饰与IS小胶质细胞表型的转变密切相关。IS发生后,SUMO2与ANXA1第113、161和257位的赖氨酸3个位点的结合减弱,ANXA1 SUMO化水平降低。而将ANXA1-SUMO2的腺病毒转染至氧糖剥夺/复氧复糖(oxygen-glucose deprivation/reperfusion,OGD/R)处理的小胶质细胞中,能够增强IκB激酶α(inhibitor of κB kinase-α,IKKα)和自噬受体NBR1之间的相互作用,促进IKKα降解。这一过程能有效抑制核因子κB(nuclear factor kappa-B,NF-κB)信号通路,驱动小胶质细胞向M2表型转变[25]。另外,有研究显示,SENP6介导ANXA1去SUMO化阻断了IKKα的降解,从而激活了NF-κB信号通路,促进小胶质细胞中炎症因子的释放,加重了IS的神经损伤[26]。丝裂原活化蛋白激酶7(mitogen activated protein kinase kinase7,MKK7)是细胞因子信号传导的介质,介导c-Jun氨基末端激酶(c-Jun N-terminal kinase,JNK)和p38丝裂原活化蛋白激酶激活,引起细胞因子基因的转录激活,最终产生细胞因子[27]。在IS中,SENP3磷酸化水平增高,抑制SUMO2/3与MMK7的结合,进而激活了TLR4/p-JNK信号通路,促进小胶质细胞向促炎表型极化[28]。此外,c-Jun SUMO化修饰在IS小胶质细胞介导炎症中发挥重要作用。在OGD/R处理的小胶质细胞中,SENP3将c-Jun与SUMO2/3解偶联,增强了c-Jun转录活性,促进其与c-Fos的二聚化,形成激活蛋白1

（activatorprotein-1，AP-1）复合物，激活的AP-1复合物结合到DNA上，启动大量炎症和凋亡相关基因的转录，从而增强小胶质细胞中促炎因子的产生[10]。

2.2　线粒体动力学

线粒体动力学是指线粒体通过持续地分裂与融合，以维持其正常形态的动态过程。分裂过程的核心蛋白是动力相关蛋白1（dynamin-related protein 1，DRP1）。当分裂信号出现后，细胞质中的DRP1募集至线粒体外膜，并组装成环状寡聚体。随后，DRP1与线粒体裂变蛋白1、线粒体裂变因子（mitochondrial fission factor，MFF）等多种因子协同作用，促使线粒体断裂。而线粒体融合主要是由线粒体融合蛋白1/2（mitofusin 1 / 2，Mfn1/2）和视神经萎缩蛋白1（optic atrophy 1，Opa1）介导完成[29]。线粒体动力学是IS的发病机制之一，当IS发生后，线粒体动力学失衡，过度破碎的线粒体中呼吸复合物受损，ROS生成增加，线粒体膜电位异常，并释放细胞色素C，激活半胱天冬酶（cysteine-containing aspartate-specific proteases，caspase）蛋白酶家族，启动程序性细胞死亡[30]。

近年来大量研究发现，Drp1是SUMO化修饰的靶标，并且其SUMO化修饰在IS中发挥关键作用。不同SUMO蛋白与Drp1的偶联，产生的效果也有所不同，其中SUMO1修饰Drp1能够增强Drp1的稳定性，加剧线粒体分裂，而SUMO2/3修饰Drp1与其相反，能够抑制Drp1募集至线粒体外膜与MFF结合，抑制线粒体的裂变[31]。有研究表明，在OGD/R处理的细胞中发现，SENP3促进SUMO2/3与Drp1解偶联，增强了Drp1与B淋巴细胞瘤-xl（Bcl-xL）的相互作用。而这一作用可能导致Bcl-xL构象改变，最终促进细胞死亡[32]。另外，线粒体E3泛素连接酶1下调，可能通过调节Drp1与SUMO1结合增强以及Mfn2的泛素化，导致线粒体裂变增加，加剧了大脑中动脉栓塞/再灌注（middle cerebral artery occlusion/ reperfusion，MCAO/R）大鼠的神经功能损伤[33]。此外，去乙酰化酶sirt3 SUMO化修饰与线粒体分裂密切相关。Sirt3与SUMO1结合发生SUMO化修饰，该修饰能够抑制Sirt3的去乙酰化酶活性，导致Drp1表达水平上调，OPA1下调，促进线粒体分裂[34-35]。而在MCAO/R大鼠中，Sirt3 SUMO化水平升高，线粒体ATP含量降低，膜电位水平异常。因此推测Sirt3 SUMO化修饰引起的线粒体功能障碍可能是通过调节线粒体分裂引起的，进而造成MCAO/R大鼠的神经损伤[36]。

2.3　细胞凋亡

细胞凋亡是IS后神经元死亡的主要发病机制之一。生理条件下，细胞凋亡在促进突触的发生、可塑性以及神经的发生中发挥重要作用，并且是维持神经系统发育过程中功能完整性必不可少的部分。然而IS发生后会导致异常的细胞凋亡，引起过度的神经元、神经胶质细胞死亡以及突触功能的破坏[37]。

ANXA1与IS的神经凋亡密切相关，ANXA1结合p53并上调p53转录活性，从而促进促细胞凋亡Bid表达和caspase-3凋亡途径激活，最终导致IS后神经元凋亡[38]。而上调ANXA1 SUMO化修饰，能逆转这一情况。有研究发现，阻断SENP6介导的ANXA1的去SUMO化，抑制了瞬时受体电位通道7和蛋白激酶C对ANXA1磷酸化修饰，阻碍ANXA1进入细胞核与p53的结合，抑制了caspase-3通路的激活，减少了OGD/R原代神经元的细胞凋亡[39]。混合谱系激酶3（mix lineage kinase 3，MLK3）属于丝裂原活化蛋白激酶超家族，是IS的关键调节因子[40]。Jiang等[41]发现在IS后PIAS3与MLK3相互作用增强，促进MLK3 SUMO化，刺激其下游p38/JNK级联反应，增加了caspase-3的表达，导致细胞凋亡。另外，受体相互作用蛋白激酶1（receptor-interacting protein kinase1，RIPK1）是一种在细胞内部广泛表达的丝氨酸/苏氨酸蛋白激酶，在IS的细胞凋亡中发挥关键作用。当IS发生后，激活的RIPK1招募死亡结构域相关蛋白FADD，FADD进一步招募激活caspase-8，并且三者共同形成复合物IIa，从而促进细胞凋亡[42]。而RIPK1的去SUMO化修饰能够调控RIPK1活性，抑制细胞凋亡。Yan等[43]发现在SENP1缺陷的细胞中，RIPK1 SUMO化水平明显升高，RIPK1活性增强，促进了细胞凋亡的发生。这些均提示RIPK1 SUMO化修饰可能影响IS诱导的细胞凋亡。

2.4　氧化应激

氧化应激是指过量活性氧（reactive oxygen species，ROS）产生，导致体内氧化系统与抗氧化系统失衡，而刺激机体形成的一种有害状态，是脑卒中重要的发病机制之一[44]。当脑内ROS过度积累时会破坏血脑屏障完整性，导致微循环障碍，并且

诱发脂质、蛋白质和DNA的氧化损伤,从而导致神经元死亡,进一步加重了脑组织损伤[45]。

SUMO化修饰通过控制ROS的产生和清除,参与调节ROS稳态,是改善氧化应激的潜在治疗靶点[46]。PIAS3是SUMO E3连接酶,参与蛋白的SUMO化修饰。有研究发现,敲低PIAS3,抑制H_2O_2处理海马神经元细胞的SUMO化修饰,能够降低ROS水平,减少氧化应激诱导的细胞凋亡[47]。另外,抗氧化相关因子的SUMO化修饰与IS的氧化应激密切相关。核因子E2相关因子2(nuclear factor-erythroid2-related factor2,Nrf2)是抗氧化反应的核心调控因子,当Nrf2与Kelch样环氧氯丙烷相关蛋白-1解离时激活,转移到细胞核中,与抗氧化反应元件ARE的相应位点结合,从而激活该途径下游的抗氧化酶。上调Nrf2表达,能够抑制氧化应激和神经元细胞凋亡,对脑缺血再灌注损伤起保护作用[48]。其中SUMO2/3可与Nrf2的赖氨酸残基533结合进行SUMO化修饰,影响其抗氧化作用。Xia等[49]发现在缺血再灌注的动物以及细胞模型中,Nrf2 SUMO化水平降低,促进Nrf2的降解,氧化应激水平明显升高。过氧化物氧化还原酶6(peroxiredoxin6,Prdx6)是过氧化物氧还蛋白家族的一员,它不仅能清除细胞中ROS,还可以降低磷脂氢过氧化物,修复氧化应激引起的膜损伤[50]。有研究表明,促进Prdx6表达,明显减轻了IS中氧化应激引起的神经损伤[51]。而Prdx6与SUMO1结合,会影响其稳定性,抑制抗氧化作用[52]。提示Prdx6 SUMO化可能在IS氧化应激中发挥重要作用。

2.5 血管生成

脑血管阻塞或狭窄会导致脑部血流量不足,引发脑组织能量耗竭、氧气与营养物质缺乏,从而触发多个神经元死亡途径的激活,是IS重要的发病原因之一。血管再生是通过新血管的形成和生长,促进基础血流量的恢复,改善脑组织代谢以及缺血缺氧状态,进而促进神经功能的恢复[53]。有研究发现,SUMO1转基因小鼠,血管内皮生长因子以及CD31阳性细胞明显增多,具有更高的血管新生能力[54]。锌指蛋白580(zinc finger protein580,Zfp580)是一种转录因子,参与缺氧引起的血管生成。有研究发现,敲减MCAO/R小鼠中Zfp580基因,促进内分泌循环中胰岛素样生长因子1(insulin-like growth factor 1,IGF-1)的分泌,而IGF-1可以穿过血脑屏障参与血管生成[55]。这提示抑制Zfp580可能是改善IS恢复的靶点。Hoffmann等[56]发现,Zfp580 SUMO化修饰能够抑制Zfp580活性,而敲低Zfp580能明显增加MCAO/R小鼠血管密度和血管面积更高,减少病灶尺寸。这表明Zfp580活性下降有助于IS血管生成。SUMO化修饰可能在其中发挥重要的调控作用(表1)。

表1 缺血性脑卒中的类泛素化修饰靶点

Table 1 Identified Targets of SUMOylation in Ischemic Stroke

Mechanism	Targets	Functional effects	References
Microglia-mediated neuroinflammation	TRPC1	SUMOylation of TRPC1 promotes inflammation	[23]
	ANXA1	SUMOylation of ANXA1 inhibits inflammation	[25-26]
	MMK7	Inhibiting MMK7 SUMOylation promotes inflammation.	[28]
	c-Jun	Inhibiting c-Jun SUMOylation promotes inflammation.	[10]
Mitochondrial dynamics	Drp1	Inhibiting Drp1 SUMO2/3 modification induces cell death	[32]
		Drp1 SUMO1 promotes modification mitochondrial fission	[33]
	Sirt3	SUMOylation of Sirt3 promotes mitochondrial fission	[34-35]
Apoptosis	ANXA1	ANXA1 SUMOylation inhibits apoptosis	[39]
	MLK3	MLK3 SUMOylation promotes apoptosis	[41]
	RIPK1	RIPK1 SUMOylation promotes apoptosis	[42-43]
Oxidative stress	Nrf2	Inhibiting of Nrf2 SUMOylation promotes oxidative stress	[49]
	Prdx6	Prdx6 SUMOylation inhibits oxidative stress	[52]
Angiogenesis	Zfp580	Zfp580 SUMOylation promotes angiogenesis	[56]

3　靶向SUMO化修饰治疗IS

3.1　小分子保护剂

SUMO化修饰是一个高度动态的过程，其平衡状态主要受SENPs这一关键因子调控，进而参与IS的发生发展[15]。因此，寻找靶向SENPs的相关治疗方式，对于治疗IS具有重要意义。根据定量高通量测试筛选出SENP2抑制剂，依布硒和6-硫鸟嘌呤。将依布硒和6-硫鸟嘌呤加入OGD处理细胞以及MCAO小鼠中，能明显增强脑内SUMO化水平，并且细胞活力得到提升[57]。有研究发现，通过双报告基因检测筛选出类视黄醇AHPN以及组蛋白脱乙酰化酶（histone deacetylase ，HDAC）抑制剂，能够有效抑制OGD处理神经元细胞凋亡，并且上调SUMO水平[58]。另外，低浓度的AHPN可以抑制小胶质细胞的激活，一氧化氮合酶、趋化因子以及单核细胞趋化蛋白-1明显下调[59]。这也提示AHPN可能通过抑制小胶质细胞的激活改善IS，并且靶向SUMO化修饰。筛选出的HDAC抑制剂包括罗米地辛、帕比司他、恩替司他、贝利司他和普拉司他。其中，帕比司他和恩替司他能明显改善MCAO小鼠脑梗死面积以及运动功能[60]。这进一步提示帕比司他和恩替司他可能是靶向SUMO化修饰的潜在治疗IS靶点。但在临床中这两种药物主要用于治疗癌症，而关于神经保护方面的研究还未出现。此外，鸟苷是一种与神经保护相关的内源性神经调节剂。Dal-Cim等[61]发现鸟苷可以抑制OGD诱导星形胶质细胞产生的氧化损伤，促进谷氨酸摄取，发挥神经保护作用。而鸟苷还可以上调星形胶质细胞中的SUMO化水平[62]（表2）。这提示鸟苷可能是通过调节星形胶质细胞SUMO化修饰，改善IS的损伤。

3.2　miRNA调控

MicroRNA是一类长度约为22个核苷酸的短链、非编码RNA分子，它可与靶基因的3′-非翻译区（3′-UTR）结合并调节基因表达。其中miR-188-5p在IS中发挥神经保护作用。有研究发现，miR-188-5p靶向与*SENP3*的3′-UTR结合，抑制*SENP3*的表达，增强了SUMO2/3修饰的水平，神经元凋亡明显减弱[63]。这也为临床治疗IS提供了新思路。在机械取栓或者静脉溶栓后，配合脑内递送miR-188-5p，可能是保护神经元免受再灌注损伤的一种治疗模式。Ubc9作为唯一E2连接酶，参与SUMO蛋白与靶蛋白的赖氨酸残基结合的调控。有研究表明，Ubc9过表达的神经干细胞移植入缺血病灶处，SUMO化水平增强，神经元凋亡明显减少[64]。而miR-214可以负向调控Ubc9，并且在缺血再灌注模型中miR-214水平下调[65-66]。这提示抑制miR-214可能是调控SUMO化修饰治疗IS的潜在靶点。另外，miR-133a-3p也是治疗IS的潜在靶点。Taghvaei等[67]发现miR-133a-3p能够与*SENP1*的3′-UTR结合，下调*SENP1*表达，SUMO化修饰增强。而增强miR-133a-3p后，腺苷酸激活蛋白激酶（adenosine monophosphate-activated protein kinase，AMPK）磷酸化水平下降，进而激活哺乳动物雷帕霉素靶蛋白（mammalian target of rapamycin，mTOR），抑制缺血诱导的自噬[68]。其中AMPK具有SUMO蛋白结合位点，SUMO化水平增高时，AMPK对mTOR抑制作用减弱[69]。这提示miR-133a-3p对于AMPK/mTOR调控治疗IS的过程，可能伴随着AMPK SUMO化水平的增强。

3.3　SUMO化修饰特异性抑制剂

SUMO化修饰特异性抑制剂是一类通过干扰SUMO蛋白与靶蛋白结合过程，从而调控细胞功能的分子化合物。其中TAK-981作为一种SUMO化修饰抑制剂，与神经系统恢复密切相关。有研究发现，在脑内注射TAK-981后，SUMO2/3偶联水平下降，抑制小胶质细胞中CD36表达，血肿清除速度减缓，阻碍了脑出血神经功能恢复[70]。其中CD36在IS的恢复期中发挥吞噬作用，清除细胞碎片，抑制炎症反应[71]。这提示TAK-981可能通过影响CD36表达，进而参与IS的恢复。另外，Li等[72]发现血清中缺氧诱导因子-1α（HIF-1α）水平与IS的病变面积以及严重程度呈正相关。而经TAK-981处理后，细胞中SUMO化水平明显降低，间接增强了HIF-1α稳定性以及转录活性[73]。以上这些研究均提示TAK-981可能在IS中发挥重要作用。此外，另一种SUMO化修饰抑制剂2-D08也与IS密切相关。有研究发现，2-D08能够抑制SUMO蛋白从Ubc9转移至还原型辅酶Ⅱ氧化酶催化亚基（NADPH oxidase2，NOX2）的SUMO结合位点，导致NOX2表达上调[74]。而NOX2表达上调能够增加MCAO/R大鼠中ROS积累，促进了caspase-3和Bax表达，最终导致细胞凋亡[75]。这提示2-D08可能抑制NOX2 SUMO化修饰，减轻氧化应激以及细胞凋亡，促进IS的神经恢复。

表2 靶向SUMO化修饰的治疗措施

Table 2 Therapeutic Strategies Targeting SUMOylation

Classification	Specific therapeutic measures	Functional effects	References
Small-molecule protectant	Ebselen	SUMOylation levels were elevated in the brain, and cell viability was improved	[57]
	6-thioguanine	SUMOylation levels were elevated in the brain, and cell viability was improved	[57]
	AHPN	Upregulation of SUMO levels and inhibition of microglial activation	[58-59]
	HDAC	Upregulation of SUMO levels and inhibition of neuronal apoptosis	[58,60]
	Guanosine	Upregulation of SUMOylation and Inhibition of oxidative damage	[61-62]
MicroRNA	miR-188-5p	Increased SUMO2/3 modification and reduced neuronal apoptosis.	[63]
	miR-214	Inhibition of SUMOylation and promotion of neuronal apoptosis	[65-66]
	miR-133a-3p	Enhancement of AMPK SUMOylation and inhibition of autophagy	[67-68]
SUMOylation inhibitor	TAK-981	Decreased SUMO2/3 modification leads to suppressed CD36 and HIF-1α expression, thereby inhibiting neurological recovery	[70-73]
	2-D08	Inhibition of NOX2 SUMOylation and promotion of neurological functional recovery	[74-75]
Therapeutic hypothermia	Selective-cerebral-hypothermia	Enhancement of Drp1 SUMO2/3 modification and inhibition of mitochondrial fission	[78]
	Selective intra-arterial brain cooling	Inhibition of Sirt3 SUMOylation and improvement of mitochondrial function	[36]
Traditional Chinese medicine treatment	Astragalus-Ligusticum	Enhancement of Drp1 SUMO2/3 modification and inhibition of mitochondrial fission	[79]
	Quercetin	Upregulation of SUMOylation and amelioration of neural damage	[80]
	Buyang huanwu decoction	SUMOylation is enhanced and new synapse formation is increased	[81-82]

3.4 低温治疗

低温治疗是一种将机体或局部组织温度降低到目标水平,以达到治疗目的医疗技术。它可以通过参与多种IS的多种病理机制,发挥神经保护作用[76]。有研究发现,选择性脑低温针对IS损伤的神经保护与SUMO2/3结合的增加有关[77]。再进一步探究其具体作用机制,Yuan等[78]发现这种低温治疗方式是通过增强Drp1与SUMO2/3的偶联,抑制线粒体分裂,进而减轻大鼠局灶性脑缺血/再灌注的损伤。另外,还有一项基础研究发现,选择性动脉内脑冷却可以上调SENP1的表达,抑制Sirt3的SUMO化,改善IS的线粒体功能障碍[36]。这些证据均表明低温治疗可能是靶向SUMO化通路治疗潜在治疗措施。

3.5 中药治疗

黄芪-川芎根茎是中草药用于治疗缺血性脑卒

中的药物组合。有研究发现，提取黄芪以及川芎的活性物质干预MCAO/R大鼠，能下调Drp1与SUMO1结合，增强其与SUMO2/3的结合，抑制线粒体分裂，改善大鼠神经损伤[79]。这提示以黄芪与川芎为主要成分的中药复方，可能是靶向SUMO化修饰治疗IS的潜在靶点。槲皮素是一种广泛存在中草药中的天然黄酮类化合物。Lee等[80]发现，槲皮素可通过抑制SENP1以及SENP2的活性，上调SUMO化水平，改善OGD诱导的神经损伤。另外，脑源性神经营养因子（brain-derived neurotrophic factor，BNDF）治疗能促进SUMO蛋白的核外流，在树突上富集，影响突触后蛋白SUMO化修饰，增加新突触的形成[81]（表2）。而补阳还五汤能够上调BNDF，促进IS后突触形成[82]。这提示补阳还五汤可能在上调BNDF治疗IS时，同时伴随着SUMO修饰的调控。

4　小结

SUMO化属于蛋白质翻译后修饰之一，并且它与IS的病理机制密切相关，参与IS的发生发展。本文通过检索归纳相关文献，推断出SUMO化可能调控小胶质细胞介导的神经炎症、线粒体动力学、细胞凋亡、氧化应激以及血管生成等多种途径，影响IS的神经恢复。其中，在线粒体动力学方面，有研究证实Mfn1/2具有SUMO2结合位点，Mfn1/2 SUMO化修饰能够促进受损的线粒体在核周区域聚集、融合，并与健康的线粒体网络隔离[83]。但目前尚无相关研究探讨其在IS的作用，后续可作为探究Mfn1/2 SUMO化修饰在IS模型中神经保护作用与机制的切入点。此外不同的SUMO亚型以及不同修饰位点可能产生截然相反的效应。近年来，靶向SUMO化修饰的治疗策略，例如小分子药物、miRNA调控、低温疗法及中药活性成分等，在细胞以及动物模型中展现出了神经保护潜力，为突破当前IS治疗时间窗的限制提供了新的方向。但是，这些治疗策略的临床转化仍面临巨大挑战。在未来的研究中，可从以下几方面进行深层研究：①当前研究多聚焦于单一蛋白或通路，而SUMO化可能影响多个下游蛋白，而一个蛋白也可能被多种修饰调控。孤立研究无法揭示这些复杂的相互作用。未来可以通过蛋白质组学等技术，系统筛选出在IS不同阶段和不同细胞类型中的关键SUMO化底物，并阐明其构成的调控网络。②深入研究潜在干预措施在IS急性期、亚急性期及恢复期给药的疗效差异，确定最佳治疗时间窗。③探索靶向SUMO化疗法与静脉溶栓、机械取栓的协同作用，以及不同SUMO化调控措施的组合方案，以期实现疗效最大化。

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