REVIEW

SARM1 can be a potential therapeutic target for spinal cord injury

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Abstract

Injury to the spinal cord is devastating. Studies have implicated Wallerian degeneration as the main cause of axonal destruction in the wake of spinal cord injury. Therefore, the suppression of Wallerian degeneration could be beneficial for spinal cord injury treatment. Sterile alpha and armadillo motif-containing protein 1 (SARM1) is a key modulator of Wallerian degeneration, and its impediment can improve spinal cord injury to a significant degree. In this report, we analyze the various signaling domains of SARM1, the recent findings on Wallerian degeneration and its relation to axonal insults, as well as its connection to SARM1, the mitogen-activated protein kinase (MAPK) signaling, and the survival factor, nicotinamide mononucleotide adenylyltransferase 2 (NMNAT2). We then elaborate on the possible role of SARM1 in spinal cord injury and explicate how its obstruction could potentially alleviate the injury.

Introduction

Spinal cord injury (SCI) is a neurological disease with considerable incidence and mortality rates. The incidence rate of SCI worldwide is between 250 and 500 thousand a year [1]. Unfortunately, the current available treatment only serves to provide supportive relief for patients with lifelong disabilities [2]. SCI comprises primary and secondary injuries. Primary SCI is where an external force destructs the blood spinal cord barrier and cause local inflammatory reactions. It is often a mechanical and irreversible injury. Secondary SCI, on the other hand, is a delayed and progressive tissue injury after the primary SCI and is characterized by proapoptotic signaling, ischemia and peripheral inflammatory cell infiltration. Interestingly, current investigated SCI therapies are being aimed at secondary injury [2–4].

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The manifestations of secondary injury include Wallerian degeneration, cell permeability, apoptotic signaling, vascular injury, ischemia, edema, excitotoxicity, free radical formation, ionic deregulation, fibrous glial scar, inflammation, lipid peroxidation, demyelination, and cyst formation [1]. SARM1 is a key mediator of Wallerian degeneration [5, 6], which is a programmed self-destructive process that promotes axonal destruction in neurodegenerative diseases, and axonal injury in secondary SCI [7–9]. In the central nervous systems (CNS), the deletion of SARM1 improves functional outcomes and reduces traumatic axonal degeneration [10]. Contrastingly, the deletion of SARM1 did not inhibit axonal degeneration in the superoxide dismutase 1 G93A (SOD1G93A) amyotrophic lateral sclerosis (ALS) mouse model [11]. Recent studies have shown SARM1 to regulate the innate immune response of traumatic axonal injury in sciatic nerve injury [12]. The above studies are an indication of SARM1 playing diverse roles in different axonal injuries. Table 1 summarizes studies evidencing the role of SARM1 in disparate conditions.

This paper will review the biological roles of SARM1, with a significant emphasis on the relationship between SARM1 and Wallerian degeneration after SCI.

Table 1 Summarized studies on SARM1 in various diseases

Diseases	Species	Findings	Comment	References
Amyotrophic lateral sclerosis (ALS)	Mice	Significant attenuation of motor axon, neuromuscular junction, and motor neuronal cell body degeneration	Anti-SARM1 are potential interventional agents for diseases of the ALS- frontotemporal dementia spectrum	[13]
Parkinson's disease	Mice	SARM1 promotes the destruction of chemically lesioned dopaminergic axons, but is not involved in the retrograde degeneration of dopaminergic axons	SARM1 contributes to some, but not all types of neurodegeneration	[14]
Glaucoma	Mice	SARM1 is important for retinal ganglion cell (RGC) axonal degeneration, and axons rescued by SARM1 are electro-physiologically active. However, genetic deletion of SARM1 does not prevent or delay RGC cell death	This finding emphasizes the significance of SARM1 in RGC axonal degeneration	[15]
Metabolic neuropathy	Mice	Neuropathy caused by high-fat diet is abolished in SARM1 knocked-out mice	Genetic deletion of SARM1 prevents distal sensory axonal degeneration induced by metabolic syndrome	[16]
SCI	Mice	Conditional deletion of SARM1 inhibits neuroinflammation, and promotes axonal regeneration	SARM1 promotes neuroinflammation and inhibits neural regeneration through the NF-kappa B signaling	[17]
Diabetic peripheral neuropathy (DPN)	Mice	Deletion of SARM1 mitigates hypoalgesia, intraepidermal nerve fiber loss, and axonal degeneration	These findings demonstrate that the loss of SARM1 gene can ameliorate diabetic peripheral neuropathy	[18]
Wallerian degeneration	Mice	SARM1 deletion inhibits Wallerian degeneration after axonal degeneration	SARM1 promotes Wallerian degeneration	[19]
Mitochondrial damage	Mice	Inhibition of SARM1 by small molecules can improve axonopathies in central and peripheral nervous systems by suppressing axonal degeneration and restoring function to a metastable pool of axons	Blocking SARM1 is efficient in preventing axons from deterioration after mitochondrial damage	[20]
ALS	Human	The expression of constitutively active SARM1 allele associated with ALS is cytotoxic and promotes degeneration	High morphologic SARM1 allele is a candidate genetic risk factor for ALS	[21]
Colitis	Mouse, non-human primate, human	Deletion of SARM hinders axonal degeneration and exacerbates colitis	SARM1-mediated neurodegeneration in the intestinal nervous system alleviates local inflammation of the colon	[22]

The role of SARM1

SARM1 is a 724 amino acid protein with HEAT/Armadillo (ARM) domain, sterile alpha motif (SAM) domain and a toll/interleukin-1 receptor (TIR) domain [23, 24] (Fig. 1A). Table 2 shows the different roles of ARM, SAM and TIR domains. These three domains function individually and constitute the executioner of axonal degeneration-SARM1. SARM1 plays an important role in the neurons of the brain [34].

The ARM domain of SARM1

The ARM domains of SARM1 adopt a distinctly different conformation from other classical ARM domains. Its conformation is arched and ends bent toward each other [25]. The main function of the ARM domain is to suppress the activity of SAM-TIR and keep SARM1 in the auto-inhibition phase [26]. Under favorable conditions, nicotinamide adenine dinucleotide (NAD^+) binds to an allosteric site within the ARM domain, facilitating a "lock-in" interaction between the ARM and TIR domains, and further potentiating the

auto-inhibition of SARM1 [35]. SARM1 activation requires the deconstruction of ARM and the self-combination of TIR domain [36, 37]. The auto-inhibition of ARM needs to meet five interfaces: (1) intermolecular and intramolecular ARM-SAM interface; (2) two ARM-TIR interfaces formed between TIR alone and two different ARM domains; (3) an intermolecular ARM-ARM interface, none of which are redundant and point mutations at either interface result in the failure of auto-inhibition [26]

The SAM domain of SARM1

SAM domain is the largest protein–protein interaction motif and involves a lot of signal transduction, developmental processes, and transcriptional regulation [38]. Moreover, SAM domains mediate the polymerization of SARM1, and SARM1 is organized into ring-like octamers [29, 37, 39] that ensures the NADase stabilization in the inactive state. The ring has an inner diameter of 35 Å, an outer diameter of 200 Å, and a thickness of approximately 60 Å [25]. Interestingly, the deletion of ARM and SAM domain can prevent SARM1-mediated NAD + deletion and axonal degeneration,
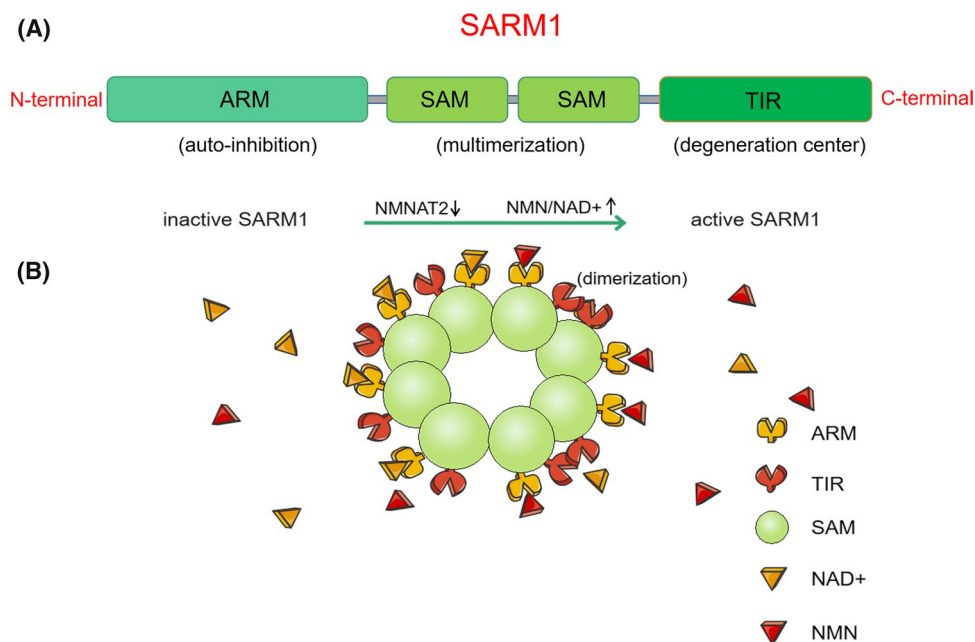

Fig. 1 The SARM1 protein structure model and SARM1 domain alterations in normal and activated states. **A** The SARM1 protein structure model. SARM1 comprises of the ARM domain, two SAM domains, and the TIR domain. Three domains are tightly bound to each other, the ARM in the protein N-terminus has an auto-inhibitory function, the two SAM in the center polymerizes the SARM1 protein, and the TIR in the protein C-terminus degrades the center of the SARM1. **B** Under normal conditions, NAD^+ binds to allosteric sites in the ARM domain, promotes the "locking" interaction between the ARM domain and the TIR domain, and reinforces the auto-inhibition function of the SARM1. Meanwhile, the SARM1 is organized into ring-like octamers to ensure the stabilization of NADase in the inactive state. After the axonal injury, NMNAT2 is rapidly consumed due to its short half-life, culminating in the inability of excess NMN to be converted to NAD^+. Therefore, the proportion of NMN/NAD^+ increases, the auto-inhibition function of the ARM domain fails, and the conformation of the ARM and TIR domains changes, causing their separation. Similarly, the instability of the ARM domain structure promotes the dimerization of the TIR domain, resulting in the activation of SARM1

Table 2 Summarized on the different roles of the three parts of SARM1

Domains	Effects	Specific roles	References
ARM domain	Auto-inhibition	1. The ARM domain suppresses the activity of SAM-TIR and keep the SARM1 in the auto-inhibition phase	[25]
		2. The ARM domain binds to NAD^+, further strengthening the connection between the ARM domain and the TIR domain	[26]
		3. The ARM domain binds to NAD + or NMN to produce allosteric regulation of the NAD + hydrolase activity	[27]
SAM domain	Multimerization	1. The SAM domain mediates the polymerization of SARM1	[25]
		2. The SAM domain forms the octamer necessary for axial mutation and promotes the enzyme activity of the TIR domain	[28]
		3. The integrity of the SAM domain determines the activity of SAMR1. Mutations in the SAM domain affect the apoptotic activity of SARM1 in cells	[29]
TIR domain	Degeneration center	1. The TIR domain is a potent NADase in SARM1, degrades NAD^+ and causes axonal destruction	[30]
		2. The TIR domain is a Ca^{2+} signaling enzyme, activated by nicotinamide mononucleotides to produce cADPR and NAADP	[31]
		3. The TIR domain is present in toll-like receptor of the innate immune system and contributes to innate immunity	[32]
		4. Bacterial TIR domains are involved in phage defense	[33]

further indicating the importance of the SAM domain to the SARM1 activity [40].

The TIR domain of SARM1

TIR domain is the most important component of SARM1, consists of alternately connected β-strands and α-helices, and forms a secondary structure architecture [30]. β-strands and α-helices are different in the TIR domain, which makes for easy discernment in the interactive functions and roles of the distinct TIR/TIR in SARM1. The TIR domain in SARM1 plays a differing role in the body. In other proteins, TIR domain is involved in innate immunity. However, TIR domain is an efficient NADase in SARM1 [41], which has the function of degrading NAD^+ and causing axonal destruction. The BB loop (named according to their adjacent β-strand in the TIR/TIR interaction loop motifs) of SARM1TIR is the determinant of NADase activity [39, 42]. SARM1TIR functions go beyond the catalysis of NAD^+, as it cyclizes NAD^+ to form cyclic ADP ribose (cADPR) that accelerates neurodegeneration [43] and facilitates base-exchange reactions with nicotinamide adenine dinucleotide phosphate (NADP) and nicotinic acid as substrates to generate nicotinic acid adenine dinucleotide phosphate (NAADP) [44]. Both cADPR and NAADP are messenger molecules that mediate the mobilization of Ca^{2+} stores [31]. Therefore, the TIR domain has a similar function to that of CD38 (a Ca^{2+} signaling enzyme) [32] (Fig. 2). Besides, the TIR domain is found in toll-like receptor of the innate immune system and contributes to innate immunity [45]. However, it is unclear whether

targeting SARM1 leads to innate immune consequences [23]. Overall, SARM1TIR is central to degeneration. In the wake of axonal injury, the TIR domain degrades NAD^+ and leads to axonal degeneration.

In summary, the auto-inhibition of SARM1 is through the action of the ARM domain. Nevertheless, axonal injury following SCI triggers the ineffectiveness of the ARM domain, leading to the degradation of NAD^+ and resulting in axonal degeneration (Fig. 1B). In addition, SARM1 is a downstream of NLRX1 (an LRR-containing protein) in the regulation of apoptosis, and SARM1 activation has an effect on apoptosis [46]. Notably, Mukherjee et al. showed SARM1 signaling was paramount to neuronal apoptosis following TLR-activation, and SARM1 deficiency inhibited TLR7/TLR9-mediated neuronal apoptosis [47].

The endogenous wallerian degeneration pathway

Wallerian degeneration is one of the detrimental effects of secondary SCI. The coding and gene expressional changes in Wallerian degeneration lead to axonal vulnerability in the human population [48–50]. Nicotinamide mononucleotide adenylyltransferase 2 (NMNAT2), mitogen-activated protein kinases (MAPK), and SARM1 are key mediators in the Wallerian degeneration (Fig. 2). The subsequent sections will detail the discovery of Wallerian degeneration and the specific role of NMNAT2, MAPK, and SARM1 in Wallerian degeneration.
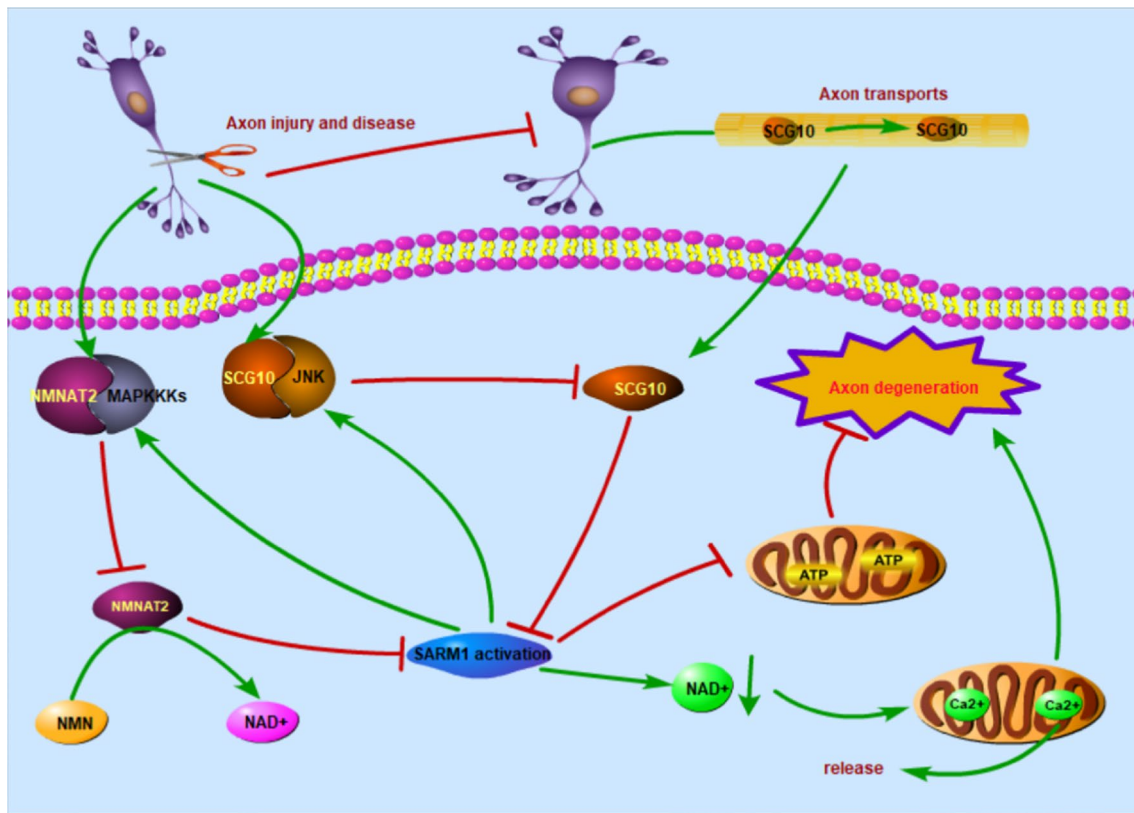
Fig. 2 The Wallerian degeneration program model. Axonal injury or disease promotes the MAPK signaling and disrupts the anterograde axonal transports of NMNAT2 and SCG10. The MAPK signaling accelerates the turnover of the survival factors, NMNAT2 and SCG10. The continual degradation of these survival factors leads to their curtailed levels below the critical threshold, which in turn stimulates the SARM1. Activated SARM1 rapidly depletes NAD$^+$, leading to intracellular Ca^{2+} dysregulation, and culminating in ATP depletion and energy metabolism crisis, and eventually, axonal degeneration

The recent findings on wallerian degeneration

Wallerian degeneration originated from an experiment in the mid-nineteenth century that was evaluating nerve fiber degeneration in frog tongue after axotomy, a programmed self-destructive process that promotes axonal destruction in neurodegenerative diseases and axonal injury [7]. In recent years, several evidences have been found to unravel the underlying mechanism of Wallerian degeneration. We elaborate on two of such evidence.

The first had to do with the discovery of Wallerian degeneration slow (Wlds)—a specific protein consisting of ube4b sequences fused to NMNAT1 [7]. In 1989, Lunn and colleagues found a spontaneous mutation that originated in mice and led to delayed Wallerian degeneration, which came to be known as Wlds. The Wlds mouse influenced a change in scientists' perception regarding axonal degeneration, resulting in the hypothesis that axons, like cell bodies, have the ability to actively self-destruct gene coding [51]. Wlds encodes the NMNAT1, which exists predominantly in the nuclei and converts nicotinamide mononucleotide (NMN) to nicotinamide adenine dinucleotide (NAD$^+$) [7,

52]. Therefore, axonal protection by Wlds could be due to the overexpression of the NMNAT1 protein's axonal localization and enzymatic activity, which also implies that there may be a link between axonal degeneration and the NAD$^+$ metabolic pathway.

The second evidence was the identification of SARM1, which is significant in Wallerian degeneration. The role of SARM1 in axonal degeneration was first identified in drosophila mutants [53]. In drosophila mutants and mouse, the loss of SARM1 provides potent cell-autonomous axonal protection similar to Wlds expression, which corroborates the importance of SARM1 in axonal degeneration [24, 54].

MAPK signaling activates SARM1 by expediting the turnover of NMNAT2

Previous studies have shown that SARM1 multimerization can activate MAPK signaling to instigate in axonal degeneration, indicating that SARM1 is located upstream of the MAPK signaling [24, 55]. However, a recent study showed the MAPK signaling to accelerate the turnover of the survival factor, NMNAT2, in order to activate SARM1. This

implies that the MAPK signaling cannot be downstream of SARM1 [56]. Particularly, there is no strict upstream and downstream relationship between SARM1 and the MAPK signal transduction. Hence, SARM1 can directly stimulate MAPK, and MAPK can also act on the NMNAT2 to activate SARM1. Although these conflicting reports remains to be clarified, it could mean that there is the existence of feedback mechanisms that potentiate the response between SARM1 and the MAPK signaling.

The MAPK signaling pathway includes mitogen-activated protein kinase kinase kinases (MAP3K), dual leucine zipper kinase (DLK), mut9p-like kinase 2 (MLK2), mitogen-activated protein 3 kinase 4 (MEKK4), mitogen-activated protein kinase kinases (MAPKKs), mitogen-activated protein kinase kinase 4 (MKK4), mitogen-activated protein kinase kinase7 (MKK7), and mitogen-activated protein kinases (MAPKs) c-Jun N-terminal kinase1-3 (JNK1-3). In this pathway, the MAPKKK, DLK/MAP3K12, MAPK-KKs, MEKK4/MAP3K4 and MLK2/MAP3K10 converge on the JNK pathway [57]. The Superior cervical ganglion 10 (SCG10) is a target of the JNK pathway. SCG10 is a microtubule regulating protein, and similar to NMNAT2, it can protect the axon by anterograde transport [58]. Interestingly, the co-expression of SCG10 and NMNAT2 enhances axonal protection after injury [56]. The phosphorylation of JNK instigates SCG10 degradation in normal conditions. Moreover, axonal injury damages the axonal transports, which in turn contributes to the loss of SCG10 and leads to axonal degeneration. This implies that SCG10 is another survival factor that is modulated by the MAPK signaling and the breakdown of SCG10 augments Wallerian degeneration [57].

In cultured neurons, the loss of NMNAT2, but not NMNAT1 or NMNAT3, triggered Wlds-sensitive axonal degeneration [59]. MAPK is a regulator of the NMNAT2 level [56]. In the wake of an injury, the anterograde transport of NMNAT2 is destroyed, resulting in its decrement along with the stimulation of the SARM1. This causes a rapid mitigation of NAD$^+$ and ATP levels, subsequently leading to axonal degeneration. Therefore, MAPK signaling may curtail NMNAT2 level to trigger the SARM1. However, the mechanism pertaining to the MAPK signaling pathway inhibiting the level of NMNAT2 remains unclear. According to recent reports, palmitoylation, localization, and the ubiquitin ligase highwire/phosphate starvation response1 (PHR1) control the NMNAT2 turnover [60–63]. Hence, it is possible that MAPK could speed up the turnover of NMNAT by influencing the aforementioned processes. Future studies focusing on the delineation of the association between these processes, MAPK and NMNAT will go a long way in possibly opening novel therapeutic targets for several medical conditions, including Alzheimer's disease, Parkinson's disease, and Amyotrophic lateral sclerosis. In view of

the fact that Serine548 resides within the SAM domain, its phosphorylation could potentially alleviate self-inhibition and promote SARM1 dimerization [64]. Besides promoting the turnover of the NMNAT2, the MAPK activates SARM1 through the phosphorylation of Serine548.

NMNAT2 suppresses the SARM1 activity

NMNAT2, the endogenous NMNAT enzyme present in healthy axons, which is of great significance to axonal survival, acts as an axonal survival factor to hinder the detrimental action of SARM1 [52, 65]. However, NMNAT2 is an unstable protein in axons that are rapidly degraded following injury prior to axonal degeneration [65]. Noteworthy is that the deletion of axonal NMNAT2 is sufficient to initiate SARM1-dependent axonal degeneration. Although the loss of NMNAT2 is fatal, it can be minimized by the conditional deletion of SARM1 or the expression of Wlds/NMNAT1 [59, 65, 66].

NMNAT2 has a short half-life [67, 68], and, therefore, requires continual supply through new protein synthesis and axonal transport. Axonal injury destroys axonal transport, leading to a decrease in local NMNAT2 levels and the onset of axonal degeneration [56]. Furthermore, axonal NMNAT2 is easy to be palmitoylated, a post-translational modification that affects its trafficking and stability [61]. An atypical E3 ligase complex (PHR1, F-Box protein 45 (FBXO45), and S phase kinase-associated protein 1 (SKP1)) modulates the non-palmitoylated axonal NMNAT2. The reduction of these genes leads to an increase in the degree of NMNAT2 and effective axonal protection [60, 69–73]. Thus, the function of PHR1, FBXO45 and SKP1 could lie in inhibiting the NMNAT2 level so as to instigate axonal degeneration. In addition, the MAP3K, DLK and its paralog, leucine-zipper kinase/LZK, can activate the neuronal JNK stress kinase pathway to control the palmitoylated axonal NMNAT2 [55, 69, 74]. Once activated, the level of NMNAT2 is markedly decreased and SARM1 is activated, promoting the progression of axonal degeneration.

The ability of NMNAT2 to protect axons is dependent on the enzymatic activity, the elevation of NMN [75–79], and the decrement of NAD$^+$ (NMNAT2 could prevent SARM1 dependent NAD$^+$ depletion in injured axons) [19, 80, 81]. The NMN can activate SARM1 [79], implying that NMNAT2 has a dual role in preventing SARM1 stimulation by converting the activator, NMN, into NAD$^+$ and acting as an axon survival factor inhibiting the role of SARM1 [36, 37]. Nonetheless, elevated NMN does not necessarily lead to axonal degeneration [35]. Figley and colleagues evidenced that the manipulation of NMN/NAD$^+$ via the augmented levels of NMN or curtailed levels of NAD$^+$ could activate SARM1. Additionally, further studies have shown that NAD$^+$ and NMN are closely related to the regulation

of SARM1's enzymatic activity [36, 82]. These findings demonstrate how NMNAT2 controls SARM1. NMNAT2 catalyzes the NMN to form NAD^+ [65], decreases the ratio of NMN/NAD^+, which is instrumental in the inhibition of SARM1.

Activated SARM1 promotes axonal degeneration

Wallerian degeneration occurs as a result of axonal damage in response to trauma or disease that promotes local clearance of the injured axonal segments [42], and SARM1 is a key mediator of Wallerian degeneration [5, 6]. Thus, SARM1 is significant in axonal degeneration. SARM1 has a TIR domain, which is necessary for the SARM1-dependent axonal degeneration. Studies have shown that forced SARM1 TIR domain dimerization is sufficient to cause local axonal degeneration [24, 55, 80]. After the axonal injury, enhanced MAPK signaling triggers a reduction in NMNAT2 levels, ultimately leading to forced dimerization of SARM1's TIR domain that provokes NAD^+ depletion. NAD^+ is significantly involved in ATP synthesis and other cellular activities [83]. The loss of sufficient NAD^+ leads to the cascade destruction of axons, in which ion imbalance causes the destruction of the cytoskeleton and axonal structure [42, 51, 80].

The role of SARM1 in SCI

Numerous studies in animals and humans have shown that the distal stump of the long-injured axons undergo irreversible damage and a degenerative process after SCI, which is known as Wallerian degeneration. Wallerian degeneration is a programmed self-destructive process, which damages axon after SCI. Therefore, mitigating Wallerian degeneration and inflammatory response could be key to the treatment of SCI. Meanwhile, inhibition of SARM1 abates Wallerian degeneration, and suppresses inflammation [17, 84]. Therefore, inhibiting SARM1 may improve SCI treatment.

SARM1 repression was potent in the treatment of traumatic brain injury [10, 85, 86], ALS, chemotherapy-induced peripheral neuropathy [16, 87, 88], and diabetic neuropathy [16]. Furthermore, following mitochondria damage, the hampering of SARM1 was effective in obviating the axons from degeneration [20]. SARM1, a protein that also regulates calpain activity, may be involved in isoflurane-induced neuro-inflammation [89]. In various neurodegenerative conditions, SARM1 champions Wallerian degeneration [68], whereas its deletion prevents neuronal deterioration [40]. Moreover, SARM1 modulates neuronal immune responses instigated by axonal injury through the regulation of the c-Jun N-terminal kinase (JNK)-c-Jun signaling pathway [12]. Additionally, SARM1 inhibition through transient RNAi via the use of a single injection of siRNA has been shown in the treatment of SCI [90].

A number of experimental and preclinical studies have shown that the potential treatment modalities concerning the inhibition of SARM1 show its significance, together with Wallerian degeneration, in SCI and neurodegeneration [14, 17, 26, 90, 91]. Some clinical studies have also shown that the inhibition of SARM1 could improve Wallerian degeneration of nerve injuries [21, 22].

Potential treatment modalities for SCI inhibiting SARM1

Regarding the in-depth study of SARM1, several methods have been proposed for the treatment of SCI by hindering SARM1. The subsequent sections delineate some of the strategies that focuses on the impediment to SARM1.

Therapeutic effect of halting SCI through the repression of SARM1

Axons need considerable energy and high-intensity metabolic activities to maintain ion gradients across the plasma membrane as well as optimal neurotransmission. Additionally, these high bioenergetic demands need to be maintained over a meter-long axon, thus, it could easily result in axonal fragility [92]. Wallerian degeneration is commonly seen following SCI [93], and SARM1 is a key mediator of Wallerian degeneration [5, 6]. Normally, SARM1 is under an inactive state [24]. In the wake of SCI, ARM domain loses its function, and the dimerization of SARM1's TIR domain activates SARM1, triggering the rapid depletion of local intra NAD^+ pools, which in turn culminates in metabolic disorders and energy imbalance [80]. Therefore, inhibiting SARM1 may be a suitable strategy for treating SCI via suppression of the Wallerian degeneration. Despite its probable prospect, studies relating to the blocking of the Wallerian degeneration via SARM1 restriction in the treatment of SCI is limited.

Conditional deletion of SARM1 downregulates the nuclear factor kappa B signaling pathway to ameliorate SCI

SARM1 promotes neuro-inflammatory response and inhibits nerve regeneration through the NF-kB signaling pathway after SCI [17]. The novelty regarding SARM1 in SCI treatment could lie in its conditional deletion in astrocytes, which in turn would curb the NF-kB signaling.

Astrocyte, the most abundant glial cells in the CNS, is a vital to brain development, function, and plasticity [94]. Subsequent to SCI, activated astrocytes lose their regulatory function, causing inflammatory response and resulting in

neuronal death. In addition, other detrimental effects, such as active astrocytes, subsequently become hypertrophic, proliferate and migrate to the injured site, eventually forming a dense network of glial scar. The glial scar is a physical and chemical barrier that prevents the regeneration of damaged neural tissue [95]. Therefore, astrocytes are significant players in inflammation in SCI. A more recent study showed the SARM1 expression to be upregulated in astrocytes during the early stages SCI [17]. Hence, conditional deletion of SARM1 in astrocytes may potentially alleviate neuro-inflammation following SCI.

Inflammation activates the secondary injury in SCI, and NF-kB is an important nuclear factor in inflammation [4]. In resting cells, the inactive NF-kappa B versus IκB (inhibitor kappa B) binds to form an inactive trimer in the endoplasm, which suppresses the nuclear translocation and activation of the NF-kB [4]. In the spinal cord, blood vessels and glia cells express the NF-kB transcriptional factors, mediating diverse mechanisms, one being inflammation [96]. Therefore, limiting the NF-kappa B signaling pathway could mitigate neuro-inflammation after SCI.

FK866 (also known as APO866) is a SARM1 feedback inhibitor that has been widely used to block nicotinamide depletion by barring the nicotinamide phosphoribosyltransferase [85]. The NF-kB signaling is the main downstream pathway of the SARM1 [97, 98]. A recent study reported that the conditional deletion of the SARM1 in astrocytes or its inhibition using FK866 leads to the upregulation of heat shock protein 70 that can significantly impede the NF-kB [99]. This then results in moderated levels of NF-kB, which in turn minimizes neuronal inflammatory.

Conclusion

Presently, thorough studies apropos to SARM1 in the treatment of SCI areinadequate. The SARM1 is an important regulator of Wallerian degeneration [5, 6]. Inhibiting SARM1 will be beneficial in preventing Wallerian degeneration and axonal degeneration. With its potential as an interventional target for SCI, extensive studies expounding on SARM1's biological characteristics and specific mechanism in nervous system injuries and repair would be worthwhile.

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