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MINIREVIEW

Resveratrol can inhibit Notch signaling pathway to improve spinal cord injury

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ABSTRACT

Spinal cord injury (SCI) is one of the severe central nervous system (CNS) diseases. Although various therapeutic approaches have been researched, there are still no effective therapeutic measures for SCI. Development of novel, safe and effective therapeutics for SCI have currently gained a lot of interest. Medicinal and chemical agents have the tendency of regulating signaling pathways. Notch signaling pathway plays an important role in neuronal cell differentiation, neuroinflammation and axonal regeneration in the wake of SCI. Resveratrol has been reported to exert neuroprotective effects in CNS conditions. Resveratrol can inhibit Notch signaling pathway to curtail SCI. Herein, we systematically review potential mechanisms of resveratrol-inhibiting Notch signaling pathway in SCI treatment.

1. Introduction

SCI is a severe CNS disease. SCI impedes normal signal transmission between CNS and the peripheral nervous system, and can culminate in long-term loss of motor- and sensory functions. Millions of people worldwide suffer from SCI. Although researchers have made great efforts in finding treatments for SCI, there are no effective therapeutic approaches yet. SCI can be divided into acute and chronic phases on the basis of the injury time, with the former divided into primary and secondary injury. Primary injury is a direct compression of the spinal cord that results in displaced bone fragments, a damaged blood vascular system, disrupted axons, disintegrated neural cell membranes and induced hemorrhage. Owing to hemorrhage, the spinal cord swells and leads to ischemia, which disrupts cell membranes and releases toxic chemicals and eventually triggers secondary injury (McDonald and Sadowsky, 2002). Secondary injury affects not only the initial lesion site, but also relative and distant regions. The development of effective SCI treatments is being focused on secondary injury as a result of the irreversibility of primary injury. Mammalian target of rapamycin (mTOR), Wnt and Notch signaling pathways participate in SCI pathogenesis (Chen et al., 2015; Lambert et al., 2016; Lin et al., 2017). Both mTOR and Wnt signaling pathways have been well studied in SCI pathogenesis; Notch signaling pathway, on the other hand, has not been systematically reviewed. Notch signaling pathway plays an important role in the neural development processes and neurodegenerative diseases. Moreover, Notch signaling pathway is activated in SCI secondary injury and inhibits functional recovery. Several studies have evidenced Notch signaling pathway to play an important role in the secondary injury of SCI, encompassing the inhibition of neural stem cells (NSCs) differentiation (Yan et al., 2018a,b), axonal regeneration and neuroinflammatory instigation (Chen et al., 2015).

The search for SCI treatment in recent years has shifted to Traditional Chinese Medicine (TCM). Resveratrol (3,4′,5-trihydroxystilbene), a Chinese medicinal monomer, present in polygonum cuspidatum, grapes and peanuts, possesses significant anti-tumor, anti-inflammatory, anti-diabetic, antioxidant and neuroprotective effects (Cote et al., 2015). Several studies have evidenced resveratrol to improve SCI recovery (Liu et al., 2011; Hu et al., 2017; Fu et al., 2018; Wang et al., 2018). Resveratrol is a Notch signaling pathway inhibitor in cancer, cardiovascular diseases and hepatopathy (Zhang et al., 2014a,b; Tanriverdi et al., 2016). Herein, we review the potential molecular mechanism of resveratrol in SCI treatment via inhibition of Notch signaling pathway.

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2. Molecular mechanisms of secondary injury following SCI

Molecular mechanisms of secondary injury following SCI include glutamate excitotoxicity, oxidative stress, neuroinflammation and immunological responses as well as glial scar formation and apoptosis. Notch signaling pathway is mainly involved in neuroinflammation, immunological responses and glial scar formation.

2.1. Neuroinflammation and immunological responses

Neuroinflammation and immunological responses are mainly driven by astrocytes and microglia. Microglia cells constitute the innate immune system of the CNS. Microglia cells are activated, and then clear up necrotic nerve cells and cellular debris at three hours post SCI. These cells, activated by glutamate and reactive species, express a range of pro-inflammatory factors such as matrix metalloproteinase-12, interleukin (IL)-1β, tumor necrosis factor (TNF)-α and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) to recruit peripheral immune cells, migrating to lesion sites (Brambilla et al., 2014). Neutrophils, macrophages and T-cells arrive at injury sites within several hours post injury (Sutherland et al., 2016). Among these recruited leukocytes, neutrophils are one of the most potent triggers of post-traumatic spinal cord damage. Neutrophils release a series of inflammatory factors, proteases, reactive oxygen intermediates and nitric oxide. These aggravate tissue damage. The suppression of neutrophils can potentially reduce the severity of secondary injury as evidenced in experimental animals (Francos-Quijorna et al., 2017). Bone marrow-derived macrophages infiltrate into the injured spinal cord and exist for several weeks. Macrophages participate in the destruction of myelin sheath and internalize myelin debris.

2.2. Glial scar formation

Generations of glia repopulate lesion sites and functionally integrate into surviving neural tissue. Glial scar acts as a chemical and physical barrier to axonal regrowth during recuperation of SCI. Astrocytes and NG2 cells are major components of glial scar (Kriyakiarana et al., 2016). Astrocyte activation is a pathological hallmark of SCI and leads to inhibitory effects via glial scar formation. Both in-vivo and in-vitro studies have evidenced astrocytes activation to be modulated by MAPK and Sirt1 signaling (Dan et al., 2017), which can potentially interact with Notch signaling.

3. Regulatory role of Notch signaling pathway in SCI

Notch signaling pathway, a highly conserved signaling mechanism, plays a critical role in development, tissue homeostasis and disease (Hasan et al., 2017). Notch signaling starts with ligand-receptor interactions between two adjacent cells, leading to series of proteolytic events of the receptor (Siebel and Lendahl, 2017).

3.1. Inhibition of Notch signaling pathway regulates neuronal cell regeneration and differentiation

There is a spontaneous partial recovery in adult mammals after SCI via mechanisms such as endogenous neural progenitor cells (ENPCs) activation. Activated ENPCs differentiate and migrate to lesions after SCI. Manipulating ENPCs potentially offers a promising means of restoring SCI-mediated neuronal dysfunction. Spinal lesion-induced ENPCs differentiate primarily into glial cells. Notch signaling pathway is a regulator of proliferation and differentiation of the ENPCs after CNS injury. An in-vivo study showed that Notch signaling pathway was activated after brain injury and the expression of Notch1 receptor increased in the hippocampus (Wang et al., 2012). Direct attenuation of Notch1 by γ-secretase inhibitor (GSI) results in ENPCs increment and induces more efficient differentiation of ENPCs into neuronal lineage in-vivo (Oya et al., 2009). On the contrary, Notch target gene Herp1, Herp4 over-activation significantly inhibits ENPCs proliferation and neuronal lineage generation, implying the response of ENPCs after CNS injury can potentially be mediated via Notch signaling pathway (Dias et al., 2012). Additionally, transplantation of exogenous neural stem/progenitor cells (NS/PCs) and mesenchymal stem cells (MSCs) promote axonal growth, nerve regeneration and neuronal survival as well as curtailment of inflammatory cell recruitment after SCI. However, a significant barrier to cell transplantation is the insufficiency of grafted cells engraftment in injured tissues. Notch signaling pathway can mediate stem cells migration in MSC therapy. Interrupting Notch signaling pathway directly by GSI or knockout of transcription factor recombination signal binding protein J (RBP-J, also known as CBF-1/CSL) can upregulate C-X-C chemokine receptor type 4 (CXCR4) expression, which is pivotal in the process of MSC homing. Interfering Notch-CXCR4 signaling can induce more MSCs to migrate into the injured tissues (Xie et al., 2013). Besides, the microenvironment of injured spinal cord is unsuitable for growth and differentiation of transplanted cells, which are limited by a line of inhibitors produced by the pathological lesions. Exogenous NSC transplantation therapy cannot achieve optimums partly due to the limited differentiation of neurons and reconstruction of neuronal networks. Leucine-rich repeat and immunoglobulin domain-containing protein-1 (LINGO-1), an upstream molecule of Notch signaling pathway, is a strong negative regulator of neural growth. With NSCs being treated by shRNA, LINGO-1 is inhibited and Notch signaling is inhibited indirectly in the aftermath of LINGO-1 inhibition. The expression of neuronal nuclei (NeuN) is increased, indicating an increment in NSC differentiation into neurons in-vitro (Wang et al., 2016). Moreover, targeted inhibition of LINGO-1 via RNA interference in-vivo not only enhances transplanted NSCs survival and neuronal differentiation but also facilitates functional recovery of SCI rats (Chen et al., 2016). Notch intracellular domain (NICD) induces NPCs differentiation from BMSCs, and the transplantation of bone marrow-derived neural progenitor cells (BM-NPCs) effectively extends neurites beyond the injured sites of the spinal cord (Aizawa-Kohama et al., 2013). Conditioned medium from cultured olfactory ensheathing cells (OECs) inhibit neuronal differentiation and promote NPCs proliferation in-vitro. Through the direct inhibition of Notch signaling pathway by *N*-[*N*-(3,5-difluorophenacetyl-L-alanyl)]-*S*-phenylglycine t-butyl ester (DAPT), effects of OEC-derived soluble factors on NPCs can be hindered (Zhang et al., 2008). Transplantation of human induced pluripotent stem cells (hiPSC) provides a promising way of treating SCI (Lu et al., 2014). However, over-proliferation and tumor-like growth of hiPSCs remain problematic. Transplantation of certain hiPSCs results in deterioration of motor function after SCI (Okubo et al., 2016). Also, Notch signaling pathway contributes to maintaining NS/PCs. Pretreatment of hiPSC-NS/PCs with Notch signaling inhibitor, GSI, promoted neuronal differentiation and maturation. In addition, effects of overgrowth diminution of hiPSC-NS/PCs as well as deterioration decrement of motor function were observed (Okubo et al., 2016). Excitatory interneurons, including V2a interneurons that control respiration and locomotion, are lost after SCI. The balance between V2b and V2a interneurons is mediated by Notch signaling pathway. Notch signaling is necessary for differentiation of V2b interneurons, and direct Notch inhibition by DAPT increases the proportion of V2a interneurons. HiPSC-derived V2a interneurons can extend neurites and form synapses with host neurons after being transplanted into the injured spinal cord (Butts et al., 2017).

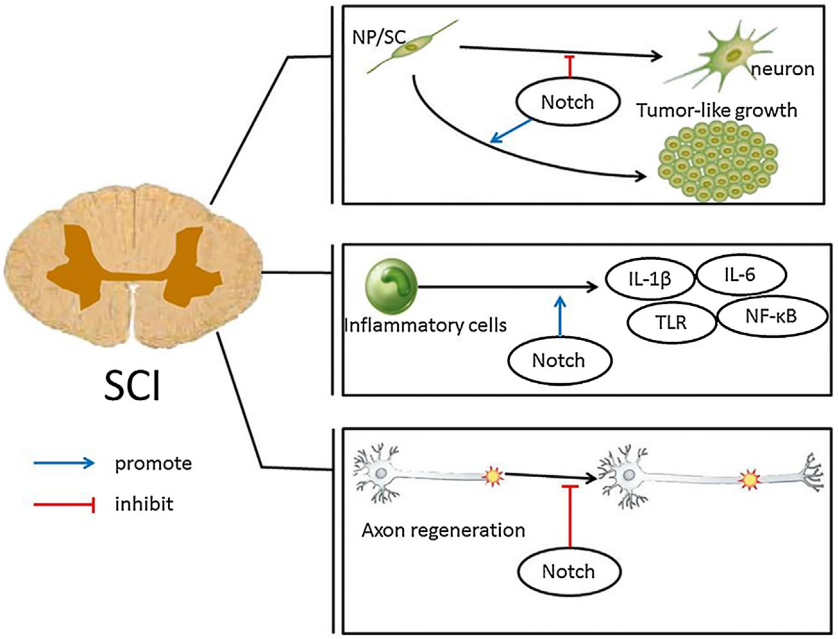

Fig. 1. Regulatory role of Notch signaling pathway in SCI. Following SCI, Notch signaling pathway is activated and participates in the recuperation process, including neural differentiation, inflammation and axonal regeneration.

3.2. Inhibition of Notch signaling pathway attenuates neuroinflammation

Persistent heightened neuroinflammation is partially responsible for continued and generalized cell death and tissue damage in secondary injury after SCI. Notch signaling pathway is involved in macrophage-mediated neuroinflammation in the wake of SCI. For example, direct inhibition of Notch signaling such as myeloid-specific Notch signaling disruption by RBP-J knockout downregulates the expression of inflammatory cytokines such as TNF-α, IL-1β, IL-6 and transforming growth factor-β (TGF-β) while upregulating IL-10 in the lesion sites after SCI in-vivo. These changes are accompanied by enhanced AKT signaling activation, which is involved in both apoptotic processes and cell survival (Chen et al., 2015). Toll-like receptor (TLR) signaling is important in inflammatory response and amalgamates with Notch signaling pathway in macrophages under inflammatory conditions (Ruiz-Garcia et al., 2016). Pharmacological promotion of TLR2 can indirectly activate Notch1 and promote Deltex and Hes-1 expression in macrophage-like cell lines in-vitro (Palaga et al., 2008). TLR5-mediated NF-κB activation is dependent on Notch signaling. Direct Notch signaling inhibition by GSI significantly decreases expression of IL-6, TNF-α and translocation of the p50 subunit of NF-κB in macrophage-like cell lines in-vitro (Zhang et al., 2012). The chemical inhibition of Notch1 signaling downregulates microglia activation and NF-κB expression through the TLR4/myeloid differentiation primary response 88 (MyD88)/TNF receptor-associated factor 6 (TRAF6)/NF-κB pathways in neuroinflammation in-vivo (Yao et al., 2013). Hypoxia can induce the activation of NICD and Hes-1, and promote astrocytic proliferation. The suppression of Notch1 signaling pathway by DAPT can hinder the enhanced effect. This process has been implicated in vascular endothelial growth factor (VEGF) or NF-κB/p65 signaling (Zhang et al., 2015). Macrophages are divided into two major types, M1 and M2. M1 macrophages initiate inflammation and aggravate tissue damage. The blocking of Notch signaling by Myeloid-Specific RBP-J knockout can reduce M1 macrophage polarization and promote neuronal survival as well as locomotive recovery improvement in SCI (Chen et al., 2015). Compared with myeloid-specific Notch signal disruption, general Notch inhibition by GSI results in opposite effects. M1 and M2 macrophage polarizations were increased and decreased respectively following GSI treatment in spinal cord injured mice. The GSI-treated mice showed significant reduction of locomotive activity after SCI (Chen et al., 2015). The effects of Notch inhibition in neuroinflammation are different in specific cells. Related mechanisms of Notch signaling with microglia cells and neutrophils in neuroinflammation warrant further research.

3.3. Inhibition of Notch signaling pathway promotes axon regeneration

A major obstacle in functional recovery after SCI is the limited regeneration of axons. Neurons regain limited capacity to regrow their axons after CNS injury. Notch signaling pathway is a negative regulator of axonal regeneration; activation of Notch signaling pathway causes neurite and axonal regeneration interference. For instance, Notch signaling inhibited injured cell growth cone initiation, which is a very early stage in axonal regeneration. However, the immediate blocking of Notch signaling after injury improved axonal regeneration in-vivo (El Bejjani and Hammarlund, 2012). The transplantation of GSI-treated hiPSC-NS/PCs into a chronically injured spinal cord can induce axonal regeneration, fiber extension and remyelination in-vivo. And these regenerative axons contributed to locomotor function recovery. P38 MAPK signaling, a key molecule axonal regeneration is involved in Notch signaling inhibition. P38 MAKP signaling is activated after Notch signaling activation during axonal regeneration (Okubo et al., 2018). Neuritin, a factor promoting neurite and synapse maturation, can significantly suppress Notch ligand Jag1 endocytosis, with this progress promoted by neutralized in-vitro (NEURL1) (Zhang et al., 2017). Axonal regeneration is impeded by glial scar and inhibitory matrix within later phase of SCI. Astrogliosis, a key factor in glial scar formation, occurs after SCI and is modulated by Notch signaling pathway. Notch signaling pathway is a promoter of astrogliosis both in-vivo and in-vitro. NICD, Hes-1, Jagged-1 and Thrombospondin-4 (a Notch modulator) can positively regulate astrogliosis and glial scar formation after CNS injury

Table 1
Neuroprotective effects of Notch signaling pathway.

Diseases	Species	Mode of administration	Dose	Results	References
Hypoxic-ischemic brain injury	Rat	Intraperitoneal injection	20 and 40 mg/kg	Resveratrol attenuates inflammatory response and oxidative stress	Gao et al. (2018)
Alzheimer's disease	Mouse	Intracerebroventricular injection	0.02 mg/kg	Resveratrol protects against neurodegeneration and cognitive deficits induced by $A\beta_{1-42}$	Qi et al. (2018, 2019)
Stroke	Rat	Intraperitoneal injection	30 mg/kg	Resveratrol decreases neuronal damage, improves and attenuates neuronal apoptosis	Hou et al. (2018)
Postoperative cognitive dysfunction	Rat	Gavage	2, 20, 40, and 60 mg/kg	Resveratrol attenuates the surgery-induced cognitive impairment and neuroinflammation	Locatelli et al. (2018)
Amyotrophic lateral sclerosis	Mouse	Intraperitoneal injection	0.068 mg/kg	Resveratrol increases the lifespan of mice and restores the acetylation state of RelA in the spinal cord.	Schiaffino et al. (2018)
Autism	Rat	Gavage	20 mg/kg	Resveratrol ameliorates prenatal progestin exposure-induced autism-like behavior via ERβ activation.	Xie et al. (2018)
Ethanol-induced neuroinflammation	Rat	Intraperitoneal injection	100 mg/kg	Resveratrol prevents the deficits of spatial reference memory and neuroinflammation by inhibiting microglial activation.	Qi et al. (2018, 2019)
Spinal cord injury	Rat	Intraperitoneal injection	100 mg/kg	Resveratrol promotes functional improvement of locomotion and reduces neuroinflammation.	Meng et al. (2018)
Diabetes mellitus	Rat	Intravenous injection	10 mg/kg	Resveratrol attenuates oxidative and nitrosative stress and decreases neuronal loss	Ferreira et al. (2018)
Intracerebral hemorrhage	Rat	intraperitoneal injection	60 mg/kg	Resveratrol reduces neural damage in the hippocampus and reduces activation of microglia	Cai et al. (2018)
Cerebellar ataxia	Rat	Intraperitoneal injection	10 mg/kg	Resveratrol ameliorates motor performance and muscle activity.	Ghorbani et al. (2018)
Pneumococcal Meningitis	Rat	Gavage	50 mg/kg	Resveratrol increases miRNAs targeting the transcription factor TEF-1.	de Queiroz et al. (2018)
Neurodegeneration	Mouse	Gavage	30 mg/kg	Resveratrol recuperates the loss of memory and learning.	Sharma et al. (2018)
Endoplasmic reticulum stress	Mouse	/	50 μM	Resveratrol reduces Sirt3 expression and prevents autophagy	Yan et al. (2018a,b)
Cerebral Ischemia/reperfusion injury	Rat	Intraperitoneal injection	50 mg/kg	Resveratrol reduces apoptosis, inflammation and enhances autophagy activation	Liu et al. (2018)
Autism	Mouse	Intraperitoneal injection	40 mg/kg	Resveratrol inhibits proinflammatory mediators and TLRs/NF-κB transcription factor signaling and improves neuroimmune dysregulation.	Ahmad et al. (2018)

(Benner et al., 2013; Zhong et al., 2018). Glial fibrillary acidic protein (GFAP) is an intermediate filament protein and a signature protein of astrocytes. NICD can demethylate the GFAP promoter, nuclear factor 1α. Astrogliosis, following SCI, can be mediated by Jagged-1/Notch signaling pathway (Kamei et al., 2012). The expression of Notch1, NICD Jagged-1 and GFAP was increased after CNS injury. The inhibition of Notch1 signaling by DAPT can suppress astrogliosis and GFAP expression in-vivo (Zhong et al., 2018) (Fig. 1).

4. Protective effect of resveratrol in SCI through the inhibition of Notch signaling pathway

As there is no effective treatment for SCI, the development of an innovative therapeutic is currently of great interest. Considering its role in NSCs differentiation, neuroinflammation and axonal regeneration, Notch signaling pathway has been hypothesized as an emerging therapeutic target for SCI. Thus, exploring the regulation of Notch signaling pathway can be an ideal strategy for SCI treatment.

4.1. Neuroprotective effects, chemistry, pharmacokinetics and pharmacodynamics of resveratrol

Resveratrol, (3,4′,5-trihydroxystilbene), is a non-flavonoid natural polyphenol agent. The chemical structure of resveratrol can be divided into trans and cis. Trans-resveratrol is more stable than *cis*-resveratrol. Resveratrol is absorbed at a high rate through small intestine via oral administration. Inside the enterocytes of the small intestine and hepatocytes of the liver, glucuronide and sulfate conjugation metabolism results in resveratrol delivery to other tissue. Resveratrol has multiple biological effects such as anti-cancer, anti-inflammatory and antioxidant (Martin, 2017). Resveratrol can be delivered across the blood–brain barrier and is available in CNS tissue. Most importantly, resveratrol can reach the lesion site and exert neuroprotective effects in several CNS diseases including SCI, cerebral ischemia, multiple sclerosis (Koronowski et al., 2017), hypoxic-ischemic brain injury (Gao et al., 2018), Alzheimer's disease (Qi et al., 2018, 2019), postoperative cognitive dysfunction (Locatelli et al., 2018), amyotrophic lateral sclerosis (Schiaffino et al., 2018), autism spectrum disorder (Xie et al., 2018), ethanol-induced neuroinflammation (Qi et al., 2018, 2019), diabetes mellitus (Ferreira et al., 2018), intracerebral

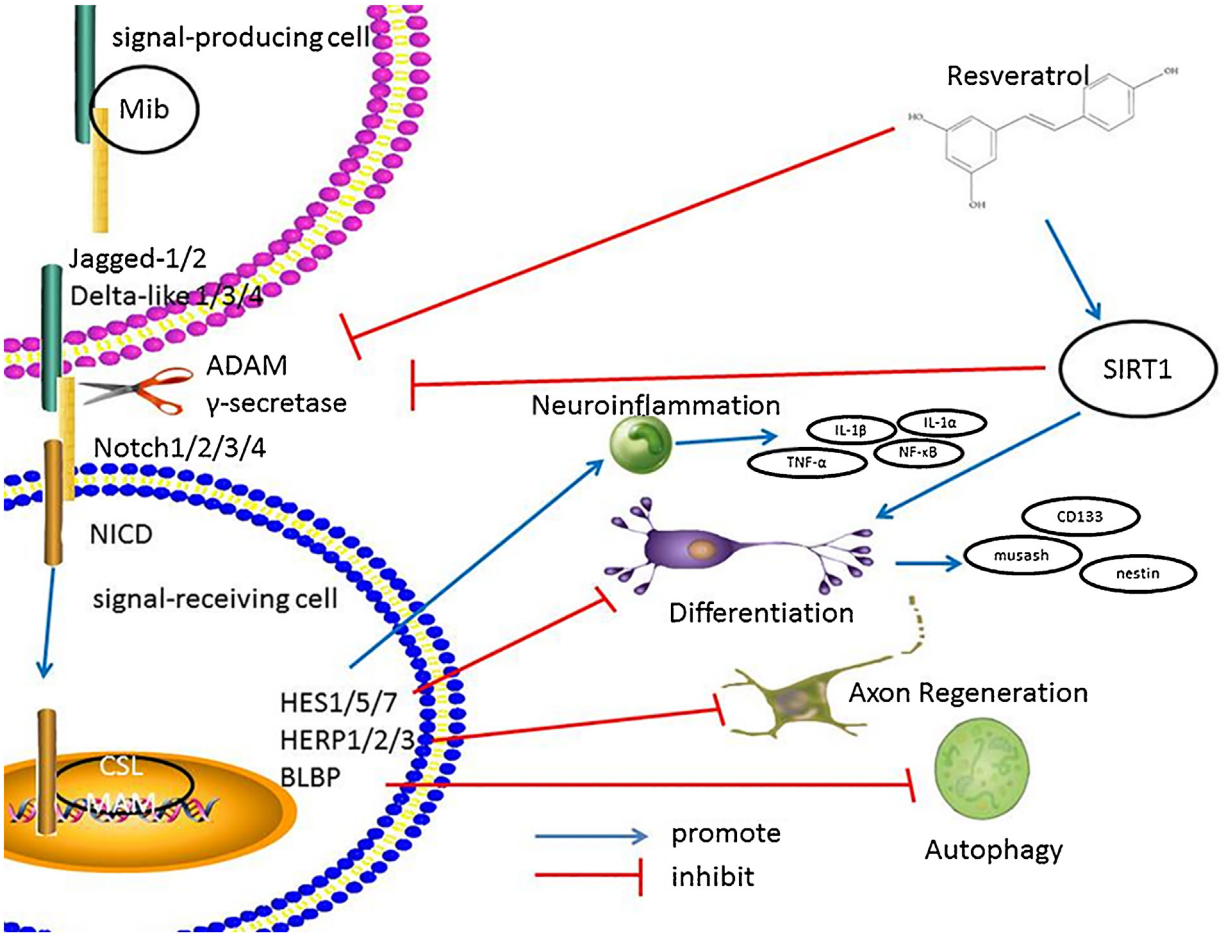

Fig. 2. Pharmacological action of resveratrol on Notch signaling pathway and potentiality of serving as SCI therapeutic.

hemorrhage (Cai et al., 2018), cerebellar ataxia (Ghorbani et al., 2018), pneumococcal meningitis (de Queiroz et al., 2018) and cerebral ischemia/reperfusion Injury (Liu et al., 2018). Owing to its neuroprotective effects and well-established safety, resveratrol is currently in phase II clinical trial for Alzheimer's disease (Turner et al., 2015) (Table 1).

A 5-mg/kg dose of resveratrol delivered in mice has a volume distribution of about 0.2 l/kg reaching the whole brain (Prakash and Young, 2016). In a study where healthy adult volunteers received resveratrol at a dose of 150–900 mg/day, the peak plasma concentrations reached around 0.8–1.5 h, with the mean peak plasma concentration being 3.89–63.8 ng/ml (Almeida et al., 2009). Resveratrol has certain limitations which include short biological half-life, extensive first pass metabolism, chemical instability and poor solubility in water. Nanotechnology can potentially enhance the delivery of resveratrol, thus, improving its medicinal activity and physical properties (Andrade et al., 2018). Several nanosized materials have been reported to encapsulate resveratrol and increase its solubility in water and reduce degradation, such as chitosan, liposomes and polymeric nanoparticles (Jeon et al., 2016).

4.2. Resveratrol inhibits Notch signaling pathway both in-vivo and in-vitro

Resveratrol is a natural Notch inhibitor and can inhibit Notch signaling pathway in different diseases. For instance, resveratrol can decrease Jagged-1, Notch-1 and Hey1/2 mRNA expressions in balloon-injured arteries in-vivo (Zhang et al., 2014a). Cervical tumor cells treated with resveratrol showed suppression of Notch signaling, concomitant with extensive apoptosis in-vitro (Zhang et al., 2014b). Resveratrol prevented liver fibrosis by inhibiting Notch signaling pathway in-vivo (Tanriverdi et al., 2016).

4.3. Resveratrol improves SCI via Notch signaling

Accumulated evidence revealed the neuroprotective effects of resveratrol in experimental SCI animals. Studies such as that of Liu et al. (2011) and Kesherwani et al. (2013) reported resveratrol treatment could improve neurological and histopathological recovery after SCI in rats. Fu et al. (2018) indicated that the protective effects of resveratrol in SCI might be related to the inhibition of p38MAPK signaling pathway, thereby inhibiting oxidative stress. Recent studies show resveratrol to exert its neuroprotection in SCI via autophagy activation. Autophagy is a highly conserved lysosomal degradation pathway, and autophagy flux after SCI has been identified as a protective mechanism. Resveratrol proselytizes autophagy flux to alleviate apoptosis after SCI in rats and mice. This process is mediated by liver kinase B1 (LKB1)/adenosine monophosphate-activated protein kinase (AMPK)/mTOR/p70 ribosomal protein S6 kinase (p70s6k) and AMPK/ sirtuin 1 (SIRT1) signaling pathway (Hu et al., 2017; Wang et al., 2018; Yan et al., 2017). Meng et al. (2018) reported that resveratrol administration results in the increment of Beclin1 (an autophagy marker) in SCI rats' model. Autophagy flux can be significantly alleviated by Notch1 signaling pathway activation; autophagy marker protein, light chain 3, was significantly inhibited by mineral trioxide aggregate-induced Notch activation (Qiu et al., 2017). In contrast, inhibiting Notch1, Notch2 and Notch3 signaling pathway by

DAPT induces more autophagy and autophagy inhibitors, chloroquine and 3-methyladenine, evidently extirpating DAPT-induced autophagy (Song et al., 2015). Also, autophagy can degrade Notch1 signaling (Wu et al., 2016). Autophagy enhancement induced by resveratrol is mediated by SIRT1/AMPK signaling pathway (Zhao et al., 2017). NICD and Notch target genes Hey1/2 can be negatively regulated by SIRT1 (Xie et al., 2012). Resveratrol also has the anti-apoptotic effect in SCI. Resveratrol administration in rats had significant lower levels of TUNEL positive cells (Senturk et al., 2018). Besides autophagy and apoptosis, neuroinflammation response is a key process in secondary injury; neuroinflammation inhibition has been evidenced to promote neuronal survival and motor function recovery. Resveratrol has been widely accepted to be an anti-inflammatory agent, with several studies indicating its inhibition capabilities in neuroinflammation in CNS disease (Yang et al., 2017). Resveratrol treatment can suppress expression of inflammatory cytokines such as myeloperoxidase, IL-1β, and TNF-α after SCI. Resveratrol significantly increased anti-inflammatory factors IL-1RA and IL-1R2 in CNS inflammatory rats model (Xu et al., 2018). Notch signaling pathway is an important regulator in neuroinflammation. Notch1 signaling can regulate T cell and M1 polarization, which in turn can adverse neuroinflammation (Sun et al., 2017). Neutralizing Dll4, one of Notch ligands, can mediate T helper (Th) 1/Th2 cell differentiation and limit neuroinflammation (Bassil et al., 2011). Another promising approach to treat SCI is stem cell transplantation. Notch signaling pathway plays a pivotal role in neuronal differentiation, with a linkage existing between resveratrol and this process. Resveratrol treatment along with neuronal induction media can significantly increase neuronal cell differentiation of dental pulp stem cells (Geng et al., 2017). Moreover, resveratrol can effectively promote BMSCs that expresses neuronal-specific markers musash, nestin and CD133 differentiated into neuronal cells by SIRT1 activation (Joe et al., 2015). Additional studies suggest SIRT1 can suppress Notch signaling pathway by reducing NICD levels (Ma et al., 2014). Also, the application of resveratrol in traumatic brain injury can minimize acute neuronal injury via reduction of astrogliosis and glial scar formation (Constant et al., 2012), which can be triggered by Notch signaling pathway. Notch1 is necessary for differentiation of astrocytes, and Notch inhibition by DAPT can decrease GFAP protein levels in CNS-injured rats. In essence, resveratrol treatment might inhibit Notch signaling pathway to exert its neuroprotective effects in SCI (Fig. 2).

5. Conclusion

Notch signaling pathway involves neuronal cell differentiation, neuroinflammation and axonal regeneration in SCI pathophysiology. Resveratrol, a natural compound, can inhibit Notch signaling pathway in several diseases. There are various studies reporting Notch signaling pathway as a potential therapeutic target of resveratrol in SCI treatment via instigation of NS/PCs; differentiating into neurons, inhibiting neuroinflammation and promoting axonal regeneration and autophagy. However, the specific mechanism of resveratrol in inhibiting Notch signaling pathway in SCI is unclear, especially in neuroinflammtion and axonal regeneration. Thus, further studies pertaining to how resveratrol curtails neuroinflammation and promotes axonal regeneration via Notch inhibition in SCI are necessary.

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Authors' contributions

XL designed the study. SZ, BOAB, YZ and XL prepared the first draft of the manuscript. SZ, BOAB, YZ and XL revised the manuscript. All authors approved the final paper.

Ethical statement

We declared that there were no ethical issues.

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