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The neuroprotective role of SIRT1 in peripheral nerve trauma

Abstract

SIRT1 has been widely associated with its potential as a neuroprotective agent. However, few studies have elucidated the mechanism of SIRT1 activity, particularly in peripheral nerve trauma. The neuroprotective mechanism of SIRT1 is largely linked to its enzymatic activity (as a deacetylase enzyme) as well as its non-enzymatic activity (related to the MAPK/ERK pathway). Deacetylation of non-histone proteins by SIRT1 in the nucleus reduces oxidative stress caused by post-trauma inflammation, while activation of the AMPK and MAPK pathways by SIRT1 in the cytoplasm prevents cell apoptosis and enhances mitochondrial biogenesis.

Keywords: neuroprotection, SIRT1, sirtuin 1, peripheral nerve trauma

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Introduction

Sirtuin 1 (SIRT1) is a class III histone deacetylase (HDAC) enzyme (nicotinamide/NAD-dependent) that plays a critical role in substrate deacetylation. The substrates of SIRT1 include both histone and non-histone proteins (transcription factors and coenzymes). Research has shown that the deacetylation of non-histone proteins by SIRT1 is crucial for neuroprotection mechanisms. Deacetylation of various transcription factors by SIRT1 activates anti-apoptotic genes and inhibits pro-apoptotic genes.[1–3] Pfister et al.,[4] reported that the neuroprotective mechanism of SIRT1 is not influenced by its intracellular location. Previous studies have shown that peripheral nerve trauma of the sciatic nerve increases the expression of active caspase 3 and SIRT1 in the anterior and posterior horns of the spinal cord. The increased expression of SIRT1 occurs after the rise in active caspase 3 expression.[5] However, recent studies providing a clear explanation of the neuroprotective mechanism of SIRT1 in peripheral nerve trauma are still limited. This article aims to further explore the neuroprotective mechanism of SIRT1 in peripheral nerve trauma.

Trauma induces cell apoptosis

Trauma will induce the peripheral nerve regeneration response. One of the cells actively involved in this regeneration is the macrophage. Macrophages act as pro-inflammatory during the acute phase to degrade nerve debris at the distal part of the trauma. This process facilitates the formation of new axon sprouts at the distal part of the trauma. One of the pro-inflammatory cytokines released by pro-inflammatory macrophages is tumor necrosis factor-alpha (TNF-α).[6,7]

Tumor necrosis factor-alpha (TNF-α) induces cell apoptosis through both exogenous and endogenous pathways. Activation of the exogenous pathway occurs through the activation of genes that produce TNF-α receptors, increased transport of TNF-α receptors to the plasma membrane surface, and direct activation of Caspase 3. Increased TNF-α leads to increased reactive oxygen species (ROS), which activate cell apoptosis through the endogenous pathway. Activation of the endogenous pathway is marked by the release of Cytochrome C from the mitochondria to the cytoplasm. This process is induced by the activation of pro-apoptotic proteins such as BH3 interacting domain death agonist (Bid), Bcl2 associated X protein (Bax), Nova, and p53 upregulated modulator of apoptotic protein (Puma). Fusion of Cytochrome C, Apoptotic protease-activating factor-1 (Apaf-1), and Caspase 9 in the cytoplasm results in the formation of the apoptosome complex. The apoptosome complex leads to the activation of Caspase 3.[8]

Peripheral nerve trauma cell apoptosis in animal models

Peripheral nerve trauma models in animal studies are widely used to explore the mechanisms of regeneration following trauma. There are three types of peripheral nerve trauma: ligation trauma, compression trauma, and transection trauma. Ligation and compression traumas are used to study cell apoptosis and neuropathic pain after trauma, while transection trauma is used to investigate axonal degeneration (Wallerian degeneration).[6,9] The effects of compression trauma differ from ligation trauma in terms of the amount and onset of TNF-α cytokine increase, as well as the occurrence of neuropathic pain after trauma. The higher the TNF-α cytokine produced, the more severe the neuropathic pain will be. Compression trauma results in greater TNF-α secretion during the acute phase, while ligation trauma results in higher TNF-α secretion during the chronic phase. Therefore, neuropathic pain from compression trauma is more severe than from ligation trauma.[6,9,10]

Trauma to the peripheral nerve induces cell apoptosis in the spinal cord. Oliveira et al.,[11] reported that transection trauma to the sciatic nerve in rats induces apoptosis of motor neurons in the anterior horn and sensory interneurons in the posterior horn of the rat spinal cord. Apoptosis of sensory interneurons occurs not only in the superficial part but also in the deep part. Scholz et al.,[12] demonstrated that sciatic nerve injury (SNI) induces apoptosis of sensory interneuron cell somas in the posterior horn of the spinal cord. The apoptosis of these neurons occurs on days 7, 14, and 21, with the peak apoptosis occurring on day 7 post peripheral nerve trauma.[12]

Interaction between SIRT1 and MAPK in the regulation of cell apoptosis

The MAPK pathway plays a role in the regulation of cell apoptosis. The administration of TNF-α cytokine to differentiating rat adrenal pheochromocytoma (PC12) cells leads to the activation of the MAPK pathway. An increase in PC12 cell apoptosis occurs when TNF-α is administered simultaneously with a MAPK inhibitor, as well as when the MAPK inhibitor is given before the TNF-α.[13] Studies show that the interaction between SIRT1 and the MAPK/ERK pathway in the cytoplasm plays an important role in the regulation of cell apoptosis after traumatic brain injury (TBI). Increased expression of active

Caspase 3, SIRT1, and MAPK were observed in both vitro and vivo studies during the acute phase after TBI. Increased expression of SIRT1 inhibits the upregulation of active Caspase 3 post-TBI.[14]

There is a bidirectional relationship between SIRT1 and the MAPK pathway following TBI. Activation of SIRT1 not only reduces the expression of active Caspase 3 but also activates the MAPK/ERK pathway. Similarly, in the MAPK/ERK pathway, activation of this pathway not only increases active Caspase 3 expression but also activates the SIRT1 pathway. Administration of SIRT1 siRNA and SIRT1 inhibitor (selermide) increases the expression of active Caspase 3 and reduces MAPK/ERK activation, while administration of the MAPK/ERK inhibitor reduces active Caspase 3 expression and decreases SIRT1 activation.[14]

Neuroprotection by SIRT1

Sirtuins (SIRT) are a family of class III HDAC enzymes that are NAD-dependent. There are 7 types of SIRT (SIRT1-7) in mammals, homologous to the silent information regulator 2 (Sir2p) in *S. cerevisiae*. Deacetylation of non-histone proteins (transcription factors and coenzymes) plays an important role in neuroprotective mechanisms.[1–3]

Sirtuins are found in different intracellular locations in neuronal cells. Pfister et al.,[4] stated that SIRT1, 6, and 7 are predominantly found in the nucleus. SIRT3 and SIRT4 are in mitochondria, while SIRT2 is found in the cytoplasm. Unlike the other six SIRT proteins, SIRT5 can be found in various intracellular locations, including the nucleus, cytoplasm, and mitochondria. The neuroprotective mechanism of SIRT1 against cell apoptosis induction occurs through increased expression of SIRT1 and SIRT5. Unlike SIRT5, the neuroprotective mechanism of SIRT1 is not influenced by its location within the cell.

Substrates of SIRT1 include histone and non-histone proteins (transcription factors and coenzymes). Studies show that deacetylation of non-histone proteins by SIRT1 plays a crucial role in neuroprotection. Deacetylation of various transcription factors by SIRT1 activates anti-apoptotic genes and inhibits pro-apoptotic genes.[1–3] Pfister et al.,[4] reported that the neuroprotective mechanism of SIRT1 is not affected by its location within the cell.

The expression of SIRT1 in the cytoplasm indicates two things: the activation of SIRT1 produced in the cytoplasm and the occurrence of SIRT1 translocation. SIRT1 translocation can occur in both directions: from the cytoplasm to the nucleus and from the nucleus to the cytoplasm. The direction of this translocation is influenced by different translocation signals. Translocation of SIRT1 to the nucleus is induced by cell differentiation events, while translocation to the cytoplasm is induced by phosphoinositide 3 kinase (PI3K) and insulin growth factor-1 (IGF-1).[15] The intracellular location of SIRT1 expression affects the form of neuroprotection provided by SIRT1. Neuroprotection in the nucleus occurs through deacetylation of nuclear substrates, while neuroprotection in the cytoplasm occurs through deacetylation of cytoplasmic substrates and interaction with pathways present in the cytoplasm.[1,14,16]

Deacetylation of non-histone proteins by SIRT1 inhibits cell apoptosis. Deacetylation of the Lupus Ku autoantigen protein p70 (Ku70) results in sequestration of the pro-apoptotic protein Bax. Deacetylation of peroxisome proliferator-activated receptor γ co-activator α (PGC-1α) enhances mitochondrial biogenesis. Deacetylation of the transcription factors p53 and forkhead box O (FOXO) inhibits pro-apoptotic genes. Deacetylation of the transcription factor nuclear factor-κβ (NF-κB) inhibits inflammation.[9,17] Pfister et al.,[4] showed that the neuroprotective mechanism of SIRT1 occurs through both enzymatic (deacetylation) and non-enzymatic actions. The non-enzymatic action of SIRT1 is demonstrated by the creation of SIRT1 mutants, H363Y and H355A. These SIRT1 mutants, which have low deacetylase activity, are also capable of providing neuroprotection against cell apoptosis induction. Administration of SIRT1 inhibitors (nikotinamide and sirtinol) in these mutants did not inhibit SIRT1's neuroprotective effects.

Peripheral nerve trauma and neuroprotection by SIRT1

An increase in TNF-α cytokines following compression trauma of the sciatic nerve induces oxidative stress. This condition is characterized by an increase in free radicals (reactive oxygen species/ROS) and a decrease in antioxidants such as superoxide dismutase (SOD) and catalase (CAT). High intracellular ROS levels activate the PI3K/protein kinase B (PKB/AKT), c-Jun N-terminal kinase (JNK), and mTOR signaling pathways. The elevated ROS levels and decreased intracellular antioxidants induce anaerobic metabolism. Activation of mTOR induces the activation of the pro-apoptotic protein Bax, while anaerobic metabolism leads to a reduction in hydrogen ion (H+) levels in the mitochondria.[15]

Activation of Bax and the decrease in H+ levels induces an increase in mitochondrial outer membrane permeability. Under physiological conditions, the permeability of the outer mitochondrial membrane is maintained by the inactivity of the permeability transition pore complex (PTPC), which connects the outer membrane to the inner membrane of the mitochondria. The activation of PTPC is influenced by several factors, including the activation of the pro-apoptotic protein Bax and a reduction in H+ ions in the intermembrane space of the mitochondria. Bax activation is influenced by the activation of the p53 protein, while the H+ ion levels in the intermembrane space are influenced by electron transport during aerobic metabolism in the mitochondria. The increase in mitochondrial outer membrane permeability through PTPC activation facilitates the release of Cytochrome C into the cytoplasm. The formation of an apoptosome complex induced by the release of Cytochrome C into the cytoplasm triggers the activation of Caspase 3, the effector caspase of cell apoptosis.[18]

Intranuclear activation of SIRT1 occurs due to increased expression of active Caspase 3 and intracellular oxidative stress (Khan et al., 2012).[11] Activated intranuclear SIRT1 induces deacetylation of non-histone nuclear proteins, which activates genes involved in the production of ROS scavengers and antioxidants like SOD and CAT. This process leads to a reduction in intracellular ROS levels and promotes aerobic metabolism. The increase in H+ levels formed during electron transport in the inner mitochondrial membrane inhibits PTPC activation. Inactivation of PTPC prevents increased mitochondrial membrane permeability, thus inhibiting Cytochrome C release from the mitochondria and the formation of active Caspase 3 in the cytoplasm.[15]

Activation of the PI3K and JNK pathways induces the translocation of SIRT1 to the cytoplasm. Neuroprotection in the cytoplasm occurs through both non-enzymatic mechanisms (interaction with AMPK and MAPK pathways) and enzymatic mechanisms (deacetylation of non-histone substrates). Induction of cell apoptosis activates both SIRT1 and MAPK pathways. There is a bidirectional relationship between the expression of SIRT1 and MAPK. The activation of SIRT1 stimulates MAPK activation, and vice versa, MAPK activation also stimulates SIRT1 activation.[14] Activation of MAPK results in the activation of the mTOR pathway. Deacetylation of liver kinase B (LKB) by SIRT1

activates the AMPK pathway, while activation of AMPK increases NAD production, which is used by SIRT1 (NAD-dependent).[16] Activation of the AMPK pathway inhibits mTOR and activates PGC-1α. Deacetylation of PGC-1α by SIRT1 and activation of PGC-1α by the AMPK pathway promote mitochondrial biogenesis and maintain low mitochondrial membrane permeability. Deacetylation of the p53 protein by SIRT1 induces its degradation via the mouse double minute 2 (MDM2)-dependent ubiquitination pathway and inhibits activation of the pro-apoptotic protein Bax. Deacetylation of Ku70 results in sequestration of the pro-apoptotic protein Bax.

The various mechanisms exhibited by SIRT1, both through its enzymatic activity on substrates and its non-enzymatic mechanisms via the activation of AMPK and MAPK pathways, demonstrate its potential as a therapeutic target for neurons at risk of death following peripheral nerve trauma. Further research is needed to explore various agents that can induce SIRT1 upregulation as a neuroprotective strategy post-trauma, such as the use of Resveratrol. By studying this, it is hoped that the adverse effects of neuronal death following peripheral nerve trauma, such as the onset of neuropathic pain or motor impairment, can be minimized.

Conclusion

The neuroprotective effects of SIRT1 in peripheral nerve trauma occur in both the nuclear and cytoplasmic compartments. In the nucleus, SIRT1 enhances antioxidant production, while in the cytoplasm, it interacts with the AMPK and MAPK pathways to regulate cellular survival. Activation of AMPK inhibits mTOR, promoting mitochondrial biogenesis and preventing apoptosis.

Acknowledgements

None.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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