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Mini Review

TXNIP and Mitochondrial Dysfunction: Effect on Nlrp3 Inflammasome Acivation and Neurodegeneration

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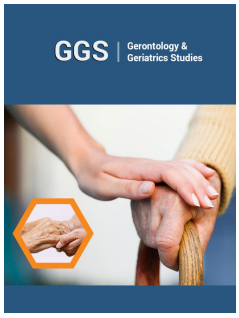

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Abstract

Mitochondrial dysfunction characterizes several neurodegenerative diseases. Several data demonstrate that altered mitochondria dynamics and function activate the NOD-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome, leading to neuroinflammation and participating to the neurodegenerative process. Thioredoxin Interacting Protein (TXNIP) the inhibitor of the ROS scavenger Thioredoxin, plays a key role on NLRP3 inflammasome assembly and activation. Indeed, TXNIP links the oxidative stress to the inflammasome activation. However, only recent studies investigated the role of TXNIP-promoted mitochondrial dysfunction on NLRP3 activation and the effect on the progression of neurodegenerative diseases of the central nervous system. In this mini review, we summarize the recent studies demonstrating the role of TXNIP-NLRP3 axis on the progression of neurodegenerative diseases, suggesting that TXNIP-NLRP3 may be considered a therapeutic target.

Keywords: Neurodegeneration; Mitochondria; Oxidative stress; Txnip; Nlrp3; Alzheimer; Parkinson; Multiple sclerosis

Introduction

Mitochondria are important plastic dynamic organelles, which play a key role in energy production through different pathways and regulate cell homeostasis, apoptosis, calcium homeostasis and reactive oxygen species (ROS)-dependent cellular response. The mitochondrial integrity and metabolism is a pathophysiologic hallmark of several disorders. The equilibrium between mitochondrial fusion and fission controls the cell integrity and metabolism [1]. Mitochondrial alterations participate in many diseases like cancer, cardiovascular disorders and neurodegeneration [2]. The link between neurodegenerative disorders and mitochondrial deficiencies is well established [3-5]. Alterations of mitochondria dynamics and activity induce the NOD-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome, an intracellular pro-inflammatory protein complex, which is the key effector of the innate immune response. NLRP3 activation leads to hyperinflammation, which is characterized by the overproduction of inflammatory cytokines like caspase 1, IL1ß and IL18 [6,7]. Many studies discovered different inflammasome complexes and the regulation of their function has been well characterized [8,9]. NLRP3 inflammasome signaling pathway is involved in the central nervous system neuroinflammatory process [10].

Role of TXNIP on NLRP3 inflammasome activation

NLRP3 inflammasome is composed of NLRP3, the apoptosis-associated speck-like protein (ASC) that holds a Caspase Recruitment Domain (CARD) and a procaspase (procaspase 1, or 4,4 and 11). Several pathogenic micro-organism or endogenous molecules can activate NLRP3 inflammasome at different levels [11]. Many Pathogen-Associated Molecular Patterns (PAMPs) and Damage-Associated Molecular Patterns (DAMPs) molecules induce the NLRP3 inflammasome activation [12]. NLRP3 inflammasome activation plays an important role on

diseases progression by giving rise of pyroptosis and cell death [13]. Thioredoxin-Interacting Protein (TXNIP) the endogenous inhibitor of the ROS scavenger protein thioredoxin (TRX), plays a major role in NLRP3 inflammasome activation [12,14]. TXNIP, a member of the α-arrestin family, modulates several processes including lipid and glucose metabolism, signaling pathways and inflammation. Enhanced TXNIP expression occurs during the onset and development of several disorders. Notably, TXNIP overexpression promotes NLRP3 inflammasome activation [15,16]. NLRP3 oligomerization requires TXNIP, leading to inflammasome activation [15,17].

TXNIP-TRX complex promotes a redox-sensitive signaling that induces NLRP3 inflammasome activation [18,19]. Oxidative stress-induced NLRP3 inflammasome activation is driven by TXNIP [20]. NLRP3 inflammasome induction is associated with mitochondrial dysfunction [21-23]. TXNIP-induced Endoplasmic Reticulum (ER) stress promotes the formation of the NLRP3 inflammasome complex into the cytoplasm [24]. Furthermore, oxidative stress induces subcellular shuttling of TXNIP into mitochondria, triggering ASK1-induced mitochondrial apoptosis [25]. TXNIP mediates inflammatory responses in neurodegenerative diseases [17,22,26-28]. In addition, TXNIP function is linked to sirtuin 1(SIRT1), which is a deacetylase that plays a key role in cellular senescence [29]. Notably, SIRT1 modulates the activity of TXNIP-NLRP3 axis [29], providing a link between the histone code and epigenetic changes and inflammasome activation. Notably, TXNIP and Sirt1play an opposite role on aging process: TXNIP promotes the aging process, while Sirt1 is considered an anti-aging gene [30]. In addition, epigenetic inactivation of anti-aging genes due to environmental factors are linked to enhanced progression of chronic diseases, further suggesting the role of Sirt1 in modulating TXNIP-NLRP3 axis [31-35].

Role of TXNIP-NLRP3 axis on parkinson disease

Parkinson's Disease (PD) is characterized by dopaminergic neurons death in the substantia nigra caused by derangements of neuronal circuits in the basal ganglia. Mitochondrial damage is the major characteristic of PD. Mitochondrial ROS increase in PD neurons, leading to neuronal dysfunction [36]. Altered mitophagy and impaired mitochondria interaction with other organelles and proteins characterize PD neurons [37]. Mitochondrial dysfunction is the major pathogenic alteration in PD [38]. Damaged mitochondrial function leads to increased oxidative stress, affecting a number of cellular pathways, which damage intracellular components, leading to cell death in PD [39]. Moreover, α-synuclein, which aggregates within Lewy bodies and is a hallmark of PD, is also present in mitochondrial enlargement and perturbed cellular membranes, leading to impaired mitochondrial complex I and IV activity [40]. The role of TXNIP in PD has been well studied [41]. TXNIP induces the accumulation of LC3II, a marker of autophagosome and affects the degradation of p62, an important substrate of autophagy, suggesting that TXNIP blocks the autophagic flux [41]. Overexpression of TXNIP in PD substantia nigra reduces the lysosomal membrane protein ATP13A2 levels, increases α-synuclein aggregation, promoting dopaminergic neuronal loss [41]. NLRP3 pathogenic role on PD dopaminergic neurons has been well elucidated [42]. Indeed, PD exhibits pyroptosis linked to the activation of TXNIP-NLRP3 axis, which induces the release of proinflammatory cytokines, including IL-1β, IL-18 and the high mobility group box 1 (HMGB1) protein [43]. Microglia play an important function in PD progression. A study demonstrated that treatment of PD animal models with the micro-RNA miR-29c-3p (miR-29c) exhibited a beneficial effect on microglia inflammation and neuronal loss *in vivo* by suppressing TXNIP-NLRP3 axis activation, demonstrating the role of TXNIP-NLRP3 axis on PD progression [44]. In addition, ER stress induced by α-synuclein accumulation activates the protein kinase C delta (PKC δ). PKC δ activation in PD leads to microgliosis, which in turn promotes dopaminergic neurons death. Interestingly, the activation of the TXNIP-NLRP3 axis can be blocked by the inhibition of PKC δ activation, resulting in diminished microglia inflammation [45].

Role of TXNIP- NLRP3 axis on alzheimer disease

Alzheimer Disease (AD) is a chronic neurodegenerative disease characterized by amyloid-beta (Aβ) plaques and Intracellular Neurofibrillary Tangles (NFT) that are constituted by hyperphosphorylated tau (τ) protein, which is associated to the neuronal cytoskeleton. The major hallmarks of inflammation in AD are lipid oxidation, protein carbonylation and mtDNA oxidation induced by ROS. ROS can be produced by the cellular oxidative metabolism or by intracellular oxidases, such as cyclooxygenase and nicotinamide adenine dinucleotide phosphate oxidase. ROS overproduction activates the NLRP3 inflammasome [46]. TXNIP mediates ROS-induced NLRP3 inflammasome activation, which participates to AD pathophysiology by promoting the neuroinflammatory cascade [21,22,47]. Recent studies underline the role of TXNIP on AD progression by showing that TXNIP is upregulated in the brain of AD mice models and AD patients [48-52]. Several data support that Aβ is carried into the mitochondria, leading to enhanced ROS production, excessive accumulation of mitochondrial Ca^{2+} and mitochondrial impairment, which limit the functionality of mitochondria and induce neuronal dysfunction [53]. It has been shown that TXNIP drives Aβ into microglial mitochondria in AD mice models, leading to mitochondrial dysfunction and oxidative stress, which promotes NLRP3 dysfunction leading to pyroptosis of AD microglia [22]. Moreover, TXNIP-driven Aβ into mitochondria affects mitochondrial dynamics by altering the function of dynamin related protein 1 (Drp1), which is involved in mitochondrial fission [22]. Thus, TXNIP-Aβ complex affects the mitochondria dynamics and function, participating to AD progression. Moreover, Aβ induces ER stress in AD hippocampus, leading to TXNIP-NLRP3 axis activation, further confirming that TXNIP is the link between ER stress and NLRP3 inflammasome activation [47]. In agreement, TXNIP is associated to NLRP3 in the brain of AD patients [17]. In addition, treatment with Chrysophanol exerts a protective effect in an AD model by modulating the ROS/TXNIP/NLRP3 cascade [54] and treatment with epitogallocatechin-3-gallate ameliorates neuroinflammation in an in vitro model of

AD by blocking the ROS/TXNIP/NLRP3 cascade [12]. These data further support the role of TXNI-NLRP3 axis on AD pathophysiology.

Role of TXNIP- NLRP3 axis on multiple sclerosis

Multiple Sclerosis (MS) is an autoimmune neurodegenerative disease. The hallmarks of MS are chronic inflammation and demyelination. Several studies analyzed the role of NLRP3 on MS pathophysiology [55] as well as the interaction between mitochondrial dysfunction and NLRP3 activation [56]. Only one study investigated the effect of TXNIP-NLRP3 axis in MS. This study reveals that treatment with Bixin, a carotenoid, exhibits beneficial effects in an *in vivo* model of MS by inhibiting the TXNIP-NLRP3 axis and reducing the oxidative stress. Bixin treatment prevents both demyelination and neuroinflammation in an in vivo model of MS, supporting that TXNIP-NLRP3 axis plays a key role on MS progression [57].

Conclusion

Although only recent studies investigated the effect of TXNIP as the major link between mitochondrial dysfunction and neurodegeneration, the data that we summarize herein strongly support that TXNIP-NLRP3 axis exhibits a key role on neurodegeneration by promoting neuroinflammation, leading to neurodegeneration. This data suggests that TXNIP-NLRP3 axis is a therapeutic target for neurodegenerative diseases.

References

1. Adebayo M, Singh S, Singh AP, Dasgupta S (2021) Mitochondrial fusion and fission: The fine-tune balance for cellular homeostasis. FASEB J 35(6): e21620.
2. Chan DC (2020) Mitochondrial dynamics and its involvement in disease. Annu Rev Pathol 15: 235-259.
3. Selfridge JE, Lezi E, Lu J, Swerdlow RH (2013) Role of mitochondrial homeostasis and dynamics in Alzheimer's disease. Neurobiol Dis 51: 3-12.
4. Bhatti JS, Kumar S, Vijayan M, Bhatti GK, Reddy PH, et al. (2017) Therapeutic strategies for mitochondrial dysfunction and oxidative stress in age-related metabolic disorders. Prog Mol Biol Transl Sci 146: 13-46.
5. Ross JM, Olson L, Coppotelli G (2015) Mitochondrial and ubiquitin proteasome system dysfunction in ageing and disease: Two sides of the same coin? Int J Mol Sci 16(8): 19458-19476.
6. Sandhir R, Halder A, Sunkaria A (2017) Mitochondria as a centrally positioned hub in the innate immune response. Biochim Biophys Acta Mol Basis Dis 1863(5): 1090-1097.
7. Hamzeh O, Rabiei F, Shakeri M, Parsian H, Saadat P, et al. (2023) Mitochondrial dysfunction and inflammasome activation in neurodegenerative diseases: Mechanisms and therapeutic implications. Mitochondrion 73: 72-83.
8. Guo H, Callaway JB, Ting JP (2015) Inflammasomes: Mechanism of action, role in disease and therapeutics. Nat Med 21(7): 677-687.
9. Zheng D, Liwinski T, Elinav E (2020) Inflammasome activation and regulation: Toward a better understanding of complex mechanisms. Cell Discov 6: 36.
10. Holbrook JA, Jarosz GHH, Caseley E, Lara RS, Poulter JA, et al. (2021) Neurodegenerative disease and the NLRP3 inflammasome. Front Pharmacol 12: 643254.
11. Chernikov OV, Moon JS, Chen A, Hua KF (2021) Editorial: NLRP3 Inflammasome: Regulatory mechanisms, role in health and disease and therapeutic potential. Front Immunol 12: 765199.
12. Xiao Y, Yang C, Si N, Chu T, Yu J, et al. (2024) Epigallocatechin-3-gallate inhibits LPS/aβo-induced neuroinflammation in BV2 cells through regulating the ROS/TXNIP/NLRP3 pathway. J Neuroimmune Pharmacol 19(1): 31.
13. Huang Y, Xu W, Zhou R (2021) NLRP3 Inflammasome activation and cell death. Cell Mol Immunol 18(9): 2114-2127.
14. Mohamed IN, Li L, Ismael S, Ishrat T, El Remessy AB (2021) Thioredoxin interacting protein, a key molecular switch between oxidative stress and sterile inflammation in cellular response. World J Diabetes 12(12): 1979-1999.
15. Cheng F, Wang N (2022) N-Lobe of TXNIP Is critical in the allosteric regulation of NLRP3 via TXNIP binding. Front Aging Neurosci 14: 893919.
16. Joaquim LS, Danielski LG, Bonfante S, Biehl E, Mathias K, et al. (2021) NLRP3 inflammasome activation increases brain oxidative stress after transient global cerebral ischemia in rats. Int J Neurosci 133(4): 375-388.
17. Li L, Ismael S, Nasoohi S, Sakata K, Liao FF, et al. (2019) Thioredoxin-interacting protein (TXNIP) associated NLRP3 inflammasome activation in human Alzheimer's disease brain. J Alzheimers Dis 68(1): 255-265.
18. Devi TS, Lee I, Hüttemann M, Kumar A, Nantwi KD, et al. (2012) TXNIP links innate host defense mechanisms to oxidative stress and inflammation in retinal muller glia under chronic hyperglycemia: Implications for diabetic retinopathy. Exp Diabetes Res. 2012: 438238.
19. Yoshihara E, Masaki S, Matsuo Y, Chen Z, Tian H, et al. (2014) Thioredoxin/Txnip: Redoxisome, as a redox switch for the pathogenesis of diseases. Front Immunol 4: 514.
20. Zhou R, Tardivel A, Thorens B, Choi I, Tschopp J, et al. (2010) Thioredoxin-interacting protein links oxidative stress to inflammasome activation. Nat Immunol 11(2): 136-140.
21. Sbai O, Bazzani V, Tapaswi S, McHale J, Vascotto C, et al. (2023) Is Drp1 a link between mitochondrial dysfunction and inflammation in Alzheimer's disease? Front Mol Neurosci 16: 1166879.
22. Sbai O, Djelloul M, Auletta A, Ieraci A, Vascotto C, et al. (2022) RAGE-TXNIP axis drives inflammation in Alzheimer's by targeting Aβ to mitochondria in microglia. Cell Death Disease13(4): 302.
23. Dagdeviren S, Lee RT, Wu N (2023) Physiological and pathophysiological roles of thioredoxin interacting protein: A perspective on redox inflammation and metabolism. Antioxid Redox Signal 38: 442-460.
24. Choi EH, Park SJ (2023) TXNIP: A key protein in the cellular stress response pathway and a potential therapeutic target. Exp Mol Med 55(77): 1348-1356.
25. Park SJ, Kim Y, Li C, Suh J, Sivapackiam J, et al. (2022) Blocking CHOP-dependent TXNIP shuttling to mitochondria attenuates albuminuria and mitigates kidney injury in nephrotic syndrome. Proc Natl Acad Sci USA 119(35): e2116505119.
26. Ishrat T, Mohamed IN, Pillai B, Soliman S, Fouda AY, et al. (2015) Thioredoxin-interacting protein: A novel target for neuroprotection in experimental thromboembolic stroke in mice. Mol Neurobiol 51(2): 766-778.
27. Ding R, Ou W, Chen C, Liu Y, Li H, et al. (2020) Endoplasmic reticulum stress and oxidative stress contribute to neuronal pyroptosis caused by cerebral venous sinus thrombosis in rats: Involvement of TXNIP/peroxynitrite-NLRP3 inflammasome activation. Neurochem Int 141: 104856.
28. Gamdzyk M, Doycheva DM, Kang R, Tang H, Travis ZD, et al. (2020) GW0742 activates miR-17-5p and inhibits TXNIP/NLRP3-mediated

inflammation after hypoxic-ischaemic injury in rats and in PC12 cells. J Cell Mol Med 24(21): 12318-12330.

29. Thapa R, Moglad E, Afzal M, Gupta G, Bhat AA, et al. (2024) The role of sirtuin 1 in ageing and neurodegenerative disease: A molecular perspective. Ageing Res Rev 102: 102545.

30. Martins IJ (2016) Anti-aging genes improve appetite regulation and reverse cell senescence and apoptosis in global populations. Advances in Aging Research 5:1.

31. Martins IJ (2017) Single gene inactivation with implications to diabetes and multiple organ dysfunction syndrome. J Clin Epigenet 3(3): 24.

32. Adjei MJ, Sun Q, Smithson SB, Shealy GL, Amerineni KD, et al. (2023) Age-dependent loss of hepatic SIRT1 enhances NLRP3 inflammasome signaling and impairs capacity for liver fibrosis resolution. Aging Cell 22(5): e13811.

33. Chen H, Deng J, Gao H, Song Y, Zhang Y, et al. (2023) Involvement of the SIRT1-NLRP3 pathway in the inflammatory response. Cell Commun Signal 21(1): 185.

34. Han Y, Sun W, Ren D, Zhang J, He Z, et al. (2020) SIRT1 agonism modulates cardiac NLRP3 inflammasome through pyruvate dehydrogenase during ischemia and reperfusion. Redox Biol 34: 101538.

35. Mousa SA, Gallati C, Simone T, Dier E, Yalcin M, et al. (2009) Dual targeting of the antagonistic pathways mediated by sirt1 and TXNIP as a putative approach to enhance the efficacy of anti-aging interventions. Aging (Albany NY) 1(4): 412-424.

36. Chen C, McDonald D, Blain A, Mossman E, Atkin K, et al. (2023) Parkinson's disease neurons exhibit alterations in mitochondrial quality control proteins. NPJ Parkinsons Dis 9: 120.

37. Chen C, Turnbull DM, Reeve AK (2019) Mitochondrial dysfunction in Parkinson's Disease-cause or consequence? Biology 8(2): 38.

38. Moon HE, Paek SH (2015) Mitochondrial dysfunction in Parkinson's Disease. Exp Neurobiol 24(2):103-116.

39. Henrich MT, Oertel WH, Surmeier DJ, Geibl FF (2023) Mitochondrial dysfunction in parkinson's disease-a key disease hallmark with therapeutic potential. Mol Neurodegener 18(1): 83.

40. Amirian R, Badrbani MA, Derakhshankhah H, Izadi Z, Shahbazi MA (2023) Targeted protein degradation for the treatment of Parkinson's Disease: Advances and future perspective. Biomed Pharmacother 166: 115408.

41. Su CJ, Feng Y, Liu TT, Liu X, Bao JJ, et al. (2017) Thioredoxin-interacting protein induced α-synuclein accumulation via inhibition of autophagic flux: Implications for Parkinson's disease. CNS Neurosci Ther 23(9): 717-723.

42. Yu J, Zhao Z, Li Y, Chen J, Huang N, et al. (2024) Role of NLRP3 in Parkinson's disease: Specific activation especially in dopaminergic neurons. Heliyon 10(7): e28838.

43. Qayyum N, Hasseb M, Kim MS, Choi S (2021) Role of thioredoxin-Interacting protein in diseases and its therapeutic outlook. Int J Mol Sci 22(5): 2754.

44. Wang R, Li Q, He Y, Yang Y, Ma Q, et al. (2020) miR-29c-3p inhibits microglial NLRP3 inflammasome activation by targeting NFAT5 in Parkinson's disease. Genes Cells 25(6): 364-374.

45. Samidurai M, Palanisamy BN, Bargues CA, Hepker M, Kondru N, et al. (2021) PKC delta activation promotes endoplasmic reticulum stress (ERS) and NLR family pyrin domain-containing 3 (NLRP3) inflammasome activation subsequent to asynuclein-induced microglial activation: Involvement of thioredoxin-interacting protein (TXNIP)/ thioredoxin (TRX) redoxisome pathway. Front Aging Neurosci 13: 661505.

46. Rosa CP, Belo TCA, Santos NCM, Silva EN, Gasparotto J, et al. (2023) Reactive oxygen species trigger inflammasome activation after intracellular microbial interaction. Life Sci 331: 122076.

47. Ismael S, Wajidunnisa, Sakata K, McDonald MP, Liao FF, et al. (2021) ER stress associated TXNIP-NLRP3 inflammasome activation in hippocampus of human Alzheimer's disease. Neurochem Int 148: 105104.

48. Wang Y, Wang Y, Bharti V, Zhou H, Hoi V, et al. (2019) Upregulation of thioredoxin-interacting protein in brain of amyloid-β protein precursor/ presenilin 1 transgenic mice and amyloid-β treated neuronal cells. J Alzheimers Dis 72(1): 139-150.

49. Hokama M, Oka S, Leon J, Ninomiya T, Honda H, et al. (2014) Altered expression of diabetes-related genes in Alzheimer's disease brains: The hisayama study. Cereb Cortex 24(9): 2476-2488.

50. Fertan E, Rodrigues GJ, Wheeler RV, Goguen D, Wong AA, et al. (2019) Cognitive decline, cerebral-spleen tryptophan metabolism, oxidative stress, cytokine production and regulation of the Txnip gene in a triple transgenic mouse model of Alzheimer disease. Am J Pathol 189(7): 1435-1450.

51. Perrone L, Valente M (2021) The emerging role of metabolism in brain-heart axis: New challenge for the therapy and prevention of Alzheimer Disease. May Thioredoxin Interacting Protein (TXNIP) play a role? Biomolecules 11(11): 1652.

52. Zhang M, Hu G, Shao N, Qin Y, Chen Q, et al. (2021) Thioredoxin-interacting protein (TXNIP) as a target for Alzheimer's disease: Flavonoids and phenols. Inflammopharmacology 29(5): 1317-1329.

53. Mishra J, Bhatti GK, Sehrawat A, Singh C, Singh A, et al. (2022) Modulating autophagy and mitophagy as a promising therapeutic approach in neurodegenerative disorders. Life Sci 311 (Pt A): 121153.

54. Zhang M, Ding ZX, Huang W, Luo J, Ye S, et al. (2023) Chrysophanol exerts a protective effect against $A\beta_{25-35}$-induced Alzheimer's disease model through regulating the ROS/TXNIP/NLRP3 pathway Inflammopharmacology 31(3): 1511-1527.

55. Brint A, Greene S, Fennig VAR, Wang S (2024) Multiple sclerosis: The NLRP3 inflammasome, gasdermin D and therapeutics. Ann Transl Med 12(4): 62.

56. Shadab A, Abbasi KM, Saharkhiz M, Ahadi SH, Shokouhi B, et al. (2024) The interplay between mitochondrial dysfunction and NLRP3 inflammasome in multiple sclerosis: Therapeutic implications and animal model studies. Biomed Pharmacother 175: 116673.

57. Yu Y, Wu DM, Li J, Deng SH, Liu T, et al. (2020) Bixin attenuates experimental autoimmune encephalomyelitis by suppressing TXNIP/ NLRP3 inflammasome activity and activating NRF2 signaling. Front Immunol 11: 593368.