Biologia Serbica, 2024, 46: 37-42

DOI: 10.5281/zenodo.14537277

Mini review

Transcription factor NRF2 as a key modulator of immune response

Suzana STANISAVLJEVIĆ

University of Belgrade, Institute for Biological Research "Siniša Stanković" - National Institute of Republic of Serbia, Department of Immunology, 11108 Belgrade, Serbia

Accepted: 12 September 2024 / Published online: 23 December 2024

Summary. Nuclear factor erythroid 2-related factor 2 (NRF2) is a transcription factor that plays a crucial role in immune regulation by promoting antioxidant defences, modulating inflammation, supporting immune cell function, and influencing autoimmune responses. Dysregulation of NRF2 signalling is implicated in the pathogenesis of autoimmune diseases and chronic inflammatory conditions. NRF2 activators, through their anti-inflammatory and antioxidant properties, have shown potential therapeutic benefits in preclinical and clinical studies for diseases characterised by dysregulated inflammation and oxidative stress such as multiple sclerosis (MS). MS is an autoimmune, neurodegenerative, and inflammatory disease of the central nervous system (CNS). In our model of MS, experimental autoimmune encephalomyelitis (EAE), we have investigated the role of NRF2 activators on several immune cell types important for the pathology of CNS autoimmunity. Ethyl pyruvate (EP), a redox analogue of MS drug dimethyl fumarate, has been proven to have beneficial effects in EAE, by suppressing encephalitogenic T cells and macrophages and inducing tolerogenic properties in dendritic cells (DCs). In a recent study, we have shown that EP achieves its effects in DCs by increasing the expression of several NRF2 downstream genes and by decreasing the expression of NF-kB genes, suggesting that the tolerogenic effect of EP is achieved through the activation of the NRF2 signalling pathway. Another tested substance, named SB140, is a derivative of cholic bile acid. This compound was tested in immune cells implicated in the pathogenesis of EAE: microglia and encephalitogenic T cells, and it was shown to have anti-inflammatory effects. These results demonstrate that both agents have potent immunomodulatory effects and suggest that they act as NRF2 activators. Both EP and SB140 are indicated as promising therapeutics in MS, but also in other diseases mediated by inflammation and oxidative stress, and thus, their role should be further investigated.

Keywords: experimental autoimmune encephalomyelitis, immunomodulation, multiple sclerosis, nuclear factor erythroid 2-related factor 2 (NRF2), transcription factor.

NRF2, AN IMPORTANT TRANSCRIPTION FACTOR FOR ANTIOXIDANT PROTECTION

Nuclear Factor Erythroid 2-Related Factor 2 (NRF2) is an important transcription factor encoded by the Nuclear Factor Erythroid 2 Like 2 (NFE2L2) gene. It plays a crucial role in cellular defence against oxidative stress. The NRF2 factor belongs to the Cap'N'Collar (CNC) subfamily of basic leucine zipper (bZIP) transcription factors, which comprises three transcription factors NRF1, 2, and 3 (Jaramillo et al. 2013). It has seven conserved NRF2 ECH homology (Neh) domains with distinct functions to control NRF2 transcriptional activity (Hayers et al. 2014). These domains modulate NRF2 stability and transcriptional activation of its target genes at multiple levels, including transcriptional, post-transcriptional, and post-translational regulation in response to various impairments (He et al. 2020).

NRF2 is expressed in all cell types and is normally bound

Invited lecture presented at the XIII Conference of The Serbian Biochemical Society, entitled "Amplifying Biochemistry Concepts", September 19-20, 2024, Kragujevac, Serbia

E-mail: ssuzana@ibiss.bg.ac.rs

to its inhibitor protein Keap1 (Kelch-like ECH-associated protein 1) in the cytoplasm under unstressed conditions, which normally keeps its basal protein level low (He et al. 2020). When NRF2 is exposed to oxidative stress, electrophilic substances, or reactive oxygen species (ROS), it dissociates from Keap1. Once dissociated from Keap1, NRF2 translocates to the nucleus, forms heterodimers with small Maf proteins, and binds to the antioxidant response elements (AREs) in the promoter regions of its target genes (Esteras et al. 2016). Binding to AREs activates transcription of a wide range of genes encoding antioxidant enzymes (such as heme oxygenase-1, catalase, and superoxide dismutase), phase II detoxification enzymes (such as glutathione S-transferases), and other cytoprotective proteins. The proteins encoded by the NRF2 target genes neutralize ROS, detoxify harmful substances, and restore the cellular redox balance. This antioxidant defence system helps to mitigate oxidative damage to biomolecules such as lipids, proteins, and DNA. This activation enables cells to maintain redox homeostasis and protect themselves from damage caused by ROS and other harmful molecules. NRF2 is, therefore, an essential component of the body's antioxidant response and has implications for various diseases, including cancer, neurodegenerative disorders, and cardiovascular diseases.

Recent studies have identified novel NRF2 target genes and uncovered several new functions of NRF2 besides redox-regulatory functions, including regulation of inflammation, autophagy, metabolism, proteostasis, and unfolded protein response (UPR) (He et al. 2020).

REGULATION OF IMMUNE RESPONSES THROUGH NRF2 ACTIVATION

As mentioned, NRF2 is expressed in all cell types, but its expression level differs among cell types. For instance, NRF2 expression is high in various immune cells, such as macrophages, dendritic cells (DCs), T cells, and B cells (Bagger et al. 2016). In the aforementioned types of cells, NRF2 activation supports their differentiation, proliferation, and survival by protecting them from oxidative stress and inflammatory insults. This ensures an optimal immune response to pathogens and other challenges.

NRF2 activation can also modulate inflammatory responses. It inhibits the production of pro-inflammatory cytokines (such as interleukin (IL)-1β, IL-6, tumour necrosis factor, TNF) and chemokines in immune cells by suppressing NF-κB signalling, a key pathway in inflammation (Saha et al. 2020). This anti-inflammatory effect helps to attenuate excessive immune activation and tissue damage under inflammatory conditions. In addition, NRF2 interacts with other cellular signalling pathways involved in immune regulation, such as the mTOR (mechanistic target of rapamycin) pathway and autophagy. These interactions contribute to NRF2's ability to coordinate cellular responses to stress and maintain immune cell homeostasis.

NRF2 signalling is implicated in the regulation of autoimmune diseases. By maintaining redox balance and controlling inflammatory responses, NRF2 activation can attenuate autoimmune responses and limit tissue damage associated with autoimmune diseases. Thus, NRF2 activators, including synthetic and natural compounds (such as sulforaphane from cruciferous vegetables), are being investigated for their potential therapeutic benefits in immune-mediated diseases. These compounds can increase NRF2 activity, boost antioxidant defences and dampen inflammatory responses, offering promising possibilities for immune modulation and disease treatment. Understanding the role of NRF2 in immune homeostasis can provide insight into potential therapeutic strategies for the treatment of immune-related diseases.

ROLE OF NRF2 IN NEURODEGENERATIVE DISEASES

Neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS) are characterized by oxidative stress-induced damage to neurons and glial cells in the brain. Increased markers of oxidative damage along with decreased activity of antioxidant enzymes have been observed in the blood and brain of these patients. Imaging studies have shown mitochondrial dysfunction in the neurons of Alzheimer's patients (Brandes et al. 2019) as well as in the dopamine neurons in the substantia nigra in Parkinson's patients (Hattingen et al. 2009), and these events occur in the early stages of both diseases. Inflammation is also a prominent feature of neurodegenerative diseases, as evidenced by elevated levels of pro-inflammatory cytokines such as TNF and IL-6 in the brain and CSF of Parkinson's patients (Hirsch et al. 2012; Dzamko et al. 2015) and in CSF of MS patients and patients with inflammatory neurological diseases (Maimone et al. 2017).

Due to its proven anti-inflammatory and antioxidant properties, NRF2 is a good target for the therapy of many diseases, including neurodegenerative diseases. Several studies provide evidence for the role of NRF2 in Alzheimer's disease, where they have reported that nuclear expression of NRF2 is decreased in Alzheimer's disease patients (Ramsey et al. 2007; Kanninen et al. 2008; Wang et al. 2017). There is also evidence of altered NRF2 expression in nigral dopaminergic neurons in Parkinson's disease patients (Schipper et al. 1998; Ramsey et al. 2007).

NRF2 activation increases the expression of antioxidant

enzymes (e.g. superoxide dismutase, catalase, glutathione peroxidase) and molecules involved in cellular redox balance. This helps to neutralize ROS and reduce oxidative damage, thereby protecting neurons from degeneration. NRF2 activation can also suppress pro-inflammatory signalling pathways such as NF-κB and reduce the production of pro-inflammatory cytokines (e.g. TNF, IL-1β). By dampening neuroinflammation, NRF2 helps to attenuate inflammatory responses that contribute to neuronal damage. Another protective effect of NRF2 in neurodegenerative diseases is to support mechanisms that promote the clearance of accumulated misfolded proteins (e.g., β-amyloid, α-synuclein), thereby reducing their accumulation and associated neurodegenerative pathology (Brandes et al. 2019).

Further research into NRF2 signalling and its modulation holds promise for developing effective treatments to combat neurodegeneration and improve the quality of life of affected individuals. Experiments in animal models and preclinical studies have shown that various NRF2 activators can be used to attenuate neurodegenerative pathology and improve outcomes in animal models of Alzheimer's disease, Parkinson's disease and ALS (Brandes et al. 2019). Clinical studies are investigating the potential of NRF2 activators for therapeutic intervention to slow disease progression or alleviate symptoms in patients with neurodegenerative diseases (Saha et al. 2022; De Plano et al. 2023).

EFFECTS OF NRF2 ON MS AND EAE

NRF2 is emerging as an important player in the pathogenesis of MS and its experimental model, experimental autoimmune encephalomyelitis (EAE). Oxidative stress is associated with the development and progression of MS and EAE. Oxidative damage is associated with activated microglial enzymes involved in the production of oxygen radicals, such as NADPH oxidases and myeloperoxidase. Increased production of ROS and impaired antioxidant defences contribute to neuron and glial cell damage, inflammation and demyelination in the central nervous system (CNS) (Vasconcelos et al. 2019). Oxidative damage is thought to be triggered by inflammation and radical production in activated microglia in the early stages of MS and is exacerbated as MS progresses. NRF2 activation increases the expression of antioxidant enzymes (e.g. superoxide dismutase, catalase, glutathione peroxidase) and thus mitigates oxidative stress and protects against CNS damage.

The role of NRF2 as an important player in the pathogenesis of MS has been shown in an animal model of MS, EAE. Nrf2-deficient mice had more severe EAE than wild-type littermates (Johnson et al. 2010). Studies using NRF2 activators or genetic models have shown that NRF2 activators can reduce disease severity and improve outcomes in EAE models (Cuadrado et al. 2018; Paladino et al. 2018). These effects are associated with NRF2-mediated enhancement of antioxidant defences. NRF2 can also contribute to reducing the severity of EAE through its anti-inflammatory effects. While the activation of NRF2 leads to the inhibition of NF-κB in homeostatic conditions, this is not the case in MS. This phenomenon, although contradictory, can be explained in several ways. Under chronic inflammatory conditions, as in MS, the ROS levels may overwhelm the NRF2 pathway's capacity to properly inhibit NF-κB. The interplay between NRF2 and NF-κB is complex. It is known that they are in competition for transcriptional coactivators like CREB-binding protein and p300 (Tonev et al. 2023). This might result in reduced transcriptional output from NRF2, diminishing its protective effects, which is particularly evident in chronic inflammatory diseases like MS, where NF-κB activity is sustained. Another explanation could be that the activity of NRF2 is downregulated. There are conflicting data on the levels of NRF2 in neurodegenerative diseases. One publication is showing an absence of NRF2 in neurons of AD patients (Maldonado et al. 2022), but in another publication, high upregulation of NRF2 was observed in active MS lesions (Licht-Mayer et al. 2015). However, the level of NRF2 in immune cells might be low. Accordingly, activation of NRF2 suppresses NF-κB activity and consequently the production of pro-inflammatory cytokines (e.g. TNF, IL-6, IL-1β) by T cells and macrophages (Saha et al. 2020). This reduces the inflammatory response and helps to stop the inflammation. NRF2 not only affects the production of pro-inflammatory cytokines, but also enhances the phagocytic activity of macrophages, improving their ability to engulf and eliminate pathogens, apoptotic cells and cellular debris (Yu et al. 2022). NRF2 may exert an immunomodulatory role by influencing the differentiation of immune cells. In EAE, NRF2 activation has been shown to influence the differentiation of T helper cells (Th cells) by promoting a shift towards regulatory T cells (Tregs) and dampening Th17 responses (He et al. 2020; Wu et al. 2024), which are known to exacerbate autoimmune inflammation. This regulatory role may help maintain immune tolerance and limit autoimmune responses in MS and EAE. NRF2 may influence DC maturation and antigen-presenting abilities (Vanconcelos et al. 2019). It can promote tolerogenic DC phenotypes that support immune tolerance rather than effector T cell activation. NRF2 activation in DCs can suppress the production of pro-inflammatory cytokines and chemokines, thereby dampening immune responses and promoting immune tolerance (Fig. 1).

Activation of NRF2 promotes neuron survival and supports the repair of damaged myelin in MS and EAE models (Brandes et al. 2020). By strengthening cellular defences against oxidative stress and inflammation, NRF2 contrib-

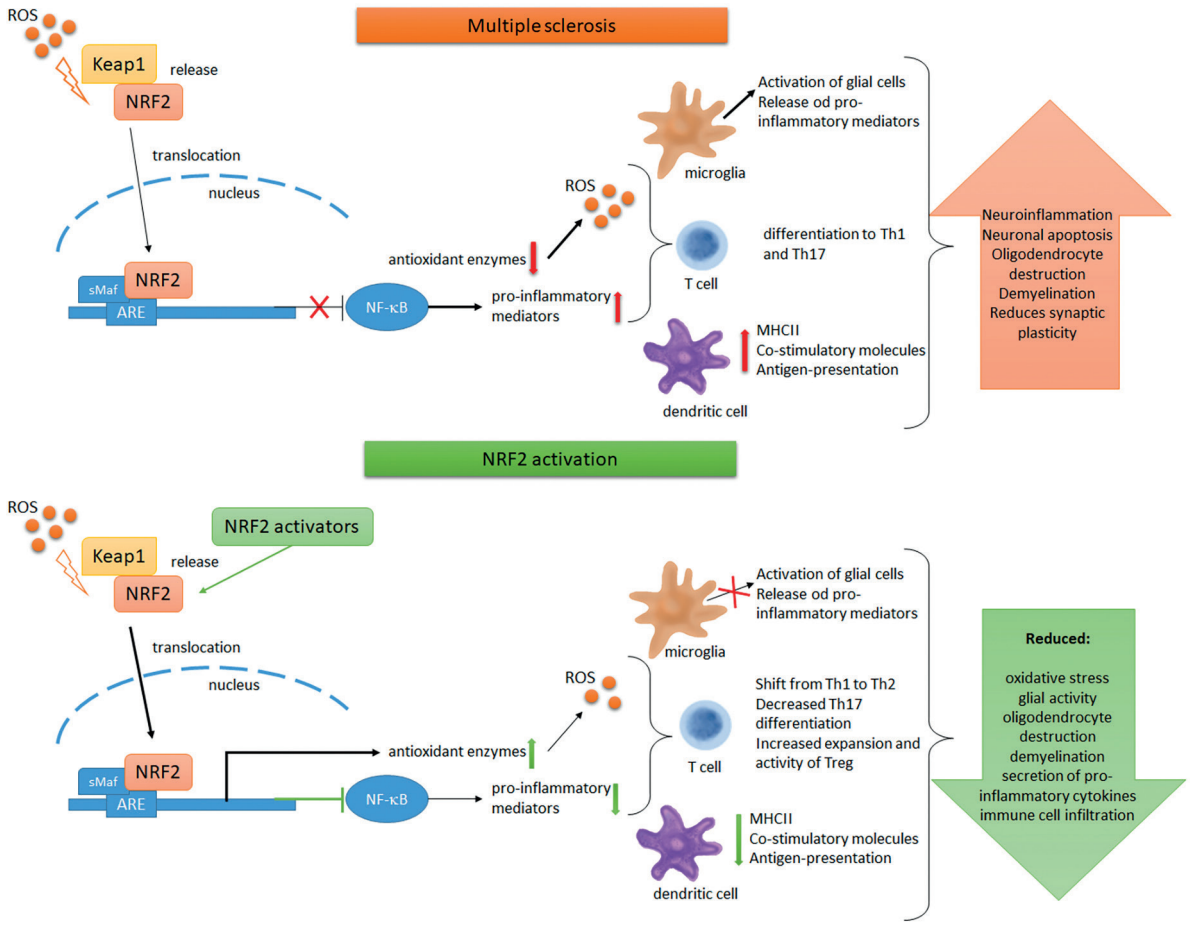

Fig. 1. Proposed mechanisms of NRF2 activators in ameliorating CNS autoimmunity.

utes to neuroprotection and maintenance of CNS integrity. Targeting NRF2 signalling pathways is therefore a promising novel therapeutic approach for the treatment of MS and related autoimmune and neuroinflammatory diseases. In our studies, we have tested several compounds that have been shown to have good therapeutic potential in EAE. One of them, ethyl pyruvate (EP), is a redox analogue of dimethyl fumarate, an approved therapeutic agent for MS (Miljkovic et al. 2015). EP has been shown to have a strong immunomodulatory effect in various animal models of autoimmune and inflammatory diseases, primarily affecting T cells, macrophages and DCc (Koprivica et al. 2022). EP was shown to improve EAE by suppressing encephalitogenic T cells and macrophages and to induce tolerogenic effects on DCs in vitro in both mice and human cells (Djedovic et al. 2019). Moreover, the effect of EP on human cells obtained from MS patients was comparable to that of the known tolerogenic agent vitamin D3 (Djedovic et al. 2019). Another study showed that EP promotes the tolerogenic properties of DCs by downregulating the expression of maturation-related Toll-like receptors 7 and 9 through a reduction in glycolysis and mitochondrial respiration in DCs (Chakhtoura et al. 2019). All of this speaks to the potential therapeutic applications of EP, which prompted us to further investigate the mechanisms by which EP achieves the above effects. We investigated the pro-inflammatory NF-kB and antioxidant signalling pathways controlled by NRF2. Analysis of NRF2 downstream genes and immunohistochemistry revealed a marked increase in the expression of the catalytic subunit of glutamate cysteine ligase (GCLC), the regulatory subunit of glutamate cysteine ligase (GCLM), heme oxygenase (HO-1), and NAD(P)H dehydrogenase quinone 1 (NQO1) in DCs treated with EP. On the other hand, gene expression of pro-inflammatory iNOS and IL-23 was reduced in DCs treated with EP. (Stanisavljevic et al. 2024)

Another compound tested in EAE, a derivative of cholic bile acid named SB140, was tested in the search for novel NRF2 activators. This compound was synthesized to increase electrophilic functionality and to improve the compound's ability to activate NRF2. Indeed, SB140 effectively activated

NRF2 signalling in myeloid-derived cells and microglia. It efficiently reduced the ability of microglial cells to produce inflammatory mediators, nitric oxide, IL-6 and TNF. SB140 also affected encephalitogenic T cells by reducing their proliferation and the production of pro-inflammatory cytokines, IL-17 and interferon (IFN)-γ. (Bjedov et al. 2024). These results indicate that SB140 is a potent Nrf2 activator and immunomodulatory agent. Therefore, further research on the application of SB140 in the treatment of neuroinflammatory diseases is warranted. Animal models for MS and other inflammatory neurological diseases are a good choice.

CONCLUSIONS

NRF2 is a master regulator of antioxidant pathways. By boosting antioxidant capacity, NRF2 protects immune cells from damage caused by oxidative stress, ensuring their proper function and longevity. Activation of NRF2 exerts significant regulatory effects on inflammation and immune responses, influencing various aspects of immune cell function and inflammatory pathways. By suppressing NF-κB activity, NRF2 inhibits the production of pro-inflammatory mediators and thus reduces inflammation. In addition, NRF2 influences the differentiation and function of various immune cells, including macrophages, DCs, T cells, and B cells. It supports immune cell survival, proliferation, and differentiation. These immunoregulatory effects are beneficial in contexts such as autoimmune diseases, chronic inflammation, and infections, where maintaining immune homeostasis and minimizing tissue damage is critical. NRF2 activation promotes neuronal survival and resilience to stressors encountered in neurodegenerative conditions. By enhancing antioxidant defences, reducing inflammation, and supporting protein quality control mechanisms, NRF2 helps to maintain neuronal function and protects against neurotoxic insults. As such, it is a promising therapeutic target. Research continues to explore pharmacological agents and natural compounds that can modulate NRF2 activity to enhance cellular defence mechanisms and combat oxidative stress-related pathologies. Our studies focusing on understanding NRF2's influence on immune cell functions provide insights into its therapeutic potential for modulating immune responses in various disease conditions.

ACKNOWLEDGEMENTS

This research was funded by the Ministry of Science, Technological Development, and Innovation, Republic of Serbia (Contract No. 451-03-66/2024-03/200007).

REFERENCES

Bagger FO, Sasivarevic D, Sohi SH, Laursen LG, Pundhir S, Sonderby CK, Winther O, Rapin N, Porse BT. 2016. BloodSpot: A database of gene expression profiles and transcriptional programs for healthy and malignant haematopoiesis. Nucleic Acids Research. 44:917–924.

Bjedov S, Stegnjaić G, Stanisavljević S, Lazarević M, Pilipović I, Sakač M, Miljković Đ. 2024. Anti-neuroinflammatory effects of a novel bile acid derivative. International Journal of Molecular Sciences. 25(13):7136.

Brandes MS, Gray NE. 2020. NRF2 as a therapeutic target in neurodegenerative diseases. ASN Neuro. 12:1759091419899782.

Chakhtoura M, Chain RW, Sato PY, Qiu CC, Lee MH, Meissler JJ, Eisenstein TK, Koch WJ, Caricchio R, Gallucci S. 2019. Ethyl pyruvate modulates murine dendritic cell sctivation and survival through their immunometabolism. Frontiers in Immunology. 10:30.

Cuadrado A, Manda G, Hassan A, Alcaraz MJ, Barbas C, Daiber A, Ghezzi P, León R, López MG, Oliva B, et al. 2018. Transcription factor NRF2 as a therapeutic target for chronic diseases: A systems medicine approach. Pharmacological Reviews. 70(2):348–383.

De Plano LM, Calabrese G, Rizzo MG, Oddo S, Caccamo A. 2023. The role of the transcription factor Nrf2 in Alzheimer's disease: Therapeutic opportunities. Biomolecules. 13(3):549.

Djedović N, Mansilla MJ, Jevtić B, Navarro-Barriuso J, Saksida T, Martínez-Cáceres EM, Miljković Đ. 2019. Ethyl pyruvate induces tolerogenic dendritic cells. Frontiers in Immunology. 10:157.

Dzamko N, Geczy CL, Halliday GM. 2015. Inflammation is genetically implicated in Parkinson's disease. Neuroscience. 302:89–102.

Esteras N, Dinkova-Kostova AT, Abramov AY. 2016. Nrf2 activation in the treatment of neurodegenerative diseases: A focus on its role in mitochondrial bioenergetics and function. Biologacal Chemistry. 397(5):383–400.

Hattingen E, Magerkurth J, Pilatus U, Mozer A, Seifried C, Steinmetz H, Zanella F, Hilker R. 2009. Phosphorus and proton magnetic resonance spectroscopy demonstrates mitochondrial dysfunction in early and advanced Parkinson's disease. Brain. 132(12):3285–3297.

Hayes JD, Dinkova-Kostova AT. 2014. The Nrf2 regulatory network provides an interface between redox and intermediary metabolism. Trends in Biochemical Sciences. 39:199–218.

He F, Ru X, Wen T. 2020. NRF2, a transcription factor for stress response and beyond. International Journal of Molecular Sciences. 21(13):4777.

Hirsch EC, Vyas S, Hunot S. 2012. Neuroinflammation in Parkinson's disease. Parkinsonism and Related Disorders. 18:S210–S212.

Jaramillo MC, Zhang DD. 2013. The emerging role of the Nrf2-Keap1 signaling pathway in cancer. Genes and Development. 27:2179–2191.

Johnson DA, Amirahmadi S, Ward C, Fabry Z, Johnson JA. 2010. The absence of the pro-antioxidant transcription factor Nrf2 exacerbates experimental autoimmune encephalomyelitis. Toxicological Sciences. 114:237–246.

Kanninen K, Malm TM, Jyrkkänen HK, Goldsteins G, Keksa-Goldsteine V, Tanila H, Yamamoto M, Ylä-Herttuala S, Levonen AL, Koistinaho J. 2008. Nuclear factor erythroid 2-related factor 2 protects against beta amyloid. Molecular and Cellular Neuroscience. 39(3):302–313.

Koprivica I, Vujičić M, Gajić D, Saksida T, Stojanović I. 2019. Ethyl pyruvate stimulates regulatory T cells and ameliorates type 1 diabetes development in mice. Frontiers in Immunology. 9:3130.

Licht-Mayer S, Wimmer I, Traffehn S, Metz I, Brück W, Bauer J, Bradl M, Lassmann H. 2015. Cell type-specific Nrf2 expression in multiple sclerosis lesions. Acta Neuropathologica. 130(2):263–277.

Maimone D, Gregory S, Arnason BG, Reder AT. 1991. Cytokine levels in the cerebrospinal fluid and serum of patients with multiple sclerosis. Journal of Neuroimmunology. 32(1):67–74.

Maldonado PP, Guevara C, Olesen MA, Orellana JA, Quintanilla RA, Ortiz FC. 2022. Neurodegeneration in multiple sclerosis: The role of Nrf2-dependent pathways. Antioxidants (Basel). 11(6):1146.

Miljković D, Blaževski J, Petković F, Djedović N, Momčilović M, Stanisavljević S, Jevtić B, Mostarica Stojković M, Spasojević I. 2015. A comparative analysis of multiple sclerosis-relevant anti-inflammatory

properties of ethyl pyruvate and dimethyl fumarate. The Journal of Immunology. 194(6):2493–503.

Paladino S, Conte A, Caggiano R, Pierantoni GM, Faraonio R. 2018. Nrf2 Pathway in age-related neurological disorders: Insights into microRNAs. Cellular Physiology and Biochemistry. 47:1951–1976.

Ramsey CP, Glass CA, Montgomery MB, Lindl KA, Ritson GP, Chia LA, Hamilton RL, Chu CT, Jordan-Sciutto KL. 2007. Expression of Nrf2 in neurodegenerative diseases. Journal of Neuropathology and Experimental Neurology. 66(1):75–85.

Saha S, Buttari B, Panieri E, Profumo E, Saso L. 2020. An overview of Nrf2 signaling pathway and its role in inflammation. Molecules. 25(22):5474.

Saha S, Buttari B, Profumo E, Tucci P, Saso L. 2022. A perspective on Nrf2 signaling pathway for neuroinflammation: A potential therapeutic target in Alzheimer's and Parkinson's diseases. Frontiers in Cellular Neuroscience. 15:787258.

Schipper H, Liberman A, Stopa EG. 1998. Neural heme oxygenase-1 expression in idiopathic Parkinson's disease. Experimental Neurology. 150(1):60–68.

Stanisavljević S, Stegnjaić G, Jevtić B, Dimitrijević M, Miljković Đ, Lavrnja I, Nikolovski N. 2024. NRF2 plays a crucial role in the tolerogenic effect of ethyl pyruvate on dendritic cells. International Journal of Molecular Sciences. 25:6195.

Tonev D, Momchilova A. 2023. Oxidative stress and the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway in multiple sclerosis: Focus on certain exogenous and endogenous Nrf2 activators. International Journal of Molecular Sciences and Therapeutic Plasma Exchange Modulation. 24(24):17223.

Vasconcelos AR, Dos Santos NB, Scavone C, Munhoz CD. 2019. Nrf2/ARE pathway modulation by dietary energy regulation in neurological disorders. Frontiers in Pharmacology. 10:33.

Wang Q, Li WX, Dai SX, Guo YC, Han FF, Zheng JJ, Li GH, Huang JF. 2017. Meta-analysis of Parkinson's disease and Alzheimer's disease revealed commonly impaired pathways and dysregulation of NRF2-dependent genes. Journal of Alzheimer's Disease. 56(4):1525–1539.

Wu H, Zhong X. 2024. Nrf2 as a therapy target for Th17-dependent autoimmune disease. The Role of NRF2 Transcription Factor [Working Title]. IntechOpen. http://dx.doi.org/10.5772/intechopen.1005037.

Yu F, Wang Y, Stetler AR, Leak RK, Hu X, Chen J. 2022. Phagocytic microglia and macrophages in brain injury and repair. CNS Neuroscience and Therapeutics. 28(9):1279–1293.