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*Review Article*

# The Role of Iron Homeostasis in Multiple Sclerosis

**Ola A. El-Feky[1,2*] , Eman S. Minesy[2], Mohamad Aboessa[2], Menna M. Elesawy[2]**

[1] Department of Biochemistry, Faculty of Pharmacy, Tanta University, Tanta 31527, Egypt.
[2] Department of Biochemistry, Faculty of Pharmacy, Alsalam University, Kafr Alzayat, Algharbia 31611, Egypt.
* Corresponding author: Ola A. El-Feky, ola.elfeqi@pharm.tanta.edu.eg, Ola.Abdelsalam@sue.edu.eg

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Iron homeostasis is a crucial component of central nervous system (CNS) function, balancing iron levels to support metabolic processes while preventing oxidative damage. In the context of neurodegenerative diseases such as multiple sclerosis (MS), disruptions in iron regulation have been implicated in disease progression and pathology. Understanding iron homeostasis in the CNS provides insight into potential therapeutic targets for MS. Iron is essential for many cellular functions, including energy production, DNA synthesis, and oxygen transport, making its regulation critical for maintaining neuronal health (Ward et al., 2014).

## Iron: An Essential Element in Neurobiology

Iron is fundamental to neuronal function, playing a role in oxygen transport, energy metabolism, and neurotransmitter synthesis. It is vital for myelin production, with oligodendrocytes—myelin-forming cells—requiring substantial iron to sustain myelination. However, excess iron, particularly in conditions of dysregulated metabolism, contributes to oxidative stress and neuronal damage (Zecca et al., 2004). Iron is also involved in the function of iron-containing enzymes such as cytochrome c oxidase, which is crucial for mitochondrial respiration, and tyrosine hydroxylase, which is essential for dopamine synthesis (Mastroberardino et al., 2009). Disruptions in iron metabolism can therefore have widespread consequences for neural function and integrity.

## Mechanisms of Iron Uptake and Storage in Microglia

Microglia, the resident immune cells of the CNS, play a key role in iron regulation. These cells acquire iron through transferrin receptor-mediated endocytosis and divalent metal transporter 1 (DMT1) (Zarruk et al., 2021). Excess iron is stored in ferritin to mitigate toxicity. In MS, microglia exhibit altered iron uptake and storage, potentially exacerbating neuroinflammation.

Microglia express key iron transport proteins, including ferroportin, which exports iron, and hepcidin, a regulatory peptide that modulates ferroportin activity (Urrutia et al., 2013). Under inflammatory conditions, hepcidin expression is upregulated, leading to ferroportin degradation and subsequent intracellular iron retention. This iron accumulation can promote the formation of reactive oxygen species (ROS), exacerbating oxidative stress and neuronal damage (Kenk et al., 2021).

Iron uptake in microglia also occurs via lactoferrin receptors and scavenger receptors, which can bind iron-containing molecules and facilitate their internalization. Additionally, microglia can acquire iron through phagocytosis of myelin debris and apoptotic cells, a process that is particularly relevant in MS lesions where demyelination is prevalent (Reinert et al., 2019). The internalized iron is either stored in ferritin or utilized in metabolic processes, but dysregulated iron sequestration can lead to iron-laden microglia, contributing to the chronic inflammatory state observed in MS.

Furthermore, microglia interact with astrocytes to modulate iron metabolism. Astrocytes can uptake excess iron through ferritin-binding receptors and sequester it in a less toxic form. However, in MS, dysfunctional astrocytes may fail to properly regulate iron homeostasis, leading to increased iron burden in microglia (Zarruk et al., 2021). This mismanagement of iron can shift microglia into a pro-inflammatory phenotype, amplifying immune responses and exacerbating neurodegeneration in MS.

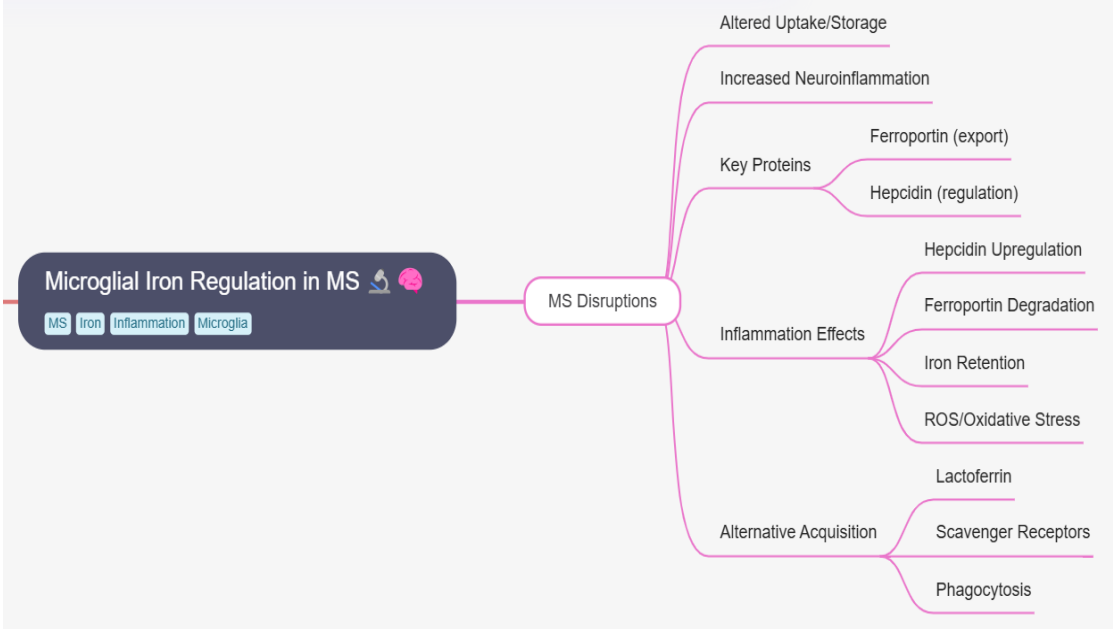


**Figure 1: Microglial Iron Regulation in MS**

**Key MRI Techniques for Iron Imaging in MS**

- **Susceptibility-Weighted Imaging (SWI)**: Sensitive to paramagnetic iron deposits in deep gray matter and MS lesions.
- **Quantitative Susceptibility Mapping (QSM)**: Provides a direct and quantifiable measure of tissue iron levels.
- *R2 Relaxometry (T2* Mapping)**: Estimates iron content by measuring transverse relaxation rates.
- **Magnetization Transfer Imaging (MTI)**: Assesses myelin integrity and its relationship with iron accumulation.

**Summary of Key Studies**

1. **Iron Deposition in Deep Gray Matter**

- **Bakshi et al. (2002, Archives of Neurology)**: Demonstrated increased iron accumulation in the basal ganglia and thalamus using T2-weighted imaging and R2* relaxometry. Higher iron levels correlated with disease severity and duration.

- **Khalil et al. (2015, Radiology)**: Used QSM to show progressive iron accumulation in the basal ganglia, particularly in secondary progressive MS, suggesting its role in neurodegeneration.

**2. Iron-Rich Lesions and Disease Progression**

- **Absinta et al. (2019, JAMA Neurology)**: Identified chronic active MS lesions with iron-rich rims using QSM and SWI. These iron-laden microglia were associated with ongoing neurodegeneration and more severe disability progression.
- **Zhang et al. (2021, Neurology)**: Conducted a longitudinal study using QSM, showing that increasing iron accumulation in deep gray matter over time correlated with worsening physical and cognitive function.

**3. Early Iron Changes in MS**

- **Stüber et al. (2016, Annals of Neurology)**: Used SWI to detect early-stage iron deposition in cortical MS lesions, suggesting that iron dysregulation begins in the initial disease stages.

**4. Implications and Future Directions**

These studies highlight the importance of MRI-based iron imaging in understanding MS progression. Key findings suggest that:

- **Iron deposition in deep gray matter correlates with disease severity.**
- **Iron-rimmed chronic lesions predict ongoing neurodegeneration and disability.**
- **Early iron dysregulation may contribute to disease onset.**

Future research should focus on integrating MRI biomarkers into clinical practice, exploring iron-targeting therapies, and further investigating the link between iron metabolism and neurodegeneration in MS.

**Ferroptosis: Iron-Dependent Cell Death and Its Role in MS**

Recent studies highlight the role of ferroptosis, a form of iron-dependent cell death, in MS pathology. Ferroptosis is characterized by the accumulation of lipid peroxides due to excessive iron levels and impaired antioxidant defenses, particularly the depletion of glutathione and inhibition of glutathione peroxidase 4 (GPX4) (Stockwell et al., 2017). Unlike apoptosis or necrosis, ferroptosis is driven by uncontrolled lipid oxidation, leading to membrane damage and cellular dysfunction.

Microglia overloaded with iron may undergo ferroptosis, releasing inflammatory mediators and further propagating neuronal damage. In MS, the presence of iron-laden microglia in active lesions suggests a heightened vulnerability to ferroptotic cell death.

This process not only contributes to neuroinflammation but also exacerbates demyelination by disrupting the microglial support of oligodendrocyte precursor cells (OPCs).

Additionally, mitochondrial dysfunction plays a crucial role in ferroptosis. Iron is essential for mitochondrial metabolism, but excessive accumulation leads to increased ROS production, further driving oxidative damage (Gao et al., 2019). The presence of dysfunctional mitochondria in MS lesions suggests that ferroptosis may be a key driver of neurodegeneration in progressive MS (Mahoney-Sanchez et al., 2021).

Targeting ferroptosis presents a novel therapeutic strategy for MS. Iron chelators, such as deferoxamine, have shown promise in reducing iron overload and mitigating oxidative stress. Additionally, GPX4 activators and lipid peroxidation inhibitors (e.g., ferrostatins and liproxstatins) have been explored as potential neuroprotective agents to counteract ferroptosis-induced damage in neurodegenerative diseases (Do Van et al., 2016). Further research into ferroptosis modulators could provide new insights into protecting neurons and oligodendrocytes from iron-mediated injury in MS.

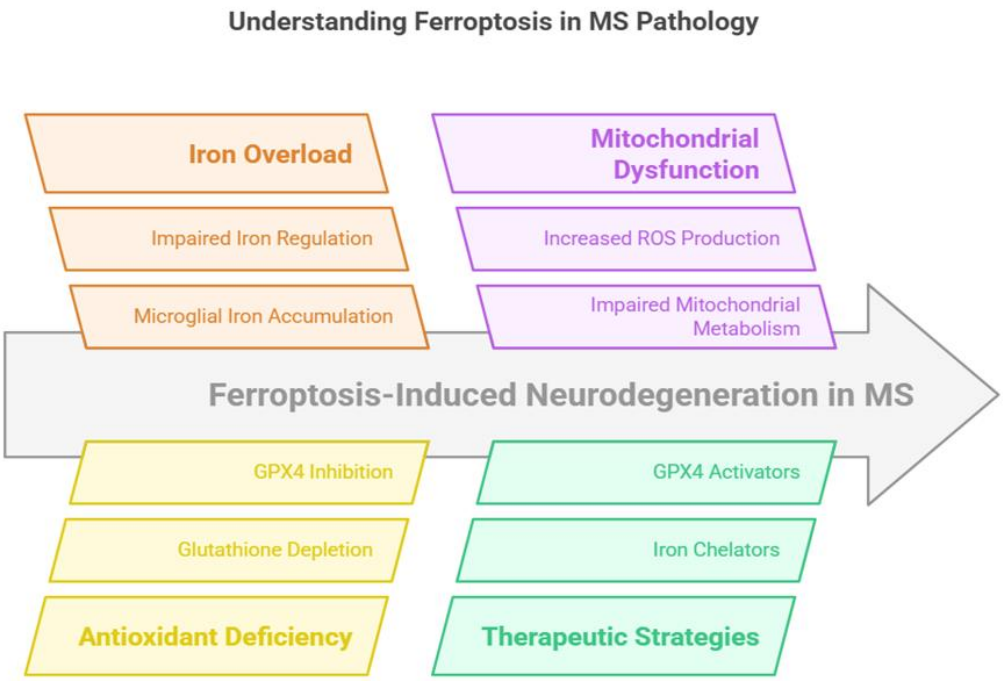


**Figure 2: Ferroptosis as a potential target for multiple sclerosis**

**The Role of Ferritin in Iron Sequestration in MS**

Ferritin is the primary iron-storage protein, maintaining iron balance within the CNS. In MS, ferritin levels are dysregulated, particularly in microglia and oligodendrocytes within demyelinating lesions. Increased ferritin expression has been observed in active MS lesions, suggesting a response to iron accumulation and oxidative stress (Hametner et al., 2013). Ferritin exists in two forms: heavy-chain ferritin (FTH) and light-chain ferritin (FTL). The heavy-chain subunit possesses ferroxidase activity, which helps convert toxic $Fe^{2+}$ to the less reactive $Fe^{3+}$ form, reducing oxidative damage. Imbalances in ferritin subunit expression could therefore contribute to increased oxidative stress in MS pathology.

Increased ferritin levels might reflect **iron deposition in the brain**, particularly in deep gray matter structures, which has been observed in MRI studies. Elevated ferritin levels have been linked to **worse disability scores (Expanded Disability Status Scale - EDSS)** and **more severe neurodegeneration** in some studies (**Batista et al., 2020)**. Differences in ferritin levels may be influenced by factors such as **age, gender, disease duration, and co-existing conditions (e.g., anemia, infections, or inflammation from other sources).**

**Clinical Implications**

**Ferritin alone is not a definitive biomarker** for MS diagnosis but may provide insights into disease activity and neuroinflammation. Combining ferritin measurements with **MRI-based iron imaging (e.g., QSM, SWI)** could offer a more comprehensive understanding of iron metabolism in MS. More research is needed to clarify **whether**

**ferritin levels can predict disease progression or response to therapy (Benarroch, E. E. (2009).**

**Oxidative Stress: Link Between Iron and Neurodegeneration**

Excess iron catalyzes the Fenton reaction, producing reactive oxygen species (ROS) that damage lipids, proteins, and DNA (Bradl & Lassmann, 2010). Oxidative stress is a key pathological feature in MS, leading to mitochondrial dysfunction and axonal degeneration. Iron-related oxidative damage is particularly detrimental in chronic MS lesions, where sustained inflammation exacerbates neuronal loss. ROS production can trigger secondary damage pathways, including lipid peroxidation, which disrupts cell membrane integrity, and protein oxidation, leading to enzyme inactivation and structural damage (Stephenson et al., 2014). The interplay between iron dysregulation and oxidative stress is therefore a major contributor to MS progression.

**Demyelination**: In MS, the immune system attacks myelin, leading to the formation of plaques or lesions in the white matter. Iron accumulation within these plaques is thought to exacerbate the damage. Iron can enhance the aggregation of myelin debris, and when iron interacts with ROS, it accelerates lipid peroxidation, damaging myelin and axonal membranes, which in turn accelerates the disease process.

**Mitochondrial Dysfunction**: Mitochondria are responsible for energy production in neurons. Oxidative stress from iron and ROS can impair mitochondrial function, leading to neuronal energy deficits and ultimately cell death. Mitochondrial dysfunction also promotes more ROS production, creating a vicious cycle of damage in MS.

**Neuroinflammation**: Activated microglia and infiltrating immune cells release pro-inflammatory cytokines, which further increase oxidative stress. The release of iron by microglia, as well as their activation during inflammation, contributes to the exacerbation of oxidative damage in MS.

**Blood-Brain Barrier (BBB) Disruption**: In MS, oxidative stress and iron overload can lead to the disruption of the BBB, which normally protects the brain from harmful substances. The breakdown of the BBB allows immune cells to enter the CNS and release ROS, further contributing to neurodegeneration.

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**Molecular Pathways of Iron-Mediated Oxidative Damage in Neurons**

In multiple sclerosis (MS), iron-mediated oxidative damage plays a critical role in the progressive neurodegeneration that characterizes the disease. The accumulation of iron, particularly in the central nervous system (CNS), can exacerbate inflammation, damage myelin, and contribute to neuronal death. This process is largely driven by the ability of iron to catalyze the formation of highly reactive reactive oxygen species (ROS) and reactive nitrogen species (RNS), which can damage cellular components such as lipids, proteins, and DNA. Below is an overview of the molecular pathways by which iron mediates oxidative damage in neurons within MS:

**Iron Accumulation and Dysregulation in MS**

- **Microglial Activation**: In MS, activated microglia (the resident immune cells of the CNS) release pro-inflammatory cytokines and ROS. During the inflammatory response, iron accumulates in the microglia, oligodendrocytes (myelin-producing cells), and astrocytes. Microglia, in particular, can release iron from their intracellular stores, leading to iron deposition in areas of demyelination and injury.
- **Iron Uptake Mechanisms**: The primary mechanisms by which iron enters neurons are via transferrin receptors (TFRC) and divalent metal transporter 1 (DMT1), both of which facilitate iron transport into cells. Once iron enters the cell, it can be stored in ferritin or released into the cytoplasm for utilization. In MS, altered iron homeostasis disrupts these pathways, leading to iron overload in CNS regions affected by demyelination.

**The Fenton Reaction and ROS Production**

- **Fenton Chemistry**: Once excess iron is available in the CNS, it can participate in Fenton chemistry, a reaction that converts hydrogen peroxide ($H_2O_2$) into highly reactive hydroxyl radicals (•OH). The Fenton reaction occurs when ferrous iron ($Fe^{2+}$) reacts with $H_2O_2$:

  These hydroxyl radicals are extremely reactive and can damage various cellular components, including lipids, proteins, and DNA, thereby promoting neurodegeneration. The Fenton reaction is a key pathway through which iron drives oxidative damage in MS.
- **Lipid Peroxidation**: The hydroxyl radicals produced through Fenton chemistry can initiate lipid peroxidation, leading to the destruction of the cell membrane and myelin sheaths. This is particularly damaging to oligodendrocytes and neurons, as myelin integrity is critical for normal neuronal function. Lipid peroxidation also generates reactive aldehydes, such as 4-hydroxy-2-nonenal (HNE), which further exacerbate oxidative damage and neuroinflammation in MS.

**Mitochondrial Dysfunction**

- **Mitochondrial Iron Accumulation**: Mitochondria are key sites of iron storage and utilization, especially for processes like cellular respiration. In MS, excess iron can accumulate in mitochondria, disrupting their function. Mitochondrial dysfunction leads to a failure in ATP production, energy deficits, and the release of ROS. Mitochondrial iron overload has been shown to amplify oxidative stress, contributing to neurodegeneration and cell death.
- **ROS and Mitochondrial Damage**: ROS generated within mitochondria can damage mitochondrial DNA (mtDNA), proteins, and lipids, further impairing mitochondrial function. This creates a vicious cycle where mitochondrial dysfunction leads to more ROS production, exacerbating neuronal injury. The resulting energy deficits contribute to axonal damage and demyelination in MS lesions.

**Neuroinflammation and Iron-Driven Cytokine Release**

- **Iron and Inflammatory Cytokines**: In MS, iron plays a role in activating neuroinflammatory pathways. The accumulation of iron in microglia and other glial cells can induce the production of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukins (IL-1β, IL-6), and interferon-gamma (IFN-γ). These cytokines not only promote further inflammation but also increase the generation of ROS, further contributing to oxidative damage.
- **Oxidative Stress and Blood-Brain Barrier (BBB) Disruption**: Neuroinflammation, fueled by iron and ROS, can lead to the breakdown of the blood-brain barrier (BBB), which is critical for protecting the brain from harmful substances. The disruption of the BBB allows immune cells, such as T-cells and macrophages, to infiltrate the CNS, further exacerbating the inflammatory response and iron-induced oxidative damage.

**DNA Damage and Cellular Dysfunction**

- **DNA Damage by ROS**: The ROS produced by iron-mediated reactions can directly damage DNA, leading to the formation of DNA adducts, strand breaks, and mutations. This genomic instability can trigger cellular responses like apoptosis (programmed cell death) and necrosis, particularly in neurons and oligodendrocytes. The accumulation of DNA damage in neurons contributes to the loss of synapses and axonal degeneration in MS.
- **Activation of Cellular Repair Mechanisms**: In response to oxidative damage, cells activate various repair mechanisms, such as the DNA repair pathways (base excision repair, nucleotide excision repair, etc.). However, these repair systems may become overwhelmed, particularly in the face of persistent oxidative stress and iron overload. This can lead to chronic neurodegeneration in MS.

**Iron and Axonal Degeneration**

- **Iron in Axons**: In MS, axonal injury and degeneration are major contributors to disability. Iron accumulation has been observed in axons in MS lesions. The iron-driven production of ROS in these axonal regions can directly contribute to axonal injury and loss. Moreover, iron interacts with neurofilament proteins and other structural components, leading to axonal dysfunction and disintegration.
- **Axonal Transport Disruption**: Iron-mediated oxidative damage can impair the axonal transport system, essential for moving molecules and organelles along the axon. The disruption of axonal transport exacerbates neurodegeneration by preventing the proper maintenance of axonal function and myelin integrity.

**Iron and Oligodendrocyte Injury**

- **Demyelination**: Iron overload can directly affect oligodendrocytes, the cells responsible for producing myelin. When oligodendrocytes are exposed to elevated levels of iron, they can undergo oxidative stress, leading to cell death and loss of myelin. This contributes to the demyelination observed in MS lesions.
- **Myelin Repair Impairment**: In addition to causing damage, iron-mediated oxidative stress can also impair the repair of myelin. Oligodendrocyte precursor cells (OPCs) are responsible for remyelinating damaged axons in MS, but oxidative stress can hinder their differentiation and maturation into mature oligodendrocytes. Iron can also interfere with the signaling pathways involved in myelin repair, further exacerbating the progression of the disease.

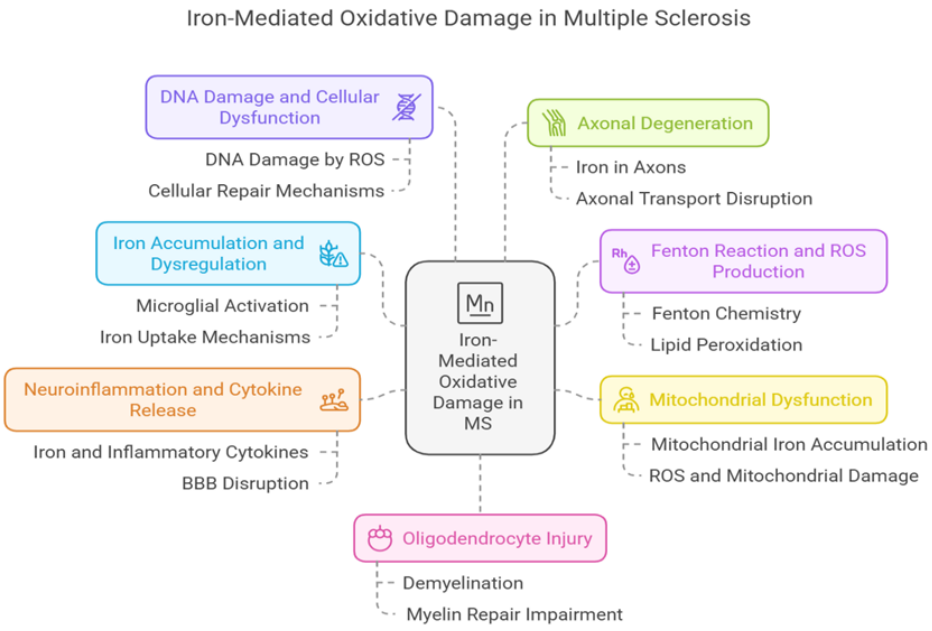


**Figure 3: Mechanisms of Iron mediated oxidative damage in multiple sclerosis**

**Therapeutic Targeting of Iron-Mediated Oxidative Damage**

- **Iron Chelation Therapy**: One approach to mitigating iron-induced damage in MS is the use of iron chelators, which bind free iron and prevent its involvement in Fenton chemistry. Iron chelation can help reduce oxidative stress and inflammation, potentially slowing the progression of the disease. Drugs like deferoxamine and deferasirox have been studied in MS, although clinical trials have produced mixed results.
- **Antioxidant Therapy**: Another strategy is the use of antioxidants to neutralize ROS and reduce oxidative stress. Antioxidants, such as glutathione, coenzyme Q10, and vitamins C

and E, can help counteract the damaging effects of iron-induced oxidative stress. However, the effectiveness of antioxidant therapy in MS remains uncertain, and more research is needed.

- **Dimethyl fumarate (DMF) is an FDA-approved oral disease-modifying therapy (DMT)** for relapsing forms of multiple sclerosis (MS). It is widely used due to its **anti-inflammatory and neuroprotective properties**, which are largely mediated by its activation of the **nuclear factor erythroid 2-related factor 2 (Nrf2) pathway** (Gold et al., 2012).

**Mechanism of Action and Role in Oxidative Stress**

- DMF exerts its therapeutic effects by activating **Nrf2**, a key transcription factor that regulates the expression of antioxidant and cytoprotective genes (Linker et al., 2011). **Nrf2 activation enhances the cellular defense mechanisms against oxidative stress** by upregulating antioxidant enzymes such as heme oxygenase-1 (HO-1) and glutathione

synthesis. This is particularly relevant in MS, where oxidative stress contributes to **neuroinflammation, demyelination, and neurodegeneration** (Scannevin et al., 2012).

**Potential Effects on Iron Metabolism and Neurodegeneration**

- Iron dysregulation is a hallmark of **progressive MS**, where iron accumulation in deep gray matter contributes to neurotoxicity. Through its antioxidant and anti-inflammatory effects, DMF may **mitigate iron-induced oxidative stress**, thereby **reducing neurodegeneration** (Hemmati-Dinarvand et al., 2019). Some studies suggest that Nrf2 activation can help regulate **iron metabolism**, potentially influencing iron uptake and storage in MS lesions (Ghoreschi et al., 2011).

**Clinical Implications:** DMF has demonstrated efficacy in reducing **relapse rates, disability progression, and MRI lesion activity** in MS patients (Fox et al., 2012). Due to its ability to reduce oxidative stress and inflammation, DMF might also impact **iron-mediated neurotoxicity**, although further research is needed to confirm its role in iron homeostasis.

**Conclusion**

Iron dysregulation is a significant factor in MS pathology, contributing to oxidative stress, inflammation, and neurodegeneration. A deeper understanding of iron homeostasis in the CNS may unlock new therapeutic avenues. Future research should focus on targeted iron-modulating therapies to mitigate disease progression while preserving essential iron-dependent processes. Understanding the interplay between iron metabolism, immune responses, and oxidative damage in MS will be key to developing effective therapeutic interventions.

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