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Research Progress on Solute Carrier Family 7 Member 11 Protein Regulation of Ferroptosis in Neurodegenerative Diseases

Jiaxian Liang, Jianwen Zhi, Bo Ning *

Department of Neurosurgery, Guangzhou Red Cross Hospital Affiliated to Jinan University, Guangzhou, Guangdong, 510220, China
*** Corresponding author:** Bo Ning (Email: ningbo1974@126.com)

Abstract: Solute carrier family 7 member 11 (SLC7A11) plays a crucial role in regulating ferroptosis and is closely associated with neurodegenerative diseases (NDDs) such as Alzheimer's disease and Parkinson's disease. As a key component of the cystine/glutamate antiporter (System Xc−), SLC7A11 inhibits lipid peroxidation and ferroptosis by mediating cystine uptake and glutathione synthesis. In NDDs, downregulation or dysfunction of SLC7A11 leads to decreased neuronal antioxidant capacity and exacerbated ferroptosis, thereby promoting disease pathogenesis and progression. Therefore, targeting SLC7A11 or ferroptosis-related pathways may represent novel therapeutic strategies for NDDs. This review systematically summarizes the specific mechanisms of SLC7A11 in NDDs, linking its function to the pathological mechanisms of NDDs through the emerging concept of "ferroptosis," thereby constructing an "SLC7A11-ferroptosis-neurodegenerative disease" association model and identifying SLC7A11 as a potential key molecular node connecting disease pathology with this mode of cell death.

Keywords: SLC7A11; System Xc−; Ferroptosis; Neurodegenerative Diseases; Oxidative Stress; Glutathione Metabolism.

1. Introduction

Neurodegenerative diseases (NDDs) are a group of disorders characterized by progressive neuronal loss and functional decline, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS), among others [1, 2]. With the aging global population, the incidence of NDDs is increasing annually. However, their pathogenesis is not fully understood, and effective disease-modifying therapies are lacking. Therefore, in-depth exploration of the molecular mechanisms of NDDs and the identification of new therapeutic targets are of significant scientific and clinical importance. In recent years, ferroptosis, a novel form of regulated cell death, has become a hotspot in NDD research due to its close association with oxidative stress and lipid peroxidation [3]. The core feature of ferroptosis is iron-dependent accumulation of lipid peroxides (LPO), ultimately leading to loss of membrane integrity and cell death [4]. Solute carrier family 7 member 11 (SLC7A11) is the light chain subunit of the cystine/glutamate antiporter (System Xc−) [5]. It mediates the uptake of extracellular cystine and release of intracellular glutamate [6], participating in glutathione (GSH) synthesis, thereby inhibiting lipid peroxidation and ferroptosis [7]. Growing evidence indicates that SLC7A11 expression is dysregulated in NDDs, and its impaired function may contribute to neuronal death and disease progression by promoting ferroptosis [8]. This article systematically reviews the molecular mechanisms of SLC7A11 in regulating ferroptosis and its research progress in NDDs, focusing on the expression changes, functional regulation, and potential therapeutic value of SLC7A11 in AD, PD, and other diseases, aiming to provide new insights into the mechanisms and targeted therapy of NDDs.

2. Structure and Function of SLC7A11 and System Xc−

SLC7A11 (also known as xCT) is a member of the solute carrier family 7 (SLC7), located on human chromosome 4q28-31 [9]. The SLC7A11 protein consists of 502 amino acids and contains 12 transmembrane domains (TMDs), with both N- and C-termini located on the cytoplasmic side [10]. The function of SLC7A11 depends on its association with the heavy chain subunit SLC3A2 (also known as 4F2hc or CD98hc) to form a heterodimeric complex. SLC3A2 connects to SLC7A11 via a disulfide bond, anchors the complex to the plasma membrane, and may participate in substrate binding and transport regulation [11].

System Xc− is a cystine/glutamate antiporter composed of SLC7A11 and SLC3A2, functioning to exchange extracellular cystine for intracellular glutamate in a 1:1 ratio [12]. Upon entering the cell, cystine is rapidly reduced to cysteine, which is a rate-limiting substrate for GSH synthesis [13]. GSH is one of the most important intracellular antioxidant molecules. It acts as a cofactor for glutathione peroxidase 4 (GPX4), which catalyzes the reduction of lipid peroxides to non-toxic lipid alcohols, thereby inhibiting ferroptosis [14]. Thus, SLC7A11 plays a key role in maintaining cellular redox balance by regulating cystine uptake and GSH synthesis. The activity of System Xc− is regulated by various factors, including oxidative stress, inflammatory signals, nutritional status, and pharmacological interventions [15]. For example, nuclear factor erythroid 2-related factor 2 (Nrf2) is an important transcriptional activator of System Xc− [16]. Under oxidative stress, Nrf2 dissociates from Keap1 and translocates to the nucleus, binding to the antioxidant response element (ARE) to promote the expression of SLC7A11 and other antioxidant genes. Additionally, transcription factors such as p53, ATF4, and BACH1 can also regulate SLC7A11 expression directly or indirectly [16].

3. Role of SLC7A11 in Regulating Ferroptosis

Ferroptosis is an iron-dependent, non-apoptotic form of cell death characterized by iron accumulation and lipid peroxidation [17]. The occurrence of ferroptosis involves several key molecules and pathways. Iron ions enter cells via transferrin (Tf) and transferrin receptor 1 (TfR1) and are released in acidic lysosomes. Free iron (Fe^{2+}) catalyzes the Fenton reaction, converting hydrogen peroxide (H_2O_2) into hydroxyl radicals (·OH), which attack polyunsaturated fatty acids (PUFAs) to initiate lipid peroxidation [18]. PUFAs are oxidized by lipoxygenases (LOXs) or non-enzymatic reactions to generate lipid peroxides (LPO). The accumulation of LPO leads to decreased membrane fluidity, increased permeability, and ultimately cell death. GPX4 is a key enzyme inhibiting ferroptosis, and its activity depends on GSH. When SLC7A11 function is impaired, leading to reduced cystine uptake, GSH synthesis is limited, GPX4 activity declines, and LPO cannot be cleared promptly, thereby triggering ferroptosis [19].

SLC7A11-mediated cystine uptake is the first step in GSH synthesis. Inhibiting SLC7A11 (e.g., with Erastin or Sorafenib) significantly reduces intracellular GSH levels, leading to GPX4 inactivation and ferroptosis. GSH, as a cofactor for GPX4, directly participates in the reduction of LPO [20]. By maintaining GSH supply, SLC7A11 ensures sustained GPX4 activity, thus inhibiting ferroptosis. SLC7A11 clears LPO via the GSH/GPX4 axis, preventing their accumulation to lethal levels [21]. Furthermore, SLC7A11 may indirectly inhibit ferroptosis through non-GPX4-dependent pathways (e.g., the FSP1/CoQ10 axis), but the specific mechanisms require further study. Beyond the GSH/GPX4 axis, SLC7A11 may indirectly regulate intracellular iron levels by influencing iron metabolism-related proteins (e.g., TfR1, FPN1) [22]. SLC7A11 can interact with redox-sensitive transcription factors like Nrf2 and p53, forming feedback regulatory loops to dynamically control cellular antioxidant capacity [23]. By regulating glutamate/cystine exchange, SLC7A11 affects intracellular amino acid metabolism and energy production, thereby indirectly influencing ferroptosis sensitivity [24].

4. Expression and Function of SLC7A11 in Neurodegenerative Diseases

4.1. Alzheimer's Disease (AD)

AD is a neurodegenerative disease first described by Alois Alzheimer in 1907. It is a progressive disorder with various brain complications, characterized pathologically by β-amyloid (Aβ) deposition, hyperphosphorylated tau protein, and neuronal death [25]. Excessive Aβ deposition and tau hyperphosphorylation may lead to the formation of senile plaques and neuronal death. Abnormal iron metabolism might cause post-translational abnormal modification of Aβ, leading to increased Aβ oligomers. Iron accumulation in the cerebral cortex is closely related to AD pathogenesis, and the role of ferroptosis in AD is increasingly recognized. Multiple studies have shown significantly downregulated SLC7A11 expression in the brain tissues of AD patients [26-28]. A transcriptomics-based study found that SLC7A11 mRNA levels in the hippocampus and temporal cortex of AD patients were significantly downregulated compared to healthy controls, with an average reduction of 40% ± 5.2%. This abnormal expression was region-specific, highly coinciding with core pathological areas of the disease [27]. Immunohistochemical quantitative analysis confirmed significantly weakened SLC7A11 protein immunoreactivity in neuronal somata and processes of AD patients. The positive staining area was significantly negatively correlated with Aβ plaque density in brain tissue, suggesting that loss of SLC7A11 expression might accelerate oxidative stress damage and neuronal degeneration induced by Aβ deposition by weakening the neuronal antioxidant defense system [28].

Downregulation of SLC7A11 may lead to the following consequences. *Reduced GSH synthesis:* GSH levels in the cerebrospinal fluid of AD patients are significantly decreased and correlate with cognitive decline. GSH deficiency weakens neuronal antioxidant capacity, promoting Aβ-induced lipid peroxidation and ferroptosis [29]. *Aggravated iron accumulation:* Iron deposition increases in the brains of AD patients, especially in the hippocampus and basal ganglia. Impaired SLC7A11 function may affect the expression of iron metabolism-related proteins, leading to iron overload and enhanced Fenton reactions [30]. *Neuronal death:* Animal model studies indicate that inhibiting SLC7A11 exacerbates Aβ-induced neuronal death, whereas overexpressing SLC7A11 or supplementing with N-acetylcysteine (NAC, a GSH precursor) significantly alleviates neuronal damage and cognitive deficits [31]. SLC7A11 expression levels may serve as a biomarker for AD. SLC7A11 gene polymorphisms are associated with AD susceptibility, suggesting its potential involvement in AD genetic risk.

4.2. Parkinson's Disease (PD)

PD is a common neurodegenerative disease in the elderly, with symptoms divided into motor and non-motor symptoms [32]. The most prominent pathological change is the degeneration or death of dopaminergic (DA) neurons in the substantia nigra pars compacta, leading to a significant decrease in striatal DA content [33]. The role of ferroptosis in PD pathogenesis has been widely confirmed. SLC7A11 expression is significantly reduced in the substantia nigra and putamen of PD patients. A proteomics-based study found that SLC7A11 protein expression levels in the substantia nigra of PD patients were significantly reduced by approximately 30% compared to healthy controls, and its expression level was significantly negatively correlated with the motor score of the Unified Parkinson's Disease Rating Scale Part III, suggesting that SLC7A11 downregulation may participate in disease progression [34]. Animal experiments further validated this finding. In the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD mouse model, both SLC7A11 mRNA and protein expression in the substantia nigra showed time-dependent downregulation, significantly correlating with the reduction in tyrosine hydroxylase-positive neurons. This indicates that abnormal SLC7A11 expression may lead to selective loss of nigral dopaminergic neurons by weakening cellular antioxidant defense capacity and promoting the ferroptosis cascade [35].

Impaired SLC7A11 function may contribute to PD pathogenesis through the following mechanisms. *Enhanced oxidative stress:* Levels of oxidative stress markers (e.g., 8-hydroxydeoxyguanosine, 4-hydroxynonenal) are elevated in the brains of PD patients. SLC7A11 downregulation leads to reduced GSH synthesis, impairing the clearance of α-synuclein (α-Syn)-induced lipid peroxides, thereby

promoting ferroptosis [36]. *Iron metabolism dysregulation:* Iron deposition is significantly increased in the substantia nigra of PD patients and correlates with the severity of motor symptoms. SLC7A11 may affect intracellular iron balance by regulating the expression of iron transport proteins (e.g., DMT1, FPN1). *Mitochondrial dysfunction:* SLC7A11 downregulation can lead to decreased mitochondrial membrane potential and respiratory chain complex activity, further exacerbating oxidative stress and ferroptosis [37]. SLC7A11 expression level is associated with the prognosis of PD patients. PD patients with higher SLC7A11 expression respond better to levodopa treatment and have a lower incidence of motor complications. Furthermore, SLC7A11 gene polymorphisms (e.g., rs10117) are associated with PD susceptibility, suggesting it may act as a genetic modifier for PD [38].

4.3. Huntington's Disease (HD)

HD is an autosomal dominant, late-onset neurodegenerative disease. Its core pathological features include selective loss of medium spiny neurons (MSNs) in the striatum, cerebral cortical atrophy, and the presence of nuclear inclusions formed by aggregated mutant huntingtin protein (mHTT) [39]. The main clinical symptoms are choreiform movements, followed by motor impairment, aphasia and dysphagia, cognitive and psychiatric disorders, eventually leading to death [40]. HD-related mechanisms include loss of glial cells, neuronal death, and brain atrophy, primarily occurring in the striatum and cerebral cortex [41]. Clinical MRI detects significant iron accumulation in the basal ganglia of HD patients, accelerating with disease progression [42]. Recent research has focused on the key role of SLC7A11 in HD pathogenesis, finding significantly reduced SLC7A11 protein expression in striatal MSNs of HD patients compared to healthy controls [43]. This downregulation has dynamic pathological significance; longitudinal follow-up data showed that SLC7A11 expression levels were significantly negatively correlated with the rate of increase in the Unified Huntington's Disease Rating Scale motor scores and strongly negatively correlated with the rate of decline in Montreal Cognitive Assessment scores. This suggests that loss of SLC7A11 expression may accelerate disease progression by weakening neuronal antioxidant defense capacity, manifesting as progressive motor function decline and widespread cognitive impairment [44].

Mechanistically, SLC7A11 may participate in HD pathogenesis through the following pathways. *Inhibition of ferroptosis:* As a key subunit of the System Xc-/GSH axis, downregulation of SLC7A11 leads to reduced glutathione synthesis, impairing the clearance of mHTT-induced mitochondrial ROS burst, thereby promoting lipid peroxide accumulation and ferroptosis [45]. Overexpression of SLC7A11 can restore GSH levels and block this pathological process. *Regulation of iron metabolism balance:* Striatal iron deposition is significantly increased in HD patients and positively correlates with motor symptom severity. SLC7A11 may inhibit iron influx and promote iron efflux by regulating iron transporter expression (e.g., transferrin receptor TfR1, ferroportin FPN1), thereby alleviating intracellular iron overload and Fenton reaction-induced oxidative damage [46]. *Alleviation of excitotoxicity:* SLC7A11 dysfunction reduces extracellular glutamate uptake, leading to increased striatal glutamate concentrations, which can induce excitotoxicity via overactivation of NMDA receptors. Overexpression of SLC7A11 can lower glutamate levels and protect neurons from excitotoxic injury [47]. Furthermore, SLC7A11 expression level is closely related to HD patient prognosis. Clinical data analysis shows that HD patients with higher striatal SLC7A11 expression experience slower motor function decline and respond better to dopaminergic medications (e.g., tetrabenazine) [48]. These findings provide new therapeutic targets for HD. Upregulating SLC7A11 expression or enhancing its function may represent a potential strategy to delay disease progression and improve patient outcomes.

4.4. Other Neurodegenerative Diseases

ALS is a neurodegenerative disease characterized by selective death of motor neurons. SLC7A11 expression is downregulated in spinal motor neurons of ALS patients and is associated with shortened survival [49]. Studies in superoxide dismutase 1 (SOD1) mutant ALS mouse models show that SLC7A11 overexpression delays disease progression and extends survival. Friedreich's ataxia (FRDA) is another neurodegenerative disease primarily caused by deficiency of the mitochondrial protein frataxin [50]. Clinical manifestations of FRDA include ataxia, dysarthria, reading difficulties, and sensory loss, with diabetic symptoms potentially appearing as a terminal syndrome. FRDA cells are highly sensitive to Erastin, and SLC7A11 overexpression can alleviate Erastin-induced cell death in FRDA models.

5. Conclusion and Discussion

SLC7A11, as the core component of the System Xc−, a key antioxidant defense system, plays an indispensable role in maintaining physiological homeostasis in the nervous system. By precisely regulating cellular cystine uptake, it provides the essential precursor for GSH synthesis, thereby strongly promoting GSH production. GSH, as one of the most important intracellular antioxidants, effectively scavenges excess reactive oxygen species, acting as a central hub in inhibiting ferroptosis and maintaining neuronal redox balance. In the complex pathological process of NDDs, the downregulation of SLC7A11 expression or impairment of its normal function is a critical event. This abnormality directly leads to decreased cystine uptake capacity, resulting in reduced GSH synthesis. Consequently, intracellular antioxidant defense capacity is compromised, unable to effectively counter oxidative stress damage, ultimately leading to exacerbated ferroptosis. Excessive ferroptosis causes significant neuronal loss, a hallmark pathological feature of NDDs, which further promotes disease progression and deterioration, severely affecting patients' neurological function and quality of life. Based on these findings, targeting SLC7A11 or ferroptosis-related pathways opens new strategic directions for NDD treatment. Developing drugs that upregulate SLC7A11 expression or enhance its function, or intervening in key molecules and signal transduction within the ferroptosis pathway, holds promise for effectively inhibiting ferroptosis, reducing neuronal death, thereby delaying NDD progression, and improving clinical symptoms and prognosis. However, many aspects of the specific regulatory mechanisms of SLC7A11 in NDDs remain unknown. Future research needs to integrate various advanced experimental techniques and methods, such as gene editing, single-cell sequencing, and proteomics, to further elucidate the regulatory networks, post-translational modifications, and interactions with other signaling pathways

of SLC7A11 at molecular, cellular, tissue, and whole-animal levels.

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