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REVIEW

Biochemical potential of laccase in preventing protein aggregation in rare diseases

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Abstract

Rare diseases are a group of disorders that typically arise from genetic mutations and often follow a progressive clinical course. In many of these diseases, protein aggregation represents a critical pathological mechanism that can lead to neuronal cell loss. Protein aggregation occurs when misfolded proteins accumulate within cells and form insoluble structures. This study addresses the potential biochemical role of laccase, an enzyme with high oxidative capacity, in preventing protein aggregation. Laccase catalyzes the oxidation of suitable substrates while reducing molecular oxygen to water; however, whether this activity reduces net oxidative stress or protein aggregation in neuronal cells remains to be determined. Within this framework, aggregation mechanisms observed in rare neurodegenerative diseases, such as Niemann–Pick disease type C, neuronal ceroid lipofuscinosis, and spinocerebellar ataxia type 7, have been examined, and the theoretical impact of laccase on these processes has been discussed. Given its broad substrate specificity, redox potential, and effects on cellular homeostasis, the potential use of laccase as a therapeutic agent has been emphasized. In conclusion, laccase may offer a novel biotechnological approach to mitigating cellular damage associated with protein aggregation.

Keywords: Laccase, Neuronal Ceroid Lipofuscinosis, Niemann-Pick disease type C, Protein aggregation, Rare diseases, Spinocerebellar Ataxia Type 7 (SCA7)

Introduction

Rare Diseases: Definition, prevalence and clinical significance

Rare diseases comprise a heterogeneous group of disorders that individually affect a small proportion of the population but collectively represent a significant global public health challenge (C. M. Wang et al., 2024). Despite their low individual prevalence, these disorders are associated with substantial morbidity and mortality and pose significant challenges for diagnosis, clinical management, and therapeutic development (Gopal-Srivastava & Kaufmann, 2017). Furthermore, due to their low prevalence, marked clinical heterogeneity, and frequently overlapping clinical manifestations, rare diseases are often underdiagnosed or misdiagnosed, resulting in delayed diagnosis, limited access to appropriate treatment, and poorer patient outcomes (Chung et al., 2022).

The concept of rare diseases began to attract attention in the 19th century, particularly with the emergence of medical specialization and the development of nosological classifications; however, such conditions remained primarily of clinical interest and were not systematically addressed beyond individual cases. By the mid-20th century, the social isolation and limited access to treatment experienced by individuals affected by rare disorders prompted the formation of patient advocacy groups and grassroots movements. These movements gained institutional recognition with the enactment of the Orphan Drug Act in the United States in 1983, which introduced legal and economic incentives to encourage the development of treatments for rare diseases. In parallel, similar initiatives were launched in Europe, culminating in the implementation of the European Union Orphan Medicinal Products Regulation in 2000. Multistakeholder interactions among patient organizations, researchers, and public authorities have since played a critical role in shaping both the clinical definition of rare diseases and their recognition within health policy frameworks. In recent years, advances in genomic technologies, including molecular genetics, next-generation sequencing, and precision medicine, have enabled the molecular characterization of previously unidentified rare diseases, substantially improving disease classification and diagnostic approaches (Rodríguez-Sánchez & Morgado, 2022). The historical development of rare disease research and the recognition of selected rare disorders are summarized in Figure 1.

Despite these significant advances, effective therapeutic options remain unavailable for the majority of rare diseases. This unmet clinical need has shifted research efforts toward identifying common pathogenic mechanisms shared among genetically distinct disorders and developing mechanism-based therapeutic strategies that target these underlying molecular processes (Boycott & Ardigó, 2017).

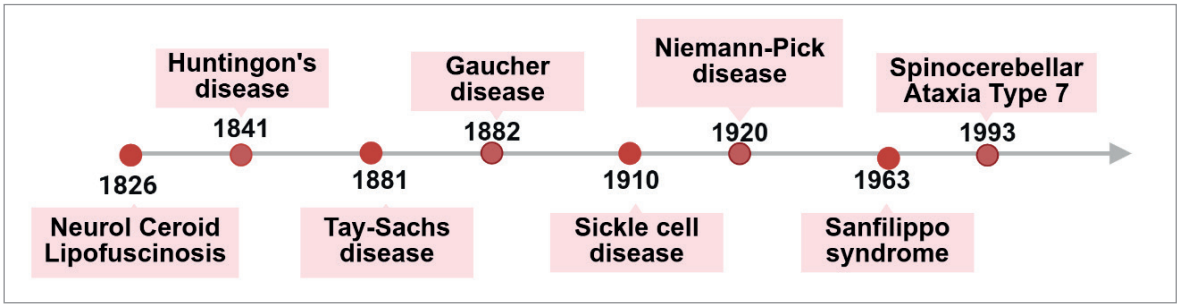

Figure 1. Timeline of protein aggregation research in rare diseases. Beginning with Neuronal Ceroid Lipofuscinosis in 1826, subsequent findings including Huntington's disease, Tay-Sachs disease, and Niemann-Pick disease have revealed the central role of misfolded proteins and lysosomal dysfunctions in neurodegeneration. The timeline presents selected historical milestones, including Spinocerebellar Ataxia Type 7 in 1993, rather than a comprehensive account of subsequent discoveries.

Protein homeostasis and protein aggregation

Protein homeostasis, also referred to as proteostasis, is a dynamic cellular network responsible for regulating protein synthesis, folding, trafficking, and degradation, thereby maintaining protein quality and cellular function (Shukla & Narayan, 2024). Disruption of proteostasis compromises protein quality control and increases the likelihood of protein misfolding, particularly under conditions of cellular stress. Maintaining proteostasis is therefore essential for preserving normal cellular function, especially in post-mitotic cells such as neurons.

Proteins fold into specific conformations to achieve stable structures by reaching their lowest energy states under physiological conditions within the cell. This process culminates in the polypeptide chain acquiring its native three-dimensional structure. In addition to electrostatic forces, van der Waals interactions, hydrogen bonds, and other physical interactions, hydrophobic interactions also play an important role in determining protein conformation. The tertiary conformation of proteins determines their cellular function (Rehman et al., 2024). Proper protein folding depends on the amino acid sequence and the conditions of the cellular environment.

Various environmental and cellular conditions can alter protein conformation. These alterations directly affect protein function and, in some cases, may contribute to disease pathogenesis. If misfolded proteins are not recognized and degraded in a timely manner, they tend to interact with one another, forming insoluble intracellular inclusions or extracellular plaque structures (Juković et al., 2024).

Protein aggregation is the process by which proteins misfold within the cell and subsequently assemble into large, typically insoluble structures (Stefani & Dobson, 2003). In soluble proteins, hydrophobic side chains are typically buried within the protein core, allowing domains to pack together in a manner that minimizes the exposure of these hydrophobic residues to the aqueous environment (Pelley, 2012). Misfolded proteins interact uncontrollably with other proteins due to the exposure of their hydrophobic regions. Over time, these interactions lead to nonspecific protein aggregation, resulting in the formation of aggregates. This process represents a significant biological event that disrupts cellular homeostasis and underlies the pathogenesis of various diseases (Weids et al., 2016).

The progressive accumulation of these aggregates is a hallmark of numerous neurodegenerative disorders and is closely associated with neuronal dysfunction. Protein aggregation is classified into two main types: amyloid and amorphous (Sheng et al., 2020). During aggregate formation, oligomeric structures typically emerge as initial intermediates. These oligomers can develop into larger structures within the cell, forming amyloid fibrils or inclusion bodies. Amyloid structures, in particular, exhibit regular β-sheet arrangements and are associated with diseases such as Alzheimer's disease and Parkinson's disease. Uncontrolled protein accumulation leads to neuronal apoptosis and cell death (Ajmal, 2023). Because neurons are long-lived post-mitotic cells with limited regenerative capacity, they are particularly susceptible to the toxic effects of protein aggregates. Consequently, progressive aggregate accumulation contributes to synaptic dysfunction, neuronal degeneration, and the progression of numerous neurodegenerative diseases.

Oxidative stress in protein aggregation

Although multiple intracellular stressors contribute to protein aggregation, oxidative stress is considered one of the principal mechanisms driving protein misfolding and aggregate formation. Protein aggregates can form in response to various intracellular stressors, including heat shock, oxidative stress, errors in post-translational modifications, pH fluctuations, and elevated protein concentrations (Cox et al., 2020).

Reactive oxygen species (ROS) are oxygen-derived molecules generated during oxygen metabolism in aerobic organisms (Sachdev et al., 2023). ROS include oxygen-derived molecules such as the superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and the hydroxyl radical (•OH) (Averill-Bates, 2024). These species are generated during redox reactions or electron transport processes. Exposure of proteins to ROS can lead to the formation of protein aggregates over time (Grune, 2020).

ROS not only disrupt the intracellular redox balance but also directly impair the structural integrity of proteins. Oxidative modifications induced by ROS can cause proteins to lose their native three-dimensional conformation, resulting in protein misfolding and functional impairment (Sies & Jones, 2020). Oxidized proteins are often not efficiently eliminated by cellular quality control systems and gradually interact with one another to form toxic protein aggregates. Moreover, oxidative modifications may impair the activity of cellular proteostasis mechanisms, including molecular chaperones and the ubiquitin–proteasome system, thereby further promoting the accumulation of damaged proteins. Therefore, oxidative stress is widely recognized as one of the major mechanisms that initiate and accelerate protein aggregation (Pajares et al., 2015). Protein aggregation and oxidative stress are linked through a bidirectional relationship. While oxidative stress promotes protein aggregation, the resulting protein aggregates further impair mitochondrial function, leading to increased intracellular ROS production. Consequently, oxidative damage progressively accumulates, cellular protein quality control systems become overwhelmed, and additional protein aggregates form. This establishes a self-perpetuating pathological cycle between oxidative stress and protein aggregation. Such a vicious cycle accelerates synaptic dysfunction, disrupts cellular energy metabolism, and promotes neuronal cell death, particularly in neurodegenerative diseases (Carija et al., 2017).

Protein Aggregation in Rare Neurodegenerative Diseases

Protein aggregation and lipid dysregulation in niemann-pick type c

Niemann–Pick disease type C (NPC) is a rare autosomal recessive neurovisceral disorder, with approximately 95% of cases resulting from mutations in the NPC1 gene and the remainder attributed to mutations in the NPC2 gene (Newton et al., 2018). A hallmark of disease pathogenesis is the abnormal accumulation of lipids within late endosomes and lysosomes; however, the precise mechanisms underlying this accumulation remain incompletely understood (Wheeler & Sillence, 2020). Although cholesterol has long been considered the primary storage lipid in NPC disease, recent studies have demonstrated that sphingomyelin and glycosphingolipids also play significant roles in the pathogenesis of the disorder (Newton et al., 2017). Following the identification of the NPC1 and NPC2 genes, it became evident that their gene products are critically involved in lysosomal cholesterol trafficking. Under normal physiological conditions, neurons internalize cholesterol from lipoprotein sources, and this cholesterol is transported from lysosomes to the Golgi apparatus and the endoplasmic reticulum for further metabolism. During this process, NPC2 binds cholesterol and transfers it to the N-terminal domain of NPC1, thereby facilitating its exit from the lysosome (Wang et al., 2010). However, when either of these proteins loses its function, cholesterol accumulates within lysosomes, disrupting intracellular cholesterol homeostasis and adversely affecting various biological processes.

Beyond disrupting intracellular cholesterol homeostasis, excessive cholesterol accumulation within lysosomes profoundly impairs cellular proteostasis, thereby promoting the accumulation of misfolded and aggregation-prone proteins (Servín Muñoz et al., 2024). Increasing evidence indicates that defective cholesterol trafficking in NPC disease adversely affects several protein quality control

pathways, including the autophagy–lysosome pathway, the ubiquitin–proteasome system, and protein folding mechanisms within the endoplasmic reticulum (ER). Dysfunction of these pathways prevents the efficient removal of misfolded and aggregation-prone proteins, leading to their gradual accumulation in neuronal cells. Furthermore, impaired autophagic flux and reduced lysosomal degradative capacity promote the persistence of toxic protein species within the intracellular environment. Chronic ER stress and prolonged activation of the unfolded protein response (UPR) further aggravate protein misfolding, thereby accelerating neuronal dysfunction. Collectively, disruption of these protein quality control mechanisms facilitates the formation of intracellular protein aggregates and represents a key contributor to the neurodegenerative pathology observed in NPC disease.

Cholesterol is a critical lipid that not only maintains the structural integrity of cellular membranes but also plays a key role in regulating various signaling pathways. Therefore, disruptions in cholesterol homeostasis are believed to contribute to functional impairments, particularly within the central nervous system, potentially initiating progressive neurodegenerative processes (Arenas et al., 2017). Studies have indicated that the neuronal loss observed in NPC disease is associated not only with alterations in synaptic vesicle composition and structure but also with defects in endosomal trafficking pathways (Schultz et al., 2016). In this context, the high vulnerability of Purkinje cells to NPC pathology aligns with clinical manifestations such as ataxia, which is characteristic of cerebellar degeneration (Malnar et al., 2014). For instance, NPC1 mouse models faithfully recapitulate the neuropathological features of the disease, including mitochondrial cholesterol accumulation in both the brain and liver. This finding suggests a direct link between lysosomal cholesterol transport and mitochondrial function (Lopez et al., 2011).

Moreover, several molecular features, such as cholesterol accumulation, endolysosomal dysfunction, tau hyperphosphorylation, and β-amyloid (Aβ) deposition, have been identified as shared pathologies between NPC and Alzheimer's disease. Excess cholesterol in NPC1-deficient cells has been shown to impair amyloid precursor protein (APP) metabolism, leading to the accumulation of Aβ and C99 fragments, which can be reversed by cholesterol-lowering interventions. These findings highlight that cholesterol imbalance in NPC may contribute to Alzheimer's-like pathologies and support the utility of the NPC1 model in elucidating the molecular mechanisms underlying these processes (Borroni et al., 2018). ***Genetic and lysosomal mechanisms in neuronal ceroid lipofuscinosis***

Neuronal ceroid lipofuscinosis (NCL) is a rare, progressive, inherited neurodegenerative disorder (Guelbert et al., 2022). The most common forms of NCL typically begin during infancy or childhood and follow an autosomal recessive pattern of inheritance. The disease is characterized by progressive vision loss, epileptic seizures, motor dysfunction, cognitive decline, and ultimately premature death (Zhang et al., 2025). Based on age of onset and subtype, NCL is classified into four major groups: infantile, late-infantile, juvenile, and adult-onset forms (Nicolaou, 2024). The infantile form usually manifests during the first year of life and is marked by rapid neurological deterioration. During this period, visual impairment, seizures, muscle tone abnormalities, and regression in developmental milestones are commonly observed. In the juvenile form, symptoms typically appear during school age, with vision loss often being the earliest sign. As the disease progresses, patients experience ataxia, cognitive impairment, speech difficulties, seizures, and behavioral changes. In the less common adult-onset forms, disease progression tends to be slower; however, memory loss, motor dysfunction, and personality changes remain prominent clinical features (Mole & Cotman, 2015).

The pathogenesis of the disease begins with impaired lysosomal function due to genetic mutations. In this process, mutations, particularly in genes such as CLN1, CLN2, and CLN3, lead to deficiencies in lysosomal enzymes (Naseri et al., 2020). These enzymatic deficiencies result in the accumulation of lipofuscin within cells. Lipofuscin, a storage material, accumulates to toxic levels, especially in neurons, disrupting cellular function and ultimately leading to neurodegeneration. In addition to lipofuscin accumulation, lysosomal dysfunction also impairs the autophagy–lysosome pathway, compromising intracellular protein quality control. Consequently, misfolded and aggregation-prone proteins cannot be efficiently degraded, promoting their accumulation within neurons and further contributing to neurodegeneration.

The majority of NCL genes encode proteins associated with secretory and endolysosomal pathways within the cell. Among these are various lysosomally localized enzymes and soluble proteins, including CLN1/PPT1, CLN2/TPP1, CLN5, CLN10/CTSD, and CLN13/CTSF. Additionally, transmembrane proteins such as CLN3, CLN6, CLN7/MFSD8, and CLN12/ATP13A2 are involved in lysosomal membrane function. On the other hand, CLN6 and CLN8 are localized to the endoplasmic reticulum and function in compartments specific to the secretory pathways. Progranulin, encoded by the CLN11/GRN gene, is another protein shown to function within the secretory pathway (Gardner & Mole, 2021). Two other NCL-related proteins, encoded by CLN4/DNAJC5 and CLN14/KCTD7, are localized in the cytoplasm and are peripherally associated with cellular membranes. A major limitation in understanding the biological functions of soluble lysosomal enzymes involved in NCL is the incomplete characterization of their natural substrates. To address the enzymatic deficiencies associated with this disease, therapeutic strategies such as enzyme replacement therapy (ERT) and gene therapy are currently being developed and show considerable clinical promise (Neverman et al., 2015). ***Epigenetic dysregulation and aggregation in spinocerebellar ataxia type 7***

Spinocerebellar ataxia type 7 (SCA7) is an inherited, progressive neurodegenerative disorder characterized primarily by cerebellar coordination deficits, pyramidal system dysfunction, and vision loss resulting from retinal degeneration. The primary molecular cause of this disease is the expansion of CAG trinucleotide repeats beyond the normal range within the ATXN7 gene, located on chromosome 3p12–13. These expanded repeats lead to the accumulation of misfolded proteins that impair neuronal function, resulting in clinical manifestations such as impaired fine motor skills, dysarthria, and dysphagia (Horton et al., 2013). At the transcriptional level, functional impairments in the SAGA (Spt-Ada-Gcn5 acetyltransferase) complex, which interacts with RNA polymerase II, are considered among the key mechanisms contributing to disease pathogenesis. Mutant ATXN7 accumulates in the nucleus and disrupts the activity of the SAGA transcriptional regulatory complex, leading to alterations in histone modifications and dysregulation of gene expression. These transcriptional abnormalities not only disrupt neuronal gene expression but also impair cellular proteostasis, creating conditions that favor protein aggregation and neuronal degeneration.

The accumulation of polyglutamine (polyQ)-containing ATXN7 in the nucleus interferes with protein function and promotes the buildup of cellular waste (Niewiadomska-Cimicka & Trottier, 2019). These aggregates can trigger mitochondrial dysfunction in neurons, increase oxidative stress, and ultimately initiate neurodegenerative cascades leading to apoptosis. In addition to transcriptional defects, mutant ATXN7 compromises intracellular protein quality control mechanisms. Both the ubiquitin–proteasome system (UPS) and the autophagy–lysosome pathway contribute to the removal of misfolded proteins under physiological conditions. However, polyQ-expanded ATXN7 interferes with these degradation pathways, reducing the efficiency of abnormal protein clearance and promoting the

progressive accumulation of toxic aggregates within neurons. A pathological hallmark of SCA7 is the formation of intranuclear inclusions composed of mutant ATXN7, together with ubiquitin, molecular chaperones, and transcription-associated proteins. Although these inclusions were initially regarded as inherently toxic, increasing evidence suggests that they may also represent a protective cellular response aimed at sequestering misfolded proteins and limiting their toxicity (Zoghbi & Orr, 2000).

Studies have shown that epigenetic alterations may also occur in human cells expressing mutant ATXN7. In neuronal and retinal cell models derived from SCA7 patients, significant changes in histone acetylation levels at the promoters of various genes have been observed (Switonski et al., 2021). In this context, epigenetic modifications, particularly those that increase chromatin accessibility, are thought to contribute to transcriptional dysregulation. Moreover, disturbances in the deubiquitination process, such as alterations in the ubiquitination status of histone H2B, have also been reported in human cellular models (Lee et al., 2007). These epigenetic and transcriptional abnormalities are proposed to affect downstream gene expression, leading to imbalances at the protein level and ultimately triggering neurodegenerative processes. Collectively, current evidence suggests that mutant ATXN7-induced epigenetic dysregulation, impaired proteostasis, mitochondrial dysfunction, and oxidative stress cooperate to promote progressive neuronal degeneration in SCA7. Nevertheless, further studies using human disease models are required to clarify how these molecular alterations contribute to protein-level changes and aggregate formation (Mohan et al., 2014).

As illustrated in Figure 2, protein aggregation represents a shared pathological feature across several rare neurodegenerative diseases, including NPC, NCL, and SCA7. Multiple factors, such as mutations, chaperone system dysfunction, post-translational modification defects, and oxidative stress, can contribute to protein aggregation. In this context, laccase enzymes may have the potential to modulate oxidative stress and thereby limit aggregation-associated processes.

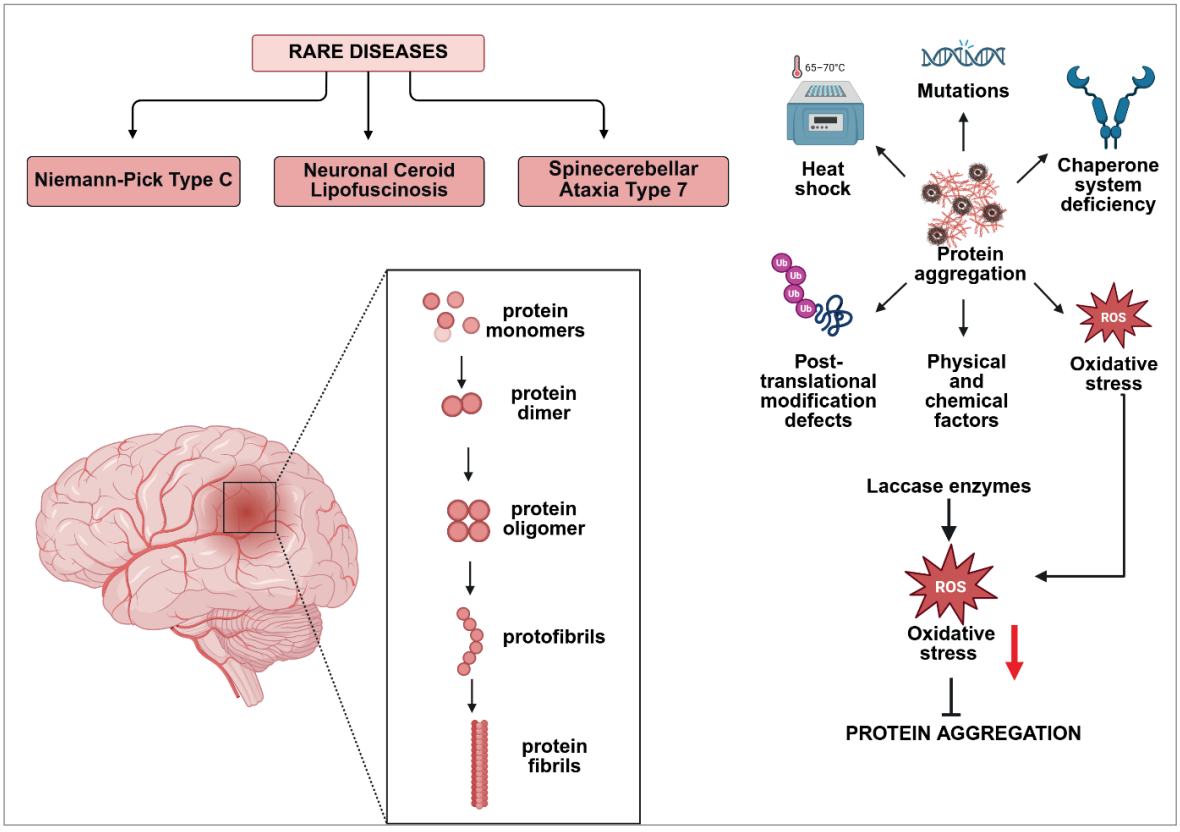

Figure 2. This diagram shows the stages of protein aggregation and the molecular factors that trigger this process in rare neurodegenerative diseases such as Niemann-Pick Type C, Neuronal Ceroid Lipofuscinosis, and Spinocerebellar Ataxia Type 7. The left section shows that misfolded monomers, which form the starting point of protein aggregation, transform into amyloid-like fibrils by forming intermediate structures such as dimers, oligomers and protofibrils throughout the process, and these structures lead to pathological accumulation in the brain tissue. The right section shows how various intracellular stress factors, such as genetic mutations, cellular stress (e.g., heat shock), molecular chaperone deficiencies, post-translational modification defects, and oxidative stress caused by reactive oxygen species, are effective in disrupting protein homeostasis and triggering aggregate formation. Laccase oxidizes suitable substrates while reducing molecular oxygen to water. Its net effect on neuronal ROS and protein aggregation remains hypothetical and requires experimental validation.

Biochemical properties and therapeutic potential of laccase

Structure, catalytic mechanism and substrate specificity of laccase

Laccase (p-diphenol oxidoreductase; EC 1.10.3.2) is a powerful copper-containing oxidase found in bacteria, plants, fungi, and some invertebrates (Yang et al., 2017). In addition, laccases are classified within the multicopper oxidase (MCO) superfamily, along with enzymes such as ascorbate oxidase (EC 1.10.3.3) and ferroxidase (EC 1.16.3.1). In particular, white-rot fungi, which are capable of decomposing all lignocellulosic components, produce high levels of laccases (Kijpornyongpan et al., 2022). This enzyme catalyzes the oxidation of monophenolic and polyphenolic compounds through single-electron transfer while reducing molecular oxygen to water.

Each enzyme molecule contains a total of four copper ions: one T1, one T2, and two T3 copper ions. Electron transfer is initiated at the T1 center, and the electrons are subsequently transferred to molecular oxygen through the trinuclear copper complex (TNC) (Jones & Solomon, 2015). The T1 site acts as the primary redox center, receiving the first electron from the substrate. This electron is then transferred via a conserved His-Cys-His tripeptide motif to the TNC, which consists of T2 and T3 copper ions. Located within a broad binding pocket on the enzyme surface, the T1 ion enables interactions with a wide range of substrates. It functions as a gate that regulates the entry of substrate-derived electrons into the enzyme's active site and plays a role in determining the catalytic rate. Ultimately, the four electrons collected at this cluster enable the complete reduction of molecular oxygen to two molecules of water. For a representative phenolic substrate, the overall reaction is $4\ ArOH + O_2 \rightarrow 4\ ArO\bullet + 2\ H_2O$, where ArO• denotes a phenoxyl radical (Walde et al., 2019). Therefore, the reduction of molecular oxygen to water does not, by itself, demonstrate the removal of cellular ROS; whether laccase reduces net oxidative stress in neurons remains to be determined.

The reduction of the T1 copper ion is considered the rate-limiting step in laccase catalysis. The redox potential of this ion ranges from 420 mV to 790 mV versus the standard hydrogen electrode, indicating that laccases primarily interact with compounds within this redox range. The triangular geometry formed by the T2 and T3 copper ions facilitates the binding of molecular oxygen to the enzyme's

active site. This structure enables the reduction of molecular oxygen and the formation of water using the four electrons transferred through the T1 site (Jiang et al., 2022). The unique multicopper active site of laccase underlies its broad substrate specificity and high catalytic efficiency, making it one of the most extensively studied oxidoreductases.

Laccases exhibit considerable substrate diversity and share functional similarities with other oxidase enzymes, such as bilirubin oxidase and tyrosinase. A wide range of compounds, including both high- and low-molecular-weight molecules, can serve as substrates for these enzymes. Substrate preference depends, in part, on the structure of the substrate-binding pocket and the redox properties of the enzyme and substrate (Ezike et al., 2021). However, broad substrate specificity does not establish the selective oxidation of disease-associated molecules in neurons. For the proposed neuronal application, the substrates and oxidation products of a defined laccase would need to be identified under physiologically relevant conditions, alongside potential effects on endogenous neuronal compounds. In this context, laccases possess the catalytic ability to oxidize mono-, di-, and polyphenols, aromatic and aliphatic amines, certain structural carbohydrate fractions, as well as various inorganic and organic complexes and metal species (Karaki et al., 2016).

Classification, distribution and biological functions of laccase

Generally, laccases are classified into two groups based on their structural organization: three-domain laccases (3D) and two-domain laccases (2D). Three-domain laccases are widely distributed in nature and have been identified in various organisms, including certain insect species, higher plants, fungi, bacteria, archaea, and crustaceans. In contrast, two-domain laccases have a more limited distribution and are predominantly produced by bacteria belonging to the genus Streptomyces (Giardina et al., 2010).

Although laccases have been reported in higher plants, microorganisms, and certain insect species, the majority of studies on laccases have focused on fungal groups belonging to the Ascomycetes, Basidiomycetes, and Deuteromycetes, as well as cellulolytic fungi (Viswanath et al., 2014). Among these, saprophytic fungi from the Basidiomycetes group have been particularly well studied as prolific laccase producers (Baldrian, 2006). Notable examples include Cariolapsis polyzona, Coprinus cinereus, Lentinus edodes, Phlebia radiata, Pycnoporus cinnabarinus, and Trametes spp. (Baldrian, 2006; Yang et al., 2017). The first laccase isolated from an ascomycete species was obtained from Monocillium indicum, paving the way for the recognition of the laccase-producing potential of this fungal group as a promising enzyme source (Widsten & Kandelbauer, 2008). Fungal laccases are generally known to play physiological roles in processes such as toxin detoxification, pathogenicity, lignin degradation, and sporulation (Patel et al., 2022). The widespread distribution of laccases across different kingdoms reflects their diverse physiological functions and evolutionary conservation.

Industrial applications and therapeutic potential of laccase

Laccases are widely employed in a range of sectors, such as biofuel production, environmental remediation, food, textiles, pharmaceuticals, and cosmetics (Jeon et al., 2012). Due to their compatibility with sustainability principles, laccases play a key role in supporting environmentally friendly production processes. However, the large-scale industrial application of laccases is often limited by high production costs and suboptimal enzyme performance. To overcome these challenges, current strategies focus on the use of recombinant microorganisms or the selection of microbial strains that naturally produce high levels of laccase. Additionally, various immobilization techniques and protein engineering approaches are being explored to enhance enzyme stability and efficiency (Upadhyay et al., 2016).

The synthesis and secretion of laccases are influenced by various environmental and physiological factors, including nutrient availability, culture conditions, and the developmental stage of the organism. In particular, certain heavy metal ions (e.g., Cu^{2+}, Ag^{+}, Mn^{2+}) and lignin-derived aromatic compounds (e.g., ferulic acid, veratric acid, and xylidine) are known to significantly induce laccase production (Khatami et al., 2022). Beyond inducing gene expression, these compounds may also trigger the involvement of laccases in cellular defense mechanisms against oxidative stress arising from the accumulation of ROS. Consequently, laccases are considered essential not only for lignin degradation and environmental applications but also for maintaining intracellular redox homeostasis (Liu et al., 2022). The proposed therapeutic effects of laccase on oxidative stress, cellular proteostasis, and protein aggregation are summarized in Figure 3.

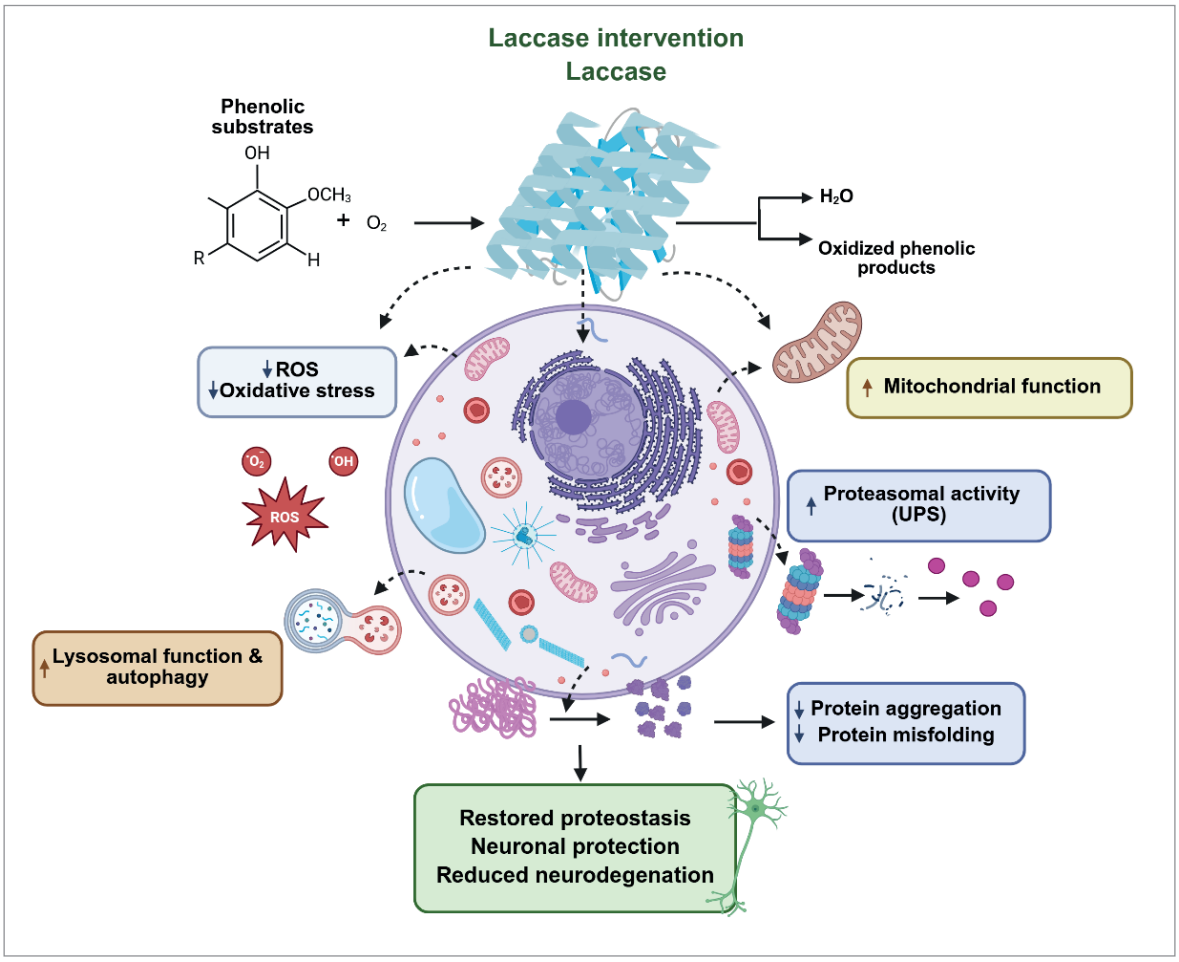

Figure 3. Proposed mechanism of laccase-mediated regulation of protein aggregation in rare neurodegenerative diseases. Laccase reduces oxidative stress through the oxidation of phenolic substrates, thereby promoting mitochondrial function, lysosomal autophagy, and ubiquitin–proteasome system activity. These effects may enhance proteostasis, reduce protein misfolding and aggregation, and contribute to neuronal protection. The illustrated pathway represents a hypothetical mechanism derived from the current literature.

Future Perspectives

Laccase is a multicopper oxidase enzyme that has emerged as a promising biocatalyst in biotechnology and biomedical research due to its high catalytic efficiency, broad substrate specificity, and strong oxidative capacity (Janusz et al., 2020). Its ability to oxidize a wide range of both phenolic and non-phenolic compounds has enabled its extensive application across various industrial processes. In particular, laccase plays an important role in biomass pretreatment and bioethanol production by facilitating the efficient degradation of lignin. Moreover, it is considered a sustainable biocatalyst in the pulp and paper industry, where it can reduce the use of environmentally harmful chemicals during bleaching processes (Moreno et al., 2015). Furthermore, advances in enzyme engineering, immobilization technologies, and heterologous expression systems have improved the stability, catalytic efficiency, and industrial applicability of laccase, thereby expanding its biotechnological applications. However, whether laccase affects protein aggregation, oxidative stress, or cellular proteostasis in neurodegenerative diseases remains to be determined. Therefore, its proposed role in these processes should be investigated in relevant neuronal models before therapeutic applications are considered.

Several limitations should be considered before proposing laccase for neuronal applications. Its catalytic activity depends on properly assembled copper centers, so the copper content and activity of the selected enzyme would need to be verified (Osipov et al., 2015). Because molecular oxygen is required for the catalytic reaction, its activity should also be tested under oxygen conditions relevant to the target tissue. Finally, the immunogenicity of administered laccase, particularly with repeated dosing, remains to be evaluated. Immune responses have been observed with other therapeutic enzymes, but this does not establish that laccase causes the same response (Tsukimura et al., 2020).

Protein aggregation is one of the major pathological hallmarks of neurodegenerative diseases and is driven by closely interconnected cellular mechanisms, including oxidative stress, mitochondrial dysfunction, defects in the autophagy–lysosomal pathway, and impairment of the ubiquitin–proteasome system (Schützmann & Hoyer, 2025). Considering the complexity of these processes, therapeutic strategies targeting a single molecular pathway may not be sufficient to halt disease progression. Therefore, the development of biological agents capable of simultaneously modulating multiple cellular mechanisms has gained increasing attention as a promising approach for the treatment of neurodegenerative diseases (Hu et al., 2025).

Given its redox activity and demonstrated ability to catalyze oxidative modifications of proteins, laccase may represent a potential candidate for further investigation in the context of protein aggregation-associated neurodegenerative diseases (Mardiyono et al., 2026; Steffensen et al., 2008).

Significant advances have been made in recent years in therapeutic strategies targeting protein aggregation, with pharmacological agents, gene therapy, immunotherapy, and nanoparticle-based drug delivery systems emerging as promising approaches for the treatment of neurodegenerative diseases (Barthel et al., 2022). These strategies aim not only to prevent the formation of misfolded proteins but also to promote the clearance of existing protein aggregates and restore cellular protein quality control mechanisms, including the ubiquitin–proteasome system and the autophagy–lysosomal pathway (Harris & Rubinsztein, 2011). However, the limited ability of therapeutic agents to effectively cross the blood–brain barrier, challenges in delivering treatments to the target tissue, and the complex molecular nature of neurodegenerative diseases remain major factors limiting the clinical efficacy of current therapeutic approaches (Thomsen & Moos, 2022).

Recent advances in targeted protein degradation strategies, the identification of novel autophagy receptors, and nanoparticle-based delivery systems have provided promising approaches for the more efficient clearance of toxic protein aggregates. Therefore, future research should focus on improving our understanding of the molecular mechanisms underlying protein aggregation and identifying novel biomarkers that support early diagnosis and therapeutic intervention (Assali et al., 2019). The therapeutic potential of laccase in neurodegenerative diseases has not yet been fully elucidated. Therefore, future studies should investigate the effects of laccase on the formation and clearance of protein aggregates using advanced cellular and animal models, improve its bioavailability through appropriate drug delivery systems, and evaluate its clinical applicability (Figure 4). Findings from these studies may establish laccase as a promising biological candidate for the development of innovative and multifunctional therapeutic strategies targeting protein aggregation.

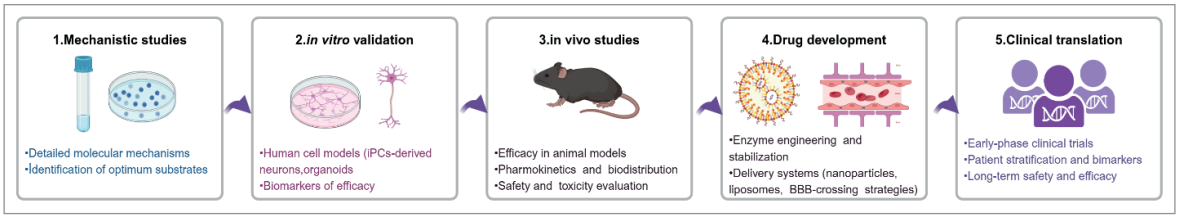

Figure 4. Proposed research roadmap for the clinical translation of laccase as a therapeutic strategy for rare neurodegenerative diseases. Future research should progress through sequential stages, including mechanistic studies to elucidate the molecular actions of laccase, in vitro validation in human cell models, in vivo evaluation of efficacy, pharmacokinetics, and safety, optimization through enzyme engineering and drug delivery systems, and ultimately clinical translation through early-phase clinical trials. This roadmap highlights the key research priorities required to facilitate the development of laccase-based therapies for protein aggregation-associated rare neurodegenerative diseases.

Conclusion

This review comprehensively evaluated the potential therapeutic role of laccase in rare neurodegenerative diseases characterized by protein aggregation. In neurodegenerative disorders such as Niemann–Pick disease type C (NPC), neuronal ceroid lipofuscinosis (NCL), and spinocerebellar ataxia type 7 (SCA7), the accumulation of misfolded proteins, often triggered by cellular stress factors, leads to the formation of toxic protein aggregates, ultimately resulting in neuronal cell death. Through its oxidative catalytic activity, laccase oxidizes suitable phenolic and aromatic substrates while reducing molecular oxygen to water; however, this reaction alone does not establish a reduction in cellular free radicals. Whether laccase affects oxidative stress, protein misfolding, or aggregate formation in neuronal cells remains to be determined. Therefore, the possible effects of laccase on aggregate-associated neuronal toxicity require direct experimental investigation.

In rare neurodegenerative diseases such as NPC and NCL, lysosomal dysfunction is commonly associated with intracellular protein aggregation. Whether laccase affects reactive oxygen species

(ROS) levels or lysosomal homeostasis in NPC and NCL has not yet been established. In SCA7, where expanded polyglutamine tracts promote aggregation, the possible effects of laccase also remain unexplored. Thus, laccase should be considered a candidate for mechanistic investigation rather than an established treatment for NPC, NCL, or SCA7.

Future studies should identify relevant neuronal substrates and reaction products, determine whether laccase alters cellular ROS levels or protein aggregation, and assess enzyme stability, delivery, and safety in appropriate cellular and animal models. Such evidence is necessary before its therapeutic potential can be evaluated.

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Conflict of interest

The authors declare no conflict of interest.

Data availability statement

Data sharing is not applicable to this review article as no datasets were generated or analyzed during the current study.

Ethics committee approval

Ethics committee approval is not required for this study

Authors' contribution statement

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