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Navigating Neuroscience with Research Antibodies

Key Aspects and Principles of Neurodegenerative Diseases & Overview of Related Research Reagents

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Neuroscience is a captivating field that delves into the intricate workings of the brain and nervous system. It encompasses a wide array of disciplines aimed at unraveling the complexities of the human mind and addressing neurological disorders. With millions of people affected by these conditions worldwide, the need for ongoing research is paramount. Despite remarkable progress in neuroscience, there is still much to uncover about the mechanisms underlying brain function and dysfunction, and to develop innovative treatments.

This e-book is designed to offer an insightful exploration of neuroscience research, with a particular focus on neurodegenerative diseases and underlying common principles. It provides an in-depth analysis of these foundational principles, shedding light on the critical neural pathways and cellular processes involved. Additionally, it gives an overview of the brain tissues and important markers involved.

As a provider of top-quality research materials, we recognize the significance of dependable tools for neuroscience research. This comprehensive guide provides a range of research materials available, including antibodies, proteins, and assay kits tailored to neuroscience studies, plus valuable insights into the selection and utilization of these resources, underlining their pivotal role in advancing our knowledge of the brain and its intricate functions.

Contents

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Neurodegenerative Diseases

Key Processes in Neurodegenerative Diseases

The term neurodegenerative disease describes a heterogeneous group of disorders that are characterized by the progressive degeneration of structure and function of the central nervous system (CNS) or peripheral nervous system, leading to loss of brain functions, including memory, movement, and cognition. Because there is no known way to reverse the progressive degeneration of neurons, these diseases are considered to be incurable. The late manifestation of clinical symptoms, usually years or even decades after disease onset, continues to impede therapies to prevent disease progression or regenerate or replace affected neurons.

Neurodegenerative diseases may occur due to age, i.e., Alzheimer's disease (AD), Parkinson's disease (PD), or due to genetic mutations, which impact nerve system cell function, i.e., Huntington's disease (HD), early-onset AD or PD, and Amyotrophic Lateral Sclerosis (ALS). Furthermore, neurodegenerative diseases show a variety of pathological overlaps. Here we provide an overview about selected key processes reoccurring in neurodegenerative diseases, including proteinopathies, neuroinflammation, mitochondrial dysfunction, errors in RNA, and altered cell signaling.

These similarities suggest that therapeutic advances against one neurodegenerative disease might be effective against other diseases as well. Research on this topic is highly relevant especially in the context of our aging population, as aging is an important trigger factor of neuronal diseases.

Proteinopathies

Biomedical research revealed similarities on a subcellular level, including atypical protein assemblies like proteinopathy (a single type of proteinopathy can be associated with multiple diseases) and induced cell death. The proteinopathies include diseases such as AD, PD, Creutzfeldt–Jakob disease, and other prion diseases, such as amyloidosis, multiple system atrophy, and a wide range of other disorders. In most, if not all proteinopathies, a change in the three-dimensional folding conformation increases the tendency of a specific protein to bind to itself. The misfolding of the protein may result in a loss of its usual function as well as a toxic gain-of-function. In this aggregated form, the protein is resistant to clearance. These deposits of insoluble peptides or proteins accumulate with time, and they become more toxic when neurons age.

Certain risk factors can promote the self-assembly of a protein and therefore proteinopathy. These include increased expression, destabilizing changes in the primary amino acid sequence of the protein, post-translational modifications, and changes in temperature or pH. Advancing age is a strong risk factor—in the aging brain, multiple proteopathies can overlap. The following table gives an overview of different proteinopathies and their link to neurodegenerative diseases.

Long-COVID: "Brain fog"

Brain fog describes symptoms brought into focus in the post-COVID progression. In addition to concentration problems, word-finding disorders and forgetfulness, and other symptoms, such as general mental fatigue may also occur. These "long-haul" symptoms can persist for months.

SARS-CoV-2 may rarely invade brain tissue directly; most neurological damage is thought to stem from the indirect effects of infection, such as inflammation, stroke, and lack of oxygen. Inflammatory chemicals can travel from the lungs to the brain, where they disrupt microglia cells. When microglia are inflamed, their efforts become destructive thus loosing their supportive function towards neurons. This leads to fewer fresh neurons as many existing neurons lose their insulating sheats, impeding electric signal transduction.

Explore SARS-CoV-2 Hub

Disease	Pathology	Component Proteins
Alzheimer Disease	Senile plaques Neurofibrillary tangles Lewy bodies Neuronal inclusions	Tau α-Synuclein TDP-43
Parkinson's Disease	Lewy bodies	α-Synuclein
Amyotrophic Lateral Sclerosis	Neuronal inclusions	TDP-43 FUS/TLS SOD1
Huntington's Disease	Neuronal intranuclear inclusions	Huntingtin

Neuroinflammation

Microglia, the primary immune cells in the CNS, are activated upon disruption of the physiological homeostasis. Activated microglia destroy pathogens, remove damaged cells, eliminate toxic substances, prevent spread of infections and injury, release neurotrophic factor, and promote tissue repair and regrowth. However, tight coordination among activated microglia, astroglia, and neurons is essential for tissue repair and for fighting off infection of healthy CNS cells. In neurodegenerative diseases, beneficial effects of neuroinflammation appear to be reduced and excessive inflammation leads to neuronal loss instead. Reactive microgliosis or the chronical activation of microglia, is a hallmark of several neurodegenerative diseases and is implicated in progression of AD and PD. Driving factors include aggregated α-synuclein and A-β-amyloid or imbalanced neurotransmitters.

Mitochondrial Dysfunction

Because of their high energy requirements, neurons are especially vulnerable to injury and death from dysfunctional mitochondria. Pathological and physiological evidence reveals mitochondrial dysfunction in all major neurodegenerative diseases. Catalyzed by iron, copper, and trace redox-active metals, metal-mediated oxidative stress plays a key role in mitochondrial dysfunction. Questions remain as to whether mitochondrial dysfunction is causal to neurodegenerative disease. Even if is not causal, mitochondrial dysfunction is still highly important and likely contributory to disease.

Altered Cell Signaling

Cellular communication and signaling are keys to coordinate the functions of the different cell types that constitute organisms. These systems control processes, such as inter- and intracellular transport, changes in cell morphology, energy consumption and accumulation, cell differentiation, cell migration, and cell proliferation or cell death. Based on the theory of the neurovascular unit, abnormal cell-to-cell communication, e.g., disrupted presynaptic input and disrupted intracellular signaling, contribute to the pathogenesis of neurodegenerative disease. Although the undeerlying mechanism is not yet fully understood, astrocyte dysfunction is thought to play a central role. Understanding the signal transduction pathways that regulate gene expression will help efforts to develop therapeutic interventions.

Neurovascular Unit

The concept of the neurovascular unit emphasizes that cell-to-cell signaling, among the various neuronal, glial, and vascular compartments underlies the homeostasis of normal brain function. Conversely, dysfunctional signaling like disrupted presynaptic input, as well as disrupted intracellular signaling within the neurovascular unit should contribute to the pathogenesis of neurodegenerative disease.

Errors in RNA

Various neuromuscular and neurodegenerative diseases—including certain types of ALS, frontotemporal dementia, and AD—feature toxic RNA or RNA-binding proteins. Non-coding RNAs are diverse classes of RNA molecules that are not translated into proteins. They are disproportionately expressed within the CNS, where they have roles in gene expression, development, neural network plasticity and connectivity, stress response, and brain aging. Antisense oligonucleotides (ASOs) are being tested to treat RNA errors in human neurodegenerative disease. Additionally, ASOs are designed to hybridize and then to block disease-related RNA sequences.

Alzheimer's Disease

Alzheimer's disease (AD) is the most common form of dementia with about 50 million people worldwide affected. A further increase in the number of cases is expected by 2050 partly due to the fundamental rise in life expectancy. The clinical picture is characterized by a progressive loss of cognitive abilities. The neurological hallmarks are the presence of neuritic plaques and neurofibrillary tangles of proteins in brain tissue. Ultimately, the disease leads to death.

The majority of sporadic AD cases remain genetically unexplained and are thought to be primarily influenced by contributing nongenetic factors, such as oxidative stress, mitochondrial dysfunction, neuroinflammation, or microbial factors (e.g. HSV-1).

However, in some forms of early-onset and late-onset AD, underlying pathogenic mutations in several genes and their respective proteins have been identified as genetic risk factors to develop familial AD. For example, the presence of the ε4 allele of the apolipoprotein E (APOE4) gene increases a person's risk for late-onset AD from the mid-60s on. Early-onset AD occurring as early as the mid-30s is less frequent and gene alterations observed in this context are in the amyloid precursor protein (APP) gene and the Presenilin 1 (PSEN1) and 2 (PSEN2) genes. Aβ and hyperphosphorylated Tau (pTau) oligomers are considered determinants of AD pathophysiology, although the exact mechanism is not yet understood.

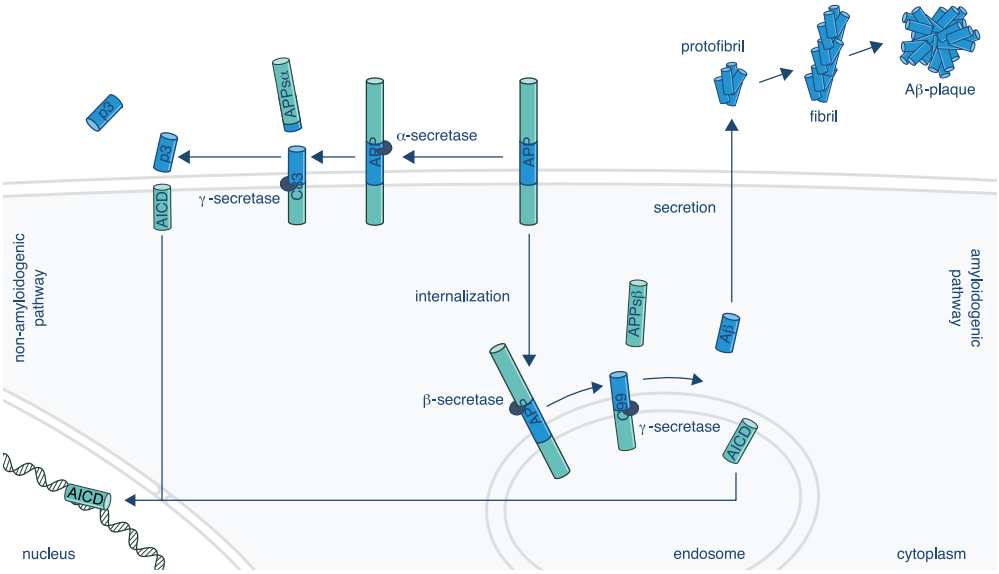

Fig. One of the key factors for AD and central to the amyloid hypothesis as underlying cause for the disease is APP. It is predominantly proteolytically processed by α-secretase and γ-secretase in the plasma membrane (non-amyloidogenic pathway, left). End products are soluble extracellular N-terminal fragment (APPsα) and p3 peptide and the N-terminal APP intracellular domain (AICD). Processing in the endosome membrane via the amyloidogenic pathway (right) by Aβ- and Aγ-secretase into N-terminal APPsβ, Aβ peptides, and AICD. AICD acts as transcription factor upon transport into the nucleus. The Aβ peptides with 38 to 43 amino acids are secreted into the intracellular space where they form fibrils and ultimately the Aβ-plaques characteristic for AD.

Key Factors in AD

Apolipoprotein E

The APOE4 variant of the apolipoprotein E gene on chromosome 19 is the principal genetic risk factor for late-onset AD. It is one of three different versions of the APOE gene: APOE2 is the rarest of the three variants and is associated with a decreased AD risk; APOE3 is the most common variant and is not thought to influence developing AD; APOE4 is a major risk factor for late-onset familial AD as it causes changes in the blood-brain barrier that lead to problems in synapses.

The prevalence of the APOE4 variant in the general population is 9% to 23%. In comparison, at least one copy of APOE4 is present in 24% to 45% of AD patients and 2% to 3% have two copies of the allele (homozygosity) depending on ethnicity. Homozygosity for this allele causes earlier disease onset than in heterozygous carriers and predicts AD by age 80.

Amyloid Precursor Protein

Proteolysis of transmembrane surface receptor APP gives rise to various amyloid-beta (Aβ) peptides. Mutations in the APP gene on chromosome 21 can impair β-secretase (BACE1) and γ-secretase (PSEN1, PSEN2, NCSTN, APH1A, APH1B, PSENEN) protease cleavage sites and increase the total amount of Aβ in the cell or the ratio of the Aβ42/Aβ40. Similarly, mutations in the APP promotor or duplication of the gene cause an elevated Aβ concentration. Protective mutation in the AAP gene, on the other hand, can reduce AD risk. Several proteins are also known to modulate APP expression, e.g., APOE, ABCA7, BIN1, clusterin, PICALM, and SORLA.

Both the increase of total Aβ and Aβ42/Aβ40 ratio lead to the formation of the extracellular neuritic amyloid plaques that are characteristic for AD because of the proteins' tendency—

in particular Aβ42—to oligomerize and from insoluble fibrils. The amyloid hypothesis posits that this clumping of Aβ peptides are the primary driver of AD. Anti-AD drugs, such as lecanemab, donanemab, aducanumab, and gantenerumab monoclonal antibodies aim to clear amyloid from the brain. Some of these have shown lackluster effects in alleviating the effects of AD in later stages, but slowed cognitive and functional decline in people with early symptomatic AD in clinical trials. Alternative pharmacological approaches target β-secretase and γ-secretase to prevent APP proteolysis.

APP and Aβ peptides also influence synapse stability through interaction with the Wnt signaling pathway. On one hand, APP activates canonical Wnt-b-catenin, which is important for synapse stability, through induction of the Wnt inhibitor Dkk1 by Aβ. On the other hand, Aβ can also activate non-canonical Wnt signaling which leads to synapse retraction. Activation of this non-canoncial Wnt signaling pathway also increases Aβ production, resulting in a positive feedback loop that ultimately leads to synapse loss.

Neuroinflammation cause by APP proteolysis products is an additional aspect to AD. Aβ also binds to pattern-recognition receptors (PRRs) on microglia, the primary immune cells in the central nervous system. Upon recognizing Aβ as damage-associated molecular patterns (DAMP), resting microglia are activated. This triggers release of cytokines to enhance phagocytosis and Aβ uptake and clearance, inhibit inflammatory processes, and promote tissue repair. However, long-term activation of microglia gives rise to neuroinflammation causing synaptic dysfunction and neurotoxicity that exacerbates neurodegeneration.

β- and γ-Secretase

The mechanisms of Aβ generation and prevention are subject of intensive research. APP, as well as β- and γ-secretases, are the principal players involved in Aβ production, while α-secretase cleavage on APP prevents Aβ deposition. Inhibitors or modulators that target β- and γ-secretases, as well as α-secretase activators, are promising candidates for AD treatment.

PEN2 | APH1A | APH1B | BACE1 | NCSTN

Tau

Tau is a microtubule-associated phosphoprotein abundant in axons involved in promoting polymerization and stabilization of microtubules. Many neurodegenerative diseases show Tau alterations and a pathology that is characterized by intraneural neurofibrillary tangles composed of pTau oligomers. AD is considered a secondary tauopathy because the primary driver of the disease is clumping of Aβ proteolysis products.

Many kinases, including GSK3β, CDK5, MAPK, JNK, and p38, finely regulate protein Tau hypermethylation. This leads to a conformational change, which impairs its association with microtubules. Consequently, Tau becomes soluble and can undergo dimerization and self-association into higher-order oligomers, filaments (aka paired helical filaments, PHF), and ultimately NFTs (neurofibrillary tangles). Chaperones such as Hsp70 and DNAJA1 can reduce aggregation of Tau and are in turn modulated by Cereblon (CRBN).

α-synuclein

The presynaptic protein α-synuclein (αSyn) is traditionally associated with synucleopathies like PD or dementia with Lewy bodies (DLB). More recently, it has been suggested that αSyn may also play a role in AD because of elevated levels of the protein in the cerebrospinal fluid of individuals at elevated risk for sporadic AD and experimental evidence linking αSyn to tau hyperphosphorylation.

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Antibodies Used in Alzheimer's Disease Research

Publication	Target	Overview	Antibody
Somatostatinergic systems: an update on brain functions in normal and pathological aging	Somastatin	SST is implicated in multiple brain functions like olfaction, vision, cognition and locomotion, as well as in pathologies such as AD, schizophrenia, and major chronic depression.	SST Antibody

Publication	Target	Overview	Antibody
Mechanistic Insight into the Inhibition of Choline Acetyltransferase by Proton Pump Inhibitors	Choline O-Acetyl -transferase	Patients with AD have reduced cerebral content of choline acetyltransferase, which leads to a decrease in acetylcholine synthesis and impaired cortical cholinergic function. Cholinesterase inhibitors increase cholinergic transmission by inhibiting cholinesterase at the synaptic cleft and provide modest symptomatic benefit in some patients with dementia.	CHAT Antibody
Brain angiogenesis in developmental and pathological processes: mechanism and therapeutic intervention in brain tumors	serpin Peptidase Inhibitor, Clade F	The primary role of SERPINF1 in neuroscience is to promote the survival and health of neurons. It exerts neuroprotective effects by inhibiting the activity of certain enzymes and factors that can lead to neuronal damage, inflammation, and oxidative stress. Additionally, SERPINF1 has neurotrophic properties, which means it can promote the growth, differentiation, and maintenance of neurons. In AD, for example, the loss of neurons and the accumulation of harmful proteins like beta-amyloid can contribute to cognitive decline. SERPINF1's neuroprotective and neurotrophic properties make it a target for research into treatments that could slow down or mitigate the progression of such neurodegenerative disorders.	SERPINF1 Antibody
A Comprehensive Analysis of the CaMK2A Gene and Susceptibility to Alzheimer's Disease in the Han Chinese Population	Calcium/ calmodulin-Dependent Protein Kinase II alpha	The paper suggests an important role for CaMK2A in the pathophysiology of AD.	CAMK2A Antibody
Selective loss of cortical endothelial tight junction proteins during Alzheimer's disease progression	Occludin	Publication highlights the presence of prominent endothelial tight junction pathology in AD. Loss of cortical tight junction proteins in AD is associated with insoluble amyloid-β40 and loss of synaptic markers.	OCLN Antibody
Parvalbumin interneuron vulnerability and brain disorders	Parvalbumin	Parvalbumin-expressing interneurons are highly vulnerable to stressors and have been implicated in many neuro-psychiatric diseases such as schizophrenia, AD, autism spectrum disorder, and bipolar disorder.	PVALB Antibody

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a late-onset fatal motor neuron disease with an incidence of about 1 to 5/100,000 that was first described in 1869 by the French neurologist Jean-Martin Charcot (Charcot disease) and became well known in the late 1930 when baseball player, Lou Gehrig, was diagnosed with it (Lou Gehrig's disease).

Most ALS cases are sporadic (SALS), but 5 to 10% of the cases are familial ALS (FALS) with an underlying genetic cause. Typically, symptoms emerge around 60 years of age for SALS and around 50 years for FALS. Both SALS and FALS caused by a progressive degeneration of cortical and spinal motor neurons, leading to paralysis and ultimately respiratory failure because of muscle impairment. Mutations in numerous genes have been associated with mechanisms causing neuronal degeneration, such as RNA dysregulation, impaired protein homeostasis, or the formation of cytoplasmic aggregates. Many of these genetic marks are shared with the closely related disease frontotemporal dementia. Non-neuronal cells, such as astrocytes and microglia, exacerbate neurodegeneration via the secretion of neurotoxic mediators and the modulation of glutamate receptor expression. Dysfunction of oligodendrocytes and Schwann cells cause damage to the myelin.

Besides genetic predisposition, environmental factors are thought to contribute to developing ALS given that the disease typically manifests in adulthood. Suspected risk factors include smoking, head trauma, athletic propensity, and neurotoxic chemicals (e.g. b-N-methylamino-L-alanine (BMMA)), among others.

So far, there is no effective treatment for ALS. The principal options are neuroprotective treatment, symptomatic and supportive treatment, as well as some unproven disease-modifying therapies, such as stem cell transplantation and gene therapy.

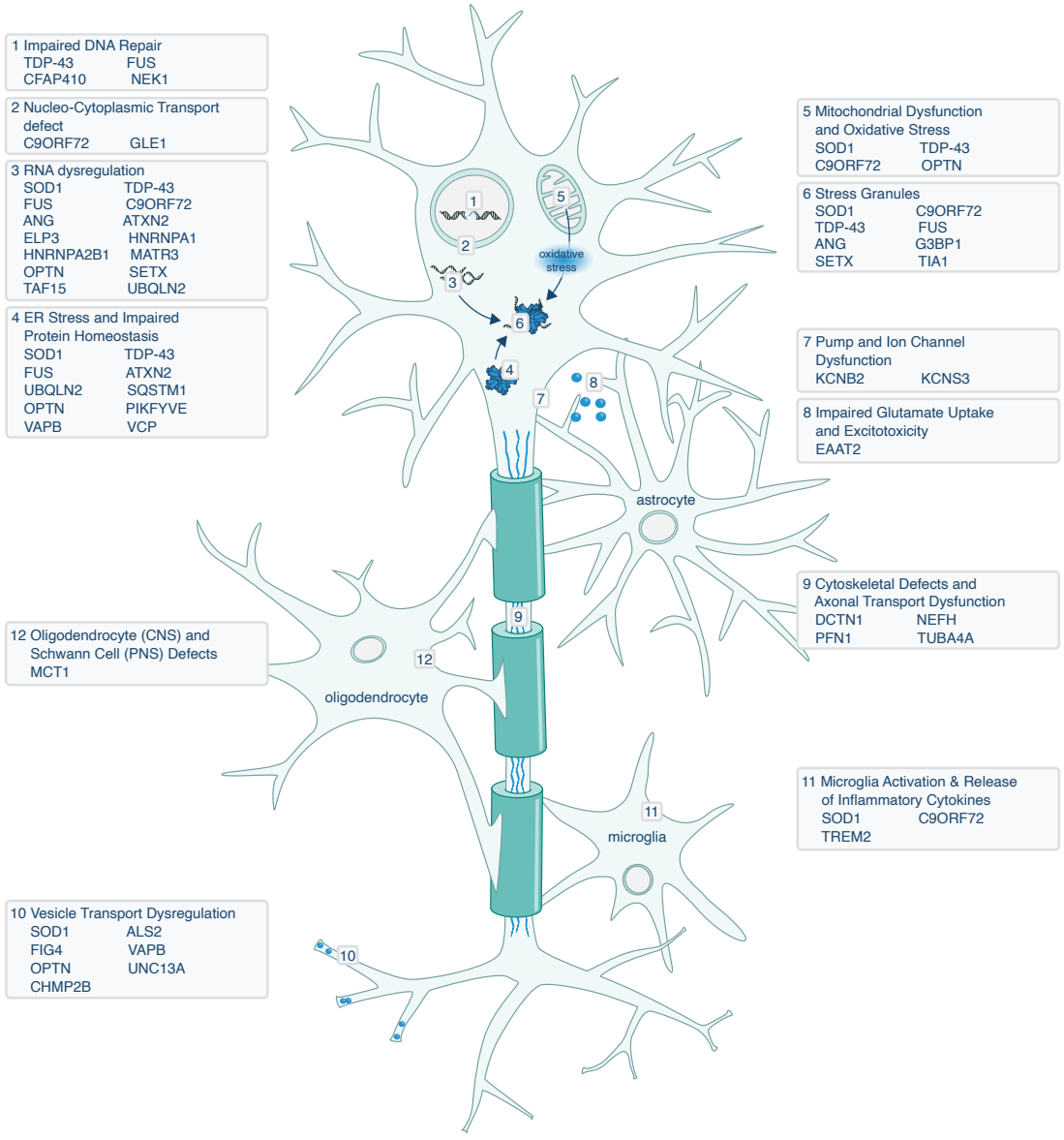

Fig. Mechanisms causing motor neuron degeneration in ALS and some of the involved proteins.

Key Factors in ALS

C9ORF72

C9ORF72 is a protein abundant in neurons that are a part of the C9ORF7-SMCR protein complex. It is thought to facilitate guanine nucleotide exchange factor (GEF) activity, regulate autophagy, and play a role in endosomal trafficking. Mutations in the C9orf72 gene are most frequently associated with ALS (up to 50% of FALS and 10% of SALS cases).

Three mechanisms are thought to contribute to the ALS pathology depending on C9ORF72 mutations. Firstly, the expansion of a GGGGCC repeat within the C9orf72 promotor leads to decreased protein expression and consequently a loss of function. Secondly, the accumulation of GGGGCC repeat-containing RNA transcripts leads to the formation of toxic RNA aggregates, which further sequester additional RNA-binding proteins and lead to dysregulation of the protein homeostasis and the formation of stress granules. And thirdly, a toxic gain of function when the GGGGCC hexanucleotide repeats are translated into dipeptide repeat (DPR) containing proteins. These poly-GA, poly-GP, poly-GR, poly-PA, and poly-PR peptides (depending on the reading frame) form DPR inclusions that impair nucleocytoplasmic transport and can cause neurodegeneration. These proposed mechanisms are not mutually exclusive and their relative contributions are still being investigated.

SOD1

Genetic studies have identified mutations in superoxide dismutase (SOD1) as the second-most common cause for FALS with a proportion of 10 to 20%.

SOD1 is a highly expressed, primarily-cytosolic enzyme that catalyzes the conversion of superoxide into hydrogen peroxide and oxygen. Mutant SOD1 binds to mitochondria and compromises respiration by blocking protein import. This causes oxidative stress, an imbalance in the cellular Ca^{2+} homeostasis, the formation of intracellular aggregates, and stress granules. These aggregates lead to neurofilament aggregation and adversely affect axonal transport processes. Ultimately, mutant SOD1 can induce apoptosis via Bcl-2 inhibition.

TDP-43/TARDBP

Mutations in the TAR-DNA binding protein 43 kDa (TDP-43), encoded by the TARDBP gene, are less common than the C9ORF72 DPR or the SOD1 mutations. However, its mislocalization to the cytoplasm is a characteristic feature in many ALS cases.

TDP-43 is an essential DNA- and RNA-binding nuclear protein involved in regulating transcription and modulating gene splicing, RNA metabolism, and stress granules. In both familial and sporadic ALS and other neurodegenerative diseases, such as the closely related Frontotemporal Dementia or AD, mutated TDP-43 forms are a major component of the insoluble ubiquitinated protein aggregates in the cytoplasm. These TDP-43 aggregates sequester miRNAs and proteins, thus impairing protein homeostasis. Dysregulation of nuclear-encoded mitochondrial proteins leads to mitochondrial dysfunction and oxidative stress.

Knocking down TDP-43 is not a viable therapeutic approach because of the proteins' critical cellular function. However, reducing the expression of ataxin 2 (ATXN2) using antisense oligonucleotides (ASOs) has also been shown to reduce TDP-43 toxicity.

FUS

Similar to TDP-43, fused in sarcoma (FUS) is an RNA-binding protein involved in transcription by RNA processing. Consistent with its function, wild type FUS is located in the nucleus. However, in ALS, mutated forms of the protein are mislocalized to the cytoplasm. Here, gain of function mutations can cause aggregation of FUS and associated RNA binding proteins, thus leading to an imbalance in protein homeostasis, RNA dysregulation, and the formation of stress granules, which ultimately lead to motor neuron loss.

FUS mutations are present in approximately 5% of FALS and less than 2% of SALS cases. They are frequently associated with early-onset ALS. Because of the dose-dependent toxic effect of mutated FUS variants, the protein is a potential therapeutic target for antisense oligonucleotide silencing.

Huntington's Disease

Huntington's disease (HD) is a neurodegenerative disorder characterized by a triad of motor, cognitive, and psychiatric symptoms. The pathology of HD primarily affects the basal ganglia and cortex, leading to motor symptoms, such as chorea, dystonia, and bradykinesia. Cognitive impairment includes deficits in executive function, memory, and attention, while psychiatric symptoms may manifest as depression, anxiety, and psychosis.

HD is caused by a mutation in the huntingtin (HTT) gene, leading to the abnormal expansion of a CAG repeat in the gene's coding region. This expanded repeat results in the production of a mutant huntingtin protein that accumulates in neurons and disrupts their function. Although the disease is triggered by the mutation of a single gene, intensive research has linked numerous other genes to its pathogenesis. Transcription factors such as CBP and p53 are sequestered, VDACs and TOMs are impaired, and dopamine and glutamate signaling is disturbed.

HD is inherited in an autosomal dominant manner, meaning that individuals with a single mutant HTT allele are at risk of developing the disease, with symptoms typically appearing in mid-adulthood. Approximately 2.71 people per 100,000 worldwide are affected by the disease. In the following, the biochemical core processes of HD are described and important targets for therapeutic research are presented, alongside with suiting antibodies and proteins to carry on research.

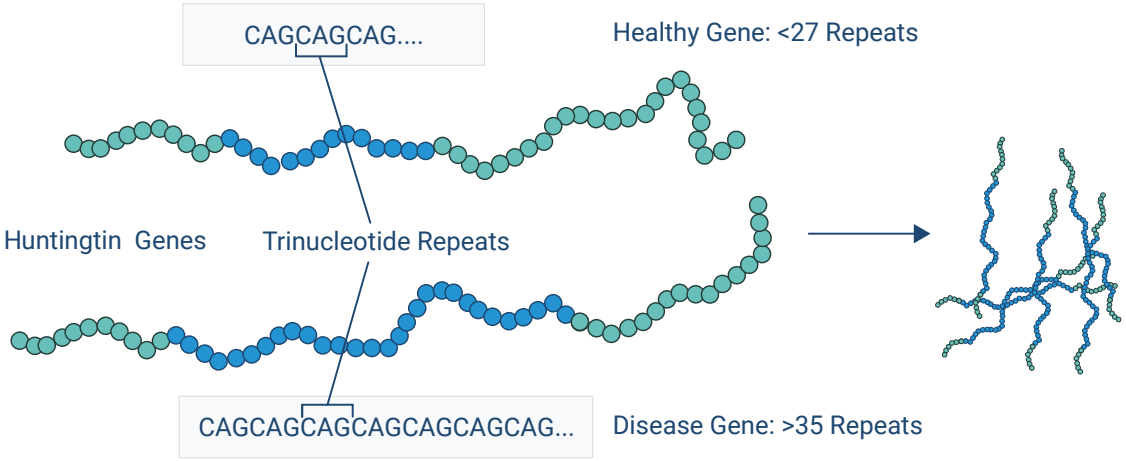

Fig. The mutant huntingtin protein in HD contains an expanded polyglutamine tract, making it prone to misfolding and aggregation.

Key Processes in HD

Transcriptional Dysregulation

Mutant Huntington can sequester essential transcription factors, such as CREB-binding protein (CBP) and p53. CBP is a co-activator involved in the regulation of multiple genes critical for neuronal survival and function. Its sequestration by mutant Huntington impairs its ability to activate gene expression. Mutant Huntington can also affect histone acetylation, a critical epigenetic modification that regulates gene expression. It has been shown to reduce histone acetylation levels, leading to condensed chromatin and decreased accessibility of genes for transcription.

HTT | CBP/CREBBP | p53 | SP1 | HSF1 | KAT2B | NFYB | FOXO3

Altered Protein Folding

The mutant Huntington protein in HD contains an expanded polyglutamine tract, making it prone to misfolding and aggregation. The polyQ stretch is on exon 1, which is cleaved off with the resulting N-terminal fragment—enough to cause aggregation. These aggregated mutant proteins overwhelm the cell's protein degradation machinery, including the ubiquitin-proteasome system and autophagy pathways.

Pathways Connected to HD

Huntington's disease is connected to a variety of pathways. Cytotoxicity, apoptosis, and calcium signaling are frequently linked to HD, but also found strong indications for other potentially disease-relevant mechanisms that have been less intensively studied in the context of HD (such as the cell cycle and RNA splicing, as well as Wnt and ErbB signaling).

- Autophagy
- Cell Division Cycle
- Ubiquitin Proteasome Pathway
- Unfolded Protein Response
- WNT Signaling

Impaired Protein Degradation

As a result the cell's chaperone network overloads, other metastable proteins misfold, producing a complex loss-of-function phenotype that leads to neurodegeneration. This impaired protein clearance leads to cellular dysfunction and ultimately neuronal death, contributing to the progressive neurodegeneration observed in HD.

Efforts to enhance protein degradation pathways or facilitate the removal of aggregated proteins are promising strategies in HD research, with the potential to alleviate the toxic effects of protein accumulation and slow the progression of HD.

HTT | p63 | STUB1 | HSP70 | DNAJA1

Polyglutamine (polyQ) Diseases

The polyglutamine diseases are a group of neurodegenerative disorders caused by expanded cytosine-adenine-guanine (CAG) repeats, encoding a long polyQ tract in the respective proteins. To date, a total of nine polyQ disorders have been described: six spinocerebellar ataxias (SCA) types 1, 2, 6, 7, 17; Machado-Joseph disease (MJD/SCA3); Huntington's disease; dentatorubral pallidoluysian atrophy; and spinal and bulbar muscular atrophy, X-linked 1. PolyQ diseases are characterized by the pathological expansion of CAG trinucleotide repeat in the translated region of unrelated genes. The translated polyQ is aggregated in the degenerated neurons leading to the dysfunction and degeneration of specific neuronal subpopulations.

Mitochondrial Dysfunction

In HD, mitochondria become less efficient at producing energy through oxidative phosphorylation, leading to energy deficits in affected neurons. Mutant Huntington protein can interact with and affect the function of several key mitochondrial antigens, such as voltage-dependent anion channels (VDACs) and translocase of the outer membrane (TOM) proteins. These interactions lead to impaired mitochondrial membrane integrity and compromised energy production. Furthermore, antibodies against these mitochondrial antigens have been detected in the blood of HD patients, suggesting an autoimmune response against dysfunctional mitochondria.

This dysfunction results in increased oxidative stress, which damages cells and exacerbates neurodegeneration in HD. Moreover, impaired mitochondrial dynamics and transport disrupt the distribution of healthy mitochondria within neurons, further contributing to their degeneration.

HTT | VDAC1 | VDAC2 | VDAC3 | TOMM20

Disrupted Neuronal Circuitry

Mutant Huntington protein can directly interfere with various neuronal antigens, resulting in the breakdown of essential connections in the brain. Preferred targets of mutant Huntington protein are synaptic vesicle release and neurotransmitter receptors, like the NMDA receptor. They are adversely affected, ultimately impairing synaptic plasticity and connectivity.

Protein Phosphatase 1, Regulatory Subunit 1B (PPP1R1B/DARPP-32) regulates the transmission of dopamine and glutamate signals in striatal neurons. Mutant Huntington in HD disrupts the function of DARPP-32, which contributes to abnormal signaling in the striatal circuits. This disruption has direct consequences for motor control and cognitive functions affected in HD.

Another possible target for the mutated Huntington protein is the dopamine D2 receptor (DRD2). Similarly to DARPP-32, altered expression and function of DRD2 can lead to imbalances in dopamine signaling, impacting motor control, and potentially contributing to the characteristic chorea seen in HD.

HTT | DARP-32 | NMDAR1 | NSMF | DRD2

Therapeutic Approaches for HD

The mechanism and modality, in which cysteine-adenosine-guanine expansion leads to a poisonous effect on the neuron, is yet to be clearly understood. Since HD is an inherited monogenic disorder, lowering the mutant Huntingtin represents a promising therapeutic strategy. Huntingtin lowering strategies mostly focus on nucleic acid approaches, such as small interfering RNAs (siRNAs) and antisense oligonucleotides (ASOs). Currently, no effective remedy has been found for HD, though.

ModDetect Panels

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Learn more

A new approach identifies essential features of the polyQ amyloid nucleus. This pattern encodes a four-stranded steric zipper with interdigitated Q side chains. Once formed, the zipper poisons its own growth. The self-poisoning may be exploited to block amyloid formation, by genetically oligomerizing polyQ prior to nucleation and thereby decelerate the disease.

Parkinson's Disease

Parkinson's Disease (PD) is the second most common neurodegenerative disease. It is a chronic progressive disorder of the central nervous system, characterized by four cardinal motor symptoms: tremor, bradykinesia, rigidity, and postural instability. With disease progression, non-motor symptoms may also arise, including cognitive decline, altered behavior, and sleep disorders. PD typically emerges at 60 years of age and older with an incidence of approximately 150 to 200/100,000 individuals. It is more prevalent in men than in women. Most cases of PD are caused by environmental factors. However, 10 to 15% of the cases are early-onset familial PD and genome-wide associated studies have identified more than 40 genetic risk factors.

On a cellular level, PD is characterized by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNc), a region of the midbrain responsible for motor control. Degeneration of these neurons leads to decreased dopamine production and altered signaling in the striatum of the basal ganglia, contributing to fine motor control. Motor symptoms typically appear when 50 to 80% of the SNc dopaminergic neurons have degenerated. Each side of the human SNc only contains 400,000 to 500,000 dopaminergic neurons.

The predominant risk factors for PD are aging and environmental factors including mitochondrial poisons, heavy metals, pesticides, or traumatic brain injuries. Oxidative metabolism of dopamine in the dopaminergic cells by mitochondrial monoamine oxidase isoforms (MAOA and MAOB) leads to reactive oxygen species (ROS) generation, oxidative damage, and ultimately cell death. Because of their high metabolic activity, dopaminergic neurons of the SNc are thought to be particularly sensitive to oxidative stress.

Besides idiopathic causes, mutations in several genes have been identified as susceptibility factors for PD or found to be associated with autosomal dominant or recessive forms of the disease.

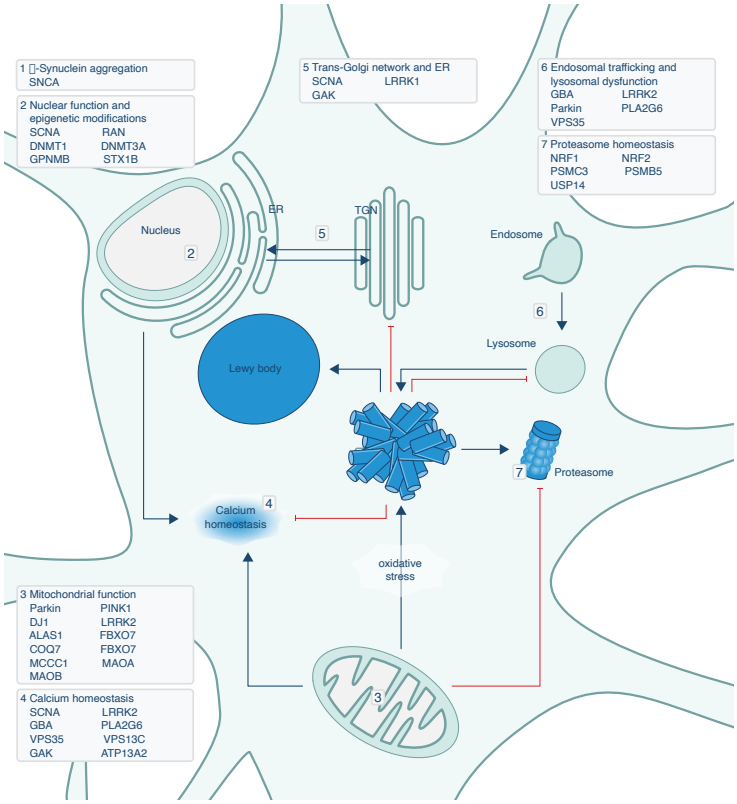


Fig. Mechanisms causing motor neuron degeneration in ALS and some of the involved proteins.

Top Parkinson-related Targets

SNCA

Alpha-synuclein (SNCA, autosomal dominant locus PARK1) is a neuronal protein abundant in the human brain that regulates synaptic vesicle trafficking and subsequent neurotransmitter release. PD is classified as a synucleopathy because of the characteristic aggregation of misfolded alpha-synuclein.

Under pathological conditions, ROS can mediate conformational changes of normal alpha-synuclein into non-fibrillar, misfolded aggregates. Typically, misfolded alpha-synuclein protein is tagged and degraded by the ubiquitin-proteasome system, and the larger aggregates undergo lysosomal degradation. However, they can also form larger aggregates and insoluble clumps known as Lewy bodies.

Lewy bodies (LB) are also present in the neurodegenerative disease dementia with Lewy bodies, which share symptoms with PD. The extent of the LB pathology is considered in the Braak staging of PD.

Misfolded alpha-synuclein in one neuron can induce the misfolding of alpha-synuclein in neighboring neurons. This spreading pathology possibly underlies the progressive nature of PD. Misfolded alpha-synuclein can disrupt various cellular processes, such as protein degradation and mitochondrial function, leading to cellular dysfunction and additional oxidative stress, further driving the pathology. Neuronal toxicity caused by the accumulation of misfolded alpha-synuclein is believed to contribute to the degeneration of dopaminergic neurons in the SNc.

Lastly, aggregates of misfolded alpha-synuclein hyperactivate MAPK signaling, thus promoting neuroinflammation. Inflammation further contributes to the degeneration of neurons and the progression of the disease.

The initial formation of alpha-synuclein aggregates is usually triggered by factors causing cellular and oxidative stress. However, formation of these aggregates can also be favored by certain point mutations in the SNCA gene. Epigenetic factors, such as a low level of methylation of two CpG islands in the SNCA gene, have been implicated as contributing factors to PD.

GBA

The GBA gene encodes the lysosomal enzyme beta-glucocerebrosidase (Beta-GC), which has a central role in cell membrane turnover and the degradation of complex lipids. Mutations in this gene are the most common genetic PD risk factor: up to 10% of PD patients have a mutation in GBA compared to 1% of the unaffected population. Heterozygous GBA mutation increases the PD risk five- to eightfold. Overall, more than 100 variants of the GBA gene are known that reduce the protein's enzymatic activity, destabilize the protein, or alter its lysosomal localization.

The accumulation of Beta-GC's substrate glucocerebroside in lysosomes leads to lysosomal dysfunction and is thought to contribute to alpha-synuclein aggregation and to further exacerbate neuroinflammation.

Heterozygous GBA mutation carriers have a five- to eightfold increased PD risk depending on the variant. Homozygous mutations in the GBA cause Gaucher's Disease (GD), a lysosomal storage disorder that mainly affects the liver, spleen, and bones. Beyond these organs, GD can also manifest in the central nervous system and GD patients are classified into three types based on brain involvement and neurological symptoms.

LRRK2

Leucine-Rich Repeat Kinase 2 (LRRK2, autosomal dominant locus PARK8) is a complex 253 kDa protein with multiple domains and activities that is expressed in the brain, lungs, kidneys, and immune system. LRRK2 has both GTPase and kinase activities. Mutations in the LRRK2 gene are the second most common genetic risk factor for sporadic PD and account for up to 1% of PD cases. LRRK2 mutations are also among the most common causes of familial PD, and individuals who inherit gain of function mutations in LRRK2 are at higher risk to develop the disease in later life. Increased kinase activity is thought to drive the pathogenic effect of LRRK2 variant associated with PD.

Because of the wide range of kinase substrates, LRRK2 neuropathology is very diverse. LRRK2 mutations may influence alpha-synuclein and have been linked to neuroinflammation, and mitochondrial and ubiquitin-proteasome dysfunction—all contributing factors to PD.

Recent investigations have shown that small-molecule LRRK2 inhibitors can be neuroprotective, suggesting that therapies targeting LRRK2 could be beneficial in a larger population of patients.

VPS35

The vacuolar protein sorting 35 (VPS35, autosomal dominant locus PARK17) is part of the retromer protein complex, which is responsible for sorting of proteins from the endosome to the cell membrane and trans-Golgi network. VPS35 recruits the WASH complex to the endosomal membrane which is necessary for endosomal protein sorting.

The VPS35 D620N mutation is present in 0.1 to 1% of patients with familial PD. This mutant has been shown to associate poorly with the WASH complex and compromise its recruitment to the endosome. VPS35 D620N has also been implicated in mitochondrial dysfunction. Therefore, mutations in VPS35 might contribute to PD through disrupted lysosomal activity, and consequently, the accumulation of alpha-synuclein aggregates and increases oxidative stress through mitochondrial dysfunction.

PRKN

The E3 ubiquitin protein ligase parkin (PRKN, autosomal recessive locus PARK2) coordinates mitochondrial control mechanisms and modulates lysosomal homeostasis under cell stress. It also regulates mitochondria-lysosome contact sites.

Mutations in PRKN are the most common cause of early-onset Parkinson's. Loss of parkin's E3 ligase activity is thought to play a pathogenic role in both inherited and sporadic PD.

Key Concepts in Neurodegenerative Diseases

Tau Immunotherapy

Alzheimer's Disease International estimates that dementia affects about 57 million people worldwide as of 2019, which is expected to nearly triple by 2050. Alzheimer's disease (AD) is characterized by the presence of β-amyloid peptide and phosphorylated tau protein (short for tubulin-associated unit). Under normal conditions, tau is a microtubule-associated protein (MAP) involved in microtubule stabilization. Tau is found primarily in axons, where it regulates microtubule polymerization and stabilization. In disease, tau becomes hyperphosphorylated and can no longer adequately stabilize the microtubules. Kinases such as GSK3β, CDK5, MAPK, CaMKII, and p38 carry out the phosphorylation step. Hyperphosphorylated tau forms insoluble filaments which accumulate as neurofibrillary tangles (NFTs). The resulting neurodegenerative diseases are called tauopathies and include progressive supranuclear palsy (PSP), Pick's disease (PiD), PD, and AD.

Several tau antibodies and tau vaccines are currently in clinical trials or late-stage preclinical development. A large proportion of these are targeted for the treatment of AD, whereas most of these anti-tau antibodies are whole antibodies that work both intracellularly and extracellularly, blocking the spread of tau pathology via different mechanisms for a review on past and present clinical trials). Recently, the results of another phase 1b study using a tau-targeting antisense oligonucleotide (MAPTRX) to reduce tau in patients with mild AD were published in Nature Medicine. While this is good news in itself, what is particularly noteworthy is that this is the first antisense oligonucleotide (ASO) treatment evaluated in a clinical study of patients with Alzheimer's. In this context, our recently introduced ModDetect™ Antibody Panels that allow for the detection of modified nucleic acids could further advance this innovative technology.

As we continue to identify interaction partners and modulators of tau, new opportunities will emerge to further improve efficacy. For example, another recent publication in Science showed that tau immunotherapy relies mainly on the intracellular antibody receptor TRIM21, which contributes to the neutralization of tau-antibody complexes. Despite the rapid development in this field, tau immunotherapies are of exceptional complexity.

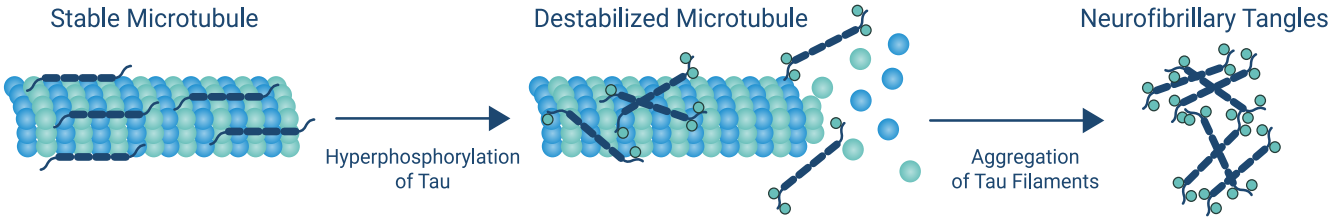


Fig. Formation of neurofibrillary tangles. Under pathological conditions, tau becomes hypephosphorylated and destabilizes microtubules. Phosphorylated tau aggregates, builds filaments, and forms NFTs.

Key Tau Antibodies & Proteins

Tau Pathway Antibodies	
Target	CAMK2A CaMk11 CDK5 Mapk1 GSK3B MAPK8 MAPK14 RPS6KB1 MAPT Mapt TRIM21

Tau Proteins		
Protein	Tau-316 Tau-352 Tau-381 Tau-383	Tau-410 Tau-412 Tau-441
Mutation	S198A A198E S199E S214A K257T L266V G272V N279K dK280	dN296 PS01L P301S S305N V337M S352L S404A S404 R406W

Amyloid-β Deposition Linked to Myelin Dysfunction

The prevalence of Alzheimer's disease (AD), the primary contributor to dementia, increases significantly with age. One of the distinctive features of AD involves the accumulation of extracellular plaque formations containing amyloid-β (Aβ), along with neurofibrillary tangles (NFTs) composed of tau. However, the precise connection between brain aging and the deposition of Aβ remains elusive. A recent publication by Depp et al., 2023 examined whether age-related structural myelin defects are a risk factor for neuronal Aβ deposition.

In this study, the researchers propose a working model, where myelin dysfunction, specifically modeled through the premature aging of white matter in myelin mutant mice, triggers a cascade of events. The dysfunction leads to the activation of microglia, which interferes with the clearance of Aβ deposits and promotes plaque formation. Simultaneously, aging myelin loses its supportive functions for axons, causing axonal distress. This distress leads to increased levels of neuronal BACE1 (Beta-Site App-Cleaving Enzyme) and APP CTF (Amyloid Precursor Protein-derived C-Terminal Fragment), suggesting enhanced Aβ production.

The study highlights the interconnectedness of plaque-promoting factors, microglial activation, and axonal distress as downstream consequences of myelin injury. The researchers emphasize that it is challenging to isolate these phenomena due to their tight linkage. They note that microglia depletion in certain mice models can alleviate axonal swellings, indicating that axonal distress and APP metabolism changes might be downstream of microglia activation. Interestingly, the amyloid-promoting effect observed with myelin dysfunction differs from nonspecific microglia activation induced by lipopolysaccharide, indicating the unique role of myelin defects in microglia activation.

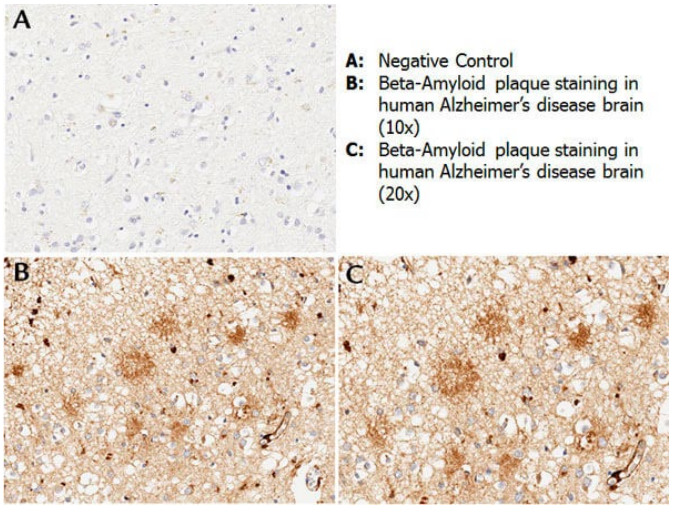


Fig. Immunohistochemistry with anti-beta amyloid antibody showing amyloid beta plaque staining in human AD brain at 10x and 20x (B & C). Staining was performed on Leica Bond system using the standard protocol.

An important clinical implication of the study's findings is the potential connection between AD and multiple sclerosis (MS). The researchers suggest an increased risk of AD as a comorbidity of MS based on their experiments and recently published data. Due to the limited dataset however, further epidemiological studies need to explore this comorbidity.

The findings of this study establish a causal link between myelin deterioration and AD progression, contributing molecular evidence to the existing amyloid hypothesis and the role of neuroinflammation in AD. It positions age-dependent loss of myelin integrity as an upstream initiator of AD pathology, potentially explaining why age is a major risk factor for the disease.

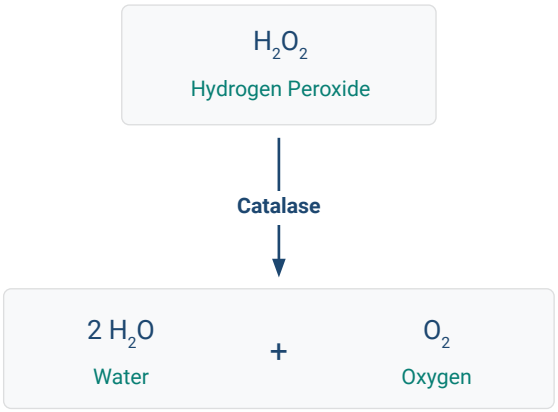
Key Amyloid-β Antibodies & Proteins

Amyloid-β Antibodies	
Target	APBA2 APP APPBP2 BACE1 BACE2 MBP

Amyloid-β Proteins	
Fragment	1-16 3-11 3-40 3-42 11-40 11-42 25-35
Mutation	pyrE Arctic Mutant Dutch Mutant Flemish Mutant Italian Mutant Iowa Mutant

Catalase in Neurodegenerative Diseases

Reactive species like oxidants emerge as byproducts of routine cellular metabolism. They can react with cellular biomolecules and cause damage through oxidative stress. Conditions like Alzheimer's disease (AD) and Parkinson's disease (PD) have been correlated with oxidative stress, underlining its role in certain neurodegenerative disorders (Reviewed by Nandi et al., 2019). Fortunately, cells have evolved an array of protective strategies to counteract reactive oxygen species, such as hydrogen peroxide. One of these defense mechanisms involves the action of an enzyme called catalase, which breaks down hydrogen peroxide into water and oxygen.



Catalase in Alzheimer's Disease

AD is characterized by the accumulation of amyloid-β peptides and tau protein in the brain, forming plaques and neurofibrillary tangles, respectively. Research has demonstrated the neurotoxic effects of these amyloid-β peptides in cultured neurons. These peptides, derived from the amyloid precursor protein (APP), are initially soluble components present in plasma and cerebrospinal fluid. However, in AD, soluble amyloid-β transforms into insoluble fibrils within plaques through protein-protein interactions.

Notably, *in vitro* studies have shown that while newly formed amyloid-β is non-toxic, aged forms become harmful to neurons. Evidence suggests that amyloid-β peptides trigger the buildup of hydrogen peroxide in neuroblastoma and hippocampal neuron cultures. This phenomenon is likely attributed to direct binding of amyloid-β to catalase, leading to diminished enzyme activity. These findings have led to a hypothesis proposing that the interaction between catalase and amyloid-β significantly contributes to increased hydrogen peroxide levels within cells, thus linking amyloid-β accumulation and the onset of oxidative stress in AD.

The current prevailing hypothesis regarding the mechanism of amyloid-β-induced oxidative damage suggests that amyloid-β directly binds to catalase, deactivating its catalytic function and subsequently fostering conditions of oxidative stress. Additionally, complete amyloid-β peptides interact with Cu^{2+} ions at their N-terminal segments, reducing them to Cu^{+}. This amyloid-β Cu^{+} complex has been shown to promote the generation of hydrogen peroxide. Consequently, catalase exhibits both direct and indirect associations with the pathogenesis of AD, playing a pivotal role in the intricate interplay between amyloid-β, oxidative stress, and neuronal dysfunction.

Catalase in Parkinson's Disease

PD, an age-related neurological disorder, initially presents as subtle hand tremors that progress to impair overall body movements, significantly diminishing quality of life. As the disease advances, motor control difficulties intensify, characterized by muscle rigidity and slowed movement initiation. The root cause lies in dopamine depletion due to damage to dopamine-producing neurons in the substantia nigra pars compacta (SNpc), resulting in the loss of around 100-200 neurons daily.

A central player in the disease's cytopathology is the protein α-synuclein. Mutations in the α-synuclein gene lead to the production of a mutant protein that disrupts dopamine synthesis and storage, causing its accumulation within neuron cytoplasm. This aberrant process triggers the auto-oxidation of dopamine, which generates reactive oxygen species like hydrogen peroxide with toxic dopamine-quinone species, culminating in oxidative stress.

Furthermore, mutant α-synuclein also interferes with catalase. This inhibition is attributed to α-synuclein's disruption of peroxisome proliferator-activated receptor γ (PPARγ) transcription activity, which regulates catalase gene expression. Collectively, these findings suggest that the altered catalase activity and elevated hydrogen peroxide levels in PD may be attributed, in part, to α-synuclein's indirect impact on catalase expression. This intricate interplay unveils new insights into PD progression and offers potential avenues for therapeutic exploration.

Markers for Neurobiology

Protein Markers of Dementia Risk

Various neurodegenerative disorders and contributing factors play a pivotal role in the pathogenesis of dementia, leading to a gradual and irreversible decline in neuronal integrity and brain function. Early detection of dementia holds significant promise for effective intervention in these severe conditions. Notably, the deposition and aggregation of amyloid-β and tau neurofibrillary tangles within the central nervous system (CNS) have been recognized as crucial hallmarks of Alzheimer's disease (AD). Moreover, emerging evidence indicates that systemic factors and biological processes outside the CNS influence dementia risk. In a recent large-scale study conducted by Walker et al., 2023 and published in Science Translational Medicine, a proteomic signature associated with increased dementia risk has been identified, astonishingly detectable up to two decades before the manifestation of clinical symptoms.

The study included 10,981 participants, of whom 1,874 (17%) developed dementia by the end of the study period. Analysis of 4,877 plasma proteins found 26 proteins significantly associated with 25-year dementia risk. GDF15, a protein that plays a role in metabolic and immunoregulatory functions, exhibited the most significant correlation with the risk of dementia. Follow-up analysis revealed an additional 6 proteins associated near-term (<15 years) and another 6 asscociated with long-term (≥15 years) dementia risk (see table below). The dementia-associated proteins were found to be predominantly associated with four overlapping biological processes: proteostasis, immunity, synaptic function, and extracellular matrix (ECM) organization.

Remarkably, several of the leading dementia-associated proteins identified in this study, such as GDF15, were present in low abundance or were undetectable in postmortem brain tissue. Despite their limited presence in the brain, these proteins, along with peripherally secreted proteins and genetic regulators, could still play a crucial role in influencing the expression of genes that show abnormal expression in AD brains. This intriguing discovery highlights the significance of investigating peripheral sources and genetic regulatory mechanisms in understanding the pathogenesis of AD.

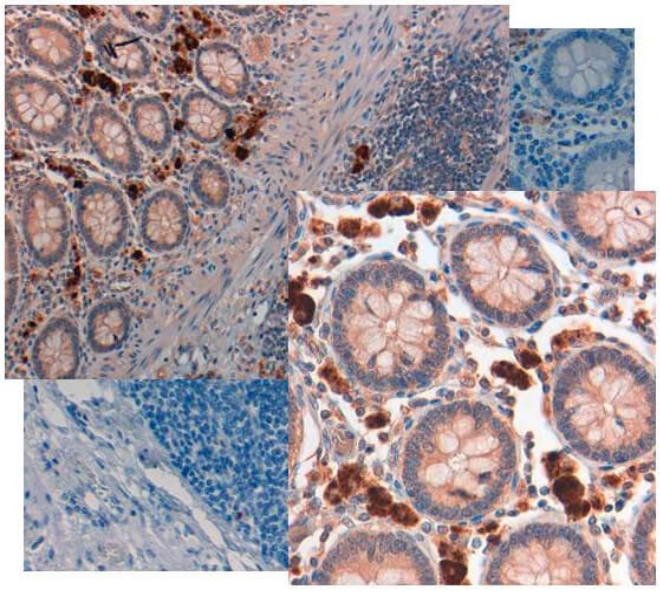


Fig. IHC of anti-NAG1 antibody (C-terminal specific). Tissue: Human Colon at 20X in colon tissue at pH9. Negative control of human colon tissue pH9 is shown in the background.

The researchers propose that the identified proteins serve as a promising foundation for future investigations, as they hold potential as predictive markers for dementia. Moreover, their findings offer valuable insights into relevant biological pathways, and may aid in the discovery of early-stage markers and underlying molecular factors contributing to the disease.

Proteins Identified in Walker et al. Study

Dementia-associated Protein	Pathway	Associated with Dementia	Antibodies
GDF15	Immune, Metabolism	All follow-up times	NAG-1 Antibody NAG-1 Antibody NAG-1 Antibody NAG-1 Antibody NAG-1 Antibody NAG-1 Monoclonal Antibody NAG-1 Monoclonal Antibody NAG-1 Monoclonal Antibody NAG-1 H Variant Monoclonal Antibody
MMP12	ECM, Immune, Proteostasis	25-year follow-up	MMP12 Antibody
EPHA10	Synaptic	25-year follow-up	EphA10 Antibody
GLUL	Synaptic	25-year follow-up	GLUL Antibody
GPLX2	Synaptic	25-year follow-up	-

Dementia-associated Protein	Pathway	Associated with Dementia	Antibodies
FCRL4	Immune	25-year follow-up	FCRL4 Antibody
ABHD14A	-	25-year follow-up	ABDH14A Antibody
HSPA1B	Proteostasis, Immune	25-year follow-up	Hsp70 Antibody
HTRA1	Immune, ECM, Metabolism	25-year follow-up	HTRA1 Antibody
PSIP1	Immune, Synaptic	25-year follow-up	PSIP1 Antibody
GRID2	Synaptic	25-year follow-up	GRID2 Antibody
GABARAPL1	Proteostasis	25-year follow-up	GABARAPL1 Antibody
SMC3	-	25-year follow-up	SMC3 Antibody
MB	Vascular	25-year follow-up	Mesothelin Antibody
MMP19	ECM, Immune	25-year follow-up	MMP19 Antibody
CPLX1	Synaptic	25-year follow-up	Complexin 1 Antibody
NDST1	Metabolism	25-year follow-up	NDST1 Antibody
DNAJB12	Proteostasis	25-year follow-up	DNAJB12 Antibody
CRLF1	Immune	25-year follow-up	CRLF1 Antibody
ADAMTSL2	ECM	25-year follow-up	ADAMTSL2 Antibody
LEFTY2	Immune	25-year follow-up	LEFTY A Antibody
F8	Vascular	≥15 years	Factor VIII Antibody
CLSTN3	Synaptic	≥15 years	Calsyntenin 3 Antibody
ALB	-	≥15 years	Human Serum Albumin Antibody
FBLN5	ECM	≥15 years	Fibulin 5 Antibody
DNAJB9	Proteostasis	≥15 years	DNAJB9 Antibody
CBLN4	Synaptic	<15 years	CBLN4 Antibody
EGFR	Immune, ECM	<15 years	EGFR Antibody EGFR Antibody EGFR phospho Y1197 Antibody
IGFBP2	Metabolism, Immune	<15 years	IGFBP2 Antibody
GHR	Metabolism, Immune	<15 years	Growth Hormone Receptor Antibody
FAP	ECM	<15 years	Fibroblast Activation Protein Antibody
SERPINA3	Immune, Proteostasis	<15 years	SERPINA3 Antibody

Central Nervous System Cell Markers

Neural stem cells acting as a source of various cell types are a subpopulation of cells that can self-renew and proliferate identical cells. They are multipotent to generate diverse neural lineages, encompassing neurons, astrocytes, and oligodendrocytes. Central Nervous System (CNS) cell markers are fundamental in elucidating the functions of different neural cell types and their involvement in various neurological diseases and disorders. Researchers and clinicians rely on these antibodies to gain insights into the cellular composition of the CNS and to develop therapies and diagnostic tools for conditions, such as neurodegenerative diseases, brain injuries, and neuroinflammatory disorders.

These antibodies are used in various experimental techniques, including immunohistochemistry and immunofluorescence, to visualize and study the distribution of specific cell types within the CNS. We offer an outstanding selection of marker antibodies and kits for detection of neurons, microglia and astrocytes, as well as proteins, peptides, and reagents for neuroscience research.

Types of Cell Markers

Cell Type	About	Cell Markers	
Neural Progenitor Cells	Neural progenitor cells (NPCs) are the progenitor cells of the CNS that give rise to many, if not all, of the glial and neuronal cell types that populate the CNS.	Nestin OTX2 PAX3 PAX6	SOX1 SOX2 SMARCA4
Microglia	Although microglia were first described as ramified brain-resident phagocytes, research conducted over the past century has expanded considerably upon this narrow view and ascribed many functions to these dynamic CNS inhabitants. Microglia are now considered among the most versatile cells in the body, possessing the capacity to morphologically and functionally adapt to their ever-changing surroundings.	CD11b CD45RB CD45RO CX3CR1	CD40 CD68 NOS2 TMEM119
Astocytes	Astrocytes are specialized glial cells that outnumber neurons by over fivefold. They contiguously tile the entire CNS and exert many essential complex functions in the healthy CNS.	Aldolase ALDH1L1 AQP4 GFAP GLN1	IGFBP3 S100B SLC1A2 SLC1A3
Immature Neurons	Immature neurons, also known as neural precursor cells or neuroblasts, represent an early stage in the development of the nervous system. These cells have not yet fully differentiated into mature, functional neurons and retain the capacity for further development. Immature neurons are often found in specific regions of the brain, such as the subventricular zone and the dentate gyrus of the hippocampus, where they can contribute to neurogenesis and brain plasticity.	DCX TBR1 Stathmin NSMCE2	CD56 NEUROD1 Tubulin B3
Oligodendrocytes	Oligodendrocytes are the myelinating cells of the CNS. They are the end product of a cell lineage which has to undergo a complex and precisely timed program of proliferation, migration, differentiation, and myelination to finally produce the insulating sheath of axons.	AchE ChAT CNP ELK3 MOBP	MOG NMDA OLIG1 OLIG2 OMG
Mature Neurons	Mature neurons promote survival at all costs by employing multiple, often redundant, strategies to prevent cell death by apoptosis. This dramatic shift from permitting cell death to ensuring cellular survival is critical, as these post-mitotic cells must provide neuronal circuitry for an organism's entire lifetime.	DLG4 FoxA2 GABA GABRA1 GAD65+GAD67 GAP43	MAP2 NeuN Nrp1 Synaptophysin Tau

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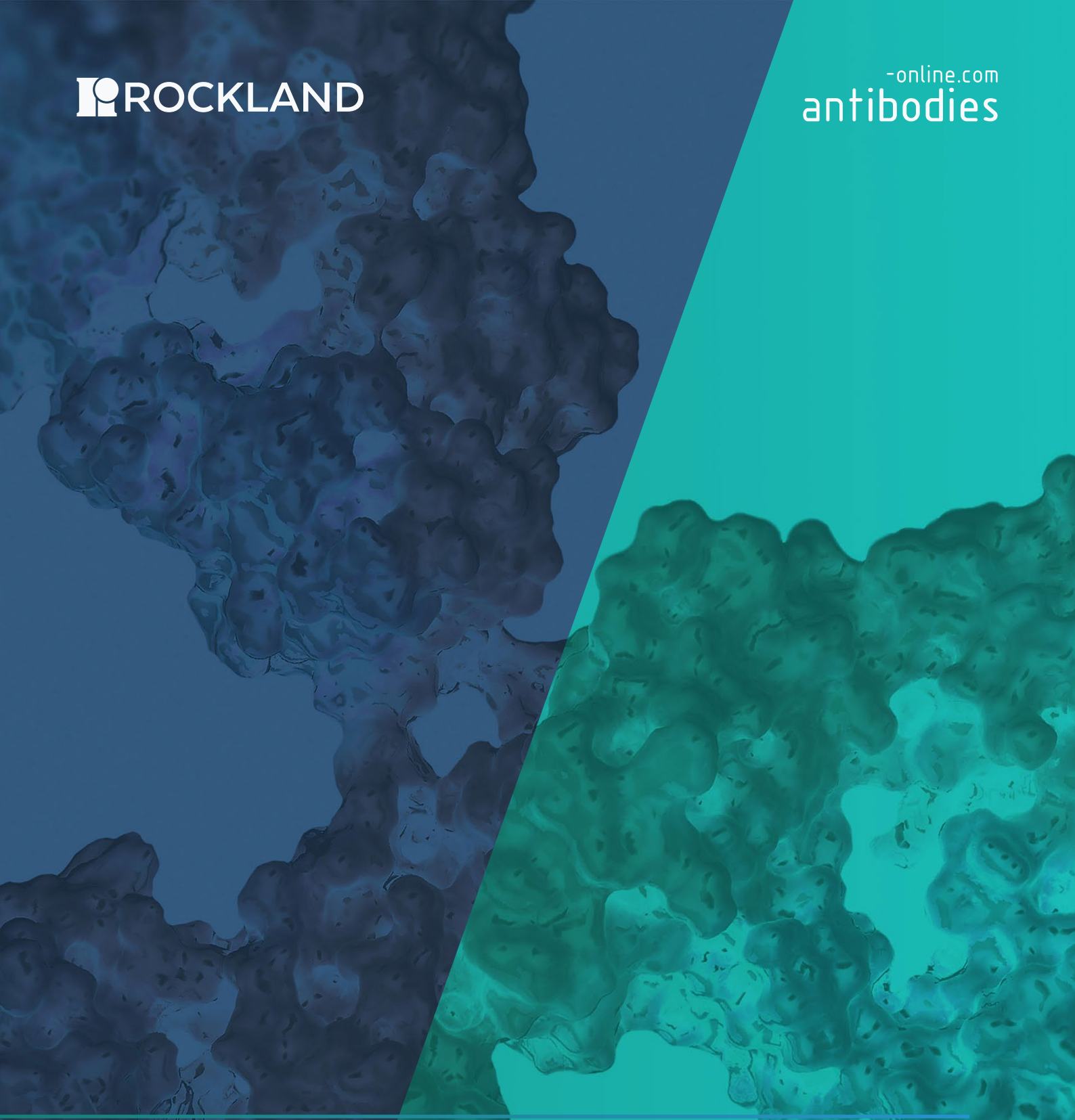

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