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A Novel Review: Association of Alzheimer's Disease with the SUMO Protein Family

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Abstract
Neurodegenerative diseases are conditions marked by the gradual deterioration and loss of neurons. In more advanced stages, this results in impairments in cognitive function and motor activity. These disorders may arise from a combination of internal and environmental causes, including genetic predisposition, the natural process of aging, dietary habits, and psychological stress. Multiple studies have shown that protein aggregation is a prevalent characteristic of neurodegenerative disorders. Misfolded or inadequately expressed proteins have a substantial influence on the advancement of many disorders. Recent investigations have shown that certain paralogs of SUMO proteins have a substantial impact on neurodegenerative disorders. This study specifically examines Alzheimer's disease, a well-known neurodegenerative disorder, and investigates the influence of SUMO proteins on the development and progression of this illness. Empirical evidence indicates that this group of proteins governs cellular processes by means of post-translational changes, exerting both beneficial and detrimental effects on Alzheimer's disease. Several factors contribute to Alzheimer's disease, a complex neurological ailment that causes brain function to degrade. It is becoming more common worldwide due to the rising number of elderly individuals. Examining the impact of SUMO proteins from this standpoint provides encouraging insights into future therapies for these now-untreatable conditions.

Keywords: Alzheimer's, Neurodegenerative, SUMO protein family, Apo-E4, Ubiquitin.

Introduction
Neurodegenerative diseases are characterized by the progressive loss of neurons, leading to the subsequent degeneration of specific brain regions and resulting in the loss of nervous system functions associated with this neuronal decline[1]. A common feature in the pathophysiology of these diseases is the aggregation of misfolded proteins [2]. The inability to maintain protein stability can arise due to the expression of mutated genes or post-translational modifications, leading to misfolding [3]. Therefore, post-translational modifications are crucial within the cell. Examples of neurodegenerative diseases include Dentatorubral-Pallidoluysian Atrophy, Spinobulbar Muscular Atrophy, Neuronal Intranuclear Inclusion Disease, Parkinson's Disease, Alzheimer's Disease, and Huntington's Disease [4]. In Alzheimer's disease, this review article will examine the role of the sumoylation cycle, a post-translational modification involving the attachment of SUMO (Small Ubiquitin-related modifier) proteins to lysine residues of target proteins. The sumoylation process often affects events involved in neurodegeneration, such as protein aggregation, mitochondrial dysfunction, oxidative stress, RNA transcription, and metabolism [5].

Protein Aggregation Mechanisms in Alzheimer's Disease
Alzheimer's Disease (AD) is characterized by the extracellular accumulation of amyloid plaques (Aβ plaques) and the intracellular aggregation of neurofibrillary tangles (NFTs) within the brain. The aggregation of Aβ plaques and NFTs is recognized as a hallmark of AD pathology, as these structures interfere with neuronal communication at synapses. In the amyloidogenic pathway, Aβ plaques is produced through the sequential cleavage of amyloid precursor protein (APP) by β-secretase and γ-secretase, whereas in the non-amyloidogenic pathway, α-secretase acts as the key enzyme, preventing Aβ formation [53]. In addition to Aβ, hyperphosphorylated tau proteins, resulting from the action of various kinases, lead to the formation of abnormal filamentous bundles, which are also present in the AD brain. Early-onset AD is associated with rare autosomal dominant mutations in three genes: APP, presenilin 1 (PSEN1), and presenilin 2 (PSEN2), while late-onset AD is strongly correlated with polymorphisms in the apolipoprotein E (APOE) gene. These mutations influence the production of Aβ peptides, a major component of senile plaques. Beyond APOE, other risk variants in genes such as ADAM10, ADAMTS1, MAPT, GRN, ARSA, and CSF1R are implicated in APP and tau metabolism in late-onset AD [54].

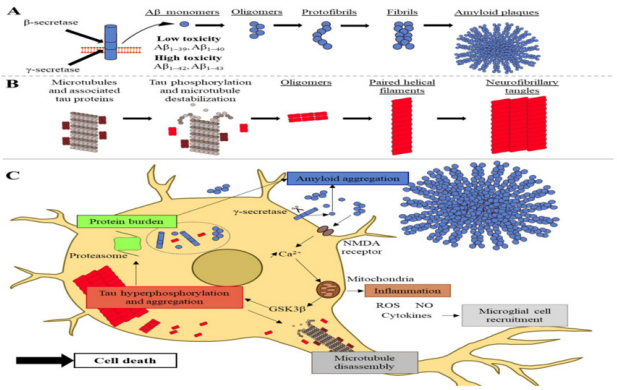

Figure1: Molecular Features of Alzheimer's Disease. (A) Production and Aggregation of Amyloid Peptides: The amyloid precursor protein (APP) is cleaved by β- and γ-secretases, forming Aβ peptides. These peptides aggregate into toxic oligomers, protofibrils, fibrils, and amyloid plaques under pathological conditions. (B) Tau Protein Aggregation: Tau proteins, normally associated with microtubules, become hyperphosphorylated during disease progression, dissociate, and aggregate into oligomers, paired helical filaments, and neurofibrillary tangles (NFTs). (C) Molecular Interactions in Neurons during AD and the Tau–Aβ Feedback Loop: Aβ oligomers increase calcium levels, triggering inflammation, microglial activation, and promoting tau aggregation. Hyperphosphorylated tau destabilizes microtubules, enhances tau aggregation, and interferes with Aβ degradation, contributing to neuronal death. Abbreviations: NMDA, N-methyl-D-aspartate; GSK3β, glycogen synthase kinase 3 beta; ROS, reactive oxygen species; NO, nitric oxide. (Vignon A., Salvador-Prince L. et al., Int. J. Mol. Sci. *2021)*[60]

As seen in Figure 1,the clearance of Aβ and tau proteins occurs through several mechanisms, including lysosomal degradation, ubiquitination and proteasomal degradation, microglial phagocytosis, and transport via interstitial fluid (ISF), the blood-brain barrier (BBB), and cerebrospinal fluid

(CSF). Two transmembrane receptors on endothelial cells, the lipoprotein receptor-related protein (LRP) and the receptor for advanced glycation end products (RAGE), are involved in the transport of soluble Aβ from the brain to the bloodstream, as well as vice versa. Additionally, the ATP-binding cassette transporter P-glycoprotein (P-gp) mediates the translocation of soluble Aβ across neuronal endothelial cells into the circulatory system. Conversely, the gp330/megalin receptor is involved in returning circulating Aβ to the brain through its interaction with apolipoprotein J (ApoJ) [55]. In AD brains, LRP-mediated Aβ efflux is downregulated, while RAGE-mediated influx is upregulated, exacerbating Aβ accumulation. Enzymatic degradation of Aβ is facilitated by various peptidases, notably zinc metalloproteases such as neprilysin and insulin-degrading enzyme (IDE), as well as members of the matrix metalloproteinase (MMP) family, including angiotensin-converting enzyme (ACE) and endothelin-converting enzyme (ECE). Several epidemiological studies have reported that levels and activities of neprilysin, IDE, and ACE are reduced in aging and AD-affected brains [56].

The amyloid precursor protein (APP) is a well-known integral membrane protein localized at neuronal synapses, playing a pivotal role in both Aβ production and its subsequent pathological aggregation. APP spans the lipid bilayer of the neuronal membrane, featuring a large glycosylated extracellular N-terminus and a shorter cytoplasmic C-terminus. Proteolytic processing of human APP occurs via two alternative pathways: amyloidogenic and non-amyloidogenic, both resulting in peptides of varying lengths, including the amyloid β-peptide (Aβ), which consists of 37 to 49 amino acids and is the primary component of amyloid plaques in AD brains [57]. In the amyloidogenic pathway, APP is first cleaved by β-secretase (BACE-1) at the Asp site, producing a membrane-bound C-terminal fragment (C99 or CTFβ) and a secreted N-terminal fragment (sAPPβ). Subsequently, γ-secretase cleaves CTFβ at multiple sites, generating fragments of varying lengths (43, 45, 46, 49, and 51 amino acids), which ultimately lead to the formation of extracellular Aβ peptides, predominantly Aβ40 and Aβ42 [58]. In contrast, the non-amyloidogenic pathway involves cleavage of APP by α-secretase at the Leu site, producing the secreted N-terminal fragment sAPPα and the membrane-bound C-terminal fragment C83 (CTFα). CTFα is further processed by γ-secretase, resulting in the extracellular P3 peptide and CTFγ. These Aβ monomers can aggregate into various forms, including oligomers, protofibrils, and mature amyloid fibrils, which are most commonly observed in the neocortex of AD patients [59].

Post-translational modifications serve as rapid and reversible mechanisms for maintaining protein stability, responding to extracellular stimuli, and facilitating various cellular processes. The SUMO proteins and the sumoylation process were recently discovered and recognized for their significant roles within the cell [6]. SUMO proteins have garnered interest for their roles in both the central and peripheral nervous systems. As a result, research has accelerated on the impact of SUMO proteins and the sumoylation process, a post-translational modification, on neurodegenerative diseases. However, many pathways remain to be elucidated [7].

General Characteristics of SUMO Proteins and Sumoylation:
Discovered in 1996, SUMO, or Small Ubiquitin-Related Modifiers, expresses itself in a variety of eukaryotic cell systems, from yeast and nematodes to fruit flies and mammals [8]. These proteins share an 18% sequence similarity in their three-dimensional structure and function. SUMO proteins, through a metabolic cycle known as sumoylation, play roles in maintaining cellular homeostasis, controlling transcriptional activity, replication, defense responses to factors like inflammation and stress, and regulating gene expression [9]. In yeast and Saccharomyces cerevisiae, there is a single SUMO paralog, Smt3p, while mammals are known to have five paralogs, including SUMO1, SUMO2, SUMO3, and SUMO4. These paralogs have been found to exhibit homology with each other. Molecularly, SUMO2 and SUMO4, and SUMO2 and SUMO3, show homology, whereas functionally, SUMO1 and SUMO4 are homologous. The SUMO proteins' substrates are mostly intracellular proteins. SUMO proteins bind to their substrates via isopeptide bonds, playing roles in numerous biochemical events. Through this binding, they regulate the localization of their substrates within cells, increasing the stability and activity of these proteins [10]. SUMO1, like SUMO2 and SUMO3, shows widespread tissue distribution, but SUMO4 is pre-dominantly found in the spleen, kidney, and lymph nodes [11].

The deconjugation process of SUMO1 is slower than that of SUMO2/3 [12]. Additionally, SUMO-1 is generally found in the nuclear membrane and nucleus, whereas SUMO-2/3 is located in the nucleoplasmic fluid (caryolymph) [11]. SUMO-1 and SUMO-2/3 can act on both the same and different substrates, with studies indicating significant functional differences between them [13]. For example, SUMO-1 forms mono-sumoylation chains, while SUMO-2/3 forms poly-sumoylation chains. SUMO-1 has been shown to serve as a terminal cap in SUMO-2/3 polymer chains [14].

Despite all this information, much remains to be discovered about the recently identified SUMO-4 protein. Studies have shown that SUMO-4 is 86% similar to SUMO-2 [15]. Sumoylation refers to the reversible covalent bonding of any member of the SUMO protein family to lysine groups on substrates (target proteins). To date, over 3,600 SUMO substrates have been identified in sumoylation studies to date [16]. Furthermore, some studies have observed that many proteins bind to SUMOs through non-covalent interactions. This type of binding involves intermediaries known as SUMO interaction motifs (SIMs). These SIM-mediated bonds are especially found in neuronal and synaptic proteins [5]. The bonds formed with target proteins provide temporal and spatial regulation, which is crucial for cell viability. Additionally, studies suggest that disruptions in neuronal sumoylation can lead to or predispose to many diseases [17]. When not in use, SUMO proteins are inactive, and their expression from SUMO genes occurs as inactive precursor molecules [18]

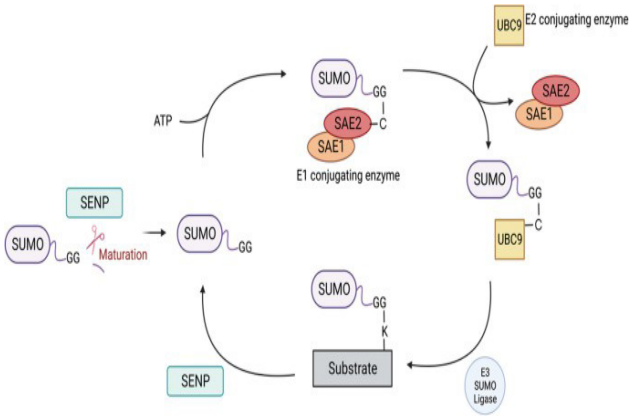

Figure2: Sumoylation Pathway Diagram. (Huang C., Yang T., Lin K.; Journal of Biomedical Science (2024))[52]

As seen in Figure 2, the sumoylation signaling pathway involves the following steps: The function of sumoylation proteins in the sumoylation cycle is assumed to be "protein solubility enhancement." This function has been shown to be effective in regulating protein aggregation and the pathogenesis of neurodegenerative diseases. SUMO has been demonstrated to have direct effects on protein solubility for α-synuclein, DJ-1, Huntington, and STAT1 [19]. The sumoylation process consists of conjugation and deconjugation phases. Three enzymes play key roles in this process: E1 (activating enzyme), E2 (SUMO-specific conjugating enzyme, Ubc9), and E3 (SUMO ligase) [20]. The binding process in mammals begins with the E1 enzyme, a heterodimer of SAE1 and SAE2, activating SUMO proteins in an ATP-dependent manner. During activation, a thioester bond is formed between the glycine residue at the C-terminal of the SUMO protein and the cysteine residue in the active site of SAE2. Immediately after, the SUMO protein is transferred to the active cysteine site of the E2 (Ubc9) conjugating enzyme via the thioester bond [21]. E3 ligase enzymes serve as a bridge between the SUMO-loaded Ubc9 gene and substrate proteins. Additionally, for SUMO transfer to occur, the SUMO-Ubc9 thioester bond must be maintained. SENP enzymes facilitate both sumoylation maturation and deconjugation. Mammals have multiple SENP enzymes. SENP1 and SENP2 enzymes are responsible for the maturation phase of SUMO proteins. Furthermore, these enzymes are involved in breaking the bonds between SUMO-1 and SUMO-2/3 proteins and their substrates. SENP3/5 enzymes are thought to be responsible for monomeric SUMO-2/3 proteins' substrates, while SENP6/7 are involved in the regulation of SUMO-2/3 protein chains [5, 22].

Relationship between SUMO and Ubiquitination

Ubiquitin is a post-translational regulatory protein that consists of approximately 76 amino acids. First identified in 1978, this protein plays a role in various biological pathways. Its primary function is to label proteins for degradation in the 26S proteasomes. Ubiquitination consists of two successive steps: tagging the protein with multiple ubiquitin molecules, and then degrading the tagged protein by the proteasome complex, releasing free or reusable ubiquitin. Generally, ubiquitination and sumoylation share similar enzymatic structures [23].

As previously stated, ubiquitination is a post-translational modification that aims to degrade proteins in the 26S proteasomes by marking them. This process results in the release of free and reusable ubiquitin through two consecutive steps [24] .The ubiquitin systems primarily involve three different enzymes, enabling ubiquitin to covalently bind to substrate proteins or itself from the C-terminus. These enzymes are E1 (activating enzyme), E2 (conjugating enzyme), and E3 (ligating enzyme) [25]. In the first step, E1 activates ubiquitin through an ATP-mediated reaction, resulting in the high-energy thiol ester intermediate E1-S*. The activated ubiquitin is then transferred to a specific substrate via a member of the ubiquitin protein ligase family, E3 ligase, through one of several E2 enzymes, forming the high-energy thiol intermediate E2-S*[26,27] .The E3 enzyme classes, particularly RING-finger-containing types, directly transfer the active ubiquitin from E2 to the substrate bound to E3. In contrast, in HECT domain-containing E3s, the activated ubiquitin is transferred from E2 to the active cysteine residue on E3, forming the high-energy thiol ester intermediate E3-S*, which is subsequently transferred to the ligase-bound substrate. This regulation depends on protein phosphorylation, believed to influence E3 enzyme activity. Ubiquitination typically entails transferring ubiquitin to one of the substrate's seven lysine residues or the N-terminus, forming a covalent isopeptide bond that results in a variety of ubiquitin chain types and lengths [28]. Numerous ubiquitination types exist, forming different structured chains based on binding types recognized as specific signals by ubiquitin-binding proteins, which regulate the modified protein's enzymatic activity, stability, and localization [29] .

The molecular diagrams of ubiquitin, SUMO1, SUMO2, and SMT3, the single SUMO paralog found in Saccharomyces cerevisiae, are provided in Figure 3. (referee1 reccomendation.)

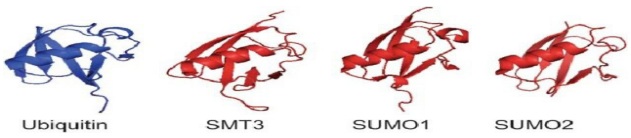

Figure 3: A Diagram of SUMO paralogue and Ubiquitin. (Alonso A., Greenlee M. Et al.; Cytoskeleton, 2015.)[49]

SUMO Protein Family and Alzheimer's Disease

Risk factors for AD include age, gender, dementia, genetic factors (presence of the Apolipoprotein E (Apo E) e4 gene), Down syndrome, atherosclerosis, diabetes mellitus, systemic diseases, metabolic factors (amyloid-β metabolism), hypertension and hypotension, smoking, infectious factors, poisoning, history of major depression, and head trauma [31, 32]. As they age, people may experience forgetfulness, slower speech, fatigue, and unhappiness, which can be normal aging signs or symptoms of AD. AD significantly complicates patient lives, leading to substantial declines in quality of life [33].

The clinical course of AD is divided into three stages based on the severity of symptoms and findings: Early stage, middle stage, and advanced stage. The early stage is characterized by memory disorders, difficulty learning new information, repeatedly asking questions, and misplacing items [34]. Since

forgetfulness is considered normal in elderly individuals, there can be delays in seeking medical help, resulting in a late diagnosis. In the middle stage, there is a functional loss in many daily activities due to the worsening of early-stage symptoms [35]. Information from the recent past starts to fade slowly. Patients may get lost when going out and become unable to manage financial processes. In the advanced stage, patients require assistance with basic daily activities. "2023 Alzheimer's Disease Facts and Figures" mentions that patients become completely dependent on basic needs such as dressing, bathing, and eating. Communication is reduced to meaningless sounds and words, making understanding the patient difficult. Complications from diseases like pulmonary embolism, bed sore infections, and nutritional disorders are among the primary causes of death [36].

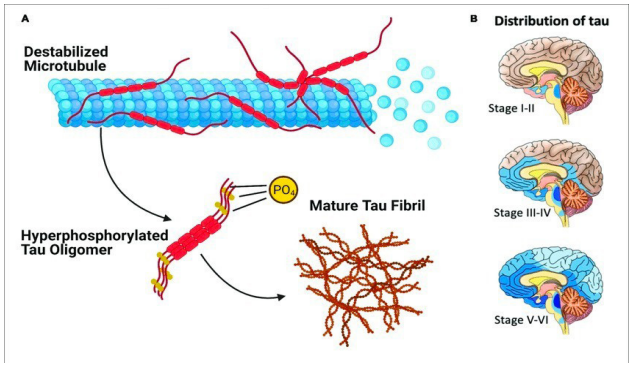

Figure 4: A Diagram of Alzheimer's Disease and Tau Proteins Aggregation Motifs, (Mah D., Zhao J. Et al.; Frontiers in Molecular Biosciences, 2021.)[50]

As shown in Figure 4, alzheimer's disease is a progressive condition characterized by neuron and synapse loss in certain parts of the central nervous system (CNS). Genetic predisposition is a significant factor in AD development. It is a complex disease that presents at multiple levels and is influenced by various pathways. Two primary pathological findings in AD are amyloid plaques and neurofibrillary tangles [37]. Genes associated with AD include amyloid precursor protein (APP), Presenilin 1 (PS1), Presenilin 2 (PS2) (responsible for AD before age 65), and ApoE (responsible for AD after age 65) [38]. The APP gene is located on chromosome 21, and the PS2 genes are on chromosome 1. Mutations in these chromosomal regions increase amyloid-β peptide levels in AD. These mutations result in abnormal APP cleavage, toxic amyloid-β production, Tau protein hyperphosphorylation, and neurofibrillary tangle (NFT) formation. Early-onset AD develops due to APP (2–3%), PS1 (70–80%), and PS2 (20%) gene mutations [35].

For late-onset AD, the ApoE gene on chromosome 19 is influential. The e2 allele of this gene is protective and reduces AD risk, while the ApoE e4 allele increases AD risk by promoting amyloid plaque and NFT formation. Mutations in the ApoE gene account for 50–80% of late-onset AD. However, ApoE e4 alone is not sufficient to cause AD [36]. The most known pathological finding in AD is amyloid plaques. Amyloid-β peptides, which result from the proteolytic breakdown of the amyloid precursor protein, are linked to the disease. The APP protein is metabolized by proteolytic enzymes called α-, β-, and γ-secretases. In the first step, APP is cleaved by either α-secretase (non-toxic, normal cleavage) or β-secretase (toxic, abnormal cleavage). Subsequently, γ-secretase generates amyloid-β and AICD (APP intracellular domain) fragments from C99 [39].

Current methods do not offer an effective therapeutic pathway to alter disease progression or slow or halt cognitive decline. To address this gap, a better understanding of the disrupted signaling pathways underlying AD pathology, including the regulatory mechanisms that typically control these networks, is essential. One such mechanism involves sumoylation, a post-translational modification that regulates many aspects of cell biology and has several critical neuron-specific roles. Connections with the ubiquitin proteasome system (UPS) and, more recently, autophagy have been a focal point [40]. Conjugation with SUMO and the pathways regulated by SUMO have been less studied in relation to AD pathology and neuronal physiology. However, sumoylation's involvement in these areas has gained momentum in recent years [41]. The diagram in Figure 5, illustrating the roles of Alzheimer's disease and SUMO proteins, also supports this paragraph. (Referee1 Reccomendations.)

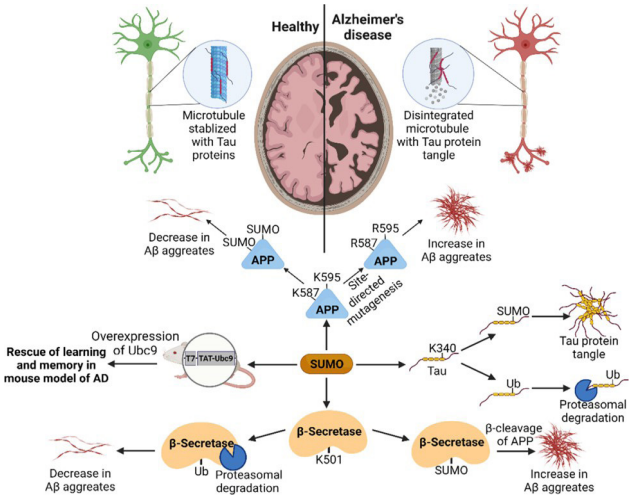

Figure 5: A Diagram of Alzheimer Disease's and SUMO Proteins. (Mandel N., Agarwal N.; Cells, 2022.)[51]

Given the numerous proteins subjected to sumoylation in neurons, it is unsurprising that any disruption in this post-translational modification affects Alzheimer's disease [42, 43, 44]. Evidence from genetic studies supports this hypothesis. A single nucleotide polymorphism (SNP) on chromosome 6 (rs6907175) linked to the SUMO-activating enzyme (E1) subunit 2 homolog (SAE2) has been found to be significantly associated with AD in multiple independent sample sets. The SNP was later confirmed to be significant in another genetic study on sporadic AD [45].The mechanism by which the SAE2 homolog SNP influences AD pathogenesis is unclear.

Another SUMO enzyme, protease SENP3, showed altered expression in microarray analyses of the inferior parietal lobules of sporadic AD patients [46]. In AD, there is a significant downregulation of SENP3 expression; RT-PCR confirmed that

AD tissue had about half the average SENP3 expression of controls. The SUMO-conjugated enzyme Ubc9 is the third sumoylation protein linked to AD. Genomic DNA analysis of late-onset AD patients revealed an SNP (rs761059) in intron 7 of the Ubc9 gene (UBE2I) that is significantly associated with the disease [47,48]. These studies indicate that changes in sumoylation likely play a role in AD, although research into the underlying mechanisms continues.

Conclusion and Recommendations

This review has examined the precise impacts of the SUMO protein family on Alzheimer's disease, with a focus on the noteworthy influence of post-translational modification systems on intricate neurodegenerative conditions. The SUMO system is a post-translational modification system that has significant involvement in the development of neurodegenerative illnesses. This involvement occurs via its metabolic cycles, which are referred to as sumoylation. Although the significance of these systems has been recently uncovered, they have been discovered to play a crucial role in the development of several disorders. SUMOs, via a metabolic cycle and processes akin to ubiquitination, govern cellular function by managing factors such as intracellular localization and protein homeostasis resulting from gene expression. A thorough investigation and future discoveries about these routes are essential. Gaining a comprehensive understanding of SUMO pathways would greatly enhance the progress of research aimed at developing therapies for complex neurodegenerative illnesses such as Alzheimer's, which now lack a definite cure.

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