

The Roles of Liquid-Liquid Phase Separation in Cellular Function and Neurodegeneration

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ABSTRACT

Liquid-Liquid phase separation (LLPS) is a biological process in which biomolecules like proteins and RNA separate into distinct liquid phases, forming membraneless organelles called biomolecular condensates. LLPS is found to be involved in many cellular organization processes under physiological conditions. However, if LLPS is dysregulated, it can lead to harmful solid aggregates that contribute to disease formation, such as Alzheimer, Parkinson, ALS, cancer, and immune disorders. The neurodegenerative diseases are driven by complex interactions between gene, environmental, and cellular stress factors, which collectively contribute to protein aggregations. This paper offers a brief review on the importance of LLPS, explores the examples of the diseases caused by LLPS, and suggests several potential ways to disrupt these pathological protein aggregates that may alleviate neurodegenerative disease symptoms

1. INTRODUCTION

Liquid-liquid phase separation (LLPS) is a biological process in which a single uniform liquid spontaneously separates into two distinct liquid phases—much like how oil droplets form in water¹. In cells, this separation enables the formation of membraneless organelles, or biomolecular condensates, which concentrates on specific proteins and nucleic acids in certain regions without the need for lipid membranes. LLPS has become a key focus in biological research, emerging as a crucial method utilized by many scientists. It is also recognized as a fundamental mechanism for organizing cellular compartments in eukaryotic cells². In fact, these condensates play important roles, such as helping regulate the timing and location of critical biochemical reactions by concentrating key molecules, increasing reaction speed, and responding rapidly to changes in the cellular environment.

It is important to note that proteins participating in LLPS typically possess modular domains or intrinsically disordered regions (IDRs) and often engage with RNA molecules, which are critical in both initiating and regulating the phase separation process³. The range of biological functions controlled by LLPS continues to expand. LLPS is crucial for a variety of cellular processes, including chromatin organization and gene transcription, the DNA damage response, X-chromosome inactivation, and paraspeckle formation⁴. It also plays a key role in the formation of PML nuclear bodies, stress granules,

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and ribonucleoprotein granules, as well as the assembly of proteasomes and autophagosomes, and the formation of synaptic vesicle active zones in neurons⁵. In this article, we will cover the importance and the functionality of LLPS in biological systems.

2. METHODS

This review is based on a literature search of peer-reviewed publications investigating LLPS in cellular biology and neurodegenerative diseases. Articles were identified through searches of PubMed, Google Scholar, and PubMed Central (PMC) using combinations of search terms including “liquid-liquid phase separation,” “stress granules,” “protein aggregation,” “Alzheimer’s disease,” “Parkinson’s disease,” “amyotrophic lateral sclerosis (ALS),” “oxidative stress,” “neuroinflammation,” and “proteostasis.”

Priority was given to recent peer-reviewed research articles and review papers published primarily between 2014 and 2025, alongside seminal studies that established the fundamental principles of LLPS. Additional relevant literature was identified through citation tracking of key review papers.

Studies were selected based on their specific relevance to the physiological functions of LLPS, the mechanisms of biomolecular condensate formation, pathological phase transitions, cell-specific vulnerability, and potential therapeutic approaches. The findings were synthesized narratively to provide a comprehensive overview of the current understanding in the field, rather than through a quantitative meta-analysis.

3. PHYSIOLOGICAL FUNCTIONS OF LLPS

3.1 Mechanism and Importance of LLPS

At the molecular level, and in typical physiological contexts, LLPS occurs when weak, reversible interactions between proteins and nucleic acids become strong enough to overcome the entropy that normally favors a mixed state. In the state that LLPS is activated properly, it will cause the uniformed solution to separate into two distinct liquid-like phases: one rich in specific biomolecules (the condensate) and one depleted of them (Figure 1, left and middle).

Despite the fact that LLPS is essential for normal cell function, dysregulation of this process can contribute to disease. If the interactions between biomolecules become too strong or irreversible, the liquid-like condensates will harden into rigid, solid aggregates (Figure 1, right). These aggregates provide a difficult time towards the cells and the proper working of the cellular processes, such as transcriptions, signal transductions, and protein degradations.

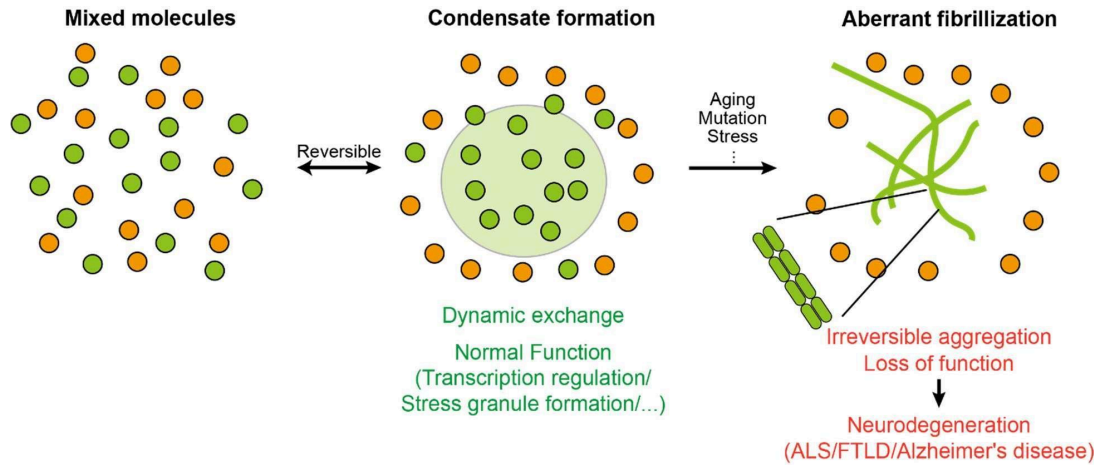


Figure 1. Schematic for LLPS and aberrant fibrillization that could lead to neurodegeneration.

Such misregulation of LLPS is now linked to the development of multiple diseases: neurodegenerative disorders (e.g., Alzheimer's, Parkinson's, ALS), cancers, immune system dysfunction and viral infections (Figure 1, right). In these conditions, that are caused by abnormal LLPS, the proteins that normally undergo LLPS under controlled conditions begin to form persistent, toxic assemblies that interfere with cell function. In fact, it has been founded that the same attractive force that drives the LLPS will transform helpful, reversible compartments of the organelles into pathological aggregates⁵. Taken together, the discovery and disregulation of LLPS have given scientists new insights on how cells organize complex biological processes and how this organization can go wary to develop pathological states.

3.2 Cellular Organization

Inside cells, biomolecular condensates formed through LLPS, serve as dynamic hubs for organizing proteins and nucleic acids. Unlike traditional organelles such as the nucleus or mitochondria, LLPS do not require membranes to function. By acquiring these benefits, it allows cells to rapidly reorganize their internal structures in response to stress, signaling cues, or developmental changes—without building new organelles from scratch.

An accumulated body of evidences indicates that these condensates act as a “mini workstations,” that compartmentalizes the cellular reactions and facilitating biochemical efficiency². Similarly, it has been proposed that the LLPS allows cells to quickly respond towards the stress by reversibly forming and dissolving these condensates⁶. For instance, stress granules that are formed by LLPS can sequester untranslated mRNAs and regulatory proteins during environmental stress, temporarily halting translation and protecting essential components until normal conditions are restored. These protective roles are crucial for maintaining cell viability. In addition, LLPS plays essential roles in regulating gene expression by assembling transcriptional machinery—such as RNA polymerase II and coactivators—into concentrated hubs at super-enhancer regions⁷. These dynamic structures allow cells to rapidly activate genes in response to internal and external cues, allowing cells to adapt to ever changing environments.

LLPS also helps shape genome organization and is essential for immune responses and synaptic signaling in neurons^{8,9}.

3.3 Immune Regulation

Another function of LLPS is that it plays a regulatory role in both innate and adaptive immune systems by forming signaling condensates that enhance the precision and speed of immune responses. Moreover, phase separation facilitates the rapid concentration and activation of immune factors that involved in DNA and RNA sensing pathways¹⁰. For example, during viral infection, LLPS allows for the assembly of antiviral signaling hubs that drive cytokine expression and interferon production. However, viruses can also exploit LLPS mechanisms. Some viral proteins mimic host factors that undergo phase separation, thereby interfering with immune signaling. Disruption of LLPS in immune responses may also contribute to autoimmunity or chronic inflammation, underlining the dual-edged nature of this mechanism.

In short, LLPS offers a flexible, efficient, and elegant way for cells to organize themselves and respond to their environment. LLPS has become a powerful concept for explaining both the dynamic nature of healthy cells and the mechanisms underlying many human diseases. The next sections of this review will explore how LLPS becomes misregulated, and how this misregulation contributes to the progression of neurodegenerative diseases and other disorders.

4. LLPS DYSREGULATION IN NEURODEGENERATIVE DISEASES 4.1 FROM PHYSIOLOGICAL CONDENSATES TO PATHOLOGICAL AGGREGATES

Although LLPS is essential for normal cellular function, its dysregulation contributes to disease through three principal mechanisms: increased propensity for phase separation, liquid-to-solid material transitions, and the seeding of toxic protein.

1. **Increased Propensity for LLPS:** Disease-associated mutations may cause proteins to phase separate excessively or under inappropriate conditions.
2. **Material State Transitions:** Condensates may harden from a liquid-like to a solid-like state, reducing their reversibility and leading to aggregate formation.
3. **Seeding of Toxic Aggregates:** Proteins confined within condensates can nucleate amyloid fibrils, triggering a cascade of misfolding.

It has been reported that proteins such as TDP-43, FUS, tau, and α -synuclein further described how these proteins undergo normal LLPS in physiological contexts but become pathological under stress, aging, or mutation⁹. These transitions are particularly implicated in neurodegenerative diseases like amyotrophic lateral sclerosis (ALS), Alzheimer's and Parkinson's.

4.2 Early Mechanisms: IDPs, LLPS, and Aggregation in Neurodegeneration

Neurodegenerative diseases are characterized by the gradual dysfunction and death of neurons in the central nervous system. These diseases—such as Alzheimer's, Parkinson's, ALS, and Huntington's—are influenced by a complex interplay of genetic, environmental, and cellular stress factors. LLPS contributes

to these diseases by promoting harmful protein aggregation and impairing cellular homeostasis under stress. Protein homeostasis (proteostasis) depends on finely tuned folding, trafficking, and degradation¹¹. However, when these mechanisms are overwhelmed—especially under stress or during aging—misfolded proteins can accumulate. LLPS facilitates the initial clustering of these proteins, but when misregulated, it can trigger irreversible aggregation, such as amyloid fibril formation. Insights from the National Institutes of Health (NIH) databases illustrate how LLPS plays a pivotal role in the initial stages of protein aggregation underlying neurodegenerative diseases like Alzheimer's, Parkinson's and ALS^{12,13}. These conditions are frequently marked by the buildup of intrinsically disordered proteins (IDPs), which lack fixed threedimensional structures in normal physiological environments. NIH resources highlight that cellular toxicity can emerge prior to the formation of large aggregates, implying that nascent phase-separated protein condensates may trigger early damage¹⁴.

It is further found that IDPs engage in LLPS to create dynamic droplets, which can mature into harmful aggregates like amyloid fibrils—hallmarks shared across various neurodegenerative disorders¹³. These pathological aggregates underscore the transition from reversible liquid-like states to irreversible solid-like forms, contributing to disease progression. Complementing this, studies have provided a detailed examination of protein misfolding and aggregation, revealing that these processes are not stochastic but shaped by tissue-specific molecular contexts¹¹. Under healthy conditions, molecular chaperones facilitate proper protein folding; however, dysfunction of this quality-control system leads to misfolding, aggregation, and self-perpetuating cycles that amplify pathology. This framework is essential for comprehending LLPS dysregulation in diseases such as Alzheimer's and Huntington's, where misfolded proteins nucleate polymorphic amyloid structures that exert cellular toxicity¹¹.

4.3 Neuroinflammation

Neurons do not function in isolation. They rely on support from glial cells—including microglia and astrocytes—and protection from the blood-brain barrier (BBB). Chronic neuroinflammation, often triggered by glial cell activation, is a major contributor to neurodegeneration¹⁵. While glial responses are meant to protect the brain, prolonged activation can cause damage instead.

Microglia, in particular, can transition from neuroprotective to neurotoxic states under persistent stress, aging, or systemic inflammation. Microglia can shift from a neuroprotective to a neurotoxic phenotype. Chronic inflammatory states, associated with conditions such as arthritis or diabetes prime, microglia for exaggerated immune responses, increasing vulnerability to Alzheimer's disease. Likewise, systemic factors including viral infections obesity, and depression promote glial mediated neuroinflammation, which disrupts neuronal function and accelerates neurodegeneration^{16,17}. Importantly, stress-induced inflammatory signaling is modulated by LLPS. For example, stress granules formed via LLPS can trap RNA-binding proteins like TDP-43 and FUS, which later transition into pathological aggregates if the stress response is not resolved.

4.4 Environmental and Cellular Stressors

Beyond cellular stress, neurodegenerative diseases are shaped by lifestyle and environmental exposures. As the lifestyles were recorded with people's sleeping and dieting patterns along with the injuries from sudden accidents and environmental exposures, it demonstrated the pattern of aging, poor diet, chronic psychological stress, and sleep disturbances all contribute to cellular dysfunction and may exacerbate LLPS-related aggregation¹⁸¹⁹.

Oxidative stress—a key consequence of aging and environmental insults—plays a particularly damaging role. Studies have consistently and repetitively focused and recorded tediously how LLPS related aggregation is affected through people's lifestyle, highlighting the sensitivity of the hippocampus to oxidative stress, with implications for learning, memory, and overall brain health²⁰. Under oxidative pressure, proteins that normally undergo reversible LLPS may instead form persistent toxic assemblies.

Not only do people's sleeping and dieting patterns matter, but injuries that accidentally occur also play a significant role in affecting LLPS. For instance, traumatic brain injury (TBI) is another important environmental risk factor. It is demonstrated how even mild head injuries can initiate prolonged inflammatory responses in the brain²¹²². These responses include cytokine release and BBB disruption, which in turn exacerbate LLPS misregulation and aggregation. Furthermore, scholars and researchers have attempted to connect TBI injuries to chronic conditions, such as Chronic Traumatic Encephalopathy (CTE). It is a progressive, degenerative brain disease that is found in the people with a history of repetitive head impacts or concussions. Other diseases that the researchers have attempted to connect was Alzheimer disease and Parkinson's disease²³.

Lifestyle-related metabolic disorders also impact neurodegeneration via LLPS mechanisms. In addition to the sleeping patterns and injury history, dieting and choice of food also significantly impacts the LLPS activities as a result. It has been studied how highfat diets, exposure to environmental pollutants, smoking, and alcohol abuse influence neuronal signaling ²⁴. These factors increase the burden of cellular stress and impair proteostasis, indirectly promoting pathological LLPS and protein aggregation.

Studies regarding the lipid peroxidation—oxidative damage to polyunsaturated lipids—showcased that it affects phase behaviors that is inside the cell membranes. Using giant plasma membrane vesicles as a model, the study demonstrated that lipid oxidation enhances phase separation and promotes the disordered phase, altering the organization of proteins and lipids. Specifically, identifying and selecting proteins that typically prefer lipid rafts (ordered domains) were found to translocate into disordered domains after peroxidation, indicating a breakdown in compartmental integrity. This disruption impairs membrane raft function and composition, potentially contributing to pathological conditions such as ferroptosis and neurodegenerative diseases, including Alzheimer's disease²⁵.

Overall, these findings suggest that LLPS does not act in isolation. It operates at the interface of cellular biology and environmental context, where both internal and external stressors can disrupt its balance—paving the way for disease.

5. REPRESENTATIVE EXAMPLES OF LLPS IN NEURODEGENERATIVE DISEASES

5.1 Alzheimer's Disease (AD)

AD is the most prevalent neurodegenerative disorder, marked by the accumulation of misfolded proteins—especially tau and amyloid- β ($A\beta$)—in the brain. These proteins can undergo LLPS under physiological conditions, but under prolonged stress or aging, they form toxic aggregates²⁶. Tau proteins initially form liquid-like condensates through LLPS, but these droplets can mature into insoluble fibrils, especially in the presence of metal ions or interacting proteins.

$A\beta$ peptides also become concentrated within LLPS droplets, accelerating their aggregation into neurotoxic oligomers and fibrils. Importantly, tau and $A\beta$ can co-localize in the same condensates, mutually enhancing their aggregation—a process that amplifies disease progression. This highlighted how persistent stress granules formed via LLPS serve as nucleation sites for these aggregates, linking cellular stress responses to AD pathogenesis²⁷.

The impact of LLPS in AD is far-reaching: it influences tau aggregation, $A\beta$ dynamics, and even the interaction between these proteins within shared condensates. These findings underscore the importance of LLPS in shaping both early-stage toxicity and later structural degeneration in Alzheimer's.

5.2 Parkinson's Disease (PD)

PD is a progressive disorder primarily affecting motor function, caused by the death of dopamine-producing neurons in the substantia nigra. The hallmark of PD is the accumulation of α -synuclein into Lewy bodies—aggregates that disrupt neuronal signaling. Studies have shown that α -synuclein undergoes LLPS under normal conditions, but genetic mutations or oxidative stress can drive the condensates toward solid aggregation²⁸. Moreover, PD patients often experience degeneration in additional brain regions, losing not only dopamine but also norepinephrine-producing nerve endings. This broadens the disease's impact on non-motor functions, such as blood pressure regulation and mood stability. The pathological LLPS of α -synuclein has been implicated in both familial and sporadic forms of PD.

Many patients with PD also present symptoms that overlap with other disorders, such as multiple system atrophy and Lewy body dementia—conditions sometimes grouped under “Parkinson's-plus syndromes.” These shared features suggest a common molecular origin, potentially tied to dysregulated LLPS and protein aggregation.

6. DISCUSSION AND OUTLOOK

Although LLPS occurs in many cell types throughout the body, neurodegenerative diseases display a phenomenon known as selective vulnerability, targeting specific populations of neurons. For instance, Alzheimer's disease primarily damages neurons within the hippocampus and cerebral cortex, whereas Parkinson's disease predominantly affects dopaminergic neurons in the substantia nigra. The molecular

basis for this cell-specific sensitivity remains unclear. While current research focuses heavily on individual disease-associated proteins, fewer studies have examined whether intrinsic differences in condensate composition, RNA metabolism, baseline metabolic activity, or cellular stress responses drive this vulnerability. Future investigations comparing LLPS dynamics across different neuronal populations may reveal why certain cells undergo pathological aggregation while neighboring cells remain resilient, even when expressing the exact same proteins. Growing evidence supports LLPS as a promising therapeutic target for neurodegenerative diseases. However, a major challenge arises because LLPS carries out numerous essential physiological functions within the cell. Broadly inhibiting phase separation would likely disrupt normal cellular organization, transcriptional regulation, RNA metabolism, and vital stress responses, such as the formation of protective stress granules. Consequently, future therapeutic strategies must precisely distinguish between healthy, physiological condensates and aberrant, pathological aggregates. One innovative approach involves engineering "protein surfactants," which fuse IDRs with large, highly soluble proteins. The fused IDRs act as a targeting mechanism, driving the entire surfactant protein to partition into specific condensates. Once inside, the protruding soluble proteins exert repulsive forces against one another primarily due to steric hindrance, which minimizes molecular crowding. These dual-action interactions work together to cap condensate growth at a specific upper size limit. In experiments testing this feasibility using maltose-binding protein (MBP) as the soluble domain, increasing the surfactant protein concentration markedly reduced the overall size distribution of the protein droplets. In *in vivo* applications, these protein surfactants could keep naturally small, physiological condensates intact while selectively preventing pathological ones from growing abnormally large or transitioning into harmful, solid-state aggregates.

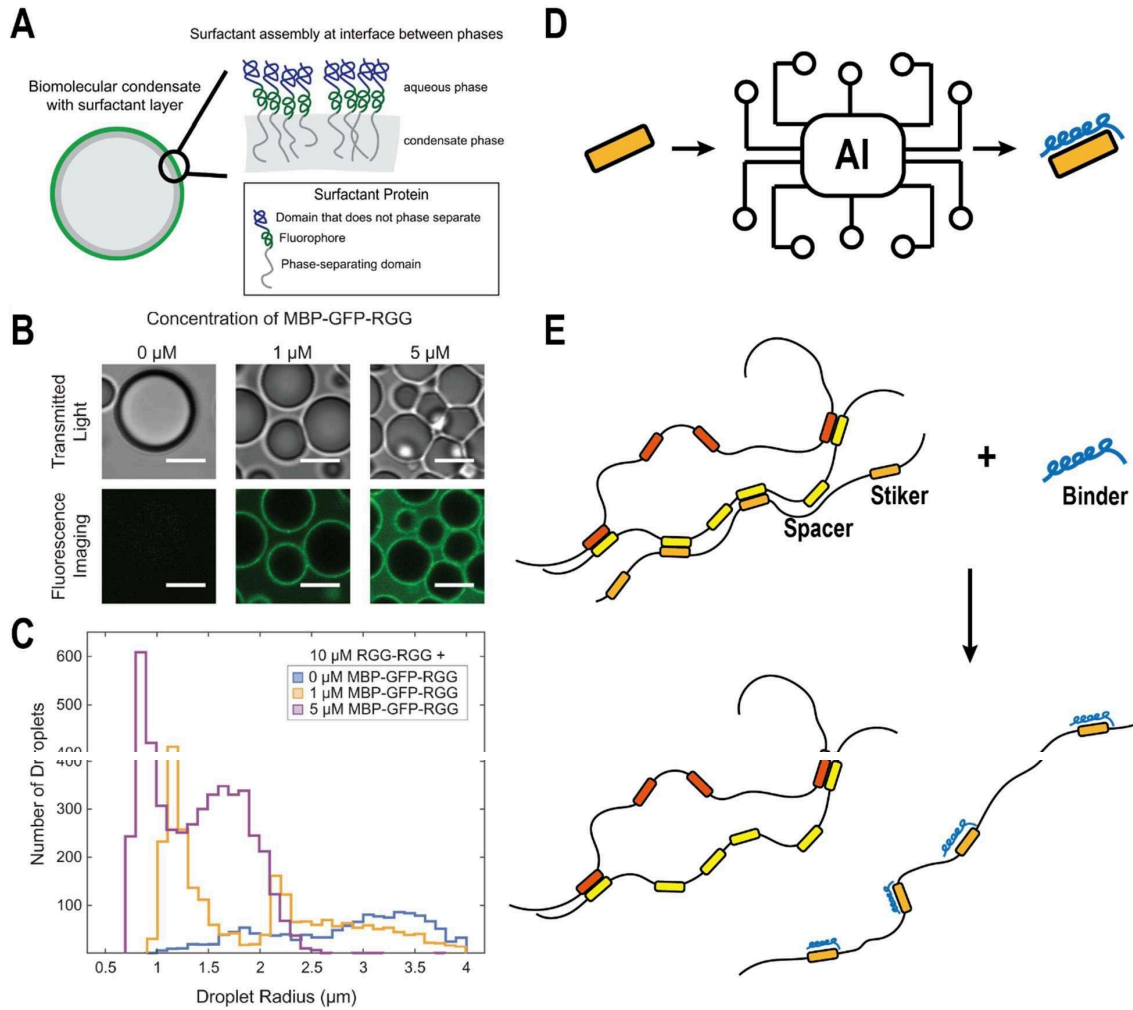


Figure 2. (A) Schematic for protein surfactants. (B and C) When protein surfactants that fuse MBP and green fluorescent protein (GFP) with condensate-forming RGG IDR are added at increasing concentrations, the observed condensates increasingly span lower radius regions. (D and E) Schematic for artificial intelligence-based design of mini proteins that selectively bind to the sticker parts in protein condensates.

Another emerging strategy utilizes generative artificial intelligence for de novo protein design. The formation of biomolecular condensates can be modeled by a polymer physics framework known as the "stickers and spacers" model. "Stickers" (such as aromatic amino acid residues) form weak, transient, non-covalent crosslinks, while "spacers" dictate the flexibility of the protein chain and the overall volume of the condensate. Instead of trying to block an entire functional binding site on a protein, it may be more effective to saturate the system with small, monovalent proteins designed to bind specifically to these

stickers. Because these monovalent components occupy the stickers without offering any multi-directional bridging architecture, they effectively lower network connectivity. This shifts the phase boundary and prevents the system from reaching its percolation threshold, causing the condensate to dissolve. Advanced generative AI tools, such as diffusion models, can design small protein structures with complementary shapes to these specific stickers, while inverse-folding AI models evaluate structure-sequence fitness to generate the exact amino acid sequences required. Thanks to their compact size, these engineered binders can easily penetrate dense condensates to disrupt sticker interactions. If these small protein binders are engineered to target pathological stickers—such as those rich in beta-strand components prone to forming rigid amyloid fibrils—they could selectively dissolve disease-associated condensates without harming healthy ones. Looking forward, research should focus on selectively stabilizing healthy, reversible condensates while accelerating protein clearance pathways to degrade damaged ones. Additionally, identifying reliable biomarkers capable of detecting pathological LLPS before irreversible neuronal damage occurs remains a critical priority. Ultimately, combining advances in high-resolution live-cell imaging, biomarker discovery, and targeted molecular therapies will significantly improve early diagnosis and therapeutic intervention for neurodegenerative diseases.

7. CONCLUSION

LLPS is now recognized as a fundamental organizational principle in cellular biology, enabling the formation of membraneless compartments that regulate transcription, translation, immune signaling, and stress responses. When finely regulated, LLPS enhances biochemical efficiency and adaptability. However, under stress, aging, or genetic mutation, this same mechanism can trigger pathological protein aggregation and drive disease.

Neurodegenerative diseases, such as Alzheimer's, Parkinson's, ALS, and Huntington's, share a common feature: the transformation of liquid-like protein condensates into toxic fibrils. Environmental influences like oxidative stress, traumatic brain injury, and chronic inflammation can exacerbate this transformation. At the same time, glial cells and systemic immune responses play critical roles in shaping the cellular environment where LLPS operates.

Thus, LLPS lies at the crossroads of molecular biology, cellular stress, and environmental influence. Its dual role—as both a regulator and a risk factor—makes it a compelling target for future therapeutic strategies. Better understanding of the triggers that convert beneficial LLPS into pathological aggregation could pave the way for early interventions that prevent or reverse neurodegeneration.

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