Proceedings of the 6th International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/2026.39139

Research Frontiers of Biomolecular Condensates from Function to Disease

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Abstract. Biomolecular condensates are a class of dynamic membrane-less cellular compartments in cells that lack a lipid membrane envelope and are driven by liquid-liquid phase separation (LLPS). Through multivalent weak interactions they enrich specific biomacromolecules and occupy a key position in core physiological processes such as gene transcriptional regulation, RNA processing and metabolism, and signal transduction. In recent years, with the rapid development of super-resolution microscopy imaging, single-molecule tracking in living cells, and bioinformatics technologies, researchers' understanding of the multivalent assembly rules, dynamic exchange properties, and functional realization mechanisms of condensates has continued to deepen. However, once the homeostasis of phase separation is unbalanced, functional droplets can gradually turn into pathological solid aggregates through maturation and aging, which in turn triggers protein misaggregation, signaling pathway disorder, and dysregulation of gene expression; related abnormalities have been widely confirmed in neurodegenerative diseases, tumors, and autoimmune diseases. This paper systematically sorts out the main logical line of biomolecular condensates evolving from formation mechanisms and physiological functions toward pathological mechanisms, and reviews frontier strategies such as targeted phase separation regulation, post-translational modification intervention, and autophagic clearance, in the hope of providing a theoretical basis and practical reference for biomarker discovery, drug target establishment, and intervention development for related diseases.

Keywords: Biomolecular condensates, liquid-liquid phase separation, membrane-less organelles, physiological functions, disease regulation

1. Introduction

In recent years, methods such as super-resolution microscopy, live-cell imaging, single-molecule tracking, and bioinformatics have kept improving, and researchers have gradually seen a fact clearly: liquid-liquid phase separation (LLPS) is actually the core physicochemical mechanism driving the formation of biomolecular condensates [1]. To put it more specifically, macromolecules such as proteins and nucleic acids gather together through multivalent weak interactions mediated by intrinsically disordered regions (IDRs) and low-complexity domains (LCDs), and under the precise regulation of multiple factors such as post-translational modifications, molecular chaperones, ATPase activity, and the ionic environment, they maintain a dynamic balance between assembly and

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DOI: 10.54254/2753-8818/2026.39139

disassembly. When the local concentration of molecules crosses the critical threshold, they phase-separate out of the originally homogeneous solution and spontaneously assemble into dynamic condensed structures without a lipid membrane envelope but with their own specific chemical microenvironment and biological functions, which is what we call biomolecular condensates.

It should also be seen that abnormal condensates often bring a series of troubles such as protein misaggregation, abnormal cell signaling, and dysregulation of gene expression. Especially in diseases such as neurodegenerative diseases and cancer, condensate abnormalities have become a class of pathological mechanisms that researchers pay close attention to. Precisely because of this, condensates hold promise as new disease biomarkers, drug targets, and even intervention objects. What this paper wants to do is to sort out the transition process of condensates from physiological function to pathological mechanism, and provide some theoretical basis for the treatment of related diseases.

2. Formation mechanisms and structural characteristics of biomolecular condensates

2.1. Thermodynamic and molecular interaction basis of liquid-liquid phase separation

LLPS is the core physical mechanism by which biomacromolecules spontaneously form membrane-less compartments (that is, biomolecular condensates) in cells, and it is essentially a self-organization process driven by thermodynamics and regulated by weak intermolecular interactions [2, 3]. From the perspective of statistical thermodynamics, the occurrence of LLPS depends on the competitive balance between mixing entropy and the enthalpy of intermolecular interactions: when specific multivalent interactions overpower the resistance of conformational entropy and mixing entropy, the originally homogeneous solution undergoes a phase transition, splitting into a dense phase rich in biomolecules and a relatively poor dilute phase [4, 5]. This process follows the classical Flory-Huggins theoretical framework for polymer solutions, and also shows strong dynamism and regulability in biological systems; later, with the help of modern theories such as the "sticker-spacer" model (Sticker-Spacer Model), the molecular logic behind it was explained more clearly [6, 7].

2.2. Dynamic assembly and maturation of condensates

The dynamic assembly and maturation of biomolecular condensates is the core physicochemical mechanism by which cells achieve membrane-less compartmentalization, regulate biochemical reactions, and cope with environmental stress. It is not a static structural generation, but a complex dynamical system driven by LLPS, regulated by multivalent weak interactions, and undergoing physical state evolution over time. Recent studies suggest that the transition of condensates from initial liquid droplets to final solid-like or gel-like aggregates (a process called "maturation" or "aging") not only determines the specificity of their physiological functions, but is also the key pathological basis for the occurrence of various neurodegenerative diseases and cancers [8-10]. As shown in Figure 1, this main line from homogeneous solution to pathological aggregates is presented intuitively.

DOI: 10.54254/2753-8818/2026.39139

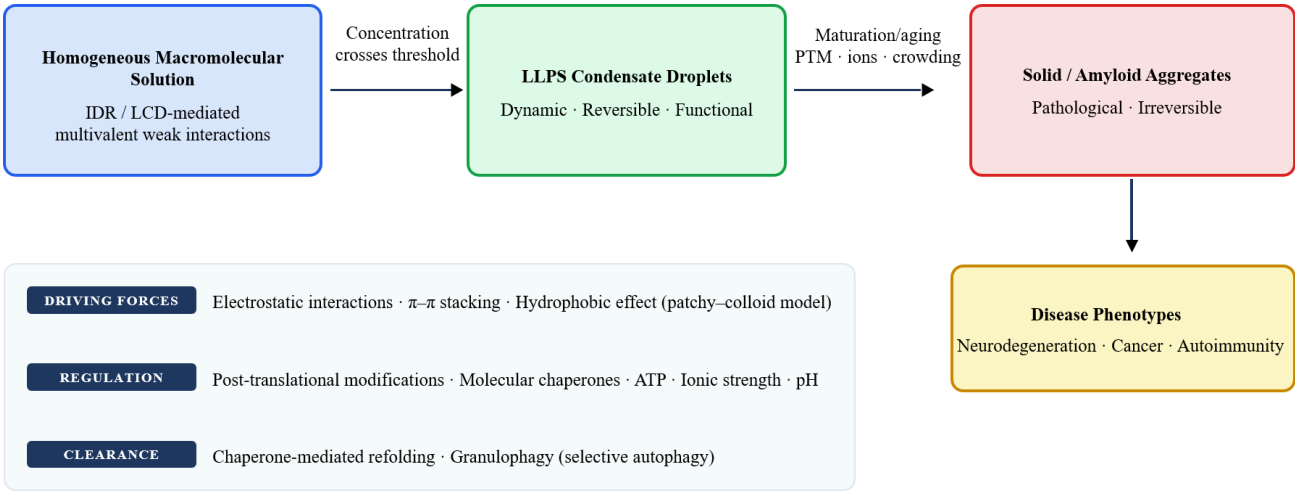


Figure 1. LLPS-driven formation and pathological transition of biomolecular condensates

2.3. Regulation of the environmental microenvironment by post-translational modifications

Post-translational modifications (PTMs) of proteins are a sophisticated set of molecular regulatory languages in cells. They not only profoundly affect the functional state of individual proteins, but also occupy a central position in shaping and responding to complex microenvironments—especially the tumor microenvironment (TME). By dynamically modifying key signaling proteins, structural proteins, and immune regulatory molecules, this regulatory network directly participates in determining the physical properties, biochemical composition, and intercellular communication patterns of the microenvironment, thereby affecting disease progression and therapeutic response.

In the tumor microenvironment, hypoxia is a widespread characteristic stress, and it can obviously reshape the intracellular PTM landscape. Studies have shown that under hypoxic conditions, the acetylation levels of histones and non-histones undergo global changes, forming a dysregulated "abnormal acetylation regulatory network" [11]. By coordinately activating or inhibiting the expression of a batch of downstream genes, this network helps cancer cells adapt to the hypoxic environment, enhances their ability to invade and metastasize, and induces immune escape. For example, the phosphorylation of specificity protein 1 (SP1) is activated under hypoxic and other stress conditions; it can promote the production of vascular endothelial growth factor (VEGF) to support tumor angiogenesis, and can also directly mediate telomere maintenance and immune escape mechanisms of cancer cells, pushing the tumor toward malignant progression [12].

3. Core physiological functions of biomolecular condensates

3.1. Gene transcription and epigenetic regulation

By enriching components such as transcription factors, coactivators, chromatin-modifying enzymes, and non-coding RNAs, biomolecular condensates set up high-concentration microenvironments at specific genomic loci, thereby precisely regulating gene transcriptional activity. For example, super-enhancer regions can form phase-separated condensates that recruit the Mediator complex and RNA polymerase II, obviously improving the transcriptional efficiency of target genes [13]. In addition, epigenetic modifying enzymes such as histone acetyltransferase p300 and methyltransferase EZH2 can also gather at specific chromatin regions through phase separation, achieving efficient catalysis of local histone modifications, and in turn affecting chromatin open state and gene expression

DOI: 10.54254/2753-8818/2026.39139

programs [14, 15]. What deserves attention is that the synergistic action of DNA methylation and histone modifications can also be strengthened in the condensate microenvironment; this spatial co-localization helps establish stable epigenetic memory and has had a profound impact on cell fate determination and disease occurrence [16, 17]. In the aging process, the disorder of the epigenetic landscape is closely related to abnormal condensate assembly, suggesting that the two are functionally coupled in maintaining genome stability [13].

3.2. RNA processing, metabolism, and transport regulation

RNA-binding proteins (RBPs) generally carry low-complexity domains (LCDs) or intrinsically disordered regions (IDRs), which makes it easy for them to drive phase separation through multivalent weak interactions and form RNA-related condensates such as nuclear speckles, nucleoli, and stress granules (SGs). These structures provide an efficient reaction platform for the splicing, editing, tailing, and nucleocytoplasmic transport of precursor mRNA. For example, nuclear speckles are rich in splicing factors such as SC35 and SR proteins, and the phase separation properties they display ensure the rapid assembly and recycling of the splicing machinery [18]. In the cytoplasm, stress granules form rapidly under conditions such as heat shock, oxidative stress, or viral infection; by temporarily storing non-essential mRNA and suppressing its translation, they help the cell save energy and prioritize the synthesis of stress proteins [19]. However, the abnormally persistent existence or misassembly of SGs will lead to dysregulation of RNA metabolism, a point that many studies have repeatedly mentioned in neurodegenerative diseases and blinding eye diseases [20]. In addition, some long non-coding RNAs (lncRNAs) can also act as scaffold molecules, guiding specific RBPs to form functional condensates and thereby regulating the fate of target mRNAs [21].

3.3. Cell signal enrichment, stress response, and autophagy regulation

Biomolecular condensates play the role of "signal hubs" in signal transduction pathways. For example, after the T cell receptor is activated, signaling molecules such as LAT, Grb2, and SOS form microclusters through phase separation, obviously amplifying the strength of downstream Ras-MAPK signaling [22]. On the stress response side, besides SGs, P-bodies also participate in mRNA degradation and storage, and the two together regulate the cell's stress adaptability [19]. What especially needs to be mentioned is that a bidirectional regulatory relationship exists between condensates and autophagy. On the one hand, stress granules can be cleared through selective autophagy (that is, granulophagy), a process that relies on autophagy receptors such as p62/SQSTM1 to recognize ubiquitinated proteins on the SG surface [23]; on the other hand, key autophagy proteins such as the ULK1 complex can also form phase-separated condensates to promote the initiation of autophagy [24]. In a sepsis-induced cardiomyopathy model, overexpression of G3BP1 promoted the formation of SGs, which in turn inhibited the activation of the NLRP3 inflammasome by activating the autophagy pathway and reduced the production of IL-1β, playing a cardioprotective role [23]. This mechanism reveals the key position of the condensate-autophagy axis in inflammatory regulation, and also provides a new therapeutic idea for sepsis-related organ damage.

The core physiological functions of biomolecular condensates in cells and their connection to the transition into pathological condensates are shown in Figure 2. Condensates organize transcriptional and epigenetic regulation, RNA processing and transport, signal enrichment, and stress/autophagy responses through LLPS; when the dynamic balance of phase separation is broken, they can turn

DOI: 10.54254/2753-8818/2026.39139

into pathological condensates in neurodegenerative diseases, tumors, and autoimmune diseases, and become an important entry point for targeted intervention.

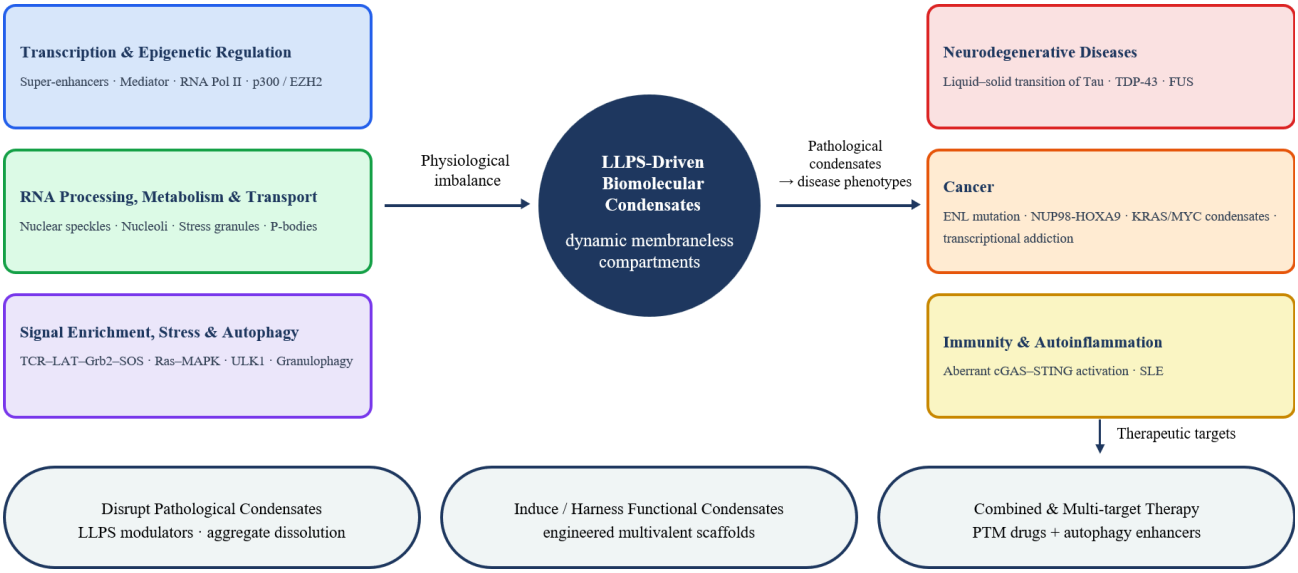


Figure 2. Physiological functions, pathological transition and therapeutic targets

4. Condensate dysfunction and the occurrence of human diseases

4.1. Pathological phase transitions in neurodegenerative diseases

For neurodegeneration-related proteins represented by Tau, the "liquid-solid" phase transition from functional droplets to pathological solid aggregates is a core frontier at the intersection of neuroscience and biophysics. This process is not simple physical solidification, but a complex cascade driven together by molecular conformational changes, post-translational modification regulation, environmental factor induction, and the failure of cellular quality control mechanisms.

In the physiological state, Tau protein, as an intrinsically disordered protein (IDP), can form dynamic and reversible biomolecular condensates through LLPS, and these functional droplets have key roles in microtubule stability, axonal transport, and the regulation of synaptic plasticity [25, 26]. Its phase separation is mainly driven by multivalent weak interactions, including electrostatic interactions, π-π stacking, and hydrophobic interactions [27, 28]. But under pathological conditions, this fine balance is broken, causing condensates to "age" and undergo an irreversible liquid-solid phase transition.

4.2. Transcriptional addiction and signaling abnormalities in cancer

Transcriptional addiction and signaling abnormalities in cancer are a core frontier of current tumor biology research, and their mechanisms are deeply rooted in the dysfunction of biomolecular condensates. Biomolecular condensates form membrane-less organelles through LLPS and spatially organize the transcription machinery and signaling pathway components, thereby precisely regulating gene expression and cell responses. When this highly dynamic and controlled process goes out of tune, it may drive the occurrence and development of tumors.

Transcriptional addiction refers to the phenomenon that cancer cells develop a pathological dependence on specific oncogenic transcription programs. This dependence is often driven by super-

DOI: 10.54254/2753-8818/2026.39139

enhancers, and super-enhancers themselves are a typical embodiment of transcriptional condensates. In the physiological state, transcription factors, coactivators (such as BRD4 and MED1), and RNA polymerase II form condensates at enhancer regions through multivalent weak interactions, efficiently enriching the transcription machinery and achieving high expression of key identity genes. But in cancer, cancer cells hijack this mechanism. For example, in acute myeloid leukemia and Wilms tumor, hotspot mutations in the YEATS domain of the ENL protein enhance the binding capacity to acetylated histones and promote the formation of aberrant transcriptional condensates, leading to sustained and excessive activation of proto-oncogenes such as MYC [29]. These mutations do not simply enhance protein function; instead, by changing phase separation properties, they create "super condensates" with higher stability and transcriptional activity, making cancer cells irreversibly dependent on them [30].

Abnormalities in signal transduction pathways are also closely related to condensates. The traditional view is that signaling pathways transmit information through linear cascades, but the latest research shows that key kinases (such as MAPK and AKT) and their substrates can form signaling condensates through LLPS under specific stimuli, thereby achieving local amplification and precise transmission of signals [31]. In cancer cells, oncogenic mutations can change the composition, stability, or localization of these signaling condensates. For example, KRAS and MYC, as the two most frequently named oncogenes, cooperate not only in the joint regulation of downstream target genes, but possibly also in the remodeling of the shared condensate microenvironment [32]. In addition, some fusion oncoproteins (such as NUP98-HOXA9) use their own intrinsically disordered regions (IDRs) to drive the formation of abnormal condensates, wrongly recruiting transcriptional coactivators to non-physiological gene loci and thereby reprogramming the entire transcriptome [33]. RNA also plays a key role in this process: it can act as a scaffold to promote the nucleation of condensates on chromatin, and can further amplify oncogenic transcription signals through positive feedback loops [34].

4.3. Immune-related diseases and autoinflammation

The role of phase separation dysregulation in the pathogenesis of autoimmune diseases is becoming a frontier focus at the intersection of immunology and cell biology. Biomolecular condensates form membrane-less compartments through LLPS and precisely regulate the spatiotemporal organization of innate and adaptive immune signaling pathways. Once this dynamic balance is broken—whether by phase separation abnormalities caused by genetic variation, environmental stress, or metabolic disorders—it may trigger the collapse of immune tolerance and push the occurrence of autoimmune and autoinflammatory diseases. Among these, the cGAS-STING pathway is a key example of phase separation regulating immune homeostasis. This pathway is responsible for sensing cytosolic double-stranded DNA (dsDNA), and its activation depends on the liquid condensates formed after cGAS binds dsDNA. These condensates not only amplify the enzymatic activity of cGAS and efficiently synthesize the second messenger cGAMP, but also act as signal hubs to recruit and activate the STING protein, finally inducing the expression of type I interferon (IFN-I) and pro-inflammatory cytokines [35]. However, in autoimmune diseases such as systemic lupus erythematosus (SLE), the abnormal accumulation of endogenous nucleic acids (such as mitochondrial DNA or DNA released by NETs) will cause sustained, non-physiological activation of the cGAS-STING pathway. This "false alarm" state driven by endogenous ligands is precisely the core driving force of chronic inflammation in many autoimmune diseases [36, 37]. Studies have confirmed that small-molecule compounds that target and inhibit the cGAS-STING pathway (such

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as Licochalcone B) can effectively relieve the pathological process in autoimmune disease models [38], which also shows the great potential of this pathway as a therapeutic target.

5. Therapeutic strategies and drug development targeting phase separation

5.1. The "disruption" strategy targeting condensates

On the "disruption" side, the research focus is placed on dissolving or preventing the formation of pathological solid condensates. In neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), RNA-binding proteins such as TDP-43 and FUS undergo abnormal phase separation due to mutations or stress, gradually turning from a dynamic liquid state into irreversible amyloid fibril aggregates [39, 40]. Against this process, small-molecule compounds can inhibit the maturation of condensates by interfering with the multivalent interaction network of proteins. For example, some aromatic compounds can bind to the LCD of proteins and block their "sticker-spacer" (sticker-spacer) interactions, thereby keeping them in a soluble state. In addition, regulating the intracellular ionic strength, pH, or degree of molecular crowding can also indirectly affect the threshold of phase separation. Worth mentioning is that the nucleocapsid protein (N protein) of SARS-CoV-2 relies on LLPS to assemble viral particles, and its mutant (such as R203K-G204R-T205I) enhanced the phase separation capacity and suppressed the host's innate immune response [41], which suggests that antiviral drugs can be designed as specific disruptors of viral protein condensates.

5.2. "Induction" and "utilization" of phase separation regulation

The "induction" and "utilization" strategies go the opposite way: they actively promote the formation of functional condensates so as to enhance specific biological pathways. For example, in the process of tissue repair, baicalin can promote the formation of new blood vessels by regulating the HIF-1α/VEGF signaling pathway, and the key components of this pathway most likely rely on phase separation to form signal transduction platforms [42]. Plant research also shows that phase separation participates in the regulation of autophagy: the ATG3 protein in Arabidopsis promotes autophagosome formation by enhancing the phase separation capacity of ATG8e [43], which provides a new idea for developing autophagy-promoting drugs.

5.3. Combined intervention and multi-target therapy

Combined intervention and multi-target therapy are the key to improving efficacy and overcoming drug resistance. Sinomenine, as the main active component of the traditional Chinese medicine Sinomenium acutum, has been confirmed to relieve chronic low back pain through the triple mechanisms of anti-inflammation, analgesia, and tissue repair [44], and its action network most likely involves the coordinated regulation of multiple phase separation-related pathways. In cancer treatment, metformin not only directly inhibits the proliferation of esophageal squamous cell carcinoma cells [45], but may also change the crowding state of intracellular macromolecules by affecting energy metabolism, indirectly regulating the assembly of oncogenic signaling condensates (such as Ras signaling clusters) [46]. In addition, targeted protein degradation technologies (TPD) such as PROTAC have a natural synergy with phase separation strategies: PROTAC molecules themselves can form condensates to enrich E3 ligases and target proteins, thereby improving

DOI: 10.54254/2753-8818/2026.39139

degradation efficiency [47, 48]. This dual mechanism of "degradation + phase separation" provides an efficient way to remove disease-causing proteins.

6. Conclusion and research prospects

As a class of membrane-less compartments driven by LLPS, biomolecular condensates have made us re-understand the compartmentalization patterns and regulatory logic inside cells. From the perspective of physiological function, it organizes transcription, RNA processing, signal transduction, and even autophagy into specific microenvironments; from the pathological perspective, the dysregulation of phase separation is tightly bound to degenerative diseases, tumors, and autoimmune diseases. Around the main line of "function-pathology", this paper has sorted out the formation mechanisms of condensates, their physiological functions, and their abnormal manifestations in several major diseases, and has also summarized strategies such as the "disruption" and "utilization" of targeted phase separation and combined intervention. The work to be done next is, first, to make the quantitative prediction of the critical conditions of phase separation more accurate, providing a fulcrum for the artificial design and regulation of condensates; second, to push the visualization methods for the dynamic changes of condensates further forward, so that processes at the living-cell level can be seen more clearly; third, to apply synergistic ideas such as "degradation + phase separation" to more disease models, to see whether they can truly be transformed into usable intervention means. It can be expected that, with mechanistic research and technical means advancing on both fronts, condensates have a good chance of moving from a basic concept to the clinical targets in the outlook.

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