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Review Article

An Insight into Cancer from Biomolecular Condensates

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Abstract

Understanding the characteristics of cancer cells is critical for developing enhanced therapies and diagnoses. The super-enhancer notion has been given from the angle of gene regulation in order to properly appreciate the molecular mechanisms behind the identities of distinct cell types. A variety of distinguishing features of super-enhancers have contributed to the findings which link gene regulation and biomolecular condensates. This is typically mediated via liquid-liquid phase separation. Several lines of evidence have pointed to alterations in molecular and biophysical principles in cancer cells, notably those linked to gene regulation and cell signaling. All these findings hint to biomolecular condensate change as a major mechanism by which cancer cells acquire distinct cancer characteristic traits and offer functional innovation for cancer initiation and progression. Liquid-liquid phase separation has recently been used for sorting all the processes taking place in the cell for the formation of biomolecular condensates (membrane-free organelles). Recent studies on biomolecular condensates have found that their production and regulation are associated with cancer. Here, we review the evidence that production and degradation of biomolecular condensates are linked to cancer development and progression. As they are linked to cancers, they can be used in cancer research and to devise new cancer therapies, for example, condensate perturbation.

Introduction

For decades, research on the pathophysiology of cancer has shown that various cellular pathways become dysregulated throughout the malignant stage. This includes transcription, chromatin structure, proliferative signaling, RNA processing, and other activities, as well as the maintenance of genomic integrity.[1] These processes occur across the cellular environment and involve precise spatial and temporal interactions between DNA, protein, and RNA molecules. These cellular activities have been intensively researched, resulting in a deep mechanistic understanding of how cells control themselves in both healthy and changed cells, as well as the creation of therapeutic hypotheses that have progressed medical research.[2] Recent research, however, has shown that the bulk of biological processes are compartmentalized in biomolecular condensates, which have physicochemical properties that contribute to regulatory mechanisms that go beyond what classical molecular biology would anticipate.[3] This new information has prompted us and others to study the function of condensate biology in oncogenesis and to consider fresh therapy options that might benefit cancer patients. Nonmembrane-bound organelles, known as biomolecular condensates, compartmentalize and concentrate components involved in related cellular functions. In contrast to classic membrane-bound organelles such as the nucleus, mitochondria, and Golgi apparatus, these structures are not restricted by a lipid bilayer and are not fundamentally stable components of the cell.[4] Instead, they often occur because of phase separa-

Keywords: Cancer; Condensates; Mutations; Genomic instability; Therapies; Biomolecular; Liquid-liquid phase separation.

Abbreviations: ALS, amyotrophic lateral sclerosis; AML, MYC gene 3′ end; Atg1, Autophagy-related 1; ATL, alternative telomere lengthening; BRD4, bromodomain containing 4; CDC6, cell division cycle; CDK7, Cyclin-Dependent Kinase 7; cGAS, cyclic GMP-AMP synthase; CTD, carboxy-terminal domain; DDX4, DEAD-Box Helicase 4; ER, estrogen receptor; EWS, Ewing sarcoma; FUS, fused in sarcoma; hnRNPA1, Heterogeneous nuclear ribonucleoprotein A1; IDR, intrinsically disordered region; LLPS, liquid-liquid phase separation; LLPT, liquid-liquid phase transition; MALAT1, Metastasis associated lung adenocarcinoma transcript; MED1, Mediator of RNA polymerase II transcription subunit 1; NEAT1, nuclear paraspeckle assembly transcript 1; NPM, Nucleophosmin; Nups, nucleoporins; OCT4, Octamer-binding transcription factor 4; P-body, processing body; PGL3, Polygalacturonase 1 beta-like protein 3; PKA, protein kinase A; PML, promyelocytic leukemia; RARa, retinoic acid receptor-alpha; RAS, reticular activating system; RNA, Ribonucleic acid: SG, stress granule; RTK, receptor tyrosine kinase; SIM, SUMO-interacting motif; SPOP, speckle-type POZ protein; SRSF2, Serine/arginine-rich splicing factor 2; TCR, T-cell receptor; TF, transcription factor.

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Table 1. Mechanisms that control the creation of condensate, as well as its physical characteristics and content

Mechanism	Effect on condensate	Example	Reference
RNA			
Splicing determines this	Paraspeckle production requires a subdomain of the long noncoding RNA NEAT1 2, an alternate splice variant of NEAT1	Paraspeckles	10
Abundance	Condensate formation is influenced by RNA levels	PGL-3 condensates, FUS, TAF15, hnRNPA1, FIB-1, Whi3, EWS	9,11
RNA structure determines this	BNI3 and CLN3 mRNA secondary structures influence the generation of cytoplasmic Whi3 condensates with different molecular makeup	Condensates of BNI1 mRNA/ Whi3 and CLN3 mRNA/Whi3 in the fungus *Ashbyagossypii*	12
Governed via modifications	Polymethylated m6A-mRNAs serve as a scaffold for the m6A-binding protein YTHDF2 to phase separate and improves the partition of YTHDF2-m6A-mRNA condensates into SGs and P-bodies	condensates of YTHDF2-m6A-mRNA	13
Protein			
Methylation	Protein methylation interferes with condensate formation	DDX4, FUS, hnRNPA2 and condensates	14
Composition of amino acid	Saturation concentration of phase separation is governed by arginine and tyrosine arginine; glycine preserves fluidity, while glutamine and serine increase hardness	condensates of FUS family proteins	15
Repeat length	Number of heptapeptide repetitions effects condensate formation and physical characteristics	RNA Pol II-CTD condensates	16
Citrullination	FUS citrullination prevents the formation of condensate	Condensates of FUS	17
Phosphorylation	Phase separation disrupts by FUS phosphorylation	RNA Pol II-CTD and FUS condensates	18
Membrane association			
ER membrane	TIGER domains cluster to form TIS Granules	TIS granules	19
Association plasma membrane	Transmembrane protein phosphorylation Nck/ nephrin/N-WASP and Grb2/LAT/Sos1 membrane signaling clusters are formed by nephrin and LAT	LAT and nephrin clusters	20
Small molecules			
ATP	FUS phase separation and aggregation are prevented by ATP	FUS condensates	21
Poly ADP-ribose	hnRNPA1 and TDP43 condensates	Poly ADP-ribosestimulates the production of hnRNPA1 and TDP43 condensates	9

DDX4, DEAD-Box Helicase 4; EWS, Ewing sarcoma; FUS, fused in sarcoma; hnRNPA1, Heterogeneous nuclear ribonucleoprotein A1; NEAT1, nuclear paraspeckle assembly transcript 1; P-body, processing body; PGL3, Polygalacturonase 1 beta-like protein 3; RNA, Ribonucleic acid: SG, stress granule.

tion in a reversible and dynamic way. A recent study has shown that a huge number of cancer-related biological processes occur in biomolecular condensates. Therefore, scientists have begun to investigate how oncogenic alterations impact condensate biology and contribute to novel research indicating condensates impact the pharmacodynamic behavior of small-molecule medications also suggests new cancer therapy techniques.[5] In this review, we provide an overview of the methodologies used in condensate analysis to generate novel therapeutic strategies and expand our understanding of cancer. We cover many cellular condensates that have already been detected and explore the traits that they share.[6] Following that, the many ways in which condensates are altered in cancer are discussed, with a focus on how the physicochemical properties of condensates may impact dysregulated cellular functions. Condensates influence the pharmacodynamics of antineoplastic medications, and we discuss how to use this to develop a new class of cancer therapies.[7] We end by listing critical future research themes and speculating on how condensates may help cancer biology research.

Biomolecular condensates

The nucleus and mitochondria are two examples of membrane-bound cell compartments. Numerous nonmembrane condensates are also found throughout the cytoplasm and nucleus. In contrast to standard biological complexes, which have a well-clear stoichiometry, condensates are nonstoichiometric assemblies made up of biomolecules with feeble multivalent interactions.[8] As a result, they generate a tiny concentration of molecules which exchange continually with the majority phase surrounding them as shown in Table 1.[9,10–21] Simple thermodynamic models that provide insight into condensate and component part behavior can be used to describe how polymers behave in solutions. Some of these behaviors have been explained using the Flory-Huggins hypothesis, which

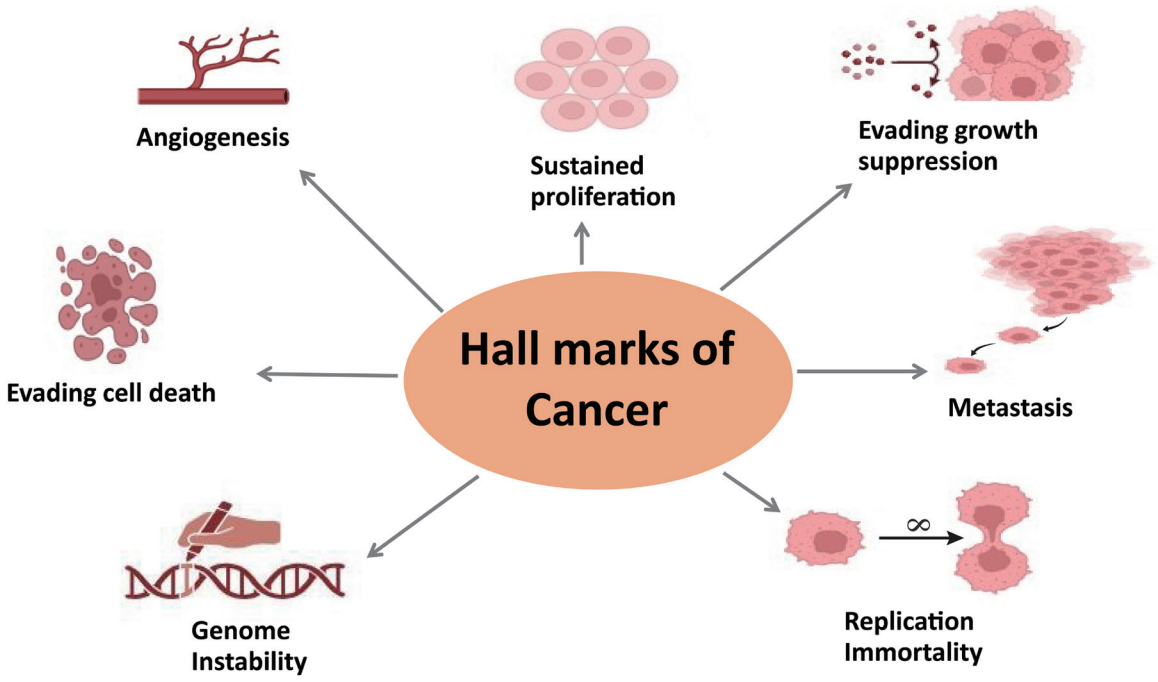

Fig. 1. Seven cancer hallmarks. Clockwise in the figure: sustained proliferation, growth suppression evasion by suppressing p53 and Rb, cell death evasion, replication immortality, genomic instability stimulation by damaging DNA, invasion of tumor and progression, and angiogenesis to form vasculature.

defines the free energy of mixing polymers in a solvent.[22] Certain weak and dynamic interactions between molecules, such as salt bridges, pi-cation, pi-pi, and hydrophobic contacts, have been proposed to be responsible for the creation of condensates and the selective division of biomolecules into condensates.[3] Condensates arise when the concentration and strength of biopolymer connections reach a critical level and the interactions overcome conflicting forces.

Cancer development and metastasis

Some rogue cells overcome the barrier of tissues and become cancer cells with the ability to proliferate, dodge growth suppression, avoid natural cell death, rearrangements of genes, travel distant organs (metastasis), and grow vascular structure to take up nutrients. The traditional hallmarks of cancer include genome mutations and alterations as shown in Figure 1. It interferes with lock-and-key type interaction of protein binding regions. Several cancer mutations happen because of the abnormal arrangement of domain structures. These disorganizations cause the production of biomolecular condensates that are involved in cellular formations. These facts have made researchers scrutinize whether any mutation causing cancer phenotypes is associated with the production and modulation of these condensates and if this could be used in cancer therapy.[23]

Localized condensates are very dynamic. They reorganize within condensates and interchange with outside molecules allowing reversible assembly/disassembly protein aggregation. Disorder in these dynamics causes diseases by altering their function and producing abnormal masses such as amyotrophic lateral sclerosis, fronto-temporal dementia, and multisystem proteins pathology, as shown in Figure 1. The production and modulation of these condensates are making researchers consider it as cancer diagnostics and therapeutics.[24] For instance, researchers are now considering biomolecular condensates instead of point mutations in tumorigenesis. This article summarizes the formation of cancer through biomolecular condensates and their role in therapeutics such as association of condensates production and pathogenesis in cancer.

Role of biomolecular condensates in proliferative signaling

In normal tissue, homeostasis is controlled by cell growth. In cancer, cells overrule this mechanism and divide profusely causing mutations and activation of receptor tyrosine kinases (RTKs). It leads to profuse cell division through downstream signaling of reticular activating system (RAS). The extracellular ligands stimulate RTKs, sequestered in the cell membrane by dimerizing them and triggering RAS proteins. During RTK activation, RTK and RAS adapters (i.e. SOS, LAT, and GRB2) separate by LLPS and SOS dwell time rise with RTK/RAS for proofreading mechanisms. This proofreading mechanism avoids SOS membrane localization for RAS activation and downstream signaling. This mechanism is disrupted by cancer-causing mutations in RTKs by LLPS of RAS signaling molecules and SOS as shown in Figure 2.

Growth suppression evaded by biomolecular condensate disassembly

Besides elevating cell growth, cancer cells overcome growth restrictions by changing endogenous tumor suppressor pathways. Speckle-type POZ protein (SPOP) is substrate adaptor for cullin3-RING ubiquitin ligase. It is the main protein in tumor suppressor pathway which captures tumor-causing substrate at ligase for ubiquitination and degradation in proteosomes for protection from tumor in healthy cells. This SPOP mutation occurs in solid mutations such as breast and prostate cancer. SPOP usually concen-

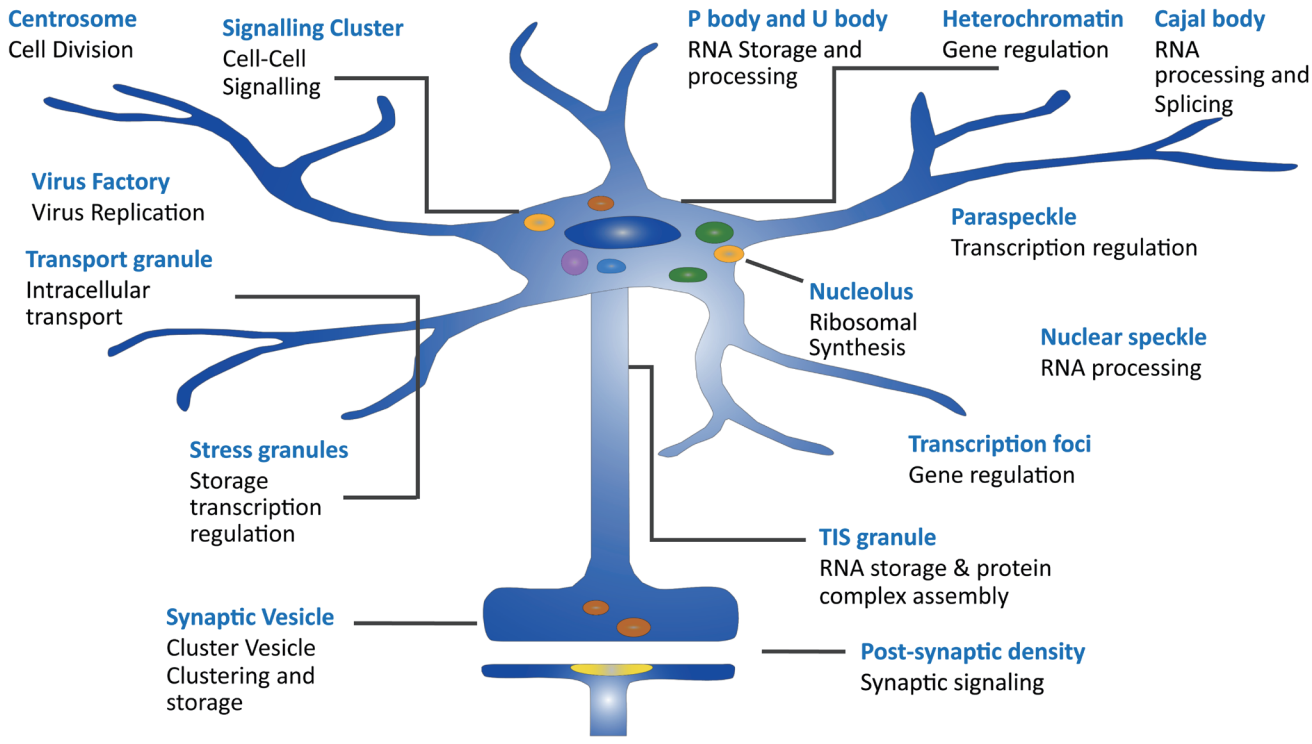

Fig. 2. Functions of biomolecular condensates.

trates at nuclear speckles, Bouchard and colleagues discovered that oligomerization and substrate interaction of SPOP enhance phase separation in SPOP-containing bodies.[25]

In cancer, this recruitment is disrupted which halts SPOP/DAXX production and concentration of DAXX. DAXX suppresses the transcription of p53 leading to cancer cell survival and SPOP mutant build-up. These events describe the association between biomolecules condensates and cancer progression and indicate of disintegration of these condensates leading to cancer.[26] Furthermore, the therapeutic applications can be determined by identifying molecular determination and signals for the localization of proteins to SPOP nuclear bodies.

Repair of foci-resistance from cell death by DNA damage

Apoptosis is a programmed mechanism that is used to remove abnormal/unwanted cells which prevents cancer formation. DNA damage, especially double-stranded nicks stimulate apoptosis.[27] TP53 is activated by DNA damage leading to Noxa and Puma BH3-onlyproteins upregulation. This causes the apoptotic cascade or cell cycle arrest which can be avoided by repairing DNA by forming membrane-free repair foci. MRE11-RAD50-NBS1 (MRN) complexes stimulate the production of repair foci. Foci are formed by recognizing double-stranded breaks of exposed DNA ends. The basal transcriptional machinery is recruited to double-stranded break via MRN complexes for transcription of long noncoding RNAs (damage-induced) which further recruits 53BP1 (damage-response factor). It stimulates molecule phase separation in repair foci that grow bigger, fused, and exchange with molecules outside the foci. In this way, cancer cells avoid DNA double-stranded nicks and cell death.[28] DNA damage is repaired by phase separation by accumulating PARP1 [pol (ADP-ribose) polymerase 1] on the double-stranded nicks which produce the long poly (ADP-ribose) chains. It assembles fused in sarcoma (FUS), RNA-binding protein, to produce foci by phase separation. Repair foci are then recruited by 53BP1 with the help of FUS to repair double-stranded nick. Therefore, dysfunctional FUS in tumor leads to apoptosis disruption. Both of the repair mechanisms involve 53BP1. A recent study revealed that repair foci have p53 and 53BP1-dependent induction of p53 is also disturbed by disrupted phase separation. It decreases p53-dependent targeted gene expression leading tumor progression.[29] These responses and induction of apoptosis/cell cycle arrest can stimulate the synthesis of repair foci in cancer. These inductions give a deeper idea of 53BP1 phase separation and gene activation through global p53.

Wild-type p53 and specific p53 mutants have been observed to undergo liquid-like phase separation independently, in a protein-autonomous manner, in addition to their functional association with phase-separated biomolecular condensates.[30] According to *in vitro* experiments, it has been observed that the fluid-like characteristics of p53 can be influenced by its interaction with ATP and nucleic acids.[31] Additionally, it has been found that the formation of droplets is disrupted by a specific mutant of p53, known as p53S392E, which mimics the effects of phosphorylation.[32] Several additional mutations frequently observed in patients have been discovered to induce the amyloidogenic properties of the protein. The formation of amyloid fibers by the mutant protein has the ability to sequester the wild-type p53 protein, resulting in a dominant-negative effect and subsequent impairment of p53 normal function.[33] Peptide inhibitors that hinder the assembly of amyloid have the ability to impede cell proliferation and reinstate the tumor-suppressing function of p53 in ovarian carcinoma cells that possess these specific mutations.[34]

Biomolecular condensate material states LLPS characteristics and LLP transition

Biological systems exhibit a remarkable degree of complexity and dynamism, prompting researchers to investigate the behavior and characteristics of biomolecular condensates as a burgeoning field of study. Biomolecular condensates refer to compartments that lack a membrane and are formed through the process of liquid-liquid phase separation (LLPS) involving biomolecules, including proteins, nucleic acids, and their complexes.[35] LLPSdescribes the phenomenon where a uniform solution spontaneously separates into two separate liquid phases. Biomolecular condensates possess the ability to undergo assembly and disassembly in response to a diverse range of cellular signals and environmental stimuli.[36] The inherent dynamism of these entities facilitates their rapid assembly and disassembly, thereby empowering cells to swiftly adapt to diverse physiological circumstances. Biomolecular condensates arise as a consequence of the phase separation of biomolecules, which is facilitated by the presence of weak, multivalent interactions such as protein-protein, protein-nucleic acid, or RNA-RNA interactions. The aforementioned interactions can be facilitated by a range of forces, such as hydrophobic interactions, electrostatic interactions, and pi-stacking interactions.[2] Biomolecular condensates frequently demonstrate characteristics reminiscent of liquids, such as the swift movement of molecules within the condensate, the alteration of shape in response to external forces, and the merging of condensates upon contact. The observed traits indicate that the condensed phase exhibits properties akin to those of a liquid droplet or a viscoelastic substance.[37] Biomolecular condensates possess the ability to demonstrate specificity and selectivity in their composition, thereby indicating that certain biomolecules display a greater affinity for the condensate while others are excluded. The selectivity observed in this context is a result of specific interactions between proteins or between proteins and RNA molecules. These interactions drive the formation of distinct condensates with varying compositions and functions within the cellular environment. Liquid-liquid phase transition (LLPT) denotes the phenomenon wherein a system undergoes a transition from one liquid phase to another, resulting in the presence of two distinct liquid phases. In the field of biomolecular condensates, occurs when biomolecules in a solution go through phase separation, which causes liquid droplets or compartments to form.[38] LLPTs are usually caused by a combination of weak multivalent interactions and changes in concentration, temperature, or pH in the environment. Through the LLPT process, biomolecules are brought together to form small droplets of liquid, or condensates. These droplets are then separated from the surrounding solution. The transition may exhibit reversibility, wherein condensates dissolve back into the solution, or irreversibility, resulting in the formation of stable condensates.[39] The investigation of LLPS and LLPT in biomolecular condensates is currently a highly active field of research. Scientists are actively studying the fundamental principles that govern the formation, properties, and functions of these phenomena. The above studies are very important because they give us a full picture of how biomolecular condensates are involved in many cellular processes, such as gene regulation, signal transduction, and stress response, among others.[40]

The method by which cells compartmentalize is known as phase separation.[2] Macromolecules like nucleic acids and proteins separate within cells into a dilute phase and a dense phase during the physiological process of phase separation, which involves a density transition. By permitting the concentration of a particular set of macromolecules and the development of various habitats, phase separation provides an appropriate architecture for controlling and compartmentalizing biochemical activity inside cells. A molecule or biomolecule can physically change states via a process known as phase transition. The cooperative transition known as phase transition is caused by the combined interactions of multiple multivalent protein modules. Although the two processes are difficult to separate, they happen in a similar state of matter, whereas phase transition is irreversible.[41] Many different forms of material states can occur from phase separation and transition, including hydrogels (solid-gels, liquid-gels), liquid droplets, amyloids, and aggregates in cells. The capacity of liquids to agglomerate, leak, and fuse in liquid assemblies is a common emergent property. Through phase separation, the droplet formation is frequently reversible, and molecules in moving droplets are extraordinarily mobile both inside the dense phase and among the light and dense phases.[42] The biomolecule condensates may also transform into crystal patterns through crystal-like states arrayed, as well as hydrogels formed of amyloid-like filaments, which typically grow indefinitely. Protein sequences are assumed to be the main force behind these transitions because specialized protein sequences have changed to utilize liquid-to-solid changes for functional transitions. When proteins with solid-like states are present, protein combinations that might be highly organized fibrils of amyloid or disordered gels that mimic crystals are commonly encountered in cells under stress. An increasing corpus of studies has linked sickness to these protein solid-like states formed by phase transitions.[9]

Abnormal phase transitions and phase separations in cancer

Biomolecular condensate changes have been associated with cancer and neurodegeneration. As a result of abnormal gene amplifications, chromosomal translocations, and missense mutations, the external signals and cellular environment are disturbed.[35] Cells then gain the capacity to proliferate unrestrained because of oncogene or tumor suppressor gene activity dysregulation caused by altered gene expression patterns.[3] Several clinical conditions can cause transition or phase separation in tumor tissue, which can affect the state by regulating the affinities and concentrating the core protein and interactions of scaffold RNAs and/or proteins. Recent studies show that the phase separation of cancer-associated proteins, which are involved in signal transduction, translation, epigenetic protein degradation, and transcriptional regulation, plays a critical role in cancer formation.[43]

Biomolecular condensates and cancer

Changes in biomolecular condensates, according to growing studies, are connected to both cancer and dementia. Cancer is characterized by unrestrained cell proliferation, which is determined by oncogene or tumor suppressor gene activity that is dysregulated because of genomic instability, incorrect protein degradation, or gene expression.[44] Furthermore, when malignant cells metastasize, they are extremely resistant to severe conditions (such as chemotherapy) and readily adapt to new environments. These disease phenotypes are linked to the actions of various condensates, which are just now being studied in connection to cancer.

Bodies of promyelocytic leukemia

Promyelocytic leukemia (PML) bodies have dynamic nuclear structures that play crucial roles in apoptosis, transcription, cell cycle regulation, and DNA damage response.[45] PML, the protein scaffold of PML bodies, contains the RBCC domain, which promotes self-oligomerization. SUMO-interacting motif (SIM) and

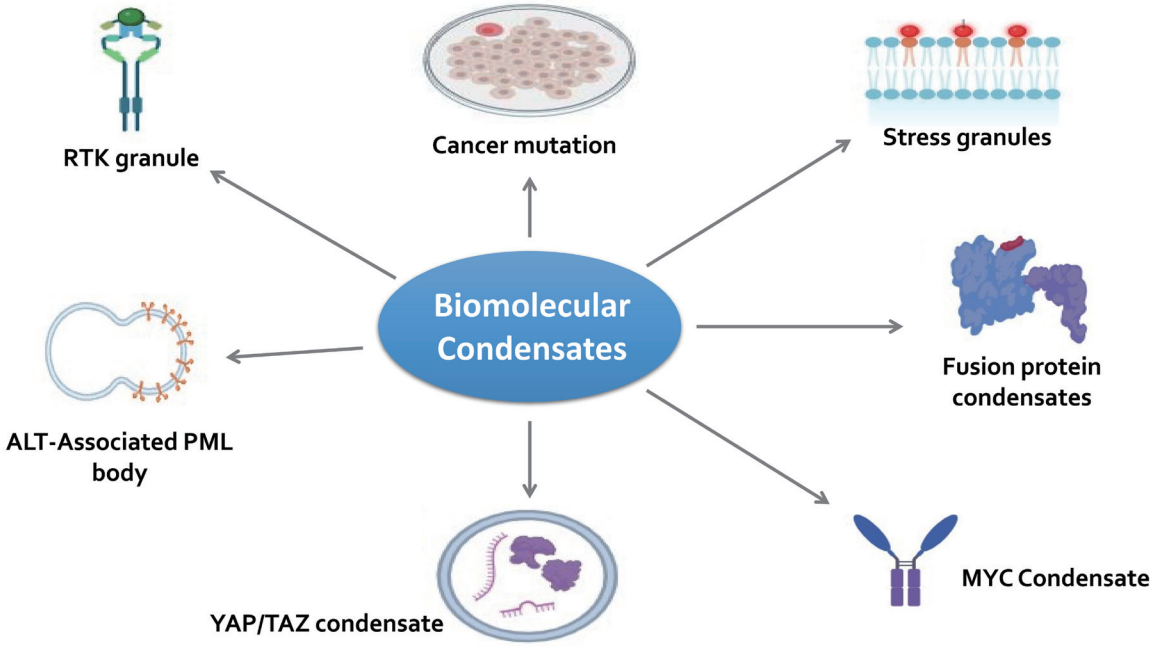

Fig. 3. Examples of biomolecular condensates in the literature that are involved in cancer genesis and development. ATL, alternative telomere lengthening; RTK, receptor tyrosine kinase; PML, promyelocytic leukemia.

SUMOylation sites at the PML C-terminus aid in compartment formation. Arrays of SIM and SUMO drive the generation of liquid-like condensate with physical properties and tunable composition, emphasizing the role of the PML C-terminus in PML body formation. PML bodies have been related to cancer in a variety of ways as shown in Figure 3. A chromosomal rearrangement causes the N-terminal region and the full-length retinoic acid receptor-alpha (RARα) of PML to fuse. The absence of SUMOylation sites and C-terminal SIM in the PML-RARα fusion protein is likely to decrease PML phase separation. PML bodies are broken by the PML-RARα fusion protein, resulting in dispersed micro speckles. The composition of PML microspeckles has been changed, and transcriptional coactivators have been removed.[46] The recruitment of DNA repair proteins like 53BP1 is also delayed, resulting in a delay in ATM activation. These PML-RARα-induced compositional changes are thought to induce cancer progression by causing genomic instability. In certain sarcomas, PML bodies induce telomere extension in the absence of telomerase. Rad and bloom helicase are utilized in the so-called alternative telomere lengthening (referred to as ATL) mechanism to synthesize mitotic DNA, which lengthens telomeres. SUMOylation is required for aberrant PML body construction and Bloom helicase recruitment in several alternative telomere lengthening associated PML body elements, including SIM domains or both. Recent studies back up this model. ATL-associated PML bodies cluster telomeres such as liquid condensates through SIM-SUMO-dependent phase separation. Furthermore, PML bodies concentrate the ATPase MORC3, which has been associated with several cancers, in an SUMOylation-dependent manner. Even while PML bodies can be dysregulated in several ways in cancer, it is unknown how these faults cause cancer on their own.[47]

Transcription sites

Transcriptional regulation is often disrupted in cancer development. Super-enhancers have massive enhancer clusters thickly packed with transcriptional machinery.[48] Super-enhancers are supposed to promote cancer progression by enhancing the transcriptional activity of recognized oncogenes. Recent studies have demonstrated that RNA polymerase II may phase separate *in vitro* from transcriptional coactivators and transcription factors (TFs) containing intrinsically disordered regions (IDRs) such as the mediator-associated BRD4 and mediator complex. Furthermore, these proteins create liquid, such as condensates, around super-enhancer target genes, enhancing their expression. These discoveries provide provision for the concept that super-enhancers operate as reservoirs for active RNA polymerase II and phase-separated transcription machinery concentrators. The carcinogenic action of abnormal TFs created during chromosomal translocation proceedings seems to need phase separation as well.[49] Childhood connective tissue cancers, such as Ewing sarcoma and myxoid liposarcoma are caused by FUS and Ewing sarcoma (EWS) protein. The DNA-binding areas of TFs like CHOP and FLI1 are linked to the N-terminal IDRs of FUS and EWS, which are responsible for phase separation in these cancers. According to this study, EWS-FLI1, and FUS-CHOP may phase separate *in vitro* due to their IDRs, which indorse transcriptional activity. FUS phase separation enhances transcriptional activity via the N-terminal IDR. The IDR of the EWS-FLI fusion protein prolongs TF residence times at the GGAA microsatellites and is needed for the enlistment of chromatin remodeling complexes to the microsatellites, that have commonly originated in oncogenes.[50] Fusion proteins have been exposed to changed RNA splicing as well as transcriptional activation, suggesting that they most likely cause cancer in several ways.

Dysregulation of condensate in cancer

Malignant tumor cells develop mutations that impair transcription, chromatin structure, proliferative signaling, and other condensate-

Table 2. Dysregulated cellular processes in cancer that are associated with condensates

Protein	Dysregulated process	Biological role
EWS	Transcription	In Ewing's sarcoma, joined to FLI
MED1	Transcription	In cancer, the coactivator is overexpressed and altered
OCT4	Transcription	Master TF regulator of cell identity
CDK7	Transcription	Overexpressed and targeted kinase in cancer
MALAT1	Epigenetic regulation	In cancer, lncRNA is dysregulated
BRD4	Epigenetic regulation	In cancer, chromatin factors are increased and fused
Polycomb	Epigenetic regulation	In cancer, the gene silencing complex is changed
PKA	Cell signaling	Taking part in oncogenic signaling
B-catenin	Cell signaling	Wnt factor is the cause of colon cancer
TCR	Cell signaling	Tumor immunity mediator
NUPs	Nuclear transport	In cancer, nucleoporin is dysregulated
Cgas	Immune signaling	Participates in cancer immunity
SRSF2	Splicing	Dysfunction in myelodysplasia
NPM1	Ribosome biosynthesis	Mutated nucleolar factor in leukemia
RAD52	DNA repair	Tumor suppressor and HR factor
CDC6/ ORC/CDT1	DNA replication	Dysregulated replication
Atg1	Autophagy	Involved in cancer macromolecule recycling

Atg1, Autophagy-related 1; BRD4, bromodomain containing 4; CDK7, Cyclin-Dependent Kinase 7; cGAS, cyclic GMP-AMP synthase; CDC6, cell division cycle; EWS, Ewing sarcoma; MED1, Mediator of RNA polymerase II transcription subunit 1; MALAT1, Metastasis associated lung adenocarcinoma transcript; Nups, nucleoporins; NPM, Nucleophosmin; OCT4, Octamer-binding transcription factor 4; PKA, protein kinase A; SRSF2, Serine/arginine-rich splicing factor 2; TCR, T-cell receptor.

mediated biological activities. Despite the fact that research on condensates in tumor cells is still in its infancy, noteworthy examples of dysregulated condensates have already been documented. Furthermore, given the known effects of cancer mutations on the concentration and modification of regulatory biomolecules, condensate dysregulation is likely to be a frequent hallmark of cancer cells (Table 2).

Analyzing common oncogenic events' mechanisms

Condensate models might be used to reassess the processes involved in common oncogenic events, perhaps leading to new understanding and treatment strategies. Dysregulated signaling, metabolism, transcription, cellular connections, DNA damage, immune systems, angiogenesis, and autophagy are all common events.[51] Several signaling pathways that govern cell division, growth, and motility in cancer are changed because of signaling proteins being overexpressed, mutated, or fused. This can cause the route to be over or underactivated. Many proteins participating in tumor-related signaling pathways are discovered to condense, regulating the pathway's output. When ligand-bound membrane receptors bind and alter adaptor proteins, RAS is activated. These proteins subsequently form condensates on the cell membrane, compartmentalizing proteins and activating RAS.[52] Actin polymerization is sped up by the same adaptor protein condensates. A protein kinase A (PKA) fusion oncoprotein hinders condensation and causes incorrect signaling, whereas cAMP-dependent PKA compartmentalizes this key signaling molecule via cAMP-dependent condensate production. Nuclear signaling proteins like Wnt, STAT, and TGF-β collaborate with transcriptional coactivators to trigger their reference genes, which explains why their effects change depending on the cell type.[53] When all the pieces are put together, a novel picture of signaling that involves several signaling proteins achieving selectivity by generating various cellular compartments that have been disturbed in cancer may be developing.[53] Transcriptional dysregulation is frequent in tumor cells, and the discovery that gene regulation necessitates the creation of transcriptional condensates should lead to unique insights about unregulated regulatory mechanisms. MYC overexpression is common in different metastatic processes and may result in longer-lasting transcriptional condensates on oncogenes.[54]

Classified gene activity

Gene activation is analogous to the multicomponent, multistep biochemical formation of signaling clusters on the plasma membrane, in which local reactant retention in a condensate limits diffusion away from the signaling area and improves the pathway specific activity.[55] Similarly, portions of the gene-control system are retained near to the sites where genes are active. The RNA Pol II molecule regionally concentrated number is directly related to the amount of RNA molecules that are transcribed, and the inhibiting gene-control machinery clustering link in lower gene expression.[56] These local high concentrations functionally affect gene expression. These high local concentrations are caused by dynamic multivalent interactions between cofactors and RNA Pol II, as well as other condensate components produced at specific genomic loci. Cell-free nuclear extracts and other cofactors are partitioned in coactivator protein condensates made from RNA Pol II.[56] The observation that RNA Pol II condensate clustering in

cell nuclei and formation *in vitro* are both dependent on carboxy-terminal domain(CTD)length shows that the dynamic multivalent interactions described *in vitro* are required for the enzyme's ability to cluster. RNA Pol II is compartmentalized in the synthetic condensates formed in cells by light-induced protein domain clustering, which also boosts local RNA synthesis. Only a handful of the protein domains studied could enhance transcription, illustrating the value of condensate makeup on function, but all tested protein domains produced light-induced condensates.[57]

Multiple interactions between the genome and transcriptional machinery

The formation of transcriptional condensates is the outcome of a concerted effort of multivalent contacts between gene-control apparatus components and their interactions with the genome. RNA Pol II, regulatory enzymes, transcriptional coactivators, chromatin-linked cofactors, and DNA-binding TFs can interact with different sections of the genome as well as with one another in a variety of ways. Chromatin has numerous coordinated intra- and intermolecular interactions that result in a diverse spectrum of higher-order forms.[58] This creates at least two layers of related interactions, those involving the genome within a chromatin framework and those involving locally localized components. These two layers can collaborate to design the generation of condensates at specific genomic loci and to select the makeup of the condensed components. Condensates can form in a variety of places and with a variety of components, depending on how interactions change at either layer.[59]

Concentrated component multivalent interactions

Gene regulatory systems, signaling molecules, and cell type-defining molecules can all interact in various ways. The classic gene regulation paradigm places a strong focus on structured fundamental interactions that are generated in complexes that are firm in diluted cell-free lysates.[60] However, early protein sequencing studies revealed that stable connections with certain stoichiometries were insufficient to capture all elements of gene regulation. Because of the low complexity and inherent disorder of the CTD of RNA Pol II and the activation domains of TFs, Paul Sigler wrote an article requesting that gene activity be reorganized. Although IDRs and low complexity have been found as popular characteristics of transcription-related components, the gene-control system contains various other kinds of multivalency. Because of the abundance of annotated RNA/DNA/protein-protein interaction domains, the generality of modification-regulated reader domains, and the ability of numerous factors to achieve reversible oligomerization, most parts of the gene-control machinery may interact in higher-order systems of multivalent interactions.[61] The interaction of these two levels boosts the localized production of condensates. If the related factors are configured in such a manner that certain genomic loci become important components of the condensate, the condensate will only form at the relevant locus when the right complement of factors is present. If the constituents are preceding their saturation concentration, they will spontaneously form condensates across the nucleoplasm and finally combine at the appropriate chromosomal location.[62] The DNA-localized condensates and nucleolus are assumed to have formed because of this type of nucleation effect. This is consistent with more modern hypotheses that localized induction regulates condensate size and growth, but diffusive capture explains how condensates nucleated through designed seeds of variable valences form. These kinds of localized induction of condensates provide a method for precisely, rapidly, and powerfully moving transcriptional origins to new areas of the genome and activating novel gene programs.[63]

Gene program changes during disease: implications

In sickness, the similar multivalent connections that govern and precisely activate certain gene sets and construct mental gene programs can be hijacked and dysregulated. Neurodegeneration, developmental disorders, and cancer have all been related to multivalent interactions connecting the gene-control mechanisms that are disturbed, increased, or create novel multivalent interactions.[64] Numerous neurodegenerative illnesses are distinguished by recurrent expansions that produce aberrant condensates. Intracellular inclusions formed by glutamine repeat expansions in the Huntington's disease gene can sequester a variety of transcriptional machinery pieces, including the well-known coactivator CREB binding protein.

Superenhancement and cancer gene modification

Many pathways are involved in the aberrant proliferation of superenhancers in cancer cells. Several well-known examples of genome anomalies, such as translocation and focused amplification, may now be conceived of as superenhancer misdirection and malformation. For example, in various cancer types, distinct superenhancer-associated pathways are exploited to activate the well-known oncogene MYC.[65] In lymphomas and myelomas, chromosome translocation between the immunoglobulin locus and the MYC locus produces constitutive expression by putting immunoglobulin superenhancers adjacent to MYC. Similar situations, known as enhancer takeover, can occur in compact tumors like neuroblastomas. Furthermore, MYC is activated in a variety of cancer forms, including endometrial carcinoma, lung adenocarcinoma, acute myeloid leukemia, and acute lymphoid leukemia, by localized amplification of super enhancers located at the MYC gene 3′ end (AML). This is performed by chromatin loop rewiring and super-enhancer amplification specific to each cell type.[66] Epstein-Barr virus and human papillomavirus are two carcinogenic viral DNAs whose genomic integration might be used to create ectopic (super-)enhancers and unique chromatin loops that activate oncogenes.[67] Noncoding mutations are caused by dysregulation of superenhancers in some cancer types. In roughly 5.1% of severe T cell lymphoblastic leukemias, minor insertions (3–19 base pairs) are identified about 8.5 kb upstream of the start site for transcription of TAL1. These insertions operate as MYB oncoprotein recognition sites, resulting in the ectopic development of a superenhancer by obliging binding of additional TAL1 and TFs transcription initiation. This provides researchers with a good model for investigating by what means noncoding transformations result in the formation of ectopic superenhancers.[68] Unlike common mutations in cancer-associated gene promoters such as TERT, the functional relevance of enhancer mutations is unclear.

Biomolecular condensates and therapeutic targeting

Biomolecular condensates have garnered considerable interest within the realm of biology and are presently being investigated as prospective targets for therapeutic interventions. Biomolecular condensates that form in unusual ways or do not work right have been linked to a number of human diseases, such as neuro-

degenerative diseases, cancer, and metabolic disorders.[69] Instances of condensates have been discovered to contain proteins that are associated with diseases, such as amyloid beta in Alzheimer's disease or RNA-binding proteins in specific neurodegenerative diseases. Targeting disease-associated condensates could result in potential therapeutic interventions. One way to treat biomolecular condensates is to stop or change how they form and work.[23] The goal of stopping condensate assembly can be reached by making small molecules or peptides that are designed to interfere with the interactions that make this process happen. Disrupting the condensate may be able to restore normal cellular function and lessen disease pathology. Biomolecular condensates exhibit a high degree of dynamism, and their dynamic behaviors is of paramount importance in various cellular phenomena. Therapeutic approaches may encompass the manipulation of condensate dynamics in order to reinstate regular cellular functionality. The manipulation of condensate assembly, disassembly, or maturation kinetics can be accomplished by employing small molecules, peptides, or other interventions.[70] Condensates frequently serve as central nodes for molecular interactions, facilitating the assembly of proteins, nucleic acids, and other biomolecules. A potential therapeutic strategy involves the selective targeting of specific interactions within condensates. One potential strategy to impede the aggregation and formation of toxic species is to interfere with the interactions among disease-associated proteins within a condensate. An additional approach for therapeutic intervention entails the manipulation of synthetic condensates to selectively isolate or regulate distinct cellular constituents.[71] Synthetic condensates possess the capability to replicate the characteristics of naturally occurring biomolecular condensates and facilitate manipulation of the spatial and temporal arrangement of cellular mechanisms. The aforementioned approach has potential for various applications, including drug delivery, enzyme compartmentalization, and synthetic biology.[22] It is noteworthy to acknowledge that the domain of biomolecular condensates and their therapeutic targeting remains relatively nascent, prompting extensive ongoing investigations aimed at comprehensively elucidating their functions and potential applications. Nevertheless, the capacity to intervene in the formation and operation of biomolecular condensates presents intriguing prospects for the advancement of innovative therapeutic approaches targeting various diseases.[72] In contrast to conventional enhancer-associated genes, superenhancer-associated gene transcription is significantly dependent on transcriptional regulators like BRD4 and mediator and is particularly downregulated via the CDK7 inhibitor THZ1 and the BET-bromodomain inhibitor JQ1.[73] The superenhancer and transcriptional condensate theories, which also partially explain the molecular basis of some cancer cell types of extraordinary sensitivity to transcriptional disruption, strengthen the reasoning for treating transcription addiction and transcriptional reliance. However, because normal cells employ super enhancer transcriptional programs, it is critical to explore the origins of increased vulnerability of cancer cells to disruption, as well as techniques to specifically target transcriptional dependency. Recent research, unrelated to the pharmaceutical aim, discovered that minormolecule tumor medicines like as tamoxifen, mitoxantrone, and cisplatin concentrate in certain protein condensates.[27] These findings have the potential to be generalized to better comprehend the link between the activities, the dynamics of condensates in tumor cells and resistance of anticancer medications. Furthermore, given that a condensate-hardening medication has recently been demonstrated to inhibit in vivo replication of the human respiratory syncytial virus, the pharmacological approach for direct targeting of condensate dynamics may be appealing for cancer therapy.[74]

Drug action in cancerand condensates

Condensate biology in tumor cells provides a chance to develop novel treatment hypotheses.[27] Certain medications now appear to concentrate in certain condensates because of physicochemical interactions unrelated to the medication's affinity for its target. Furthermore, several drugs seem to selectively interrupt condensates, allowing for the modification of compartments that alter disease pathogenesis. Drugs which constrain post translational modifying enzymes may affect condensate behaviors and may be utilized to change compartmentalized carcinogenic activity in condensates.[75] The intracellular transport of medications is frequently overlooked in traditional pharmacological studies. Recent research, however, reveals that medication partitioning into certain nonmembrane condensate compartments inside cells may impact therapy effectiveness and drug resistance in cancer. Given that many normally used drug targets are now known to be found in condensates, effective drugs should be able to penetrate these compartments and interact with their appropriate targets.[27] Because of their affinity and selectivity for the separated molecules, drugs may concentrate in condensates. As a result, drug molecules can use condensate properties to concentrate in the same compartment as their target, regardless of the factors affecting target interaction.[27] There is evidence that this behaviors can reduce the efficacy of medications. Drugs' ability to partition into certain condensates may be anticipated to boost their pharmacological effects. Cisplatin, a normally used antineoplastic intercalating medication, is concentrated up to 601 times in transcriptional condensates, platinizing the super-enhancer DNA present in the condensates.[76] The diagram shows how condensate partitioning can increase a drug's pharmacological activity while also increasing target specificity for medicines that might then interact with a wider range of substrates. Because some of the greatest super-enhancers reside near driving oncogenes, it is probable that cisplatin is especially effective at inactivating the oncogenes buried in these condensates. Drug resistance might be expected if drug condensate partitioning properties contribute to their efficacy. Tamoxifen is effective in treating breast cancer with estrogen receptor(ER)positivity. Tamoxifen resistance may be caused by ER changes that reduce MED1 overexpression and drug affinity, the molecular basis of which was previously unknown. Tamoxifen, which also preferentially divides into transcriptional condensates and competes for estrogen binding, pushes ER out of the condensate and prevents it from developing in an estrogen-dependent manner.[76] The number of transcriptional condensates increased because of MED1 overexpression, which diluted the concentration of tamoxifen in the condensate and reduced its capacity to evict ER.[77] These findings demonstrate that condensate changes can impact drug resistance in tumor cells. Nonetheless, recent chemical advances provide an opportunity for pharmaceutical IDRs, potentially disturbing some condensates. Small medicines target both the MYC IDR and transcription initiation complex components. Small chemicals that bind the IDR of the p27 oncogene can interfere with its ability to engage with cell cycle machinery.[27] The low affinity of drug-IDR interactions can be compensated for by knowing how to design drugs to preferentially concentrate in specific condensates.

Hence, it is evident that the domain of drug discovery, regardless of its focus on condensate or noncondensate targets, would greatly profit from the utilization of methodologies that assess the interactions between drugs and condensates. Possible methods that could be considered relevant include using microscopy-based techniques to measure the localization of fluorescently labeled drug analogues in intact cells or in collections of reconstituted condensates.[27] This

approach is akin to using enzyme panels to investigate the selectivity of potential drugs within a specific enzymatic class. It is possible that a drug could distribute into one or multiple condensates or occupy different cellular volumes, although to varying degrees. Ultimately, the presence of condensates can potentially affect the accessibility of potential pharmaceuticals, specifically RNA therapeutics, similar to the inherent RNA storage capabilities associated with stress-induced phase separation. Due to the continuous interaction between condensate constituents and the cellular environment, the likelihood of partitioning within condensates can lead to unforeseen effects on the pharmacokinetic behaviors of drugs residing in condensates.[78] The concepts presented in this study are applicable to both small molecules and RNA therapeutics and have the potential to establish a new framework centred around condensates. This framework could enhance our understanding and facilitate the development of drugs that are both effective and safe.

Impact on cancer diagnosis and screening

Biomolecular condensates possess the capacity to exert influence on cancer diagnosis and screening through various mechanisms. Biomolecular condensates have the potential to function as a reservoir of biomarkers for the purpose of diagnosing and screening cancer. The condensates have the potential to encapsulate distinct proteins, nucleic acids, or complexes that are linked to the initiation or advancement of cancer.[27] By looking at the structure and properties of biomolecular condensates, scientists can find biomarkers that have not been found before. These biomarkers could be used to find cancer early or keep track of how a disease is getting worse. Cancer diagnosis commonly employs conventional techniques that necessitate the use of invasive tissue biopsies. Biomolecular condensates have the potential to enable liquid biopsies, which involve the analysis of specific biomarkers found in biofluids such as blood or urine for cancer detection and characterization.[79] The identification of condensates or their constituents in biofluids has the potential to offer a less invasive and more readily available method for cancer screening and monitoring. Advanced imaging techniques, such as fluorescence microscopy or super-resolution imaging, can be employed to visualize biomolecular condensates. The use of these imaging methodologies enables researchers to investigate the spatial arrangement and temporal changes of condensates within cells or tissues. The potential exists for the development of imaging-based diagnostic tools capable of early-stage tumor detection or cancer subtype characterization through the visualization of cancer-associated condensates.[80] Understanding how biomolecular condensates work in the field of cancer biology could make it easier to find new therapeutic targets. The dysregulation or dysfunction of condensates has been identified as a potential contributing factor to the formation and progression of tumors. The development of therapies that can disrupt the oncogenic signaling pathways linked to the formation and function of condensates is a potential avenue for investigation, which could involve targeting specific condensates or their components. Biomolecular condensates have the ability to manifest distinct compositions and functional characteristics that can differ among individuals or types of cancer.[71] Personalized medicine approaches can be developed by characterizing the distinct condensates that are linked to various cancer subtypes or individual patients. This approach may entail customizing treatments according to the specific condensates that are present, thereby resulting in therapies that are more efficient and focused.

Nuclear bodies without membranes have been used by histopathologists for decades to determine the type and grade of cancer cells in tissue biopsies.[81] As an example, large nucleoli are indicative of large-cell lung cancer, whereas PML bodies are indicative of acute promyelocytic leukemia. The properties and components of many biomolecular condensates change as a result of cancer-related alterations, and These modifications are now possibly used for the differentiation of cancer types.[3] Further, scientists have found that different proteins related to cancer such as catenin, TAZ, and YAP, are stable in biomolecular condenses, and that markers allowing visualization could be used to identify tumors.[4] Studies of biomolecular condensates suggest that their size may influence their functional activities, and that biomolecular condensate physical features might aid in cancer detection. The field of biomolecular condensates in cancer diagnosis and screening is currently undergoing development. However, these structures hold considerable promise in offering valuable insights and tools for the early detection of cancer, enhanced diagnostic precision, and personalized treatment approaches in cancer care.[23] Continuing investigations in this field seek to elucidate the precise functions and ramifications of biomolecular condensates in the realm of cancer biology.

Targeted cancer therapy using biomolecular condensates

The utilization of biomolecular condensates in targeted cancer therapy represents a burgeoning strategy that capitalizes on the distinctive characteristics of these formations to formulate treatments that are both more efficacious and precise. Biomolecular condensates possess the ability to selectively accumulate particular molecules or signaling constituents that play a vital role in the survival, proliferation, or immune system evasion of cancer cells.[82] Through the identification and precise targeting of these constituents present in condensates, there exists the potential to disrupt oncogenic signaling pathways or impede crucial cellular mechanisms in a cancer cell-specific manner, thereby mitigating any unintended effects on normal cells. Dysfunctional condensates, as well as condensates harboring disease-associated proteins, are implicated in the pathogenesis and advancement of cancer.[83] A potential therapeutic approach involves directing efforts toward modulating the formation or stability of these oncogenic condensates. The interference of small molecules, peptides, or nucleic acids can be strategically employed to disrupt the interactions that facilitate condensate assembly. This disruption ultimately impairs the condensate and subsequently hampers the functional capabilities of cancer cells. The inherent dynamic properties exhibited by biomolecular condensates render them highly appealing targets for therapeutic intervention. By manipulating the dynamics of condensates, it is conceivable to perturb their functionality or modify their composition in a manner that specifically impacts cancerous cells.[84] The objective can be accomplished by selectively focusing on particular enzymes, signaling molecules, or post translational modifications that play a role in the process of condensate formation or dissolution. Biomolecular condensates possess the potential to be deliberately designed or harnessed as vehicles for the precise and directed administration of pharmaceutical agents.[85] By integrating therapeutic agents into condensates or engineering synthetic condensates with tailored characteristics, it becomes feasible to directly administer medications to cancer cells or targeted tumor areas. This methodology has the potential to augment the effectiveness of pharmaceuticals, mitigate the adverse effects on the body as a whole, and enhance the accuracy of therapeutic interventions for cancer. Biomolecular condensates offer a promising framework

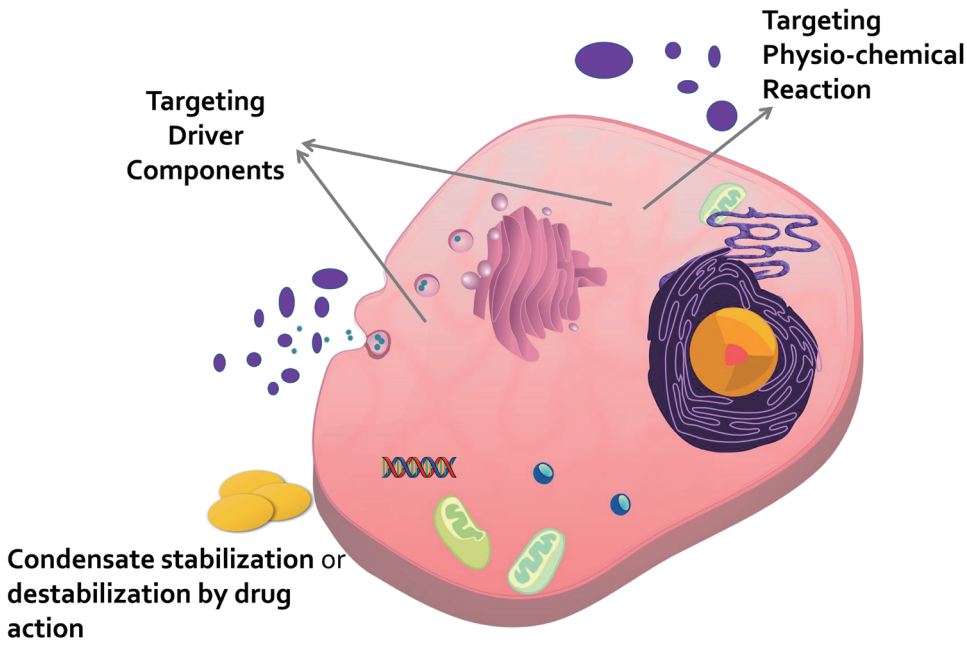

Fig. 4. Expanded view of the cellular environment demonstrating how some proteins (blue dots) and nucleic acids (purple bent lines) partition into a biomolecular condensate that can be degraded (purple circle). Targeted biomolecular condensate can be achieved in three ways. (a) (Proteins and nucleic acids) are downregulated or inactivated, and biomolecular condensates formed. (b) The physicochemical interactions (black arrows) are important for the creation of biomolecular condensates between proteins and nucleic acid. (c) Medication that partitions into a biomolecular condensate can either increase or diminish condensate activity.

for the implementation of combination therapies, wherein various therapeutic approaches are employed in a concurrent or sequential manner to address distinct facets of cancer biology.[4] The potential to achieve synergistic effects and overcome drug resistance mechanisms exists through the integration of various strategies, including the disruption of oncogenic condensates, modulation of condensate dynamics, and targeted therapy delivery.

The molecular distinctions between normal and malignant cells are used in targeted cancer therapy to remove cancer cells selectively. A mutation that causes cancer may affect an RNA or protein to be overexpressed or downregulated due to a mutation in the protein or RNA.[86] Cancer targeted therapies, as opposed to traditional cancer treatments, like chemotherapy, can be less toxic to patients. Several successful drugs target the HER-2 overexpression found in some stomach and breast cancers, as well as BRAF mutations in many melanoma cases. In these targeted therapies, portions of the protein are disrupted by small molecules that bind and break traditional lock-and-key interactions within those proteins. Biomolecular condensates can be targeted in cancer cells by focusing on their driver components.[6]

An example of such a strategy is targeting poly ADP-ribose polymerase, PARP1, which forms DNA repair foci containing FUS. It has been shown that PARP1 inhibitors interfere with DNA repair processes and therefore have been approved by the United States Food and Drug Administration as a treatment for malignancies caused by the BRCA gene mutation, such as BRCA-positive breast cancer. Biotin ligase may also be used to identify and target drivers linked with other cancer-related biomolecular condensates.

Interfering with the physicochemical characteristics of condensates is another way to disrupt them for cancer therapy as shown in Figure 4. Because weak hydrophobic interactions are common in condensates, 1,6-hexanediol, which breaks those bonds, is an excellent solvent for eliminating them. So, scientists are now considering another method of manipulating cancer-related biomolecular condensates by adding medications that directly partition into the condensate to change its properties. When specific molecular interactions such as anion or cation interactions drive condensate formation, a list of medications that are most likely to partition into a certain condensate type can be narrowed down.[7] Further, the production of condensate via weak, multivalent connections implies several synergistic drug treatments may be needed rather than one treatment approach to disrupt these connections.

Conclusions

Phase separation can be used to create biomolecular condensates that can be used to study cancer genesis and development, making this a very exciting time in cancer research. In two dimensional cancer cell models, new findings show that biomolecular condensates play a role in cancer progression even when co-occurrence does not imply causation. Many previously unexplained pathways to cancer initiation may now be understood due to protein-based phase separation, and more study into this mechanism might lead to the development of condensate-based cancer treatments. Mechanisms of phase separation that drive cancer development may be influenced by the tumor microenvironment, including mechanical stimuli, vascularization, and other factors. It will be vital in the future to determine the effectiveness of new condensate-targeting therapies by studying condensates in the natural cancer environment using *in situ* imaging methods such as intravital microscopy. Smart microscopy is also a useful technology because it employs the ability to evaluate, interpret, and respond to many forms of data via computer-assisted imaging. Achieving success in these endeavors will not be easy, but a close collaboration between micros-

copists, cancer researchers, cell biologists, computer scientists, and biophysicists might be feasible.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Concept and design of the study (QM, AS, MZS, RP, NH, MM, MWA, AW, EA), manuscript drafting (QM, AS, MZS, RP, NH, MM), data analysis (QM, AS, MZS, RP, NH, MM, MWA, AW, EA), manuscript revision (QM, AS, MZS, RP, NH, MM, MWA, AW, EA), and manuscript formatting (QM, AS, MZS). All authors made a significant contribution to this study and have approved the final manuscript.

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