Protein phase separation and its role in tumorigenesis

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Abstract Cancer is a disease characterized by uncontrolled cell proliferation, but the precise pathological mechanisms underlying tumorigenesis often remain to be elucidated. In recent years, condensates formed by phase separation have emerged as a new principle governing the organization and functional regulation of cells. Increasing evidence links cancer-related mutations to aberrantly altered condensate assembly, suggesting that condensates play a key role in tumorigenesis. In this review, we summarize and discuss the latest progress on the formation, regulation, and function of condensates. Special emphasis is given to emerging evidence regarding the link between condensates and the initiation and progression of cancers.

Introduction

Cancer is a complex disease characterized by loss of control over cell growth, proliferation, and death. In addition to sustaining proliferative signaling and an unlimited replicative potential, many cancers cells acquire the ability to evade growth suppressors, resist cell death, induce angiogenesis, and activate invasion and metastasis (Hanahan and Weinberg, 2011). Moreover, cancer cells interact with surrounding stromal cell and remodel the extracellular matrix to construct specific tumor microenvironments that support tumor growth and progression (Egeblad et al., 2010; Kessenbrock et al., 2010; Lu et al., 2012). Of note, genomic instability raises the possibility to introduce genetic mutations, thus it is often crucial for tumorigenesis (Jeggo et al., 2016). The genetic mutations in cancer-related genes frequently lead to the dysregulation of oncogene activity or they inhibit the activity of a tumor suppressor gene, which then drive the oncogenic process forward. Although significant progress has been made in identifying driver mutations and associated oncogenic processes and pathways, the precise pathological mechanisms underlying tumorigenesis are still largely unclear. Increasing evidence now suggests links between oncogenic processes and the process of condensate assembly by phase separation.

In order to achieve spatiotemporal control over complex biochemical reactions, cells must organize proteins and other macromolecules into subcellular compartments. In addition to the classical membrane-bound organelles, such as the endoplasmic reticulum and Golgi apparatus, cells possess various membraneless compartments, including nucleoli, Cajal bodies, and promyelocytic leukemia protein (PML) bodies in the nucleus (Sawyer et al., 2019) as well as stress granules (SGs) or processing bodies (P bodies) in the cytoplasm (Banani et al., 2017; Jain et al., 2016; Sachdev et al., 2019; Wheeler et al., 2016). Recent studies suggest that the assembly of these membraneless...
compartments is often driven by a physical process known as phase separation (Banani et al., 2017; Boeynaems et al., 2018).

The term biomolecular condensates is now widely used to refer to membraneless intracellular compartments and assemblies (Banani et al., 2017; Shin and Brangwynne, 2017). In contrast to other types of assemblies, condensates have no fixed stoichiometry, they are able to concentrate molecules, and frequently form through phase separation. Phase separation is a process by which a well-mixed solution of macromolecules such as proteins or nucleic acids spontaneously separates into two phases: a dense and a dilute phase. The dense phase has liquid-like properties and enriches certain macromolecules while others are depleted, allowing the dense phase to function as a compartment (Alberti et al., 2019). After their formation by phase separation, liquid condensates can mature into more solid-like states. They can thus adopt a range of different material properties, from dynamic liquid-like droplets to non-dynamic gels and solid amyloids (Woodruff et al., 2018).

Proper condensate formation is essential for homeostasis as it provides cells with spatiotemporal control over protein function. Under some conditions, such as chronic stress, aging, or disease-associated mutations, abnormal or aberrant condensates can form. These condensates have compositions or properties that deviate from those of condensates formed under physiological conditions. Early research focused on cataracts, showing that phase separation of crystallin proteins in the eye lens causes opacification and thus visual impairment (Siezen and Benedek, 1985; Siezen et al., 1985; Tanaka et al., 1977). Excess accumulation of aberrant crystallin condensates during ageing was proposed to drive the formation of cataracts (Benedek, 1997). Recent studies showed that such aberrant phase transitions are also involved in neurodegenerative diseases, affecting neuronal proteins such as Fused in Sarcoma (FUS) in Amyotrophic Lateral Sclerosis (ALS) (Patel et al., 2015), Tau in Alzheimer’s disease (AD) (Wegmann et al., 2018) and huntingtin exon 1 in Huntington’s disease (HD) (Peskett et al., 2018). For example, patient mutations in FUS were shown to accelerate a transition of reconstituted FUS droplets from a liquid to a solid-like state (Patel et al., 2015). This hardening of FUS condensates is associated with the formation of supramolecular FUS fibrils that have properties of amyloid-like aggregates. Besides neurodegenerative disorders, current research further suggests emerging roles of aberrant condensates in cancer (Alberti and Dormann, 2019; Spannl et al., 2019).

This review summarizes our current understanding and recent findings regarding the formation, regulation, and function of biomolecular condensates and highlights their emerging roles in the pathogenesis of cancer.

**Molecular features driving protein condensate formation**

Recent work shows that phase separation requires the establishment of a network of interactions through multivalent protein molecules. These multivalent interactions are promoted by proteins containing multiple-folded modular domains or intrinsically disordered regions (IDRs) (Gomes and Shorter, 2019) or oligomerization domains (Dao et al., 2018; Figure 1). Another class of phase-separating proteins containing polymerizing domains such as the DIX domain, which assemble into filaments that are crosslinked into three-dimensional condensates (Bienz, 2020).

Phase separation by proteins with folded modular domains was first established for two interacting proteins containing multiple copies of the SRC homology 3 (SH3) domains or the SH3 ligand proline-rich motifs (PRM) (Li et al., 2012). The study further demonstrated condensate formation by a three-component system containing the proteins nephrin, NCK, and neural Wiskott-Aldrich syndrome protein (N-WASP), and showed that phase separation by multiple SH3 containing protein NCK and multiple PRM containing protein N-WASP promoted Arp2/3-mediated actin assembly (Li et al., 2012). Multivalent interactions among multi-domain proteins were also shown to underlie the formation of membrane-associated phase-separated signaling clusters by T cell receptor (TCR) components (Ditlev et al., 2019; Huang et al., 2019; Su et al., 2016). The folded modular domains are often connected by intrinsically disordered linker sequences that determine the material properties of the formed condensates (Harmon et al., 2017).

Another class of proteins that has been implicated as drivers of condensate assembly is the class of proteins containing IDRs. Although IDRs lack a defined three-dimensional structure, they often
harbor multiple short amino acid motifs that mediate weak interactions. These motifs have been called stickers because of their adhesive properties (Martin et al., 2020; Wang et al., 2018a). The driving forces for sticker-mediated interactions are \( \pi-\pi \) stacking, cation-\( \pi \) interactions, or charge-charge interactions (Nott et al., 2015; Vernon et al., 2018). The stickers within IDRs are connected by short sequences that are referred to as spacers. Spacers can affect the material properties of condensates. For instance, mutations in spacer residues in FUS changed the material properties of FUS condensates: glycine residues enhanced droplet fluidity, whereas glutamine and serine residues promoted hardening (Wang et al., 2018a).

IDRs that are enriched for only a few amino acids are referred to as low-complexity domains (LCDs) (Boeynaems et al., 2018). A subset of LCDs contains polar, uncharged amino acid residues, such as glutamine (Gln), asparagine (Asn), serine (Ser), or tyrosine (Tyr), and shows a compositional similarity to yeast prion domains (Alberti et al., 2009). These LCDs are referred to as prion-like domains (PLDs) and often found in RNA-binding proteins (RBPs). Proteins with PLDs have initially gained attention because of their ability to assemble into self-templating protein aggregates. These aggregates can have infectious properties, as they can spread between cells, tissues and sometimes individuals (Chakravarty and Jarosz, 2018). More recent studies suggest that PLDs can also act as drivers of condensate assembly. For example, the isolated PLDs of FUS (Burke et al., 2015; Murray et al., 2017), heterogeneous nuclear ribonucleoprotein A1 (hnRNPA1) (Kim et al., 2013) and flowering control locus A (FCA) (Fang et al., 2019) can assemble into condensates at high concentrations in vitro. However, whether PLDs drive phase separation by promoting homotypic PLD-PLD interactions in the cellular context is still unclear. In fact, evidence is emerging that PLDs often have to interact heterotypically with other IDRs during condensate assembly or they modulate the phase behavior of a protein by affecting its overall solubility. For example, phase separation of the FUS proteins was shown to require collective interactions among tyrosine residues in the PLD and arginine residues in the RNA-binding domain (RBD) (Wang et al., 2018a). Moreover, phase
separation of the PLD-containing poly(A)-binding protein (Pab1 in yeast) is not mediated by its PLD, but by the RNA recognition motifs (RRMs). Rather, the PLD modulates condensate formation by the Pab1 RRM domains under heat shock condition (Riback et al., 2017). Thus, PLDs may not only be drivers but also modifiers of protein phase behavior (Franzmann and Alberti, 2019).

Finally, multivalent interactions can also arise from oligomerization of folded domains (Bienz, 2020; Dao et al., 2018; Fiedler et al., 2011; Madrzak et al., 2015; Schwarz-Romond et al., 2007). For example, UBQLN2, an adaptor protein required for cellular protein quality control, oligomerizes via the folded STI1-II domain and this promotes UBQLN2 phase separation (Dao et al., 2018).

One important question in the context of this review is whether proteins encoded by cancer-related genes (such as tumor-suppressors or oncogenes) can undergo the above-mentioned multivalent interactions and whether these interactions are perturbed in tumorigenesis. On the one hand, cancer-related mutations could disrupt the assembly of functional condensates by tumor-suppressors, thus contributing to the initiation of cancers. On the other hand, cancer-related mutations could promote the assembly of aberrant condensates by oncoproteins, which might stimulate tumorigenesis.

Regulation of condensate assembly

Great advances have been made in our understanding of the regulation of condensate assembly. Accumulating evidence suggests that phase separation is often regulated by post-translational modifications (PTMs) (Figure 1). PTMs, including phosphorylation, acetylation, arginine methylation, and SUMOylation, have been implicated in the assembly and disassembly of condensates, as well as the regulation of their material properties (Hofweber and Dormann, 2019). For example, recent studies showed that lysine acetylation regulates phase separation of the microtubule-binding protein Tau (Carlomagno et al., 2017; Fereon et al., 2018). Moreover, phosphorylation of serine residues or methylation of arginine residues can suppress phase separation of FUS (Hofweber et al., 2018; Monahan et al., 2017; Qamar et al., 2018). These PTMs may play an important role in the formation of pathological FUS aggregates, because many disease-associated mutations in FUS are adjacent to or directly affect amino acids that are modified by PTMs. Importantly, PTMs change not only the driving forces for condensate assembly, but also the selective partitioning of a protein into a condensate. For example, phosphorylation of the RNA polymerase II (Pol II) C-terminal domain prevents the partitioning of Pol II into transcription initiation condensates but it promotes partitioning into splicing condensates (Guo et al., 2019). SUMOylation is another additional PTM that promotes phase separation. For instance, sumoylation of SOP-2 results in an increase in both size and number of condensates in comparison to the unmodified protein (Qu et al., 2020). PTM could change the physicochemical properties of the modified amino acids, which could directly affect multivalent interactions. For instance, phosphorylation attaches a phosphate group to a hydroxyl group of an amino acid side chain, thus introducing a charge that may allow this amino acid to participate in long-range electrostatic interactions.

There now is also increasing evidence for enzymes that specifically regulate the assembly of condensates via PTMs. One example is the dual specificity tyrosine-phosphorylation regulated kinase 3 (DYRK3). DYRK3 localizes to condensates and phosphorylates multiple serine and threonine residues within IDR (Rai et al., 2018). DYRK3 kinase activity is essential for regulating disassembly of SG during stress recovery (Wippich et al., 2013), and it acts as a dissolvase of many additional membraneless condensates during mitosis (Rai et al., 2018). Many cancer-associated proteins localize to condensates and their localization and activity are regulated by PTMs, suggesting that aberrant condensate regulation by PTMs may be an important pathomechanism underlying cancer.

Another way to regulate the phase behavior of a protein is by regulating the availability of a ligand. For instance, RNA is a ligand of many phase-separating RBPs and it often regulates RBP phase behavior. The effect of RNA on RBP phase separation is concentration-dependent: low amounts of RNA often promote phase separation, whereas high amounts can inhibit it (Maharana et al., 2018). For some RBPs, this effect is independent of RNA sequence, while for others specific RNAs sequences are required (Langdon et al., 2018). Thus, it is conceivable that changes in RNA levels in cancer cells could affect the assembly of condensates. This is particularly true for non-coding RNAs (ncRNA), which are often required for the formation of RNA-protein condensates. One example is ncRNA NEAT1, which is essential for paraspeckle assembly.
More generally, ncRNAs play important regulatory roles in different cancer-related cellular processes and pathways (Anastasiadou et al., 2018). It will be interesting to determine whether altered expression patterns of ncRNAs as they are often observed during tumorigenesis mediate their effects via changes in condensate formation.

Another ligand that has been implicated in condensate regulation is polyADP ribose (PAR). PAR chains are chemically similar to RNA and they promote the condensation of FUS at low concentrations in vitro (Patel et al., 2015). Synthesis of PAR chains at the DNA sites is also required for the recruitment of FUS and the formation of DNA damage condensates in cells (Altmeyer et al., 2015; Patel et al., 2015). These data suggest that the availability of PAR regulates condensation of FUS and potentially many other PAR-binding proteins in cells. Critically, aberrant PAR assembly has been linked to many forms of cancer (Hou et al., 2019).

Studies have also implicated post-transcriptional modifications of RNAs in the regulation of phase separation (Figure 1). N6-methyladenosine (m6A) is one of the most prevalent types of mRNA modification in cells. Phase separation of the m6A-binding proteins YTHDF1, YTHDF2, and YTHDF3 was markedly enhanced by multiple m6A modifications on mRNA (Gao et al., 2019; Ries et al., 2019). Moreover, m6A modification of mRNA further enhances mRNA partitioning into different condensates. Emerging evidence also suggests that dysregulation of RNA modifications is closely associated with various human cancers (Huang et al., 2020). Notably, the expression of some oncogenic or tumor-suppressive transcripts is regulated by RNA modifications. One possibility emerging from these considerations is that these RNA modifications lead to aberrant condensate assembly and this could result in alterations of oncogene or tumor suppressor gene expression.

Functions of condensates

Although the functional spectrum of phase separation has not been fully explored, several key functions of condensates have been revealed. For instance, it has been proposed that phase separation of proteins can be used to sense changes in the environment and that the formed condensates then mount adequate adaptive responses. Indeed, the phase behavior of many proteins is very sensitive to small changes in physical-chemical conditions. For example, phase separation of Pab1 has been observed in response to thermal stress and changes in cytosolic pH (Riback et al., 2017). In addition, condensation of Sup35 is induced by an energy depletion-induced acidification of the cytosol (Franzmann et al., 2018). Another example is the RNA-binding protein Pbp1, which senses the cellular redox state and forms condensates under reducing conditions (Kato et al., 2019). In all these cases, the formed condensates play important roles in cellular stress response and adaptation. For example, Pbp1 condensates are able to sequester and inactivate TORC1, thus coupling the metabolic redox state to TOR signaling (Kato et al., 2019).

Condensates have also been shown to accelerate biochemical reaction kinetics by increasing the specific activity of reactants inside condensates. For example, the formation of miRNA-induced silencing complex (miRISC) condensates is associated with increased deadenylation activity (Sheu-Gruttadauria and MacRae, 2018). Some condensates can also sequester proteins or nucleic acids to store them for later use or downregulate enzymatic reactions. For instance, P bodies have been proposed to be reservoirs for translationally repressed mRNAs (Hubstenberger et al., 2017).

Recent work suggests that condensates can also be used to regulate gene expression. For example, super-enhancers, which are clusters of several hundred enhancers, are bound cooperatively by transcription factors to drive robust transcription of genes for defining cell identity (Hnisz et al., 2013). Several lines of evidence suggest that transcriptional coactivators and the mediator complex form condensates at super-enhancers, which may help to compartmentalize and concentrate the transcription apparatus (Boij et al., 2018; Cho et al., 2018; Sabari et al., 2018). Notably, Michnick and colleagues demonstrated that condensation by endocytic proteins can deform the plasma membrane and drive membrane invagination (Michnick et al., 2019). Very recent evidence also suggests that phase separation can buffer protein concentration noise (Klosin et al., 2020). Moreover, condensate formation has been linked to cargo sorting. In chloroplasts, the interaction among STT complex sorting factors and Tat substrate protein induces the formation of condensates, which is critical for Tat protein transport across the stroma to thylakoid membranes (Ouyang et al., 2020).

Lastly, condensates may work as compartments for protein quality control. Under stress conditions, some misfolded proteins accumulate in the granular component (GC) phase of the nucleolus, which prevents irreversible aggregation of misfolded proteins, facilitating refolding during recovery.
from stress (Frottin et al., 2019; Mediani et al., 2019). Phase separation has also been shown to be critical for the formation of proteasome-containing foci and the assembly of the autophagosome (Fujioka et al., 2020; Yasuda et al., 2020).

In summary, phase separation appears to touch on almost any fundamental process in cells. However, whether and how condensates affect the onset, progression, metastasis and drug resistance of different cancers is still largely unclear. Given the importance of condensates for normal cellular physiology, it seems reasonable to assume that aberrant condensate assembly is a frequent occurrence in tumorigenesis.

Condensate assembly by cancer-related proteins

In recent years, some oncogenic processes have been linked to condensates formed by cancer-related proteins (Table 1). These cancer-related proteins are involved in the degradation of oncogenic substrates, maintenance of genomic stability, transcriptional regulation and oncogenic signaling pathways, protein quality control and degradation.

**Speckle-type POZ protein (SPOP) condensates in degradation of oncogenic substrates**

The tumor suppressor SPOP functions as a substrate adaptor of the cullin3 (CUL3)-RING ubiquitin ligase complex, which is frequently mutated in prostate cancer (Barbieri et al., 2012; Le Gallo et al., 2012). Tumor-associated missense mutations in the substrate recognition domain of SPOP disrupt substrate binding and ubiquitination, leading to the accumulation of oncogenic substrates, such as steroid receptor coactivator (SRC3), c-MYC (Geng et al., 2017) and death-domain-associated protein (DAXX) (Kwon et al., 2006). Bouchard et al. found that multivalent interactions

| Table 1. Cancer-related proteins involved in formation and regulation of condensates. |
|-----------------------------------------------|-----------------|-----------------|-----------------|
| Biomolecular condensates | Cancer-related protein or RNA molecular | Verification of phase behavior | References |
| SPOP/DAXX bodies | SPOP | Yes | Bouchard et al., 2018 |
| DNA repair condensates | 53BP1 | Yes | Kilic et al., 2019 |
| DNA damage condensates | PARP-1 | Yes | Altmeyer et al., 2015; Patel et al., 2015 |
| DNA damage condensates | FUS | Yes | Altmeyer et al., 2015; Patel et al., 2015 |
| DNA damage condensates | EWS | Yes | Altmeyer et al., 2015; Patel et al., 2015 |
| DNA damage condensates | TAF15 | Yes | Altmeyer et al., 2015; Patel et al., 2015 |
| Transcriptional condensates | EWS-FLI1 | Predicted | Boulay et al., 2017 |
| Transcriptional condensates | YAP | Yes | Cai et al., 2019 |
| Transcriptional condensates | TAZ | Yes | Lu et al., 2020 |
| PRC1 condensates | CBX2 | Yes | Plys et al., 2019; Tatavosian et al., 2019 |
| Transcriptional condensates | β-catenin | Yes | Zamudio et al., 2019 |
| p62 bodies | p62 | Yes | Cloer et al., 2018; Sun et al., 2018; Zaffagnini et al., 2018 |
| Stress granules | KRAS | Unconfirmed | Grabocka and Bar-Sagi, 2016 |
| Stress granules | DDX3X | Yes (only in vitro) | Hondele et al., 2019; Valentin-Vega et al., 2016 |
| Stress granules | YB-1 | Unconfirmed | Somasekharan et al., 2015 |
| PML NBs | PML/RARA | Unconfirmed | de Thé et al., 2017; Dos Santos et al., 2013 |
| Paraspeckles | NEAT1_2 | Yes | Yamazaki et al., 2018 |
between SPOP oligomers and motifs in oncogenic substrate proteins drive phase separation in vitro. The same multivalent interactions are required for SPOP co-localization with oncogenic substrates in nuclear condensates. Importantly, substrate proteins such as DAXX appear to be ubiquitylated inside the condensates in a CUL3-dependent manner. Consequently, cancer-associated SPOP mutations disrupt SPOP interaction with the substrates, causing a failure to form condensates, ubiquitylate the substrates and promote their degradation (Bouchard et al., 2018; Table 1 and Figure 2). These findings reveal a direct link between the aberrant phase behavior of a tumor suppressor protein and its downstream effects on oncogenic proteins.

**Condensates in the maintenance of genomic stability**

Genomic instability usually arises from disruption of DNA repair and DNA damage response (DDR). Recent studies indicate that condensate assembly is linked to the maintenance of genomic stability. For instance, poly (ADP-ribose) polymerase 1 (PARP1) is one abundantly expressed member of the poly (ADP-ribose) polymerase (PARP) family. PARP1 synthesizes long PAR chains at DNA damage sites and plays a key role in DDR and PARP-1 has been ascribed diverse pro- or anti-tumorigenic roles (Weaver and Yang, 2013). The formation of PAR chains was shown to initiate the formation of DNA damage condensates via recruitment and assembly of FET proteins (FUS, EWS, and TAF15) (Altmyer et al., 2015; Patel et al., 2015; Table 1; Figure 3).

Additional studies have provided evidence for the involvement of condensates in maintaining genome stability. As one of the main mediators of the DNA damage response (DDR), p53-binding protein 1 (53BP1) acts as a recruitment platform for other DDR proteins (Mirza-Aghazadeh-Attari et al., 2019). 53BP1 protein was first discovered as a binding partner of the tumor suppressor proteins.
p53 (Iwabuchi et al., 1994; Vousden and Prives, 2009) and plays a direct role in p53 target gene expression, driving a cell toward an anti- or pro-tumorigenic cell fate (Cuella-Martin et al., 2016). Loss of 53BP1 has been associated with poor survival, inhibition of apoptosis, and cancer cell proliferation in colorectal cancer (Bi et al., 2015).

Recently, 53BP1 was reported to drive the formation of a DNA damage repair compartment through phase separation in response to DNA damage, which was promoted by damage-induced long non-coding RNAs (dlincRNA) synthesized at DNA double-strand breaks (DSBs) (Kilic et al., 2019; Pessina et al., 2019; Table 1 and Figure 3). Blocking dlincRNA transcription or inhibiting DNA repair condensate assembly through the chemical 1,6-hexanediol both led to a reduction in the efficiency of DNA repair, suggesting that 53BP1 repair condensates are required for DSB repair (Pessina et al., 2019). Importantly, these DNA damage repair condensates recruit downstream effectors, such as p53 and the p53 co-activator USP28, which stabilizes p53 upon DNA damage. As a consequence, disruption of DNA damage repair compartments led to impaired p53 induction and diminished p53 target gene expression as well as cell cycle arrest (Kilic et al., 2019; Figure 2). Therefore, aberrant DNA damage repair condensate assembly because of alterations in 53BP1 expression is likely to affect the central tumor suppressor protein p53 and thus the expression of many cancer-linked genes.

Intriguingly, 53BP1 is excluded from above-mentioned DNA damage condensates (Altmeyer et al., 2015). Given that 53BP1 is recruited to DNA damage sites later (Aleksandrov et al., 2018), this suggests that cells can assemble DNA damage condensates with different compositions and presumably also functions (Altmeyer et al., 2015). These studies suggest...
that condensate assembly is intimately linked to the maintenance of genome stability. Indeed, cancer-associated translocations in FET proteins appear to impair the cellular ability to interact with PAR chains, which may affect the assembly of condensates at DNA damage sites and thus undermine genome integrity (Altmeyer et al., 2015).

**Transcriptional condensates in regulation of oncogenic transcriptional programs**

Transcriptional dysregulation is a key feature of cancer (Figure 2). Recent studies have implicated condensates in the regulation of oncogenic transcription programs.

EWS-FL1 is an oncogenic transcription factor that plays key roles in Ewing’s sarcoma tumorigenesis (Delattre et al., 1992). This oncogenic factor is generated by a chromosomal translocation, in which a large portion of the prion-like domain (PLD) of EWSR1 is fused to the transcription factor FL1 in Ewing’s sarcoma (Tan and Manley, 2009; Toretsky and Wright, 2014). Rivera, Kadoch, and colleagues demonstrated that the translocated PLD was essential for recruiting the BRG1/BRM-associated factor (BAF) chromatin-remodeling complex to tumor-specific enhancers, activating an aberrant transcriptional cascades that is underlying Ewing sarcoma progression (Boulay et al., 2017; Table 1). Moreover, EWS-FL1 forms numerous nuclear foci, whereas FL1 exhibits a more diffuse pattern (Boulay et al., 2017). The hypothesis was put forward that this transcriptional program is driven by aberrant condensate formation of EWS-FL1. In addition, the PLDs of the related proteins FUS and TAF15 are often fused to transcription factors through chromosomal translocations in liposarcoma and acute leukemia, respectively (Tan and Manley, 2009). It is possible that translocated FUS and TAF15 PLDs promote the assembly of additional aberrant condensates at enhancers and promotors, thus driving abnormal tumorigenic transcriptional programs.

Evidence is now also emerging that master transcription factors and the mediator coactivator use their disordered regions to form condensates at super-enhancers, which recruit Pol II to activate transcription sites (Boija et al., 2018; Cho et al., 2018; Sabari et al., 2018). In some cancer cells, genomic alterations promote the formation of super-enhancers on oncogenes, which promote oncogenic transcriptional programs (Sengupta and George, 2017). Thus, aberrant condensation at super-enhancers might be a general mechanism that cancer cells use to sustain high oncogene expression levels.

One example of a transcription regulator implicated in the assembly of a transcriptional condensates and super-enhancer formation is the transcriptional co-activator Yes-associated protein (YAP) and its paralog transcriptional coactivator with PDZ-binding motif (TAZ). YAP and TAZ have been linked to tissue growth, stem cell activity, and tumorigenesis (Moya and Halder, 2019). They bind to a subset of highly active enhancers and super-enhancers to drive the transcription of cell proliferation genes (Galli et al., 2015). Consequently, YAP and TAZ are pervasively activated in cancers (Zanconato et al., 2016; Zanconato et al., 2019). However, YAP and TAZ not only promote tumorigenesis but also have tumor-suppressive functions. For example, activation of YAP in tumor-surrounding cells can suppress liver cancer in mice (Moya et al., 2019).

Recent evidence shows that YAP and TAZ assemble into condensates in vitro and in vivo (Cai et al., 2019; Lu et al., 2020; Table 1 and Figure 4). In cells, YAP assembles into condensates at super-enhancer regions and these nuclear condensates contain TAZ but also the transcription factor TEAD1. These condensates appear to recruit RNA polymerase II to trigger the transcription of proliferative genes (Cai et al., 2019). Furthermore, YAP and TAZ mutants defective in condensate formation, displayed reduced transcriptional activity, suggesting that transcriptional activity of YAP and TAZ is associated with their ability to assemble into condensates (Cai et al., 2019; Lu et al., 2020). Importantly, TAZ-containing condensates are negatively regulated by Hippo signaling and sensitive to mechanical signals (Lu et al., 2020). In agreement with this, a growing body of evidence suggests that YAP and TAZ could function as mechanotransducers, which detect a broad range of mechanical signals and convert them into cell-specific transcriptional responses (Panciera et al., 2017). In this way, YAP and TAZ could work as signaling hubs of the tumor microenvironment. For instance, YAP and TAZ expressed in cancer cells could sense physical cues from the surrounding microenvironment and respond by driving transcriptional programs that modify the composition and physical properties of the tumor microenvironment, thus promoting tumor development (Zanconato et al., 2019). Notably, in contrast to its diffuse localization in normal breast tissue, TAZ forms nuclear condensates in breast cancer tissue (Lu et al., 2020). Therefore, it would be interesting to investigate how the
Figure 4. YAP/TAZ condensates in the regulation of transcription. (a) YAP forms nuclear condensates during osmotic stress. These YAP condensates co-localize with TAZ and TEAD and recruit RNA Pol II to trigger transcription of YAP target gene. (b) TAZ also forms nuclear condensates which compartmentalize TEAD4, BRD4 and MED1, RNAPII, and the transcription elongation factor CDK9 for transcription. These condensates are negatively regulated by Hippo signaling and sensitive to mechanical signals and oncogenic signals from around the environment.
mechanical properties of tumor microenvironments affect YAP or TAZ phase separation and whether YAP/TAZ-driven tumorigenesis involves condensation in cancer cells.

Condensates have not only been implicated in transcription activation, but also in transcription repression via epigenetic changes of chromatin. Indeed, epigenetic alterations in chromatin are well known to drive tumorigenesis (Flavahan et al., 2017). The first condensates that have been linked to gene silencing by heterochromatin formation are assembled from heterochromatin protein 1α (HP1α) (Larson et al., 2017; Strom et al., 2017). Another set of factors that is essential for the establishment and maintenance of facultative heterochromatin are the polycomb repressive complexes (PRC) (Tatavosian et al., 2019). These complexes also have oncogenic functions or they act as tumor suppressors, depending on the specific cancer type (Koppens and van Lohuizen, 2016). Chromobox 2 (CBX2), one subunit of Polycomb repressive complex 1 (PRC1), was recently shown to assemble into condensates that recruited the core subunits of the CBX2-PRC1 complex and directed the condensation of DNA and nucleosomes (Plys et al., 2019; Tatavosian et al., 2019; Table 1). These studies suggest that PRC1 condensates contribute to chromatin compaction, thus repressing the expression of PRC1 target genes. It will be intriguing to determine whether other epigenetic regulatory factors control the formation of gene regulatory condensates and whether impairment of epigenetic condensate control results in disease.

**Signaling condensates in the regulation of signaling transduction**

Signaling pathways play an essential role in regulating gene expression. Many membrane receptors and downstream signaling molecules assemble into two-dimensional (2D) clusters upon initiation of signaling (Bienz, 2014; Wu, 2013). Well-known examples are T cell receptor signaling clusters (Ditlev et al., 2019; Huang et al., 2019; Su et al., 2016) and clusters associated with adhesion receptors (Banjade and Rosen, 2014; Beutel et al., 2019; Case et al., 2019a; Li et al., 2012). The assembly of clusters on membranes is often important for the activation of downstream signaling effectors. For instance, phase separation of phosphorylated nephrin receptor together with its downstream effector molecules NCK and N-WASP promotes actin assembly. This enhancement of actin assembly was linked to the longer membrane dwell time of N-WASP in these clusters. More generally, the dwell time of cluster components was dependent on the composition of the cluster and the concentration of the cluster constituents (Case et al., 2019b), suggesting that there is an optimal condensate composition to reach full activation. Similarly, signaling condensates formed from the phosphorylated scaffold protein linker for activation of T cells (LAT) and its two adaptors growth factor receptor-bound protein 2 (GRB2) and Son of Sevenless homolog (SOS) promoted Ras activation by increasing membrane dwell time of SOS (Huang et al., 2019). Both cases suggest that increased dwell time of signaling effectors by condensation may be a general mechanism to fully activate a signaling pathway while at the same time ensuring signaling specificity.

Notably, GRB2, SOS, and some Ras isoforms are involved in downstream signaling effectors of epidermal growth factor receptor (EGFR). EGFR is frequently mutated or overexpressed in cancer cells (Sigismund et al., 2018) and abnormal activation of Ras in the EGFR pathway results in pro-tumorigenic proliferation and migration (Martinelli et al., 2017). Given that activation of EGFR is associated with membrane-bound clusters (Liang et al., 2018), it is very likely that EGFR condensate formation regulates pro-tumorigenic activation of Ras.

Components of other oncogenic signaling pathways appear to be able to form 2D clusters at the plasma membrane (Figure 2). One example is the Wnt/β-catenin signaling pathway, which governs numerous cell fate decisions during animal development, and is deregulated in many cancers in the colon, gastric, breast, and liver (Sanchez-Vega et al., 2018; Schafer and Peifer, 2019; Zhan et al., 2017). In the absence of a Wnt signal, β-catenin is phosphorylated by a destruction complex, which is composed of Axin, tumor suppressor adenomatous polyposis coli (APC) and some additional components. Phosphorylated β-catenin is recognized by the Cullin-based E3 Ligase SCFβTrCP, promoting the degradation of β-catenin by the proteasome (Stamos and Weis, 2013). In the presence of a Wnt signal, the activity of the destruction complex is repressed. Importantly, binding of Wnt to its cell surface receptors triggers the assembly of a signalosome, which is mediated by the Dishevelled (Dvl) protein (Bienz, 2020; Bilic et al., 2007; Fiedler et al., 2011; Gammons et al., 2016; Madrzak et al., 2015; Schwarz-Romond et al., 2007). The Axin complex is subsequently recruited to the signalosome, which destabilizes the destruction complex and blocks the phosphorylation of β-catenin (Stamos et al., 2014).
Increasing evidence suggests that both the destruction complex and Wnt signalosomes have properties of condensates (Schaefer and Peifer, 2019; Figure 5). In the absence of Wnt, Axin is found in cytoplasmic puncta which also contain APC as well as other destruction complex components (Schaefer et al., 2018). By contrast, in cells receiving Wnt signals, Dvl and Axin co-localize in puncta close to the plasma membrane (Cliffe et al., 2003). The assemblies grow by fusion (Kunttas-Tatli et al., 2014; Schwarz-Romond et al., 2005) and FRAP analysis further revealed that Dvl, Axin, and APC inside the puncta exchange dynamically (Pronobis et al., 2015; Schwarz-Romond et al., 2005). Importantly, the signaling activity of Dvl is strongly correlated with the ability to form these puncta (Schwarz-Romond et al., 2005). Similarly, puncta assembly is critical for destruction complex function (Faux et al., 2008; Schaefer and Peifer, 2019). APC is required for puncta assembly and cooperates with Axin to ensure efficient β-catenin destruction (Pronobis et al., 2015). Strikingly, mutations in APC, initiate >80% of colon cancers (Zhang and Shay, 2017). The precise mechanism of how these mutations promote tumorigenesis remains to be determined. There are numbers of additional urgent questions here, for example, how APC mutations affect the assembly and

**Figure 5.** Signaling-associated condensates that may form in the Wnt/β-catenin signaling pathway. (Left) Wnt signaling triggers the assembly of 2D membrane clusters containing the receptors Frizzled and LRP as well as Dvl, Axin, and other components of destruction complex, thus disrupting destruction complex regulating degradation of β-catenin. Consequently, β-catenin accumulates and enters the nucleus, where it may localize to condensates at super-enhancers to elicit the transcription of target genes. (Right) In the absence of a Wnt ligand, Axin, and APC assemble into a destruction complex condensate that recruits kinases such as GSK3 and casein kinase I (CKI). This in turn promotes phosphorylation of β-catenin and subsequent ubiquitin-mediated degradation of β-catenin by the proteasome. Ubiquitination of phosphorylated β-catenin is mediated by the ubiquitin ligase SCFβTrCP.
properties of destruction complex condensates and the relationship between aberrant destruction complex condensates and the initiation of cancers.

Recent work has implicated condensates in another aspect of the Wnt signaling pathway. In the presence of Wnt, β-catenin accumulates in the nucleus and activates the transcription of Wnt target genes (Gammons and Bienz, 2018). Reports showed that β-catenin uses its IDRs to selectively partition into transcriptional condensates at super-enhancers (Zamudio et al., 2019; Table 1). Some cancer-related mutations in β-catenin prevent phosphorylation-dependent ubiquitination of β-catenin, leading to accumulation of β-catenin in the nucleus (Kim and Jeong, 2019). This suggests that in cancer cells, β-catenin may form aberrant nuclear condensates because of elevated protein levels and that this may promote tumorigenesis through widespread changes in gene expression.

Protein condensates associated with protein quality control and degradation

The multi-domain adaptor protein p62/SQSTM1 (p62) is defined by its role in selective autophagy, a lysosomal degradation pathway that clears misfolded proteins and damaged organelles to maintain cellular homeostasis. The regulation of p62 is complex as p62 acts as a receptor targeting cargo for degradation but it is also itself degraded by autophagy (Sánchez-Martín et al., 2019). However, when autophagy is impaired, p62 accumulates and can activate downstream signaling pathways including mTORC1, NF-κB, and NRF2, influencing nutrient sensing, inflammation and the oxidative stress response, which may all affect tumorigenesis (Moscat et al., 2016; Sánchez-Martín et al., 2019). For instance, accumulation of p62 has been shown to accelerate the development of pancreatic cancer through activating NF-κB and NRF2 signaling (Duran et al., 2008; Ling et al., 2012; Todoric et al., 2017). Similarly, p62 accumulation in chronically damaged liver cells activates NRF2 and promotes the development of hepatocellular carcinoma (Nakagawa et al., 2014; Umemura et al., 2016).

Although the mechanism of how p62 accumulates is not fully understood, p62 is often present in cellular inclusion bodies. Inclusion bodies in the brain include Lewy bodies, neurofibrillary tangles, and huntingtin aggregates; inclusion bodies in the liver include Mallory-Denk bodies, intracytoplasmic hyaline bodies, and α1 antitrypsin aggregates (Komatsu et al., 2007; Yamamoto and Simon- sen, 2011). Intriguingly, recent studies have shown that p62 assembles together with ubiquitinated proteins into condensates (Table 1), and the formed condensates are subsequently engulfed by autophagosomes and degraded (Sun et al., 2018; Zaffagnini et al., 2018). Another study found that p62 assembles into condensates together with mutant KEAP1 proteins and the transcription factor NRF2, thereby affecting NRF2-driven transcription (Cloer et al., 2018). Although this remains to be determined, it is tempting to speculate that p62 condensates are involved in the formation and autophagy-mediated disposal of various cellular condensates that promote or inhibit tumorigenesis.

Dysregulation of membraneless compartments in cancer

Accumulating evidence suggests that aberrant assembly of condensates is associated with cancer. How aberrant assembly and dysregulation of well-known membraneless compartments that form through condensation may promote tumorigenesis will be discussed in this section (Figure 6).

Stress granules

SGs, a type of stress-induced membraneless compartment, promote cell survival during stress conditions and have been shown to be formed by phase separation (Guillé´n-Boixet et al., 2020; Mollieux et al., 2015; Patel et al., 2015; Sanders et al., 2020; Yang et al., 2020). Due to the high metabolic demands of proliferation, cancer cells usually exist in a unique microenvironment characterized by hypoxia, high levels of reactive oxygen species, and nutrient starvation (Ackerman and Simon, 2014), conditions which activate the cellular stress response and trigger SG assembly. The assembly of SG promotes cancer cell adaption to adverse microenvironments and enhances cancer cell resistance to apoptosis by accumulating anti-apoptosis molecules (Arimoto et al., 2008; Thedieck et al., 2013).

Increased assembly of SG is observed in different kinds of cancers and modulated by cancer-related proteins (Figure 2). For instance, KRAS is a member of the RAS oncogene family, the most frequently mutated oncogene family in human cancers (Cox et al., 2014), has been linked to SG
KRAS mutations are detected in many highly malignant cancers, such as pancreatic ductal adenocarcinoma, colorectal adenocarcinoma, and lung adenocarcinoma (Cox et al., 2014). SG assembly was found to be induced in transformed or cancerous cells expressing mutant Kras, and this has been shown to confer a fitness advantage to cancer cells (Grabocka and Bar-Sagi, 2016). Likewise, mutations in DDX3X cause SG hyper-assembly and this has been shown to impair protein synthesis in medulloblastomas (Valentin-Vega et al., 2016). Moreover, YB-1 promotes SG assembly, which has been linked to increased invasion and metastasis (Somasekharan et al., 2015). The expression of PML/RARA leads to disruption of SG assembly and deregulated transcriptional control of senescence and differentiation in acute promyelocytic leukemia (APL) (de Thé and Chen, 2010; Dos Santos et al., 2013). Furthermore, disruption of PML bodies contributes to APL pathogenesis by increasing genome instability (Voisset et al., 2018). Recombination-based alternative lengthening of telomeres (ALT) is a key mechanism for telomerase-negative cancer cells to maintain the telomere stability and the capability for unlimited proliferation (Bryan et al., 1997). ALT-associated PML bodies (APB) facilitate telomere maintenance and thus promote cancer cell immortality (Zhang et al., 2020). IL-6/STAT3 signaling promotes paraspeckles formation, which favors overactivation of STAT3 in human hepatocellular carcinoma (HCC) (Wang et al., 2018c). Paraspeckle assembly induced by p53 has been shown to inhibit cancer initiation in pancreatic cancer models (Mello et al., 2017). Finally, inhibition of amyloid body assembly has been shown to promote tumor tissue growth (Audas et al., 2016).
example is DDX3X, which is mutated in many human tumor types (Valentin-Vega et al., 2016). In medulloblastomas (MB), mutations in DDX3X affect RNA-stimulated ATP hydrolysis and this causes SG hyper-assembly even under non-stress conditions, which results in impairing global translation (Valentin-Vega et al., 2016; Table 1 and Figure 6). In agreement with this, deleting the N-terminal IDR of MB-associated DDX3X prevented SG hyper-assembly and reversed the translation inhibitory effect (Valentin-Vega et al., 2016). In agreement with this, accumulating evidence indicates that deregulation of translation promotes cellular transformation and tumor development (Ruggiero, 2013). Therefore, perturbations in translational control caused by aberrant SG assembly may be another pathway that promotes tumorigenesis.

Another SG component that has been shown to facilitate SG assembly is Y-box binding protein 1 (YB-1). YB-1 is a member of a highly conserved cold shock domain (CSD) family and implicated in a wide variety of cellular function, such as translational regulation, DNA repair, and stress responses (Kohn et al., 2003). Increased protein levels of YB-1 are highly correlated with cancer progression and poor prognosis (Lasham et al., 2013). YB-1 was recently shown to promote SG assembly by translationally upregulating G3BP1 which is essential for SG assembly (Guillén-Boixet et al., 2020; Sanders et al., 2020; Somasekharan et al., 2015; Yang et al., 2020; Table 1 and Figure 6). Knock-down of G3BP1 severely impairs SG assembly and inhibits invasion and metastasis (Somasekharan et al., 2015). Thus, the role of YB-1 in cancer progression may be linked to SG assembly. However, how SG assembly promotes invasion and metastasis remains unclear and this aspect should be investigated by building on our improved understanding of condensate assembly.

**PML bodies**

PML bodies are stress-sensitive nuclear condensates (Banani et al., 2016; Zhu and Brangwynne, 2015). They are involved in transcriptional regulation, protein modification, apoptosis, cellular senescence, cell cycle progression, angiogenesis, and protein quality control (Hsu and Kao, 2018; Medianci et al., 2019). The formation of the PML body is driven by PML: PML interactions (Huang et al., 2014) and SUMOylation of PML, which promotes the recruitment of proteins containing SUMO-interacting motifs (SIMs) to PML bodies (Banani et al., 2016). In addition to SUMOylation-related enzymes (UBC9, RNF4), PML bodies also contain other enzymes, such as HIPK2 kinase, the CBP or MOZ acetyl transferases (Lallemand-Breitenbach and de Thé, 2018). Importantly, PML body formation regulates PTMs on p53, which are required for full p53 activity and oncogene-induced senescence (Ferbeye et al., 2000; Pearson et al., 2000).

Disregulation of PML bodies is associated with diverse cancers (Hsu and Kao, 2018; Figure 2). In acute promyelocytic leukemia (APL), PML is fused with full-length Retinoic Acid Receptor-alpha (RARA) because of a chromosomal translocation (de Thé et al., 1990). The expression of PML/RARA leads to disruption of PML bodies and deregulation of transcriptional programs that control senescence and differentiation (de Thé and Chen, 2010; Dos Santos et al., 2013; Table 1 and Figure 6). Therapeutic approaches have been developed to treat APL through a combination of retinoic acid (RA) and arsenic trioxide therapies. RA and arsenic trioxide induce PML body formation and this in turn promotes p53-driven senescence, which is required for APL eradication (Ablain et al., 2013; Ablain et al., 2014; de Thé et al., 2017). Thus, defective PML body formation promotes APL progression at least in part because APL cells cannot activate p53-driven senescence. Moreover, recent work reveals that aberrant PML body formation contributes to APL pathogenesis by increasing genome instability (Voisset et al., 2018). PML body disruption was shown to cause chromosome abnormalities and impair DNA damage response pathways.

Telomere maintenance is critical for a cancer cell to achieve the ability to proliferate in an unlimited manner (Blasco, 2005). Telomerase-negative cancer cells employ a mechanism known as recombination-based alternative lengthening of telomeres (ALT) to maintain telomere length and stability (Bryan et al., 1997). In ALT cancer cells, PML bodies associate with telomeres, their protective sheltering proteins TRF1/2 and several DNA repair proteins to form ALT-associated PML bodies (APB) (Osterwald et al., 2015; Yeager et al., 1999). A recent study suggests that the formation of APBs is driven by phase separation, thus promoting the clustering of telomere repeats and telomere lengthening (Zhang et al., 2020; Figure 6). Consequently, knocking down the PML body component PML inhibited APB formation and caused telomere shortening (Draskovic et al., 2009; Loo et al., 2020; Osterwald et al., 2015). Together, this suggests that APBs facilitate ALT telomere maintenance, eventually allowing cancer cells to grow indefinitely and become immortal.
**Paraspeckles**

Paraspeckles are nuclear bodies which regulate gene expression (Fox et al., 2018). The ncRNA scaffold NEAT1_2 drives the assembly of paraspeckles by interacting with essential paraspeckle proteins, such as NONO, SFP, FUS and RBM14 (Yamazaki et al., 2018; Table 1). Importantly, abnormal assembly of paraspeckles has been described in diverse cancers (Adriaens et al., 2016; Figure 2). In human hepatocellular carcinoma (HCC), inflammation-related IL-6 signaling increases paraspeckle formation by promoting the transcription of NEAT1_2, which is mediated by the transcription factor STAT3 and H3K4me3 histone modifications (Wang et al., 2018c; Figure 6). Increased paraspeckle formation promotes further STAT3 activation via sequestering negative regulators of STAT3 and tumor repressors, thus causing a vicious cycle that drives further paraspeckle assembly. Importantly, over-activation of STAT3 induces the transcription of various genes involved in cellular survival, inflammation, epithelial to mesenchymal transition, and cancer stem cell maintenance (Yu et al., 2014), all of which promote tumor progression.

Beyond the oncogenic role of paraspeckles in cancer progression, other studies have suggested that paraspeckles act as a tumor suppressor in certain contexts. The non-coding, paraspeckle-associated RNA NEAT1 is induced by p53 in response to various p53-activating signals (Mello et al., 2017; Figure 6). Additionally, NEAT1 overexpression suppresses the transformation of pancreatic cancer cells, and this effect was associated with an increase in the number of paraspeckles. Conversely, NEAT1 deficiency was shown to impair paraspeckle formation and promote pancreatic cancer initiation. Although this remains to be investigated, paraspeckles could regulate transcription factors associated with specific gene expression programs, thus promoting the expression of tumor suppressors and increasing the expression of developmental pancreas genes.

In addition to STAT3 and p53, NEAT1 has been shown to be regulated by other cancer-related transcription factors, such as HIF-2α (Choudhry et al., 2015), Oct4 (Jen et al., 2017), PML/RARA (Zeng et al., 2014), and c-Myc (Zeng et al., 2018). The example of PML/RARA is particularly interesting, because it not only represses NEAT1 expression (Zeng et al., 2014), but also disrupts PML bodies (discussed above). This suggests that the oncoprotein PML/RARA promotes aberrant assembly of two nuclear condensates, PML bodies and paraspeckles, to drive tumorigenesis.

Finally, NEAT1 has been reported to regulate many cancer-related microRNAs whose targets mRNAs are involved in cell proliferation, migration, invasion, metastasis, EMT, stem cell-like phenotype, chemoresistance and radioresistance (Dong et al., 2018). For instance, NEAT1 promotes metastasis by abolishing microRNA-382-3 p-mediated suppression of Rho Associated Coiled-Coil Containing Protein Kinase 1 (ROCK1) (Liu et al., 2018). However, it remains to elucidate how aberrant assembly of paraspeckles affects the activity of microRNAs.

**Amyloid bodies**

Amyloid bodies are stress-induced storage compartments in the nucleolus. The formation of amyloid bodies is seeded by non-coding RNA transcribed from loci of the rDNA intergenic spacer (rIGSRNA) and likely driven by complex coacervation of low-complexity rIGSRNA and short cationic domains in amyloid converting motif (ACM) (Wang et al., 2018b). Acidosis stress as found in tumor microenvironments was shown to induce the assembly of amyloid bodies, which involved the recruitment of many proteins involved in cell cycle regulation and DNA synthesis to amyloid bodies (Audas et al., 2016). It was postulated that amyloid body formation induces a protective state of cellular dormancy that may help cancer cells to adapt to the harsh tumor microenvironment (Wang et al., 2019). In agreement with this, inhibition of amyloid body formation by knockdown of rIGS28RNA prevented tumor dormancy and led to larger tumor sizes in cancer mouse models (Audas et al., 2016; Figure 6). However, how amyloid bodies promote tumorigenesis remains to be shown (Figure 2).

**Conclusion and future perspectives**

Condensates have now been implicated in almost all fundamental processes in living cells. Given the importance of condensates for cellular physiology and our increasingly better understanding of condensate assembly and function, we expect that condensate research will make an important contribution to unraveling the complex biology of cancers in the coming years. One example of the increasingly important role of condensates is the demonstration that transcription is regulated by condensates. Numerous cancer-related proteins function as transcription factors and assembly of
these transcription factors into aberrant condensates could drive various hallmarks of cancer cells, such as their ability to proliferate.

However, cancer cells acquire various other capabilities during tumorigenesis, such as induction of angiogenesis, activation of invasion and metastasis, deregulation of cellular energetics, avoidance of immune detection, and destabilization of the genome (Hanahan and Weinberg, 2011). Increasing evidence implicates condensates also in these processes, with confirmed roles for example in mitosis (Jiang et al., 2015; Rai et al., 2018), immune cell signal transduction (Su et al., 2016), chromatin organization (Gibson et al., 2019), and cell adhesion (Beutel et al., 2019). A future challenge will be to determine whether the corresponding physiological condensates are misregulated in cancer cells. For example, does the spindle pole regulator BuGZ (Jiang et al., 2015) form condensates in cancer cells and does aberrant BuGZ assembly promote hyperproliferation or metastasis? Does aberrant assembly of zona occludens condensates (Beutel et al., 2019) contribute to cancer cell invasion and metastasis? Such questions underscore the importance of investigating cancer-associated processes though the lens of condensate biology. Furthermore, illuminating how specific cancer-associated mutations promote aberrant phase behavior of proteins and promote condensate dysfunction will yield entirely new molecular mechanisms underlying cancer initiation and progression. We expect that the growing field of condensate biology will not only create more knowledge about the molecular underpinnings of cancer but it will also accelerate the development of new therapies, thus bringing us closer to the goal of curing cancer.

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Additional information

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References

Ablain J, Leiva M, Peres L, Fonsart J, Anthony E, de Thé H. 2013. Uncoupling RARA transcriptional activation and degradation clarifies the bases for APL response to therapies. Journal of Experimental Medicine 210:647–653. DOI: https://doi.org/10.1084/jem.20122337, PMID: 23509325

Ablain J, Rice K, Soilihi H, de Reynies A, Minucci S, de Thé H. 2014. Activation of a promyelocytic leukemia-tumor protein 53 Axis underlies acute promyelocytic leukemia cure. Nature Medicine 20:167–174. DOI: https://doi.org/10.1038/nm.3441, PMID: 24412926

Ackerman D, Simon MC. 2014. Hypoxia, lipids, and Cancer: surviving the harsh tumor microenvironment. Trends in Cell Biology 24:472–478. DOI: https://doi.org/10.1016/j.tcb.2014.06.001, PMID: 24985940

Adriaens C, Standaert L, Barra J, Latil M, Verfaillie A, Kalev P, Boeckx B, Wijnhoven PW, Radaelli E, Vermi W, Leucci E, Lapouge G, Beck B, van den Oord J, Nakagawa S, Hirose T, Sablina AA, Lambrechts D, Aerts S, Blanpain C, et al. 2016. p53 induces formation of NEAT1 long non-coding RNA-containing paraspeckles that modulate replication stress response and chemosensitivity. Nature Medicine 22:861–868. DOI: https://doi.org/10.1038/nm.4135, PMID: 27376578

Alberti S, Halfmann R, King O, Kapila A, Lindquist S. 2009. A systematic survey identifies prions and illuminates sequence features of prionogenic proteins. Cell 137:146–158. DOI: https://doi.org/10.1016/j.cell.2009.02.044, PMID: 19345193

Alberti S, Gladfelter A, Mittag T. 2019. Considerations and challenges in studying Liquid-Liquid phase separation and biomolecular condensates. Cell 176:419–434. DOI: https://doi.org/10.1016/j.cell.2018.12.035, PMID: 30682370

Alshawi H, Estrov Z, Seiden M. 2019. Liquid-Liquid phase separation in disease. Annual Review of Genetics 53:171–194. DOI: https://doi.org/10.1146/annurev-genet-112618-043527, PMID: 31403179

Aleksandrov R, Dotchev A, Poser I, Krastev D, Georgiev G, Panova G, Babukov Y, Danovski G, Dyankova T, Hubatsch L, Ivanova A, Atemin A, Nedelcheva-Veleva MN, Harms S, Sarov M, Buchholz F, Hyman AA, Grill SW, Stoynov SS. 2018. Protein dynamics in complex DNA lesions. Molecular Cell 69:1046–1061. DOI: https://doi.org/10.1016/j.molcel.2018.02.016, PMID: 29547717

Altmeyer M, Neelsen KJ, Teloni F, Pozdnyakova I, Pellegrino S, Graffe M, Rask MD, Streicher W, Jungmichel S, Nielsen ML, Lukas J. 2015. Liquid demixing of intrinsically disordered proteins is seeded by poly(ADP-ribose). Nature Communications 6:8088. DOI: https://doi.org/10.1038/ncomms9088, PMID: 26286827

Anastasiadou E, Jacob LS, Slack FJ. 2018. Non-coding RNA networks in Cancer. Nature Reviews Cancer 18:5–18. DOI: https://doi.org/10.1038/nrc.2017.99, PMID: 29170536

Arimoto K, Fukuda H, Imajoh-Ohmi S, Saito H, Takekawa M. 2008. Formation of stress granules inhibits apoptosis by suppressing stress-responsive MAPK pathways. Nature Cell Biology 10:1324–1332. DOI: https://doi.org/10.1038/nclb1791, PMID: 18836437

Audas TE, Audas DE, Jacob MD, Ho JJ, Khacho M, Wang M, Perera JK, Gardiner C, Bennett CA, Head T, Krywenko ON, Jorda M, Daunert S, Malhotra A, Trinkle-Mulcahy L, Gonzalgo ML, Lee S. 2016. Adaptation to stressors by systemic protein Amyloidogenesis. Developmental Cell 39:155–168. DOI: https://doi.org/10.1016/j.devcel.2016.09.002, PMID: 27720612

Banani SF, Rice AM, Peeples WB, Lin Y, Jain S, Parker R, Rosen MK. 2016. Compositional control of Phase-Separated cellular bodies. Cell 166:651–663. DOI: https://doi.org/10.1016/j.cell.2016.06.010, PMID: 27374333

Banani SF, Lee HO, Hyman AA, Rosen MK. 2017. Biomolecular condensates: organizers of cellular biochemistry. Nature Reviews Molecular Cell Biology 18:285–298. DOI: https://doi.org/10.1038/nrm.2017.7, PMID: 28225081

Banjade S, Rosen MK. 2014. Phase transitions of multivalent proteins can promote clustering of membrane receptors. eLife 3:e04123. DOI: https://doi.org/10.7554/eLife.04123

Barbieri CE, Baca SC, Lawrence MS, Demiches F, Blattner M, Theurillat JP, White TA, Stojanov P, Van Allen E, Stransky N, Nickerson E, Chae SS, Boysen G, Auclair D, Onofrio RC, Park K, Kitabayashi N, MacDonald TY, Sheikh K, Vuong T, et al. 2012. Exome sequencing identifies recurrent SPOP, FOXA1 and MED12 mutations in prostate Cancer. Nature Genetics 44:685–689. DOI: https://doi.org/10.1038/ng.2279, PMID: 22610119

Benedek GB. 1997. Cataract as a protein condensation disease: the proctor lecture. Investigative Ophthalmology & Visual Science 38:1911–1921. PMID: 9331254

Beutel O, Maraspini R, Pombo-Garcia K, Martin-Lemaitre C, Honigmann A. 2019. Phase separation of zonula occludens proteins drives formation of tight junctions. Cell 179:923–936. DOI: https://doi.org/10.1016/j.cell.2019.10.011, PMID: 31675499

Bi J, Huang A, Liu T, Zhang T, Ma H. 2015. Expression of DNA damage checkpoint 53BP1 is correlated with prognosis, cell proliferation and apoptosis in colorectal Cancer. International Journal of Clinical and Experimental Pathology 8:6070–6082. PMID: 26261485
Bienz M. 2014. Signalosome assembly by domains undergoing dynamic head-to-tail polymerization. Trends in Biochemical Sciences 39:487–495. DOI: https://doi.org/10.1016/j.tibs.2014.08.006, PMID: 25239056

Bienz M. 2020. Head-to-Tail polymerization in the assembly of biomolecular condensates. Cell 182:799–811. DOI: https://doi.org/10.1016/j.cell.2020.07.037, PMID: 32822572

Bilic J, Huang YL, Davidson G, Zimmermann T, Cruciat CM, Bienz M, Niehrs C. 2007. Wnt induces LRPP signalosomes and promotes disevelled-dependent LRPP6 phosphorylation. Science 316:1619–1622. DOI: https://doi.org/10.1126/science.1137065, PMID: 17569865

Blasco MA. 2005. Telomeres and human disease: ageing, Cancer and beyond. Nature Reviews Genetics 6:611–622. DOI: https://doi.org/10.1038/ng1656, PMID: 16136653

Boeynaems S, Alberti S, Fawi NL, Mittag T, Polyenmiodou M, Rousseau F, Schymkowitz J, Shorter J, Wolozin B, Van Den Bosch L, Tompa P, Fuxreiter M. 2018. Protein phase separation: a new phase in cell biology. Trends in Cell Biology 28:420–435. DOI: https://doi.org/10.1016/j.tib.2018.02.004, PMID: 29602697

Boija A, Klein IA, Sabari BR, Dall’Agnese A, Coffey EL, Zamudio AV, Li CH, Shinivas K, Manteiga JC, Hanneb NM, Abraham BJ, Afeyan LK, Guo YE, Rimel JK, Fant CB, Schuijers J, Lee TI, Taatjes DJ, Young RA. 2018. Transcription factors activate genes through the Phase-Separation capacity of their activation domains. Cell 175:1842–1855. DOI: https://doi.org/10.1016/j.cell.2018.10.042, PMID: 30449618

Bouchard JJ, Otero JH, Scott DC, Szulc E, Martin EW, Sabri N, Granata D, Marzahn MR, Lindorf-Larsen K, Salvatella X, Schuman BA, Mittag T. 2018. Cancer mutations of the tumor suppressor SPOP disrupt the formation of active, Phase-Separated compartments. Molecular Cell 72:19–36. DOI: https://doi.org/10.1016/j.molcel.2018.08.027, PMID: 30244836

Boulay G, Sandoval GJ, Riggi N, Iyer S, Buisson R, Naigles B, Awad ME, Rengarajan S, Volorio A, McBride MJ, Broye LC, Zou L, Stamenkovic I, Kadoch C, Rivera MN. 2017. Cancer-Specific retargeting of BAF complexes by a Prion-like domain. Cell 171:163–178. DOI: https://doi.org/10.1016/j.cell.2017.07.036, PMID: 2884694

Bryan TM, Engleouz A, Dalla-Pozza L, Dunham MA, Reddel RR. 1997. Evidence for an alternative mechanism for maintaining telomere length in human tumors and tumor-derived cell lines. Nature Medicine 3:1271–1274. DOI: https://doi.org/10.1038/nm1197-1271, PMID: 9359704

Burke KA, Janke AM, Rhine CL, Fawzi NL. 2015. Residue-by-Residue view of in Vitro FUS Granules that Bind the C-Terminal Domain of RNA Polymerase II. Molecular Cell 60:231–241. DOI: https://doi.org/10.1016/j.molcel.2015.09.006, PMID: 26455390

Cai D, Feliciano D, Dong P, Flores E, Gruebele M, Porat-Shliom I, Sukenis S, Liu Z, Lippincott-Schwartz J. 2019. Phase separation of YAP reorganizes genome topology for long-term YAP target gene expression. Nature Cell Biology 21:1578–1589. DOI: https://doi.org/10.1038/s41556-019-0433-z, PMID: 31792379

Carlomagno Y, Chung DC, Yue M, Castanedes-Casey M, Madden BJ, Dunmore J, Tong J, DeTure M, Dickson DW, Petrucelli L, Cook C. 2017. An acetylation-phosphorylation switch that regulates tau aggregation propensity and function. Journal of Biological Chemistry 292:15277–15286. DOI: https://doi.org/10.1074/jbc.M117.794602, PMID: 28760928

Case LB, Ditliev JA, Rosen MK. 2019a. Regulation of transmembrane signaling by phase separation. Annual Review of Biophysics 48:465–494. DOI: https://doi.org/10.1146/annurev-biophys-052118-115534, PMID: 30951647

Case LB, Zhang X, Ditliev JA, Rosen MK. 2019b. Stoichiometry controls activity of phase-separated clusters of actin signaling proteins. Science 363:1093–1097. DOI: https://doi.org/10.1126/science.aau6313, PMID: 30846599

Chakravarty AK, Jarosz DF. 2018. More than just a phase: prions at the crossroads of epigenetic inheritance and evolutionary change. Journal of Molecular Biology 430:4607–4618. DOI: https://doi.org/10.1016/j.jmb.2018.07.017, PMID: 30031007

Cho WK, Spille JH, Hecht M, Lee C, Li C, Grube V, Cisse II. 2018. Mediator and RNA polymerase II clusters associate in transcription-dependent condensates. Science 361:412–415. DOI: https://doi.org/10.1126/science.aar4199, PMID: 29930094

Choudhry H, Albukhari A, Morotti M, Haider S, Moralli D, Smythies J, Schüdel J, Green CM, Camps C, Buffa F, Ratcliffe P, Ragoisiss J, Harris AL, Mole DR. 2015. Tumor hypoxia induces nuclear paraspeckle formation through HIF-2a dependent transcriptional activation of NEAT1 leading to Cancer cell survival. Oncogene 34:4482–4490. DOI: https://doi.org/10.1038/onc.2014.378, PMID: 25417700

Cliffe A, Hamada F, Bienz M. 2003. A role of dishevelled in relocating axin to the plasma membrane during wingless signaling. Current Biology 13:960–966. DOI: https://doi.org/10.1016/S0960-9822(03)00370-1, PMID: 12781135

Cloer EW, Siessser PF, Cousins EM, Goldfarb D, Mowrey DD, Harrison JS, Weir SJ, Dokholyan NV, Major MB. 2018. p62-Dependent phase separation of patient-derived KEAP1 mutations and NRF2. Molecular and Cellular Biology 38:4606-4617. DOI: https://doi.org/10.1128/MCB.00644-17, PMID: 30126895

Cox AD, Fesik SW, Kimmelman AC, Luo J, Der CJ. 2014. Drugging the undruggable RAS: mission possible? Nature Reviews Drug Discovery 13:828–851. DOI: https://doi.org/10.1038/nrd4389, PMID: 25232972

Cuellas-Martin R, Oliveira C, Lockstone HE, Snellenberg S, Grolmusova N, Chapman JR. 2016. 53bp1 integrates DNA repair and p53-Dependent cell fate decisions via distinct mechanisms. Molecular Cell 64:51–64. DOI: https://doi.org/10.1016/j.molcel.2016.08.002, PMID: 27546791

Daeo TP, Kolaitis RM, Kim HJ, O’Donovan K, Martyniak B, Colicino E, Hehly H, Taylor JP, Castaneda CA. 2018. Ubiquitin modulates Liquid-Liquid phase separation of UBQLN2 via disruption of multiscale interactions. Molecular Cell 69:965–978. DOI: https://doi.org/10.1016/j.molcel.2018.02.004, PMID: 29526694
de Thé H, Chomienne C, Lanotte M, Degos L, Dejean A. 1990. The t(15;17) translocation of acute promyelocytic leukemia fuses the retinoic acid receptor alpha gene to a novel transcribed locus. Nature 347:558–561. DOI: https://doi.org/10.1038/347558a0, PMID: 2170850

de Thé H, Pandolfi PP, Chen Z. 2017. Acute promyelocytic leukemia: a paradigm for Oncoprotein-Targeted cure. Cancer Cell 32:552–560. DOI: https://doi.org/10.1016/j.ccell.2017.10.002, PMID: 29136503

de Thé H, Chen Z. 2010. Acute promyelocytic leukemia: novel insights into the mechanisms of cure. Nature Reviews Cancer 10:775–783. DOI: https://doi.org/10.1038/nrc2943, PMID: 2069922

Delattre O, Zucman J, Plougastel B, Desmaze C, Melot T, Peter M, Kovar H, Joubert I, de Jong P, Rouleau G. 1992. Gene fusion with an ETS DNA-binding domain caused by chromosome translocation in human tumours. Nature 359:162–165. DOI: https://doi.org/10.1038/359162a0, PMID: 1522903

Ditlve JA, Vega AR, Köster DV, Su X, Tani T, Lakudok AM, Vale RD, Mayor S, Jaqaman K, Rosen MK. 2019. A composition-dependent molecular clutch between T cell signaling condensates and actin. eLife 8:e42695. DOI: https://doi.org/10.7554/eLife.42695, PMID: 31268421

Dong P, Xiong Y, Yue J, Hanley SJ, Kobayashi N, Todo Y, Watanabe H. 2018. Long Non-coding RNA NEAT1: a novel target for diagnosis and therapy in human tumors. Frontiers in Genetics 9:471. DOI: https://doi.org/10.3389/fgene.2018.00471, PMID: 30374364

Dos Santos GA, Kats L, Pandolfi PP. 2013. Synergy against PML-RARα: targeting transcription, proteolysis, differentiation, and self-renewal in acute promyelocytic leukemia. Journal of Experimental Medicine 210:2793–2802. DOI: https://doi.org/10.1084/jem.20131121, PMID: 24344243

Draskovic I, Arnout N, Steiner V, Baccetti S, Lomonte P, Londono-Leal J, Vallejo A. 2009. Probing PML body function and topology in ALT cells reveals spatiotemporal requirements for telomere recombination. PNAS 106:15726–15731. DOI: https://doi.org/10.1073/pnas.0907689106, PMID: 19717459

Durán A, Linares JF, Galvés AS, Wikenheiser K, Flores JM, Diaz-Meco MT, Moscat J. 2008. The signaling adaptor p62 is an important NF-kappaB mediator in tumorigenesis. Cancer Cell 13:343–354. DOI: https://doi.org/10.1016/j.ccr.2008.02.001, PMID: 18394557

Egeblad M, Nakasone ES, Werb Z. 2010. Tumors as organs: complex tissues that interface with the entire organism. Developmental Cell 18:884–901. DOI: https://doi.org/10.1016/j.devcel.2010.05.012, PMID: 20627072

Fang X, Wang L, Ishikawa R, Li Y, Fiedler M, Liu F, Calder G, Rowan B, Weigel D, Li P, Dean C. 2019. Arabidopsis FLL2 promotes liquid-liquid phase separation of polyadenylation complexes. Nature 569:265–269. DOI: https://doi.org/10.1038/s41586-019-1165-8, PMID: 31043738

Faux MC, Coates J, Catimel B, Cody S, Clayton AH, Layton MJ, Burgess AW. 2008. Recruitment of adenomatous polyposis Coli and beta-catenin to axin-puncta. Oncogene 27:5808–5820. DOI: https://doi.org/10.1038/onc.2008.205, PMID: 18591934

Ferreyre G, de Stanchina E, Querido E, Baptiste N, Prives C, Lowe SW. 2000. PML is induced by oncogenic ras and promotes premature senescence. Genes & Development 14:2015–2027. DOI: https://doi.org/10.1101/gad.14.16.2015, PMID: 10950866

Ferreon J, Jain A, Choi K-J, Tsol P, MacKenzie K, Jung S, Ferreon A. 2018. Acetylation disfavors tau phase separation. International Journal of Molecular Sciences 19:1360. DOI: https://doi.org/10.3390/ijms19051360

Fiedler M, Mendoza-Topaz C, Rutherford TJ, Mieszczanek J, Bienz M. 2011. Dishevelled interacts with the DIX domain polymerization interface of axin to interfere with its function in down-regulating β-catenin. PNAS 108:1937–1942. DOI: https://doi.org/10.1073/pnas.101763108, PMID: 21245303

Flavahan WA, Gaskell E, Bernstein BE. 2017. Epigenetic plasticity and the hallmarks of Cancer. Science 357:eaal2380. DOI: https://doi.org/10.1126/science.aal2380, PMID: 28729483

Fox AH, Nakagawa S, Hirose T, Bond CS. 2018. Paraspeckles: where long noncoding RNA meets phase separation. Trends in Biochemical Sciences 43:124–135. DOI: https://doi.org/10.1016/j.tibs.2017.12.001, PMID: 29289458

Frangmann TM, Jahnel M, Pozniakovsky A, Mahamid J, Holehouse AS, Nüße E, Richter D, Baumeister W, Grill SW, Pappu RV, Hyman AA, Alberti S. 2018. Phase separation of a yeast prion protein promotes cellular fitness. Science 359:aao5654. DOI: https://doi.org/10.1126/science.aao5654, PMID: 29301985

Frangmann TM, Alberti S. 2019. Protein phase separation as a stress survival strategy. Cold Spring Harbor Perspectives in Biology 11:a034058. DOI: https://doi.org/10.1101/cshperspect.a034058, PMID: 30617047

Frottin F, Schueder F, Tiwary S, Gupta R, Körner R, Schlichthaerle T, Cox J, Jungmann R, Hartl FU, Hipp MS. 2019. The nucleolar functions as a phase-separated protein quality control compartment. Science 365:342–347. DOI: https://doi.org/10.1126/science.aaw9157, PMID: 31296649

Fujikawa Y, Alam JM, Noshiro D, Mouri K, Ando T, Okada Y, May AI, Knorr RL, Suzuki K, Ohsumi Y, Noda NN. 2020. Phase separation organizes the site of autophagosome formation. Nature 578:301–305. DOI: https://doi.org/10.1038/s41586-019-1977-6, PMID: 32053038

Galli GG, Carrara M, Yuan WC, Valdes-Quezada C, Gurung B, Pepe-Mooney B, Zhang T, Gheewala G, Gray NS, de Laat W, Calogero RA, Camargo FD. 2015. YAP drives growth by controlling transcriptional pause release from dynamic enhancers. Molecular Cell 60:328–337. DOI: https://doi.org/10.1016/j.molcel.2015.09.001, PMID: 26493901

Gammons MV, Renko M, Johnson CM, Rutherford TJ, Bienz M. 2016. Wnt signalosome assembly by DEP domain swapping of dishevelled. Molecular Cell 64:92–104. DOI: https://doi.org/10.1016/j.molcel.2016.08.026, PMID: 27692984

Gammons M, Bienz M. 2018. Multisite conjugation of Wnt signal transduction. Current Opinion in Cell Biology 51:42–49. DOI: https://doi.org/10.1016/j.cceb.2017.10.008, PMID: 29153704
Gao Y, Pei G, Li D, Li R, Shao Y, Zhang QC, Li P. 2019. Multivalent m^4A motifs promote phase separation of YTHD proteins. Cell Research 29:767–769. DOI: https://doi.org/10.1038/s41422-019-0210-3, PMID: 31388144
Geng C, Kaochar S, Li M, Rajapakse K, Fiskus W, Dong J, Foley C, Dong B, Zhang L, Kwon OJ, Shah SS, Bolaki M, Xin L, Ittmann M, O’Malley BW, Coarfa C, Mitsiades N. 2017. SPOP regulates prostate epithelial cell proliferation and promotes ubiquitination and turnover of c-MYC oncoprotein. Oncogene 36:4767–4777. DOI: https://doi.org/10.1038/onc.2017.80, PMID: 28414305
Gibson BA, Doolittle KJ, Schneider MWG, Jensen LE, Gamarra N, Henny L, Gerlich DW, Redding S, Rosen MK. 2019. Organization of chromatin by intrinsic and regulated phase separation. Cell 179:470–484. DOI: https://doi.org/10.1016/j.cell.2019.08.037, PMID: 31543265
Gomes E, Shorter J. 2019. The molecular language of membraneless organelles. Journal of Biological Chemistry 294:7115–7127. DOI: https://doi.org/10.1074/jbc.T118.011192, PMID: 30045872
Grabocka E, Bar-Sagi D. 2016. Mutant KRAS enhances tumor cell fitness by upregulating stress granules. Cell 167:1803–1813. DOI: https://doi.org/10.1016/j.cell.2016.11.035, PMID: 27984728
Guillen-Boixet J, Kopach A, Holehouse AS, Wittmann S, Jain S, Schlüessler R, Kim K, Trussina I, Wang J, Mateju D, Poser I, Maharana S, Kress M, Weil D, Shinivas K, Abraham BJ, Boija A, Decker TM, Rimel JK, Fant CB, Lee TI, Cisse II, Sharp PA, Taatjes DJ, Young RA. 2019. Pol II phosphorylation regulates a switch between transcriptional and splicing condensates. Nature 572:543–548. DOI: https://doi.org/10.1038/s41586-019-1464-0, PMID: 31391587
Hanahan D, Weinberg RA. 2011. Hallmarks of Cancer: the next generation. Cell 144:646–674. DOI: https://doi.org/10.1016/j.cell.2011.02.013, PMID: 21376230
Harmon TS, Holehouse AS, Rosen MK, Pappu RV. 2017. Intrinsically disordered linkers determine the interplay between phase separation and gelation in multivalent proteins. eLife 6:e30294. DOI: https://doi.org/10.7554/eLife.30294, PMID: 29091028
Hnisz D, Abraham BJ, Lee TI, Lau A, Saint-André V, Sigova AA, Hoke HA, Young RA. 2013. Super-enhancers in the control of cell identity and disease. Cell 155:934–947. DOI: https://doi.org/10.1016/j.cell.2013.09.053, PMID: 24119843
Hofweber M, Hutten S, Bourgeois B, Spreitzer E, Niemann NB, Schifferer M, Ruepp MD, Simons M, Niessing D, Madl T, Dormann D. 2018. Phase separation of FUS is suppressed by its nuclear import receptor and arginine methylation. Cell 173:706–719. DOI: https://doi.org/10.1016/j.cell.2018.03.006, PMID: 29677514
Hofweber M, Dormann D. 2019. Friend or foe-Post-translational modifications as regulators of phase separation and RNP granule dynamics. Journal of Biological Chemistry 294:7137–7150. DOI: https://doi.org/10.1074/jbc.T118.001189, PMID: 30587571
Hondele M, Sachdev R, Heinrich S, Wang J, Vallotton P, Fontoura BMA, Weis K. 2019. DEAD-box ATPases are global regulators of phase-separated organelles. Nature 573:144–148. DOI: https://doi.org/10.1038/s41586-019-1502-y, PMID: 31435012
Hou W-H, Chen S-H, Yu X. 2019. Poly-ADP ribosylation in DNA damage response and Cancer therapy. Mutation Research/Reviews in Mutation Research 780:82–91. DOI: https://doi.org/10.1016/j.mrrrev.2017.09.004
Hsu KS, Kao HY. 2018. PML: regulation and multifaceted function beyond tumor suppression. Cell & Bioscience 8:5. DOI: https://doi.org/10.18668/s13578-018-0204-8, PMID: 29416846
Huang SY, Naik MT, Chang CF, Fang PJ, Wang YH, Shih HM, Huang TH. 2014. The B-box 1 dimer of human PML: regulation and multifaceted function beyond tumor suppression. Annual Review of Cancer Biology 4:221–240. DOI: https://doi.org/10.1146/annurev-cancerbio-030419-033357
Hubstenberger A, Courel M, Bénard M, Souquere S, Ernout-Lange M, Chouaib R, Yi Z, Morlot JB, Munier A, Fradet M, Daunesse M, Bertrand E, Pierron G, MozziGalloch D, Poser I, Maharana S, Kress M, Weil D. 2017. P-Body purification reveals the condensation of repressed mRNA regulons. Molecular Cell 68:144–157. DOI: https://doi.org/10.1016/j.molcel.2017.09.003, PMID: 28965817
Iwabuchi K, Bartel PL, Li B, Marraccino R, Fields S. 1994. Two cellular proteins that bind to wild-type but not mutant p53. PNAS 91:6098–6102. DOI: https://doi.org/10.1073/pnas.91.13.6098, PMID: 8016121
Jain S, Wheeler JR, Walters RW, Agrawal A, Barsic A, Parker R. 2016. ATPase-Modulated stress granules contain a diverse proteome and substructure. Cell 164:487–498. DOI: https://doi.org/10.1016/j.cell.2015.12.038, PMID: 26774005
Jeggo PA, Pearl LH, Carr AM. 2016. DNA repair, genome stability and Cancer: a historical perspective. Nature Reviews Cancer 16:35–42. DOI: https://doi.org/10.1038/nrc.2015.4, PMID: 26667849
Jen J, Tang YN, Lin CC, Lai WW, Wang YC. 2017. Oct4 transcriptionally regulates the expression of long non-coding RNAs NEAT1 and MALAT1 to promote lung Cancer progression. Molecular Cancer 16:104. DOI: https://doi.org/10.1186/s12935-017-0574-2, PMID: 28615056

Jiang et al. eLife 2020;9:e60264. DOI: https://doi.org/10.7554/eLife.60264
et al. Jiang H. eLife 2020;9:e60264. DOI: https://doi.org/10.7554/eLife.60264
Jiang et al. eLife 2020;9:e60264. DOI: https://doi.org/10.7554/eLife.60264

Liu Y, Wang Y, Fu X, Lu Z. 2018. Long non-coding RNA NEAT1 promoted ovarian Cancer cells’ metastasis through regulation of miR-382-3p/ROCK1 axial. Cancer Science 109:2188–2198. DOI: https://doi.org/10.1111/cas.13647, PMID: 29790629

Loo TK, Li JSZ, Zhang Y, Azeroglu B, Boddy MN, Denchi EL. 2020. Telomere length heterogeneity in ALT cells is maintained by PML-dependent localization of the BTR complex to telomeres. Genes & Development 34:650–662. DOI: https://doi.org/10.1101/gad.339363.119, PMID: 32217664

Lu P, Weaver VM, Werb Z. 2012. The extracellular matrix: a dynamic niche in Cancer progression. Journal of Cell Biology 196:395–406. DOI: https://doi.org/10.1083/jcb.201102147, PMID: 22351925

Lu Y, Wu T, Gutman O, Lu H, Zhou Q, Henis YI, Luo K. 2020. Phase separation of TAZ compartmentalizes the transcription machinery to promote gene expression. Nature Cell Biology 22:453–464. DOI: https://doi.org/10.1038/s41556-020-0485-0, PMID: 32030417

Madzak A, Fiedler M, Johnson CM, Ewan R, Knebel A, Bienz M, Chin JW. 2015. Ubiquitination of the dishevelled DIX domain blocks its head-to-tail polymerization. Nature Communications 6:6718. DOI: https://doi.org/10.1038/ncomms7718

Maharana S, Wang J, Papadopoulos DK, Richter D, Pozniakovsky A, Poser I, Bickle M, Rizk S, Guillen-Boixet J, Franzmann TM, Jahnel M, Marrone L, Chang YT, Sternecker J, Tomancak P, Hyman AA, Alberti S. 2018. RNA buffers the phase separation behavior of prion-like RNA binding proteins. Science 360:918–921. DOI: https://doi.org/10.1126/science.aar7366, PMID: 29630702

Martin EW, Holehouse AS, Perani I, Farag M, Incicco JJ, Bremer A, Grace CR, Soranno A, Pappu RV, Mittag T. 2020. Valence and patterning of aromatic residues determine the phase behavior of prion-like domains. Science 367:694–699. DOI: https://doi.org/10.1126/science.aaw9886, PMID: 32029630

Martinelli E, Morgillo F, Troiani T, Ciardiello F. 2017. Cancer resistance to therapies against the EGFR-RAS-RAF pathway: the role of MEK. Cancer Treatment Reviews 53:61–69. DOI: https://doi.org/10.1016/j.ctrv.2016.12.001, PMID: 28073102

Mediani L, Guillén-Boixet J, Vinet J, Franzmann TM, Bigi I, Mateju D, Carrà AD, Morelli FF, Tiago T, Poser I, Alberti S, Carrà S. 2019. Defective ribosomal products challenge nuclear function by impairing nuclear condensate dynamics and immobilizing ubiquitin. The EMBO Journal 38:e101341. DOI: https://doi.org/10.15252/embj.2018101341, PMID: 31271238

Mello SS, Sinow C, Raj N, Mazur PK, Bieging-Rolett K, Broz DK, Imam JFC, Vogel H, Wood LD, Sage J, Hirose T, Nakagawa S, Rinn J, Attardi LD. 2017. Neat1 is a p53-inducible lincRNA essential for transformation suppression. Genes & Development 31:1095–1108. DOI: https://doi.org/10.1101/gad.284661.116, PMID: 28698299

Michnick S, Bergeron-Sandoval L-P, Pappu R, François P, Hendricks AG, Ehrlicher AJ, Khadivi H, 2019. A protein condensate drives Actin-Independent endocytosis. Biophysical Journal 116:161a. DOI: https://doi.org/10.1016/j.bpj.2018.11.894

Mirza-Aghazadeh-Attari M, Mohammadzadeh A, Yousefi B, Mihanfar A, Karimian A, Majdinia M. 2019. 53bp1: a key player of DNA damage response with critical functions in Cancer. DNA Repair 73:110–119. DOI: https://doi.org/10.1016/j.dnarep.2018.11.008, PMID: 30497961

Mollie A, Temirov J, Lee J, Coughlin M, Kanagaraj AP, Kim HJ, Mittag T, Taylor JP. 2015. Phase separation by low complexity domains promotes stress granule assembly and drives pathological fibrillization. Cell 163:123–133. DOI: https://doi.org/10.1016/j.cell.2015.09.015, PMID: 26406374

Monahan Z, Ryan VH, Janke AM, Burke KA, Rhoads SN, Zerze GH, O’Meally R, Dignon GL, Concilcia AE, Zheng W, Best RB, Cole RN, Mittal J, Shewmaker F, Fawzi NL. 2017. Phosphorylation of the FUS low-complexity domain disrupts phase separation, aggregation, and toxicity. The EMBO Journal 36:2951–2967. DOI: https://doi.org/10.15252/embj.201696394, PMID: 28790177

Moscat J, Karin M, Diaz-Meco MT. 2016. p62 in Cancer: signaling adaptor beyond autophagy. Cell 167:606–609. DOI: https://doi.org/10.1016/j.cell.2016.09.030, PMID: 27768885

Moya IM, Castaldo SA, Van den Moooter L, Soheily S, Sansores-Garcia L, Jacobs J, Mannerts I, Xie J, Verboven E, Hillen H, Algueró-Nadal A, Karaman R, Van Haele M, Kowalczyk W, De Vaaegeneer M, Verhulst S, Karras P, van Huffel L, Zender L, Marine JC, et al. 2019. Peritumoral activation of the hippo pathway effectors YAP and TAZ suppresses liver cancer in mice. Science 366:1029–1034. DOI: https://doi.org/10.1126/science.aaw9886, PMID: 31754005

Moya IM, Halder G. 2019. Hippo-YAP/TAZ signalling in organ regeneration and regenerative medicine. Nature Reviews Molecular Cell Biology 20:211–226. DOI: https://doi.org/10.1038/s41580-018-0086-y, PMID: 30546055

Murray DT, Kato M, Lin Y, Thurber KR, Hung I, McKnight SL, Tycko R. 2017. Structure of FUS protein fibrils and its relevance to Self-Assembly and phase separation of Low-Complexity domains. Cell 171:615–627. DOI: https://doi.org/10.1016/j.cell.2017.08.048, PMID: 28942918

Nakagawa H, Umemura A, Taniguchi K, Font-Burgada J, Dhar D, Ogata H, Zhong Z, Valasek MA, Seki E, Hidalgo J, Koike K, Kaufman RJ, Karin M. 2014. ER stress cooperates with hypernutrition to trigger TNF-dependent spontaneous HCC development. Cancer Cell 26:331–343. DOI: https://doi.org/10.1016/j.ccr.2014.07.001, PMID: 25132496

Nott TJ, Petsalaki E, Farber P, Jervis D, Fussner E, Plochowietz A, Craggs TD, Bazett-Jones DP, Pawson T, Forman-Kay JD, Baldwin AJ. 2015. Phase transition of a disordered nuage protein generates environmentally responsive membraneless organelles. Molecular Cell 57:936–947. DOI: https://doi.org/10.1016/j.molcel.2015.01.013, PMID: 25747659
Osterwald S, Deeg KI, Chung I, Parisotto D, Wörz S, Rohr K, Erhle F, Rippe K. 2015. PML induces compaction, TRF2 depletion and DNA damage signaling at telomeres and promotes their alternative lengthening. Journal of Cell Science 128:1887–1900. DOI: https://doi.org/10.1242/jcs.148296, PMID: 25908860

Ouyang M, Li X, Zhang J, Feng P, Pu H, Kong L, Bai Z, Rong L, Xu X, Chi W, Wang Q, Chen F, Lu C, Shen J, Zhang L. 2020. Liquid-Liquid phase transition drives Intra-chloroplast cargo sorting. Cell 180:1144–1159. DOI: https://doi.org/10.1016/j.cell.2020.02.045, PMID: 32169217

Panciera T, Azollini L, Cordenonsi M, Piccolo S. 2017. Mechanobiology of YAP and TAZ in physiology and disease. Nature Reviews Molecular Cell Biology 18:758–770. DOI: https://doi.org/10.1038/nrm.2017.87, PMID: 28951564

Patel A, Lee HO, Jawerth L, Maharana S, Jahnle M, Hein MY, Stoynov S, Mahamid J, Saha S, Franzmann TM, Pozniakowski A, Poser I, Magheli N, Royer LA, Weigert M, Myers EW, Grill S, Dreschel D, Hyman AA, Alberti S. 2015. A Liquid-to-Solid phase transition of the ALS protein FUS accelerated by disease mutation. Cell 162:1066–1077. DOI: https://doi.org/10.1016/j.cell.2015.07.047, PMID: 26317470

Pearson M, Carbone R, Sebastiani C, Cicco M, Fagiolli M, Saito S, Higashimoto Y, Appella E, Minucci S, Pandolfi PP, Pelicci PG. 2000. PML regulates p53 acetylation and premature senescence induced by oncogenic ras. Nature 406:207–210. DOI: https://doi.org/10.1038/350181127, PMID: 10910364

Peskett TR, Rau F, O’Driscoll J, Patani R, Lowe AR, Saibil HR. 2018. A liquid to solid phase transition underlying pathological huntingtin in exon1 aggregation. Molecular Cell 70:588–601. DOI: https://doi.org/10.1016/j.molcel.2018.04.007, PMID: 29734822

Pessina F, Giavazzi F, Yin Y, Gioia U, Vitelli V, Galbiati A, Barozzi S, Garre M, Oldani A, Flaus A, Cerbonio R, Parazzoli D, Rothenberg E, d’Adda di Fagagna F. 2019. Functional transcription promoters at DNA double-strand breaks mediate RNA-driven phase separation of damage-response factors. Nature Cell Biology 21:1286–1299. DOI: https://doi.org/10.1038/s41556-019-0392-4, PMID: 31507834

Plyas AJ, Davis CP, Kim J, Rizki G, Keenen MM, Marr SK, Kingston RE. 2019. Phase separation of Polycomb-repressive complex 1 is governed by a charged disordered region of CBX2. Genes & Development 33:799–813. DOI: https://doi.org/10.1101/gad.326488.119, PMID: 31171700

 Pronobis MI, Rusan NM, Peifer M. 2015. A novel GSK3-regulated APC:axin interaction regulates wnt signaling by driving a catalytic cycle of efficient βcatenin destruction. eLife 4:e08022. DOI: https://doi.org/10.7554/eLife.08022, PMID: 26393419

Qamar S, Wang G, Randle SJ, Ruggeri FS, Varela JA, Lin QJ, Phillips EC, Miyashita A, Williams D, Ströhl F, Meadows W, Ferry R, Dardov VJ, Tartaglia GG, Farrer LA, Kaminski Schierle GS, Kaminski CF, Holt CE, Fraser PE, Schmitt-Ulms G, et al. 2018. FUS phase separation is modulated by a molecular chaperone and methylation of arginine Cation-stabilized RNA and sumoylation. Protein & Cell 11:202–207. DOI: https://doi.org/10.1007/s13238-019-00660-y, PMID: 31894537

Qiu W, Wang Z, Zhang H. 2020. Phase separation of the C. elegans Polycomb protein SOP-2 is modulated by RNA and sumoylation. Protein & Cell 11:202–207. DOI: https://doi.org/10.1007/s13238-019-00660-y, PMID: 31894537

Rai AK, Chen JX, Selbach M, Pelkmans L. 2018. Kinase-controlled phase transition of membraneless organelles in mitosis. Nature 559:211–216. DOI: https://doi.org/10.1038/s41586-018-0129-9, PMID: 29973724

Riback JA, Katsanis CD, Kear-Scott JL, Pilipenko EV, Roejk AE, Sonnink TR, Drummond DA. 2017. Stress-Triggered phase separation is an adaptive, evolutionarily tuned response. Cell 168:1028–1040. DOI: https://doi.org/10.1016/j.cell.2017.02.027, PMID: 28283059

Ries RJ, Zaccara S, Klein P, Olarerin-George A, Namkoong S, Pickering BF, Patil DP, Kwak H, Lee JH, Jaffrey SR. 2019. m6A enhances the phase separation potential of mRNA. Nature 571:424–428. DOI: https://doi.org/10.1038/s41586-019-1374-1, PMID: 31292544

Ruggero D. 2013. Translational control in Cancer etiology. Cold Spring Harbor Perspectives in Biology 5:012336. DOI: https://doi.org/10.1101/cshperspect.a012336, PMID: 23276761

Sabari BR, Dall’Agnese A, Bovia G, Klein IA, Coffey EL, Shrivos K, Abraham BJ, Hannett NM, Zamudio AV, Mantegia JC, Li CH, Guo YE, Day DS, Schuijers J, Vasile E, Malik S, Hnisz D, Lee TI, Cisse II, Roeder RG, et al. 2018. Oncogenic signaling pathways in the Cancer genome atlas. Cell 173:321–337. DOI: https://doi.org/10.1016/j.cell.2018.02.045, PMID: 29265050

Sanders DW, Kedersha N, Lee DSW, Strom AR, Drake V, Riback JA, Bracha D, Eftens JM, Iwanicki A, Wang A, Wei MT, Whitney G, Lyons SM, Anderson P, Jacobs WM, Ivanov P, Brangwynne CP. 2020. Competing Protein-RNA interaction networks control multiphase intracellular organization. Cell 181:306–324. DOI: https://doi.org/10.1016/j.cell.2020.03.050, PMID: 32302570

Sawyer IA, Sturgill D, Dundr M. 2019. Membraneless nuclear organelles and the search for phases within phases. Wiley Interdisciplinary Reviews: RNA 10:e1514. DOI: https://doi.org/10.1002/wrna.1514, PMID: 30362243
Schaef er KN, Bonello TT, Zhang S, Williams CE, Roberts DM, McKay DJ, Peifer M. 2018. Supramolecular assembly of the beta-catenin destruction complex and the effect of Wnt signaling on its localization, molecular size, and activity in vivo. PLOS Genetics 14:e1007339. DOI: https://doi.org/10.1371/journal.pgen.1007339, PMID: 29641560

Schaef er KN, Peifer M. 2019. Wnt/Beta-Catenin signaling regulation and a role for biomolecular condensates. Developmental Cell 48:429–444. DOI: https://doi.org/10.1016/j.devcel.2019.01.025, PMID: 30782412

Schwarz-Romond T, Merrifield C, Nichols BJ, Bienz M. 2005. The Wnt signaling effector dishevelled forms dynamic protein assemblies rather than stable associations with cytoplasmic vesicles. Journal of Cell Science 118:5269–5277. DOI: https://doi.org/10.1242/jcs.02645, PMID: 16263762

Schwarz-Romond T, Metcalfe C, Bienz M. 2007. Dynamic recruitment of axin by Dishevelled protein assemblies. Journal of Cell Science 120:2402–2412. DOI: https://doi.org/10.1242/jcs.002956, PMID: 17606995

Sengupta S, George RE. 2017. Super-Enhancer-Driven transcriptional dependencies in Cancer. Trends in Cancer 3:269–281. DOI: https://doi.org/10.1016/j.trecan.2017.03.006, PMID: 28718439

Sheu-Gruttadauria J, MacRae IJ. 2018. Phase transitions of mRISC. Cell 173:946–957. DOI: https://doi.org/10.1016/j.cell.2018.02.051, PMID: 29576456

Shin Y, Brangwynne CP. 2017. Liquid phase condensation in cell physiology and disease. Science 357:aaf4382. DOI: https://doi.org/10.1126/science.aaf4382, PMID: 28395776

Siezen RJ, Fisch MR, Slingsby C, Benedek GB. 1985. Opacification of gamma-crystallin solutions from calf Lens in relation to cold cataract formation. PNAS 82:1701–1705. DOI: https://doi.org/10.1073/pnas.82.6.1701, PMID: 3856852

Siezen RJ, Benedek GB. 1985. Controlled modulation of the phase separation and opacification temperature of purified bovine gamma IV-crystallin. Current Eye Research 4:1077–1085. DOI: https://doi.org/10.3109/027136859003352, PMID: 4604730

Sigismund S, Avanzato D, Lanzetti L. 2018. Emerging functions of the EGFR in Cancer. Molecular Oncology 12:3–20. DOI: https://doi.org/10.1002/mbio.201780261, PMID: 29124875

Somasekharan SP, El-Naggar A, Leprivier G, Cheng H, Haje S, Grunewald TG, Zhang F, Ng T, Delattre O, Evdokimova V, Wang Y, Gleave M, Sorensen PH. 2015. YB-1 regulates stress granule formation and tumor progression by translationally activating G3BP1. Journal of Cell Biology 208:913–929. DOI: https://doi.org/10.1083/jcb.201411047, PMID: 25800057

Spannl S, Tereshchenko M, Mastromarco GJ, Ihn SJ, Lee HO. 2019. Biomolecular condensates in neurodegeneration and Cancer. Traffic 20:890–911. DOI: https://doi.org/10.1111/tra.12704, PMID: 31609641

Stamos JL, Chu ML, Enos MD, Shah N, Weis WI. 2014. Structural basis of GSK-3 inhibition by N-terminal phosphorylation and by the wnt receptor LRp6. eLife 3:e01998. DOI: https://doi.org/10.7554/eLife.01998, PMID: 24642411

Stamos JL, Weis WI. 2013. The β-catenin destruction complex. Cold Spring Harbor Perspectives in Biology 5:a007898. DOI: https://doi.org/10.1101/cshperspect.a007898, PMID: 23169527

Strom AR, Emelyanov AV, Mir M, Fyodorov DV, Darzaqz X, Kerpen GH. 2017. Phase separation drives heterochromatin domain formation. Nature 547:241–245. DOI: https://doi.org/10.1038/nature22989, PMID: 28635957

Su X, Ditlev JA, Hui E, Xing W, Banjade S, Okrut J, King DS, Taunton J, Rosen MK, Vale RD. 2016. Phase separation of signaling molecules promotes T cell receptor signal transduction. Science 352:595–599. DOI: https://doi.org/10.1126/science.aad9964, PMID: 27056844

Sun D, Wu R, Zheng J, Li P, Yu L. 2018. Polyubiquitin chain-induced p62 phase separation drives autophagic cargo segregation. Cell Research 28:405–415. DOI: https://doi.org/10.1038/s41422-018-0017-7, PMID: 29507397

Tan AY, Manley JL. 2009. The TET family of proteins: functions and roles in disease. Journal of Molecular Cell Biology 1:82–92. DOI: https://doi.org/10.1093/jmcb/mjp025, PMID: 19735453

Tanaka T, Ishimoto C, Chylack LT. 1977. Phase separation of a protein-water mixture in cold cataract in the young rat Lens. Science 197:1010–1012. DOI: https://doi.org/10.1126/science.87736, PMID: 87736

Tatvosian R, Kent S, Brown K, Yao T, Duc HN, Huyhn TN, Zhen CY, Ma B, Wang H, Ren X. 2019. Nuclear condensates of the Polycystic kidney disease 2 (PKD2) chromosome 2 (CBX2) assemble through phase separation. Journal of Biological Chemistry 294:1451–1463. DOI: https://doi.org/10.1074/jbc.RA118.006620, PMID: 30514760

Tauber D, Tauber G, Khong A, Van Treeck B, Pelletier J, Parker R. 2020. Modulation of RNA condensation by the DEAD-Box protein elf4A. Cell 180:411–426. DOI: https://doi.org/10.1016/j.cell.2019.12.031, PMID: 31928844

Thedieck K, Holzwarth B, Prentzell MT, Boehlke C, Klaßener K, Ruf S, Sonntag AG, Maerz L, Grellscheid SN, Kremmer E, Nitschke R, Kuehn EW, Jonker JW, Groen AK, Reth M, Hall MN, Baumeister R. 2013. Inhibition of mTORC1 by astrin and stress granules prevents apoptosis in Cancer cells. Cell 154:859–874. DOI: https://doi.org/10.1016/j.cell.2013.07.031, PMID: 23953116

Todorici J, Antonucci L, Di Caro G, Li N, Wu X, Mihalcheva A, Dhar H, Banerjee S, Fagman JB, Browne CD, Umemura T, Manley JL. 2009. The TET family of proteins: functions and roles in disease. Journal of Molecular Cell Biology 1:82–92. DOI: https://doi.org/10.1093/jmcb/mjp025, PMID: 19735453
carcinogenesis by maintaining survival of stressed HCC-Initiating cells. Cancer Cell 29:935–948. DOI: https://doi.org/10.1016/j.ccell.2016.04.006, PMID: 27211490

Valentin-Vega YA, Wang YD, Parker M, Patmore DM, Kanagaraj A, Moore J, Rusch M, Finkelstein D, Ellison DW, Gilbertson RJ, Zhang J, Kim HJ, Taylor JP. 2016. Cancer-associated DDX3X mutations drive stress granule assembly and impair global translation. Scientific Reports 6:25996. DOI: https://doi.org/10.1038/srep25996, PMID: 27180651

Vernon RM, Chong PA, Tsang B, Kim TH, Bah A, Farber P, Lin H, Forman-Kay JD. 2018. Pi–Pi contacts are an overlooked protein feature relevant to phase separation. eLife 7:e31486. DOI: https://doi.org/10.7554/eLife.31486, PMID: 29424691

Voisset E, Moravcsek E, Stratford EW, Jave A, Palgrave CJ, Hills RK, Salomoni P, Kogan SC, Solomon E, Grimwade D. 2018. Pml nuclear body disruption cooperates in APL pathogenesis and impairs DNA damage repair pathways in mice. Blood 131:636–648. DOI: https://doi.org/10.1182/blood-2017-07-794784, PMID: 29191918

Voussin KH, Prives C. 2009. Blinded by the light: the growing complexity of p53. Cell 137:413–431. DOI: https://doi.org/10.1016/j.cell.2009.04.037, PMID: 19410540

Wang J, Choi JM, Holehouse AS, Lee HO, Zhang X, Jahnell M, Maharana S, Lemaître R, Pozniakovsky A, Drechsel D, Poser I, Pappu RV, Alberti S, Hyman AA. 2018a. A molecular grammar governing the driving forces for phase separation of Priorn-like RNA binding proteins. Cell 174:688–699. DOI: https://doi.org/10.1016/j.cell.2018.06.006, PMID: 29961577

Wang M, Tao X, Jacob MD, Bennett CA, Ho JJD, Gonzalgo ML, Audas TE, Lee S. 2018b. Stress-Induced low complexity RNA activates physiological amyloidosynthesis. Cell Reports 24:1713–1721. DOI: https://doi.org/10.1016/j.celrep.2018.07.040, PMID: 30110628

Wang S, Zhang Q, Wang Q, Shen Q, Chen X, Li Z, Zhou Y, Hou J, Xu B, Li N, Cao X. 2018c. NEAT1 paraspeckle promotes human hepatocellular carcinoma progression by strengthening IL-6/STAT3 signaling. Oncoimmunology 7:e1503913. DOI: https://doi.org/10.1080/2162402X.2018.1503913, PMID: 30377567

Wang M, Bokros M, Theodoridis PR, Lee S. 2019. Nucleolar sequestration: remodeling nucleoli into amyloid bodies. Frontiers in Genetics 10:1179. DOI: https://doi.org/10.3389/fgene.2019.01179, PMID: 31824572

Weaver AN, Yang ES. 2013. Beyond DNA repair: additional functions of PARP-1 in Cancer. Frontiers in Oncology 3:290. DOI: https://doi.org/10.3389/fonc.2013.00290, PMID: 24350055

Wegmann S, Eftekharzadeh B, Tepper K, Zolotowska KM, Bennett RE, Dujardin S, Laskowski PR, MacKenzie D, Kamath T, Commens C, Vanderburg J, Roe AD, Fan Z, Mollie AM, Hernandez-Vega A, Muller D, Hyman AA, Mandelkow E, Taylor JP, Hyman BT. 2018. Tau protein liquid-liquid phase separation can initiate tau aggregation. The EMBO Journal 37:e98049. DOI: https://doi.org/10.15252/embj.201798049, PMID: 29472250

Wheeler JR, Matheny T, Jain S, Abrisch R, Parker R. 2016. Distinct stages in stress granule assembly and disassembly. eLife 5:e18413. DOI: https://doi.org/10.7554/eLife.18413, PMID: 27602576

Wippich F, Bodenmiller B, Trajkovska MG, Wanka S, Aebersold R, Pelkmans L. 2013. Dual specificity kinase DYRK3 couples stress granule condensation/dissolution to mTORC1 signaling. Cell 152:791–805. DOI: https://doi.org/10.1016/j.cell.2013.01.033, PMID: 23415227

Woodruff JB, Hyman AA, Boke E. 2018. Organization and function of Non-dynamic biomolecular condensates. Trends in Biochemical Sciences 43:81–94. DOI: https://doi.org/10.1016/j.tibs.2017.11.005, PMID: 29258725

Wu H. 2013. Higher-order assemblies in a new paradigm of signal transduction. Cell 153:287–292. DOI: https://doi.org/10.1016/j.cell.2013.03.013, PMID: 23582320

Yamamoto A, Simonsen A. 2011. The elimination of accumulated and aggregated proteins: a role for aggrephagy in neurodegeneration. Neurobiology of Disease 43:17–28. DOI: https://doi.org/10.1016/j.nbd.2010.08.015, PMID: 20732422

Yamazaki T, Souquere S, Chuo T, Kobelke S, Chong YS, Fox AH, Bond CS, Nakagawa S, Pierron G, Hirose T. 2018. Functional domains of NEAT1 architectural IncRNA induce paraspeckle assembly through phase separation. Molecular Cell 70:1038–1053. DOI: https://doi.org/10.1016/j.molcel.2018.05.019, PMID: 29932899

Yang P, Mathieu C, Kolaitis RM, Zhang P, Messing J, Yurtssever U, Yang Z, Wu J, Li Y, Pan Q, Yu J, Martin EW, Wittig T, Kim HJ, Taylor JP. 2020. G3BP1 is a tunable switch that triggers phase separation to assemble stress granules. Cell 181:325–345. DOI: https://doi.org/10.1016/j.cell.2020.03.046, PMID: 32302571

Yasuda S, Tsuchiya H, Kaiho A, Guo Q, Ikeuchi K, Endo A, Arai N, Ohtake F, Murata S, Inada T, Baumeister W, Fernández-Busnadiego R, Tanaka K, Saeki Y. 2020. Stress- and ubiquitylation-dependent phase separation. Nature 578:296–300. DOI: https://doi.org/10.1038/s41586-020-1982-9, PMID: 32052036

Yeager TR, Neumann AA, Englezoa U, Huschtscha LI, Noble JR, Reddel RR. 1999. Telomerase-negative immortalized human cells contain a novel type of promyelocytic leukemia (PML) body. Cancer Research 59:736–746. DOI: https://doi.org/10.1158/0008-5472.CAN-98-0217, PMID: 10458449

Yu H, Lee H, Herrmann A, Buettner R, Jove R. 2014. Revisiting STAT3 signalling in Cancer: new and unexpected biological functions. Nature Reviews Cancer 14:736–746. DOI: https://doi.org/10.1038/nrc3818, PMID: 25342631

Zaffagnini G, Savova A, Danieli A, Romanov J, Tremel S, Ebner M, Peterbauer T, Sztacho M, Trappanone R, Tarafder AK, Sachse C, Martens S. 2018. p62 filaments capture and present ubiquitinated cargos for autophagy. The EMBO Journal 37:e98308. DOI: https://doi.org/10.15252/embj.201798308, PMID: 29343546

Zamudio AV, Dall’Agnese A, Henninger JE, Mantegna JC, Aisean LK, Hennett NM, Coffey EL, Li CH, Oskuz O, Sabari BR, Boija A, Klein IA, Hawken SW, Spille JH, Decker TM, Cisse II, Abraham BJ, Lee TI, Taatjes DJ, Schuijers J, et al. 2019. Mediator condensates localize signaling factors to key cell identity genes. Molecular Cell 76:753–766. DOI: https://doi.org/10.1016/j.molcel.2019.08.016, PMID: 31563432
Zanconato F, Cordenonsi M, Piccolo S. 2016. YAP/TAZ at the roots of Cancer. Cancer Cell 29:783–803. DOI: https://doi.org/10.1016/j.ccell.2016.05.005, PMID: 27300434

Zanconato F, Cordenonsi M, Piccolo S. 2019. YAP and TAZ: a signalling hub of the tumour microenvironment. Nature Reviews Cancer 19:454–464. DOI: https://doi.org/10.1038/s41568-019-0168-y, PMID: 31270418

Zeng C, Xu Y, Xu L, Yu X, Cheng J, Yang L, Chen S, Li Y. 2014. Inhibition of long non-coding RNA NEAT1 impairs myeloid differentiation in acute promyelocytic leukemia cells. BMC Cancer 14:693. DOI: https://doi.org/10.1186/1471-2407-14-693, PMID: 25245097

Zeng C, Liu S, Lu S, Yu X, Lai J, Wu Y, Chen S, Wang L, Yu Z, Luo G, Li Y. 2018. The c-Myc-regulated IncRNA NEAT1 and paraspeckles modulate imatinib-induced apoptosis in CML cells. Molecular Cancer 17:130. DOI: https://doi.org/10.1186/s12943-018-0884-z, PMID: 30153828

Zhan T, Rindtorff N, Boutros M. 2017. Wnt signaling in cancer. Oncogene 36:1461–1473. DOI: https://doi.org/10.1038/onc.2016.304, PMID: 27617575

Zhang H, Zhao R, Tones J, Liu M, Dilley RL, Chenoweth DM, Greenberg RA, Lampson MA. 2020. Nuclear body phase separation drives telomere clustering in ALT Cancer cells. Molecular Biology of the Cell 31:2048–2056. DOI: https://doi.org/10.1091/mbc.E19-10-0589, PMID: 32579423

Zhang L, Shay JW. 2017. Multiple roles of APC and its therapeutic implications in colorectal Cancer. JNCI: Journal of the National Cancer Institute 109: djw332. DOI: https://doi.org/10.1093/jnci/djw332, PMID: 28423402

Zhu L, Brangwynne CP. 2015. Nuclear bodies: the emerging biophysics of nucleoplasmic phases. Current Opinion in Cell Biology 34:23–30. DOI: https://doi.org/10.1016/jceb.2015.04.003, PMID: 25942753