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Summary

Malignant transformation is characterized by dysregulation of diverse cellular processes that have been the subject of detailed genetic, biochemical, and structural studies, but only recently has evidence emerged that many of these processes occurs in the context of biomolecular condensates. Condensates are membraneless bodies, often formed by liquid-liquid phase separation, that compartmentalize protein and RNA molecules with related functions. New insights from condensate studies portend a profound transformation in our understanding of cellular dysregulation in cancer. Here we summarize key features of biomolecular condensates, note where they have been implicated – or will likely be implicated - in oncogenesis, describe evidence that the pharmacodynamics of cancer therapeutics can be greatly influenced by condensates, and discuss some of the questions that must be addressed to further advance our understanding and treatment of cancer.

Keywords

Biomolecular condensates, phase separation, cancer, dysregulated state, cancer therapeutics, instrinsically disordered protein.

Main Text

Introduction

Decades of investigation into cancer pathophysiology has revealed that diverse cellular processes become dysregulated in the malignant state. This includes maintenance of genome integrity, chromatin structure, transcription, RNA processing, proliferative signaling and others (Bradner et al., 2017; Hanahan and Weinberg, 2000, 2011; Jeggo et al., 2016; Labbé and Brown, 2018; Morgan and Shilatifard, 2015; Negrini et al., 2010; Stehelin et al., 1976; Wang and Aifantis, 2020). These processes occur throughout the cellular space, involving protein, DNA, and RNA molecules, interacting with spatial and temporal precision. These cellular processes have been the subject of much study, producing a deep mechanistic understanding of cellular regulation in both normal and

transformed cells, and providing therapeutic hypotheses that have yielded advances in medicine (Chmielecki and Meyerson, 2014; Sawyers, 2004; Vogelstein et al., 2013). Recent studies, however, have revealed that most cellular processes are compartmentalized in biomolecular condensates, which have physicochemical properties that contribute to regulatory mechanisms beyond those anticipated by conventional molecular biology (Banani et al., 2017; Choi et al., 2020; Forman-Kay et al., 2018; Hyman et al., 2014; Jiang et al., 2020; Shin and Brangwynne, 2017). This new understanding has compelled us and others to examine how condensate biology contributes to oncogenesis and consider new therapeutic hypotheses that might be exploited to benefit cancer patients.

Biomolecular condensates are non-membrane bound organelles that compartmentalize and concentrate components involved in similar cellular processes. In contrast to classic membrane-bound organelles like the nucleus, mitochondria, and golgi apparatus, these structures are not constrained by a lipid bilayer, and are not constituitive stable features of the cell. Rather, they often form reversibly and dynamically by virtue of phase separation. Biological phase separation is governed, in part, by weak, multi-valent and dynamic interactions among proteins and nucleic acid polymers (Alberti, 2017; Boeynaems et al., 2018; Riback et al., 2020). At a threshold of concentration and affinity, these biomolecules can coalesce into liquid-like droplets that compartmentalize and regulate biochemical reactions. Many of the cellular processes dysregulated in cancer have recently been shown to occur in biomolecular condensates. This has prompted investigators to begin asking how oncogenic alterations impact condensate biology and contribute to the malignant state. In addition, recent evidence that condensates influence the pharmacodynamic behavior of small molecule drugs suggests novel therapeutic approaches for cancer (Klein et al., 2020).

In this review, we summarize how the study of condensates is advancing our understanding of cancer and leading to novel therapeutic hypotheses. We survey the broad array of cellular condensates that have been described thus far and describe their shared features. We then discuss the various ways in which condensates are altered in malignancy, with a focus on how condensate physicochemical properties can contribute to dysregulated cellular processes. Condensates influence antineoplastic drug pharmacodynamics and we suggest how this can be exploited to develop a new generation of cancer therapies. Finally, we highlight key areas for future investigation and speculate on how condensates might contribute to furthering new discoveries in cancer biology.

Biomolecular Condensates

The cell is organized by diverse membrane bound compartments such as the nucleus and mitochondria, as well as dozens of non-membrane condensates located throughout the nucleus and cytoplasm (Figure 1) (Banani et al., 2017). Whereas classical biochemical complexes have defined stoichiometry, condensates are non-stoichiometric assemblies composed of biomolecules with weak multivalent interactions. Thus, they form a local concentration of molecules that continuously exchange with the surrounding bulk phase (Kato et al., 2012; Li et al., 2012; Sanders et al., 2020).

The behavior of polymers in solution can be described by simple thermodynamic models that illuminate the behaviors of condensates and their constituent components. The Flory-Huggins theory describes the free energy of mixing polymers within solvent, and has been useful in explaining some of these behaviors (Brangwynne et al., 2015; Chen and Kriwacki, 2018; Flory, 1942). At thresholds of concentration and affinity, the net attraction between polymers drives phase separation into polymer-rich and polymer-poor phases. Alterations to the polymer structure or composition, the affinity between polymers, and the environment can change the point at which a condensate forms - thus modest perturbations can result in fundamental shifts in a phase-separating system. (Banani et al., 2016; Dignon et al., 2019; Pak et al., 2016; Riback et al., 2017, 2020; Yoo et al., 2019). Applying such principles to polymer-like biomolecules and their resulting condensates can help explain their functional behaviors as well as their dysfunction in diverse disease states.

Proteins with intrinsically disordered protein regions (IDRs), repeats of short oligomerizing motifs, and nucleic acid chains are biopolymers that have been observed to promote condensate formation (Banani et al., 2016; Bienz, 2020; Gomes and Shorter, 2019; Harmon et al., 2017; Jain and Vale, 2017; Pak et al., 2016; Shrinivas et al., 2019) (Figure 2A). The formation of condensates, and selective partitioning of biomolecules into condensates, has been attributed to specific weak and dynamic interactions among the molecules, including salt bridges, pi-pi, pi-cation, and hydrophobic interactions (Brangwynne et al., 2015; Lin et al., 2017; Vernon et al., 2018; Wang et al., 2018) (Figure 2B). Condensates are formed when the concentration of, and interaction strength between, biopolymers reach a threshold level where the interactions favoring assembly overcome opposing forces (Figure 2C).

Biomolecular condensation involves multivalent interactions between an indefinite number of components that undergo self assembly via clustering, which is distinct from formation of smaller stoichiometric protein complexes with defined numbers of subunits, such as a 12-subunit RNA polymerase II complex or a viral capsid (Banani et al., 2017). Biomolecular condensates are thought to arise by either liquid-liquid or liquid-solid phase transition (Boeynaems et al., 2018; Hyman et al., 2014; Peran and Mittag, 2020; Posey et al., 2018; Woodruff et al., 2018). Thus, condensates can have properties of liquids, gels or solids, and liquid condensates can “age” to take on properties of gels or solids. These properties can produce condensates with various shapes, dimensions and behaviors (Molliex et al., 2015; Patel et al., 2015). Classic references to these nonmembrane assemblies have used diverse descriptive terms such as bodies, puncta, dots, granules, inclusions, aggregates, etc. It is likely that all of these assemblies are governed by physicochemical properties that are now under intense study in the fields of soft matter physics, chemistry, and biology.

Condensates have properties distinct from the surrounding mileu that allow for novel functions. Condensates can compartmentalize large numbers of biomolecules with related functions, thus concentrating components and accelerating biochemical reactions (Alberti et al., 2019; Banjade and Rosen, 2014; Case et al., 2019a; Huang et al., 2019; Li

et al., 2012; Sheu-Gruttadauria and MacRae, 2018; Su et al., 2016; Woodruff et al., 2017; Zhang et al., 2020c). Condensates can be localized to specific sites in cells anchored, for example, by components that interact with DNA sequences or membranes (Boija et al., 2018; Case et al., 2019a; Feng et al., 2018; Huang et al., 2019; Sabari, 2020; Sabari et al., 2020; Shrinivas et al., 2019; Zeng et al., 2018). Condensate regulation can occur through modification of concentration or affinity of components, as well as through their selective partitioning. The attributes of condensates that contribute to cellular function - compartmentalization, localization, and regulation - are discussed further below.

Compartmentalization

Condensates provide a means to organize the 5-10 billion protein molecules of the cell into distinct cellular compartments with specific functions. Cellular processes such as transcription and DNA damage repair typically involve dozens of different biomolecules that must engage with temporal and spatial precision. Compartmentalization allows for high local concentration of biomolecules and their substrates, and exclusion of other molecules that are not functionally relevant (Figure 3A) (Gibson et al., 2019; Li et al., 2020). In addition, condensates are non-stoichiometric assemblies of factors involved in shared processes so, for example, a condensate at the promoter of a gene can assemble multiple RNA polymerase molecules, thereby producing a burst of transcription (Cho et al., 2018; Guo et al., 2019; Kwon et al., 2013; Sabari et al., 2018; Wei et al., 2020). Condensates can form and dissolve in short time frames, which provides the cell with a means to produce transient compartments, thereby releasing biomolecules for use elsewhere when they are no longer needed at a specific location (Guillén-Boixet et al., 2020). Compartmentalization in condensates also serves to stabilize protein concentration in cells by buffering the inherent stochasticity in gene expression (Klosin et al., 2020). Furthermore, condensates can be organized in multiple phases, one surrounding another, to enable spatiotemporal regulation of a process. For example, nucleoli consist of distinct liquid phases where RNA Polymerase I and FIB1 occur within a larger NPM1 condensate, allowing for the synthesis of rRNA molecules and spatiotemporal regulation of pre-ribosome assembly (Feric et al., 2016; Mitrea et al., 2018).

Localization

Condensates often contain components that can anchor the body to a specific location in the cell. For example, nuclear condensates can form with proteins that bind to specific DNA or RNA sequences and cytoplasmic condensates can form at sites on the plasma membrane (Figure 3B) (Boija et al., 2018; Case et al., 2019a; Guillén-Boixet et al., 2020; Huang et al., 2019; Shrinivas et al., 2019; Su et al., 2016; Wei et al., 2020). Transcriptional condensates form at specific enhancer and promoter elements by virtue of selective transcription factor (TF) binding (Boija et al., 2018; Shrinivas et al., 2019). TFs are bifunctional proteins that contain both a structured DNA binding domain and an IDR that can condense with coactivator proteins (Sabari et al., 2020). The enhancer and promoter elements contain multiple TF binding sites, thus crowding the TFs and driving assembly of TFs and coactivators past the threshold for phase separation (Shrinivas et al., 2019). Constituituve heterochromatin condensates form at methylated satellite repeats, due in part to the binding of methylated DNA by MeCP2 and methylated histone H3K9 by HP1

proteins (Larson et al., 2017; Li et al., 2020; Strom et al., 2017). Facultative heterochromatin condensates form at sites of trimethylated H3K27 by virtue of Polycomb-repressive complex phase separation (Plys et al., 2019; Tatavosian et al., 2019). Similarly, ligand binding by cell surface signaling receptors can elevate signaling component concentration at the plasma membrane and thereby stimulate formation of condensates with signaling molecules (Case et al., 2019a; Huang et al., 2019; Su et al., 2016).

Regulation

Condensates can be regulated at many levels, as anything that changes the properties that influence formation, dissolution, viscoelasticity, and other physicochemical properties can modify condensate function (Figure 3C). We discuss specific features that play prominent roles in condensate regulation - concentration, chemical modification, selective partitioning and noncoding RNA - here because they are known, or likely, to be dysregulated in cancer cells.

The concentration of biomolecules is a key parameter in condensate formation and dissolution. Condensation occurs at a threshold concentration, which can be achieved through increased biosynthesis, reduced degradation, transport into a membrane-bound compartment, or binding to a substrate with multiple binding sites. The loss of the nuclear membrane during mitosis reduces the concentration of nuclear components and is associated with dissolution of nuclear condensates (Dammermann and Merdes, 2002; Rai et al., 2018; Sivan et al., 2007; Spector and Smith, 1986). The nuclear condensates reform when the nuclear envelope is re-established, which may in part be due to the higher concentration of components enabled by transport of proteins into the nucleus.

Chemical modification, such as the post-translational modification of histone proteins, alters the physicochemical properties of proteins and thus the condensates with which they associate. Chromatin can occur in phase-separated condensates, and the behavior of chromatin in unmodified and modified states provides an example of this type of regulation. Repressed genes are generally associated with unacetylated nucleosomes whereas active genes are associated with acetylated nucleosomes (Bradner et al., 2017). Organized into separate subdomains within the nucleus, these two types of chromatin are highly compact yet dynamically accessible to regulation by diverse modifying enzymes and proteins that bind the modified nucleosomes (Larson et al., 2017; Li et al., 2020; Sabari et al., 2018; Strom et al., 2017). Reconstituted unmodified chromatin can undergo liquid-liquid phase separation due to the IDRs of histone tails, producing dense and dynamic droplets. Acetylation of this chromatin in the presence of BRD4, a protein that binds acetylated nucleosomes at active genes, produces a different phase-separated state, with droplets that exhibit distinct physical properties. The acetylated chromatin becomes less miscible with unmodified chromatin droplets, mimicking the separation of chromatin subdomains observed in cells (Gibson et al., 2019). The histone tails are subjected to diverse chemical modifications that alter the physicochemical properties of chromatin and thus each modification has the potential to modulate chromatin condensate behavior.

RNA molecules play regulatory roles in diverse biomolecular condensates, including the nucleolus, transcriptional condensates, co-transcriptional splicing condensates, nuclear speckles, paraspeckles, and stress granules (Fay and Anderson, 2018; Guo et al., 2019; Henninger et al., 2021; Roden and Gladfelter, 2020; Sabari, 2020; Strom and Brangwynne, 2019) (Fay and Anderson, 2018; Roden and Gladfelter, 2020; Sabari et al., 2020; Strom and Brangwynne, 2019). Condensates are formed by an ensemble of low-affinity molecular interactions, including electrostatic interactions, and RNA can be a powerful regulator of condensates that are formed and maintained by these forces (Banani et al., 2017; Elbaum-Garfinkle et al., 2015; Henninger et al., 2021; Maharana et al., 2018; Peran and Mittag, 2020; Shin and Brangwynne, 2017; Zhang et al., 2015a). The functions of the vast majority of noncoding RNA species expressed in cells is not known and it seems likely that many will be found to play regulatory roles in diverse condensates.

Selective partitioning of biomolecules into specific condensates allows for high local concentration of functionally related molecules. The behaviors of proteins involved in chromatin and transcriptional condensates provide instructive examples of selective biomolecular partitioning. Some euchromatic and heterochromatic proteins selectively partition into condensates formed by other components of euchromatin and heterochromatin, and this partitioning behavior may contribute to the separation of these two compartments in the nucleus (Fasciani et al., 2020; Li et al., 2020). Phosphorylation of RNA polymerase II during transcription initiation causes the polymerase to switch between transcriptional and splicing condensates, illustrating how IDR modification can change the partitioning behavior of a macromolecule (Guo et al., 2019; Kwon et al., 2013).

Condensate Dysregulation in Cancer

Cancer cells acquire mutations that affect diverse condensate-mediated cellular processes, including transcription, chromatin structure, proliferative signaling and others. The study of condensates in cancer cells is in its infancy, but there are already notable examples of dysregulated condensates that have been reported, and the known effects of cancer mutations on the concentration and modification of regulatory biomolecules predict that condensate dysregulation is a common feature of cancer cells.

Dysregulated Compartmentalization

Cancer cells acquire genomic alterations that activate oncogenes and inactivate tumor suppressor genes (Kastenhuber and Lowe, 2017; Prior et al., 2012). Both oncogene activation and tumor suppressor inactivation involve condensate compartments that can become dysregulated in malignant cells (Figure 4A and Table 1).

Oncogene activation is often accomplished by formation of super-enhancers, which are clusters of enhancers occupied by exceptionally high densities of transcriptional components that drive high-level expression of genes (Bradner et al., 2017; Hnisz et al., 2013; Lovén et al., 2013). Super-enhancers promote formation of phase-separated condensates that draw together the clustered DNA elements into a non-membrane compartment (Figure 4A) (Cho et al., 2018; Sabari et al., 2018). These condensates are nucleated by binding of multiple TF molecules to genomic regulatory elements where TF activation domains, many of which are IDRs, condense with transcriptional coactivators

(Boija et al., 2018; Chong et al., 2018; Nair et al., 2019; Shrinivas et al., 2019). These compartments can then recruit hundreds of molecules of RNA polymerase II to effect transcription of target genes (Cho et al., 2018; Cisse et al., 2013). Thus, oncogene activation often involves condensate-mediated compartmentalization of high densities of transcription apparatus at driver oncogenes. Mutations have been observed to affect many components of these transcriptional condensates in cancer cells, and these are almost certain to cause condensate dysregulation. These mutations alter the functional levels of lineage specific master TFs, MYC, signaling TFs, transcriptional cofactors and RNA polymerase II itself (Bhagwat and Vakoc, 2015; Bradner et al., 2017).

Cancer cell sequencing has revealed recurrent mutations that affect both histones and their regulatory proteins, and these are likely to alter the landscape of chromatin condensates (Figure 4B). For example, the oncogenic histone mutation H3K27M frequently occurs in childhood brainstem gliomas and changes the chromatin landscape from poised to active at bivalent promoters, resulting in dysregulated gene expression (Larson et al., 2019; Schwartzentruber et al., 2012; Wu et al., 2014). The histone mutation H3K36M, which is recurrent in chondroblastoma and drives sarcoma development, inhibits the activity of histone methyltransferases and causes global changes in gene expression (Lu et al., 2016). Diverse chromatin regulators, including histone modifying enzymes (writers and erasers), proteins that bind selectively to modified histones (readers), and proteins involved in nucleosome mobilization are mutated in specific cancers (Bradner et al., 2017; Valencia and Kadoch, 2019). Thus, oncogenic mutations that alter chromatin condensates are likely to be a common theme in cancer cells.

Dysregulated condensate compartmentalization has also been observed with tumor suppressors. The tumor repressor SPOP (Speckle-type POZ protein) is an E3 ligase that has been implicated in a wide range of solid tumors (Kim et al., 2013). SPOP forms condensates in a substrate dependent fashion, and cancer causing mutations in SPOP prevent the protein from condensing with its substrate and diminish its enzymatic activity (Bouchard et al., 2018). Similarly, the tumor suppressor promyelocytic leukemia protein (PML) forms nuclear bodies that lack membranes and are thought to be biomolecular condensates (Banani et al., 2016). PML-bodies compartmentalize a wide variety of proteins, including p53 and DNA repair factors, and have various roles in regulating cell function, including cell death and genome stability (Lallemand-Breitenbach and de Thé, 2010). PML loss of function mutations are associated with increased tumor formation and poor prognosis, and these phenotypes are coincident with alterations to the PML bodies (Zhu et al., 2018). Such alterations might compromise the ability of PML body condensates to partition clients and degrade oncoproteins.

Condensate Mislocalization

Cancer cells acquire several different types of mutations that alter transcriptional condensate localization, including INDELs, translocations and other chromosome rearrangements. Small INDELs have been shown to create oncogenic super-enhancers at genomic loci that do not normally harbor those elements. Recurrent small INDELs near the TAL1 gene in T-ALL were found to form a binding site for a single molecule of the MYB transcription factor, whose binding was found to initiate formation of a large super-

enhancer that drives oncogenic TAL1 expression in those cells (Mansour et al., 2014). The ability of a single transcription factor molecule to cause ectopic formation of an apparatus with hundreds of transcriptional components is now understood to be a reflection of the threshold behavior that is characteristic of phase-separated condensates, where the addition of a single transcription factor binding site can create switch-like effects (Shrinivas et al., 2019).

Translocations can effect malignant transformation in leukemias, lymphomas, and solid tumors. This often occurs by juxtaposing a super-enhancer to a proto-oncogene. In aggressive B cell lymphomas translocation of the IgH super-enhancer to the MYC locus is an oncogenic event that can now be understood as bringing a transcriptional condensate to the MYC gene (Figure 4C) (Klein et al., 2011; Lovén et al., 2013). Chromosome rearrangements and translocations may also create gene fusion events that effect condensate mislocalization. One such example is the fusion oncogenic protein EWS-FLI, composed of the disordered activation domain of the RNA binding protein EWS and the DNA binding domain of the transcription factor FLI1. EWS-FLI has been shown to form condensate-like structures (or hubs) that promote transcription of genes associated with Ewing Sarcoma (Chong et al., 2018). Diverse oncogenic translocations fuse IDRs to a DNA binding domain, and the ability of the disordered region to promote formation of transcriptional condensates may contribute to the oncogenic function of these fusion onco-TFs (Kumar-Sinha et al., 2015; Winters and Bernt, 2017).

Altered Regulation

A change in the concentration of any molecule that is contained in a condensate is likely to alter the behavior of that condensate. For example, oncogenic MYC protein accumulates to very high levels in transformed cells - it has been estimated that some tumor cells harbor 500,000 MYC molecules versus 10,000 molecules for a typical transcription factor – and MYC may alter the behavior of transcriptional condensates in these cells (Figure 4D) (Lin et al., 2012).

Post-translational modifications (PTMs) can alter the condensation of chromatin. Chromatin is regulated through diverse PTMs and cancer cells harbor mutations in a broad spectrum of histone modifying enzymes, histone reader proteins, and nucleosome mobilizing proteins (Bates, 2020; Mittal and Roberts, 2020; Morgan and Shilatifard, 2015; Pastore and Levine, 2016; Valencia and Kadoch, 2019). As one example, the BET bromodomain protein BRD4, which binds to chromatin through acetylated histones, is overexpressed in some solid tumors (Filippakopoulos et al., 2010; Rhyasen et al., 2018). Although it is possible that the dysregulated transcription in these cells is due simply to canonical binding of excess BRD4 to portions of the genome, evidence that large numbers of BRD4 molecules can assemble into a super-enhancer transcriptional condensate suggest that condensate alterations are in play (Sabari et al., 2018; Shin et al., 2018; Wei et al., 2020).

Noncoding RNA (ncRNA) molecules are components of well-studied biomolecular condensates, where they have various regulatory functions (Clemson et al., 2009; Daneshvar et al., 2020; Henninger et al., 2021; Yamazaki et al., 2018). In cancer cells,

ncRNAs are overexpressed (MALAT1, HOTAIR, SRA, CCAT2, LincRNAROR, lncRNA-ATB, LncTCF7, SCHLAP1, treRNA, ZEB2-AS1, UCA1), underexpressed (LET, DRAIC, EGOT, GAS5, MEG3, NBAT-1, NKILA, PCAT), and post-transcriptionally modified (Barbieri and Kouzarides, 2020; Wang et al., 2020). The levels of the lncRNA MALAT1, a component of nuclear speckles, have been shown to be increased in lung, breast, cervical, colorectal, bladder, and liver cancers (Li et al., 2018). Cells that improperly express these ncRNAs exhibit various dysregulated functions, with inconsistent and sometimes conflicting views on mechanisms of action. It seems likely that altered expression of these ncRNAs will alter the behavior of diverse condensates.

Revisiting mechanisms in common oncogenic events

The use of condensate models to reexamine the mechanisms involved in common oncogenic events (Figure 5) could lead to new insights and therapeutic approaches. Common events include dysregulated signaling, transcription, DNA damage, metabolism, cellular interactions, immune mechanisms, autophagy and angiogenesis, and we provide here some examples of new mechanistic models that might be considered in these areas.

Diverse signaling pathways controlling cell growth, division, and mobility are altered in cancer; signaling proteins may be overexpressed, mutated, or fused, causing over- or under-activation of the pathway (Klein et al., 2011; Sanchez-Vega et al., 2018; Sever and Brugge, 2015; Vogelstein and Kinzler, 2004; Wong et al., 2010; Zhan et al., 2017). Many of the proteins involved in cancer-associated signaling pathways have been shown to form condensates, thus regulating output of the pathway (Case et al., 2019b; Chong and Forman-Kay, 2016; Su et al., 2016). RAS activation occurs when ligand-bound membrane receptors recruit and modify adaptor proteins, and these adaptor proteins form condensates at the cell membrane that compartmentalize proteins, increasing their “dwell time” and RAS activity (Huang et al., 2019; Zhu et al., 2020). These same adaptor protein condensates also accelerate the rate of actin polymerization (Case et al., 2019a). cAMP-dependent protein kinase A (PKA) undergoes cAMP-dependent condensate formation, thus compartmentalizing this key signliang molecule, while a PKA fusion oncoprotein disables condensation and causes abberant signaling (Zhang et al., 2020b). Nuclear signaling proteins such as Wnt, TGF-Beta, and STAT condense with transcriptional coactivators to activate target genes, accounting for their cell-type specific effects (Zamudio et al., 2019). Taken together, a novel picture of signaling may be emerging, in which diverse signaling proteins achieve specificity by forming distinct cellular compartments that are disrupted in cancer.

Transcriptional dysregulation is a common feature of cancer cells, and evidence that gene regulation involves formation of transcriptional condensates should prompt some new thinking about dysregulated regulatory mechanisms. For example, MYC overexpression is a common event in many metastatic processes (Dang, 2012) and may produce transcriptional condensates at oncogenes that are more long-lived. Dysregulated proliferative signaling is a general feature of tumor cells, and evidence that the terminal components of signaling pathways tend to partition into super-enhancer associated transcriptional condensates (Zamudio et al., 2019) suggests that oncogenes that acquire super-enhancers, such as *MYC*, are efficiently targeted by dysregulated proliferative

signaling through condensate-associated mechanisms. Furthermore, MYC overexpression produces a broad spectrum of cellular effects, including changes in chromatin structure, ribosome biogenesis, metabolic pathways, cell adhesion, cell size, apoptosis, and angiogenesis, among others (Amati et al., 1998; Cole and Cowling, 2008; Cowling and Cole, 2010; Dai and Lu, 2008; Dang, 2012; Eilers and Eisenman, 2008; Facchini and Penn, 1998; Frank et al., 2001; Gallant, 2005; Hanahan and Weinberg, 2011; Herold et al., 2009; Hoffman and Liebermann, 2008; Hurlin and Dezfouli, 2004; Kuttler and Mai, 2006; Lin et al., 2009; Meyer and Penn, 2008; Nieminen et al., 2007; Nilsson and Cleveland, 2003; Peterson and Ayer, 2011; Van Riggelen et al., 2010; Ruggero, 2009; Secombe et al., 2004; Singh and Dalton, 2009). It is possible that most of these cellular effects are a secondary consequence of MYC's increased binding to DNA in the regulatory regions of active genes, with consequent amplification of transcriptional output (Lin et al., 2012; Nie et al., 2012). It is also possible that high levels of MYC cause interference with condensate compartments other than those involved in transcription.

The DNA damage response acts as a barrier to the malignant transformation of preneoplastic cells. Most cancer cells display defects in the DNA damage response, and the efficacy of DNA-damaging agents used in cancer treatment is highly influenced by cellular DNA repair capacity (Gavande et al., 2016). Drugs that inhibit remaining functional DNA repair pathways in cancer can be exploited to selectively kill some malignant cells (Leung, 2020; Oshidari et al., 2020; Pessina et al., 2019). Recent studies have revealed that DNA damage response factors, and RNA produced at sites of DNA damage, promote formation of condensates at the sites of repair and have suggested that selective disruption of these condensates might produce therapeutic benefit (Altmeyer et al., 2015; Chong et al., 2018; Kilic et al., 2019; Oshidari et al., 2020; Singatulina et al., 2019).

Metabolic reprogramming is a hallmark of malignancy - cancer cells adjust metabolic and nutrient acquisition to support growth and dissemination (Dayton et al., 2016; Vander Heiden, 2011; Hopkins et al., 2016; Martinez-Outschoorn et al., 2017; Pavlova and Thompson, 2016; Schulze and Harris, 2012; Shankaraiah et al., 2018). The metabolic phenotype exhibited by tumor cells - known as the Warburg effect - is characterized by high rates of aerobic glycolysis and has been a topic of special interest in cancer research (Hsu and Sabatini, 2008; Liberti and Locasale, 2016; Warburg, 1956). Transcriptional regulators of mitochondrial biosynthesis, metabolic enzymes and small metabolites are now thought to function in biomolecular condensates. The level of the transcriptional coactivator PGC-1α, which regulates transcriptional networks associated with mitochondrial biogenesis and function, is altered in diverse cancers (Gravel, 2018); PGC-1α is known to associate with diverse TFs and transcriptional cofactors (Puigserver et al., 1999; Wallberg et al., 2003), and this is now reported to occur via interaction with transcriptional condensates in an RNA-dependent fashion (Pérez-Schindler et al., 2020). Enzymes involved in carbohydrate, nucleotide, fatty acid and amino acid metabolic pathways have been observed in diverse condensates (An et al., 2008; Jin et al., 2017; O'Connell et al., 2012; Prouteau and Loewith, 2018; Prouteau et al., 2017; Zhang et al., 2020b). Metabolites and the cellular redox state have been shown to impact condensate

formation and behavior (Franzmann et al., 2018; Kato et al., 2019; Patel et al., 2017; Riback et al., 2017). Additional insights into dysregulated metabolic processes in cancer will almost certainly come from the study of signaling, transcriptional and enzymatic condensates.

Altered cell-cell interactions are a feature of the tumor microenvironment and are characteristic of the metastatic state of tumor cells. The extracellular matrix (ECM) is involved in these interactions and provides both physical scaffolding for the cell and mediates responses to biochemical and biomechanical cues that are required for normal morphogenesis, differentiation, and homeostasis (Lu et al., 2011). Deregulation of ECM dynamics promotes cancer cell proliferation, loss of cell differentiation, the epithelial-to-mesenchymal transition, and cancer cell invasion (Henke et al., 2020; Winkler et al., 2020). The multivalent interactions characteristic of ECM components are likely to be involved in diverse condensate behaviors. Elastin is the best-characterized extracellular matrix protein whose polymeric assembly is initiated by phase separation (Bellingham et al., 2003; Kozel et al., 2006; MacEwan and Chilkoti, 2010; Muiznieks et al., 2018; Reichheld et al.; Vrhovski et al., 1997). There are additional proteins that are thought to contribute to ECM dynamics and may be involved in tumor processes; as an example, galectin-3 agglutinated glycosylated molecules in the ECM tumor stroma are thought to undergo phase separation (Chiu et al., 2020). Improved understanding of condensate components and regulation in the ECM might provide novel therapeutic avenues in cancer.

The innate immune response serves as a sensor for oncogenic events and halts malignant transformation (Corrales et al., 2017; Gajewski et al., 2013; Wellenstein and De Visser, 2018; Woo et al., 2015). As a consequence of genomic insults occurring early in the course of oncogenesis, DNA fragments translocate to the nucleus, providing a cellular “danger signal” (Dhanwani et al., 2018; Paludan and Bowie, 2013; Won and Bakhoum, 2020). Cytoplasmic DNA sensing and the downstream response is critical for anticancer immune responses and has generated excitement as a potential therapeutic opportunity (Chin et al., 2020; Pan et al., 2020). The cytoplasmic DNA sensor is now understood to be a condensate that forms in response to this cellular stress. Upon binding DNA, cGAS forms cytoplasmic condensates to generate cyclic AMP, and this in turn activates STING to induce cytokine production and an appropriate immune response (Du and Chen, 2018; Liu et al., 2018; Sun et al., 2013; Wu et al., 2013; Xie et al., 2019). The understanding that this antineoplasic process occurs by formation of a specialized phase-separated compartment opens the possibility for novel pharmacologic approaches to enhance the activity of this pathway. Consideration should be given to strategies that enhance formation of DNA sensing condensates, or improve the activity of cGAS therein.

Autophagy maintains normal cell homeostasis through the removal of unfolded proteins and damaged organelles (Bento et al., 2016; Dikic and Elazar, 2018; Glick et al., 2010; Levine and Kroemer, 2019). Dysregulation of this process contributes to cancer initiation, and once cancer is established, increased turnover of cell components that provide energy and macromolecular precursors requires autophagy for tumor survival and growth (Levy et al., 2017; Mathew et al., 2007; Mulcahy Levy and Thorburn, 2020). Thus,

targeting autophagy holds promise for cancer treatment (Amaravadi et al., 2011). Condensates are now understood to mediate this process. Modification of pre-autophagosomal structural proteins induces phagophore condensate formation, and similar to many other cellular condensates that are anchored to specific membranes, autophagy condensates are localized to vacuoles by specific proteins (Fujioka et al., 2020; Hawkins and Klionsky, 2020; Sun et al., 2018; Yamamoto et al., 2016). A deeper understanding of how autophagy condensates form and function will certainly further illuminate this critical cellular process, and may guide efforts to manipulate autophagy for therapeutic purposes.

Tumors often have an insufficient vascular supply leading to hypoxia and nutrient deprivation, environmental conditions that lead to stress granule assembly (Ackerman and Simon, 2014; Anderson et al., 2015; Protter and Parker, 2016). Stress granules facilitate high cellular proliferation rates in the face of these enviromental conditions by modulating signaling pathways, altering cellular metabolism, and activating the stress response (Buchan and Parker, 2009; Mahboubi and Stochaj, 2017). Phase separation in thought to underly the formation of stress granules - upon oxidative or osmotic stress an increase in the concentration of cytoplasmic RNA drives the condensation of RNA binding proteins such as FUS, hnRNPA1, and G3BP1/2 (Guillé N-Boixet et al., 2020; Molliex et al., 2015; Patel et al., 2015; Sanders et al., 2020; Yang et al., 2020). Stress granules compartmentalize anti-apoptotic proteins and are associated with resistance to chemotherapeutic drugs (Arimoto et al., 2008; Fournier et al., 2010; Gareau et al., 2011; Kaehler et al., 2014; Thedieck et al.). The understanding that stress granules are condensates may reveal the mechanisms by which cancer cells resist cytotoxic stressors, and imparing stress granule condensation may sensitize tumors to their own harsh enviroments or antineoplastic drugs.

Condensates and Drug Action in Cancer

An understanding of condensate biology in cancer cells presents an opportunity to develop new therapeutic hypotheses. There is now evidence that some drugs concentrate in specific condensates through physicochemicial interactions that are independent of the drug's affinity for its target (Klein et al., 2020). In addition, some drugs appear to selectively disrupt condensates, offering the opportunity to modulate compartments that contribute to disease pathology (Wheeler et al., 2019). Furthermore, drugs that inhibit post translational modifying enzymes can influence condensate behaviors and might be leveraged to alter oncogenic activities that are compartmentalized in condensates (Monahan et al., 2017; Rai et al., 2018).

Cancer drugs concentrate in condensates

Textbook diagrams of cells generally show membrane-bound organelles, implying an otherwise aqueous environment with free diffusion of macromolecules and proteins. Conventional pharmacological studies do not typically evaluate the intracellular distribution of drugs. Recent evidence, however, indicates that partitioning of drugs into specific non-membrane condensate compartments within cells can play a role in both drug efficacy and drug resistance in cancer (Figure 6A-B) (Klein et al., 2020). This new insight suggests the possibility that drugs can be designed to concentrate in specific

intracellular compartments where their targets reside, which may provide improved therapeutic index.

The targets of many commonly used drugs are now known to occur in condensates, so it might be expected that efficacious drugs can access these compartments to engage their targets. It is possible that drugs become concentrated in condensates due to their selectivity and affinity for the compartmentalized molecules. We now know that drugs can concentrate in the condensates where their targets occur, but they do this through selective partitioning due to the physicochemical properties of the drug and the condensate, independent of their target engagement. Thus, drug molecules can exploit condensate properties, independent of those governing target engagement, to concentrate in the same compartment as their target.

The ability of drugs to partition into specific condensates might be expected to enhance the pharmacological properties of drugs and indeed, there is evidence that the efficacy of drugs can be impacted by this behavior. Cisplatin, a commonly used antineoplastic intercalating agent, is concentrated up to 600-fold in transcriptional condensates, where it selectively platinates the super-enhancer DNA encompassed in these condensates (Klein et al., 2020). This example shows that condensate partitioning can enhance the pharmacological activity of a drug, but also illustrates how it can enhance target specificity for drugs that would otherwise engage a broader range of substrates. Because some of the largest super-enhancers occur at driver oncogenes, it is possible that cisplatin is especially effective at inactivating the oncogenes embedded in these condensates.

If condensate partitioning properties of drugs play a role in their efficacy, they might also be expected to play a role in drug resistance. Tamoxifen is a highly effective drug in the treatment of estrogen receptor (ER) -positive breast cancer. Tamoxifen resistance can be conferred by ER mutations that reduce drug affinity, and MED1 overexpression, which until recently did not have a mechanistic explanation (Fanning et al., 2016; Nagalingam et al., 2012). ER partitions selectively into transcriptional condensates in an estrogen-dependent manner and is evicted from the condensate by Tamoxifen, which also partitions selectively into transcriptional condensates and competes for estrogen binding (Klein et al., 2020). MED1 overexpression was found to cause an expansion of the volume of transcriptional condensates, thereby diluting Tamoxifen in the condensate, and rendering Tamoxifen less efficient in evicting ER from the condensate. These results suggest that condensate alterations can contribute to drug resistance in cancer cells.

Drugs that selectively alter condensate properties

Condensates may be selectively disrupted by small molecule drugs, suggesting a novel therapeutic hypothesis for cancers where dysregulated condensates contribute to the oncogenic state (Figure 6C). FUS and other disordered proteins are common translocation partners to TF DNA binding domains in diverse cancers (Bradner et al., 2017; Crozat et al., 1993; Kumar-Sinha et al., 2015) where they probably contribute to phase-separated transcriptional condensates at key oncogenes (Boulay et al., 2017; Chong et al., 2018). In familial ALS, mutations in FUS are characterized by accumulation of cytoplasmic stress granules containing FUS and other protein and RNA molecules

(Patel et al., 2015). A screen for small molecules that selectively affect stress granule formation revealed that lipoamide can selectively dissolve stress granules in cells (Wheeler, 2019). This evidence that a specific condensate can be sensitive to disruption by a specific small molecule drug suggests a novel therapeutic route for cancers with dysregulated condensates that contribute to disease pathogenesis.

IDR interactions mediate condensate formation, but have long been considered undruggable. This difficulty arises because IDRs lack the stable secondary and tertiary structures generally targeted by traditional medicinal chemistry approaches, and small molecules that do bind IDRs typically do so with low affinity (Csizmok et al., 2016; Dang et al., 2017; van der Lee et al., 2014; Uversky, 2011; Wright and Dyson, 2015). Nonetheless, recent advances in chemistry present an opportunity to drug IDRs, potentially disrupting specific condensates (Chen and Kriwacki, 2018; Metallo, 2010). Small molecules that target the MYC IDR and components of the transcription initiation complex have been identified (Carabet et al., 2019; Zhang et al., 2015b). The ability of the p27 oncogene to interact with the cell cycle machinery can be disrupted with small molecules that bind its IDR (Ban et al., 2017; Iconaru et al., 2015). Learning how to engineer drugs to selectively concentrate drugs in specific condensates might compensate for the relatively low affinity of drug-IDR interactions.

Modifying condensates by inhibiting post-translational modification

Condensate formation, dissolution, and function can be modified by post-translational modification of constituent proteins; the enzymes that catalyze these modifications are attractive drug targets (Figure 6D). DNA damage repair requires temporal and spatial coordination of diverse effector proteins, and is a potent antineoplastic target (Brown et al., 2017; Cleary et al., 2020; Gavande et al., 2016). DNA repair is now understood to take place in specialized condensates, the formation of which is dependent on PARylation of proteins and DNA (Kilic et al., 2019; Oshidari et al., 2020; Singatulina et al., 2019). PARP inhibiton prevents repair condensate formation, and impairs DNA repair (Singatulina et al., 2019). Diverse enzymes modify DNA repair components with functional consequences, and those impacting condensation of the DNA repair machinery may be ripe for therapeutic development. Cellular processes that effect high-fidelity mitosis are common and effective anti-neoplastic targets (Chan et al., 2012). Many cellular condensates are dissolved during mitosis and reformed after cell division by virtue of DYRK3 kinase activity (Rai et al., 2018). These condensates fail to dissolve upon chemical inhibition of DYRK3, with resulting mitotic defects. Inhibition of the enzymes that regulate cell cycle associated condensate formation and dissolution might now be considered for therapeutic discovery.

Areas for Future Investigation

Condensate regulation and dysregulation

How cancer-associated mutations give rise to the oncogenic state is understood largely from the effects of mutations on the structured regions of individual protein molecules. Understanding how mutations in protein coding sequences affect 3D protein structure has provided mechanistic hypotheses of disease causality and structure-based approaches

to medicinal chemistry that have led to valuable therapeutics. However, many proteins contain domains that lack defined, stable 3D structures, and typically contain low amino acid sequence complexity; indeed, more than 1/3 of proteins contain IDRs greater than 30 residues in length (Ward et al., 2004). The emergence of a conceptual framework and new experimental approaches to investigate condensate behaviors presents an opportunity to gain new insights into the dysregulated state of cancer cells and uncover condensate-associated mechanisms that lead to new therapeutic hypotheses.

Now that large databases of recurrent mutations have been generated for diverse cancers, it is possible to identify those that affect DNA, RNA and protein molecules whose functions are associated with condensates, thus expanding the list of cancer-associated condensate components (Table 1). To the extent that these mutant molecules create pathogenic condensate processes, the mechanisms that are dysregulated and the molecules that are involved become potential targets for therapeutic intervention. For example, it is now possible to explore how diverse modifications of DNA, RNA and protein molecules contribute to condensate behaviors and how gain or loss-of-function mutations might affect these compartments.

Drug design and development

The new understanding that the cell is organized into phase separated compartments that concentrate not only cellular components but also therapeutic drugs suggests several approaches that may improve development of novel small-molecule therapeutics. High throughput condensate assays may help discover novel perturbants of condensates and optimize drug partitioning. IDPs are difficult to target by conventional means, and robust assays for small molecules that might disrupt IDR-IDR interactions are lacking. That these domains mediate formation of phase separated condensates provides a readout to screen for drugs that perturb their interactions in cells and in vitro. Since condensates can be visualized by using fluorescent-tagged proteins, small molecule screens can be performed for perturbants of condensates key for any number of disease processes. Further, similar assays can be used to optimize partitioning of drugs into specific condensates to enhance target engagement and minimize off-target effects. While our understanding of protein partitioning is still developing, it should be possible to decipher the chemical features of a small molecule – functional groups, lipophilicity, hydrogen bond donor/acceptor count, etc. – that are responsible for selective condensate partitioning and design these into small molecules to target them to specific compartments in the cell. Mapping out the physicochemical rules of each cellular condensate will guide such efforts. Accomplishing this goal would improve the therapeutic index of drugs, allowing patients to be treated at lower doses with fewer side effects. Deploying condensate properties as a guiding principle in the design of next generation of drugs may provide a way to drug previously undruggable proteins due to their intrinsically disordered nature - a feature of TFs including the proto-oncoprotein MYC (Liu et al., 2006). The ability to produce high local drug concentrations may allow for the development of lower affinity drugs that are effective in targeting proteins whose features have rendered them “undruggable” (Yan and Higgins, 2013).

With evidence that drugs can selectively partition into specific condensates, revisiting our current understanding of drug mechanisms might provide additional insights valuable for future drug development. Super-enhancer associated oncogenes can be far more sensitive than other genes to certain drugs that should inhibit transcription generally. For example, treatment of a multiple myeloma cell line with JQ1, an inhibitor of the BRD4 coactivator, leads to selective loss of MYC expression, which is driven by a large super-enhancer (Lovén et al., 2013). Similarly, treatment of various cancer cells with THZ1, a CDK7 inhibitor, produces selective loss of expression of oncogenes that play prominent roles in those cells and that are super-enhancer driven (Chipumuro et al., 2014; Christensen et al., 2014; Kwiatkowski et al., 2014; Wang et al., 2015). These effects have been mysterious, as BRD4 and CDK7 are associated with most active genes and so it has not been clear why genes with large super-enhancers should be more sensitive than others. Condensate studies have provided a potential solution to this mystery (Hnisz et al., 2017). Larger transcriptional condensates have longer half-lives (Cho et al., 2018) and JQ1 and THZ1 are concentrated in Mediator condensates (Klein et al., 2020), so the concentration of these drugs in long-lived condensates at oncogenes provides an explanation for the gene-selective effects of these drugs.

Drug resistance

Additional condensate-associated mechanisms of drug resistance will almost certainly emerge when exploring various cancer cell resistant states. In prostate cancer, the clinical use of potent androgen receptor (AR) therapies has led to the emergence of a type of castration-resistant prostate cancer (CRPC) called ARL/negative CRPC. This cancer produces abundant AR mRNA but limited AR protein and thus cannot be targeted by hormonal therapies, resulting in poor prognosis. In ARL/negative CRPC cells, the RNA binding protein DDX3 protein is highly expressed, binds to AR mRNA and sequesters it in cytoplasmic stress granule condensates, thus limiting its translation. Inhibiting DDX3 was found to be sufficient to restore AR protein expression and sensitivity to AR signaling inhibitors (Vellky et al., 2020). Improved understanding of these mechanisms should lead to more effective strategies to minimize drug resistance for patient benefit.

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Figure Legends

Table 1: Selected protein and RNA molecules that participate in condensate-associated regulatory processes and implicated in cancer.

Figure 1. Biomolecular condensates located throughout the nucleus and cytoplasm. Cartoon depicting the cell composed of various condensates that compartmentalize biomolecules involved in shared processes.

Figure 2. Condensate promoting features of biomolecules. A) Condensate promoting features of biomolecules include intrinsically disordered regions, repeated modular domains as well as DNA and RNA. B) Electrostatic surface potential plots of interactions governing partitioning of biomolecules into condensates including hydrophobic, pi-pi, electrostatic, and pi-cation interactions.
C) Diagram showing that with higher concentration and/or increased valency the threshold of condensate formation is crossed.

Figure 3. Compartmentalization, localization, and regulation are common features of condensates.
A) Compartmentalization allows for high local concentration of biomolecules and their substrates, as well as exclusion of other molecules.
B) Localization of nuclear condensates can be mediated by proteins that bind to specific DNA or RNA sequences (left) and cytoplasmic condensates can form at sites on the plasma membrane (right).
C) Regulation of condensates can occur at many levels, for example post-translational modifications of molecules or the presence of RNA may change the properties that influence formation. The chemical environment of condensates dictates selective partitioning, e.g. HP1a is preferentially concentrated in heterochromatin condensates vs euchromatin condensates.

Figure 4. Condensate compartments dysregulated in malignant cells.
A) Cartoon depicting a transcriptional condensate with various components that have been reported to be altered in cancer.
B) Recurrent mutations affecting histones, chromatin modifiers and proteins that interact with modified biomolecules can alter chromatin condensates.
C) Translocation of the IgH super-enhancer to the MYC locus is an oncogenic event in aggressive B cell lymphomas that is likely to result in the formation of a non-membrane compartment at the MYC gene.
D) Elevated levels of the oncogenic MYC protein in metastatic tumor cells may alter the behavior of transcriptional condensates in these cells.

Figure 5. Hallmarks of cancer incorporate processes that involve diverse biomolecular condensates. Biomolecular condensates are involved in most processes that have been called hallmarks of cancer (modified from Hanahan and Weinberg, 2011).

Figure 6. Condensates and drug action in cancer.
A) Partitioning of drugs into specific non-membrane bound condensate compartments within cells can increase the concentration and efficacy of the drug.

B) Drug resistance in cancer cells might occur through overexpression of a condensate promoting protein. This mediates formation of larger condensates with resulting dilution of the drug, rendering the drug less effective.
C) Certain condensates appear to be sensitive to disruption by small molecule drugs.
D) Drugs targeting enzymes mediating post translational modifications are likely to affect condensate formation.

Tables

Table 1. Cellular processes dysregulated in cancer associated with condensates.

Dysregulated process	Protein	Biological Role	Reference
Transcription	MED1	Coactivator overexpressed and modified in cancer	(Cho et al., 2018; Nagalingam et al., 2012; Russo et al., 2019; Sabari et al., 2018)
	CDK7	Kinase overexpressed and targeted in cancer	(Klein et al., 2020; Kwiatkowski et al., 2014)
	p-tefb	Kinase implicated in ovarian cancer	(Guo et al., 2019; Kohoutek, 2009)
	YAP/TAZ	Coregulator with increased activity in various cancers	(Cai et al., 2019a; Zanconato et al., 2018)
	EWS	Fused to FLI in Ewing's Sarcoma	(Boulay et al., 2017; Chong et al., 2018)
	OCT4	Master TF regulator of cell identity	(Boija et al., 2018)
	HSF1	TF overexpressed in cancer	(Carpenter and Gökmen-Polar, 2018; Gaglia et al., 2020)
	eRNP	Implicated in breast cancer	(Nair et al., 2019)
	FUS	Translocated in sarcoma	(Crozat et al., 1993; Kato et al., 2012)
	MYC	Overexpressed in cancer	(Boija et al., 2018; Dang, 2012)
	P53	Tumor suppressor misregulated in cancer	(Kamagata et al., 2020; Lemos et al., 2020; Safari et al., 2019)
	TAF15	Cofactor implicated in cancer	(Altmeyer et al., 2015; Kwon et al.,

			2013; Shin et al., 2018; Wei et al., 2020)
	ENL	Cofactor translocated in leukemia	(Wan et al., 2017, 2020)
Epigenetic regulation	BRD4	Chromatin factor upregulated and fused in cancer	(Filippakopoulos et al., 2010; Sabari et al., 2020; Shin et al., 2018)
	Hp1a	Chromatin factor down regulated in cancer	(Larson et al., 2017; Strom et al., 2017; Vad-Nielsen and Nielsen, 2015)
	m6a	DNA modification decreased in cancer	(He et al., 2019; Ries et al., 2019)
	Polycomb	Gene silencing complex altered in cancer	(Plys et al., 2019; Tatavosian et al., 2019)
	MeCP2	Chromatin factor amplified in breast cancer	(Li et al., 2020; Neupane et al., 2016)
	MALAT1	lncRNA dysregulated in cancer	(Greig et al., 2020; Tripathi et al., 2010)
Cell signaling	B-catenin	Wnt factor driving colon cancer	(Nusse and Clevers, 2017; Zamudio et al., 2019)
	ER (Estrogen receptor)	TF and hormone receptor mutated in breast cancer	(Boija et al., 2018; Nair et al., 2019)
	PML	PML fused to RARa in APML	(Banani et al., 2016; Salomoni and Pandolfi, 2002)
	PKA	Involved in oncogenic signaling	(Sapio et al., 2014; Zhang et al., 2020b)
	TCR	Mediator of tumor immunity	(June et al.; Su et al., 2016)
	SOS	Cofactor involved in RAS signaling	(Cai et al., 2019b; Huang et al., 2019)
Immune signaling	cGAS	Involved in cancer immunity	(Du and Chen, 2018)

Ribosome biosynthesis	NPM1	Nucleolar factor mutated in leukemia	(Feric et al., 2016; Mitrea et al., 2016, 2018)
Degradation	SPOP	Tumor suppressor mutated in prostate cancer	(Bouchard et al., 2018)
DNA repair	RAD52	HR factor and tumor suppressor	(Oshidari et al., 2020)
	53BP1	DNA repair factor and tumor suppressor	(Kilic et al., 2019; Mirza-Aghazadeh-Attari et al., 2019; Pryde et al., 2005)
	FUS	Effector of transcription coupled repair	(Singatulina et al., 2019)
	PARP	Enzyme targeted for cancer therapy	(Rouleau et al., 2010; Singatulina et al., 2019)
Splicing	SRSF2	Mutated in myelodysplasia	(Guo et al., 2019; Sperling et al., 2017)
Nuclear transport	NUPs	Nucleoporin dysregulated in cancer	(Schmidt and Görlich, 2015, 2016; Simon and Rout, 2014)
DNA replication	ORC/CDC6/CDT1	Dysregulated replication	(Gaillard et al., 2015; Parker et al., 2019)
Storage	NEAT1	ncRNA of paraspeckles implicated in cancer	(Shin et al., 2019; Yamazaki et al., 2018)
Autophagy	Atg1	Implicated in macromolecule recycling in cancer.	(Fujioka et al., 2020; Mulcahy Levy and Thorburn, 2020)
Proteosome	Multiple proteins	Target of multiple myeloma therapies	(Anderson, 2016; Manasanch and Orlowski, 2017; Yasuda et al., 2020)
Telomeres	Multiple proteins	Prevents replicative senecence	(Min et al., 2019; Zhang et al., 2020a)
Stress response	FUS, hnRPNA1, G3NP1/2	Stress granules are anti-apoptitic.	(Arimoto et al., 2008; Molliex et al.,

			2015; Protter and Parker, 2016)

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Figure 1

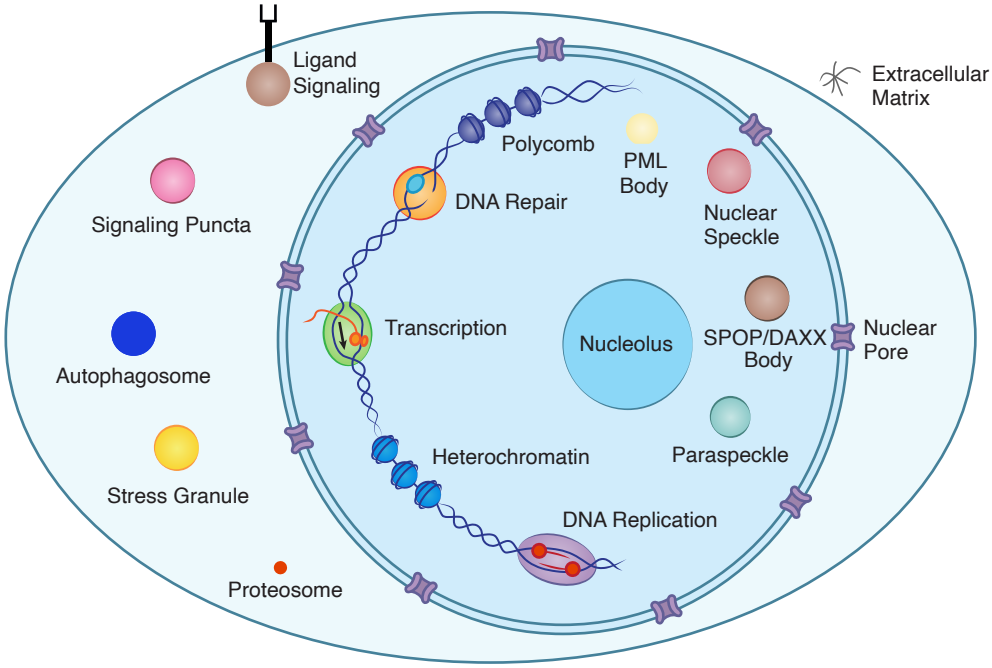

Ligand
Signaling
Extracellular
Matrix
Polycomb
PML
Body
DNA Repair
Nuclear
Speckle
Signaling Puncta
Transcription
Nucleolus
SPOP/DAXX
Body
Nuclear
Pore
Autophagosome
Heterochromatin
Paraspeckle
Stress Granule
DNA Replication
Proteosome

Figure 2

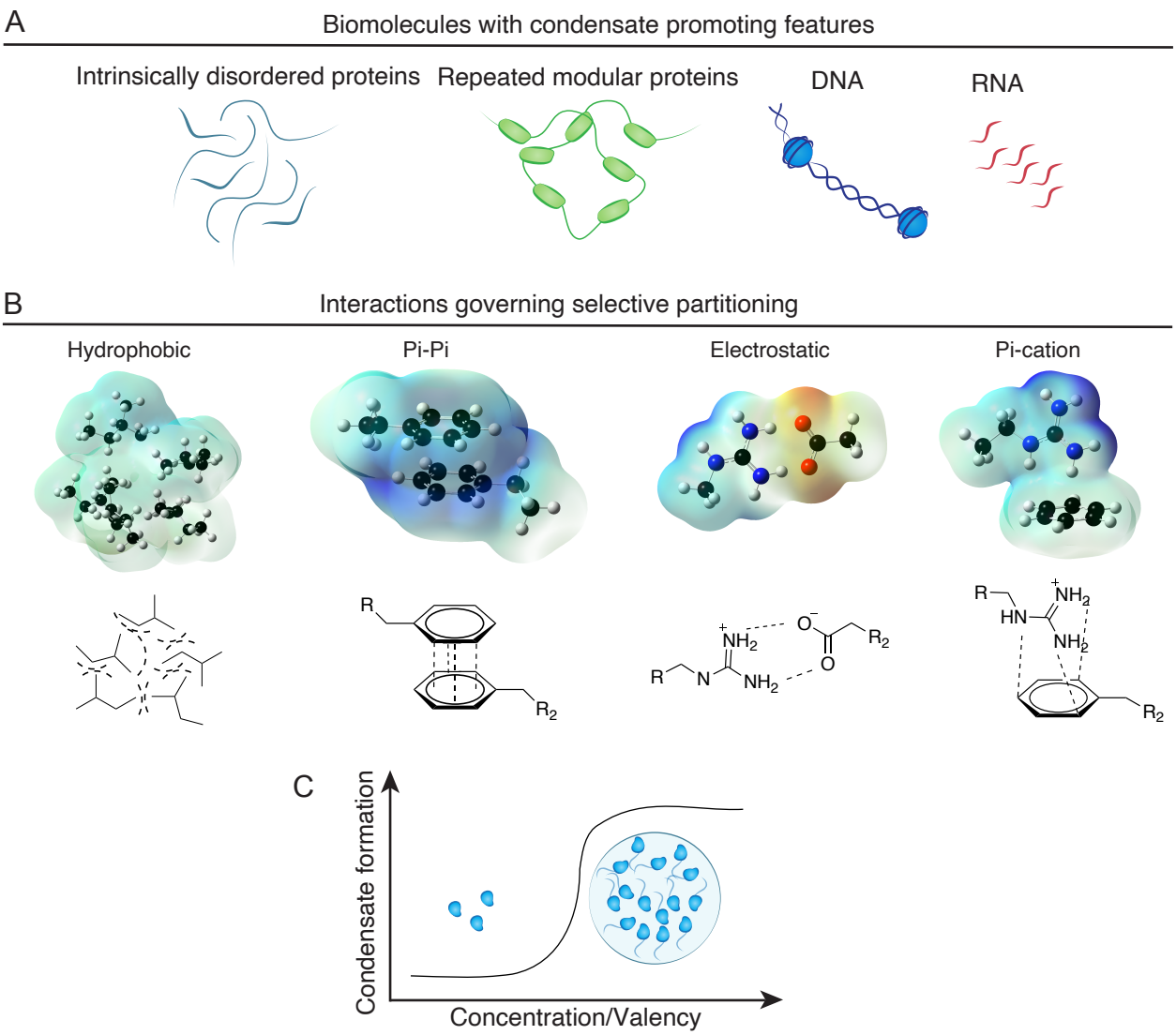

A
Biomolecules with condensate promoting features
Intrinsically disordered proteins
Repeated modular proteins
DNA
RNA
B
Interactions governing selective partitioning
Hydrophobic
Pi-Pi
Electrostatic
Pi-cation
R
R2
NH2
HN
O
N
C
Condensate formation
Concentration/Valency

Figure 3

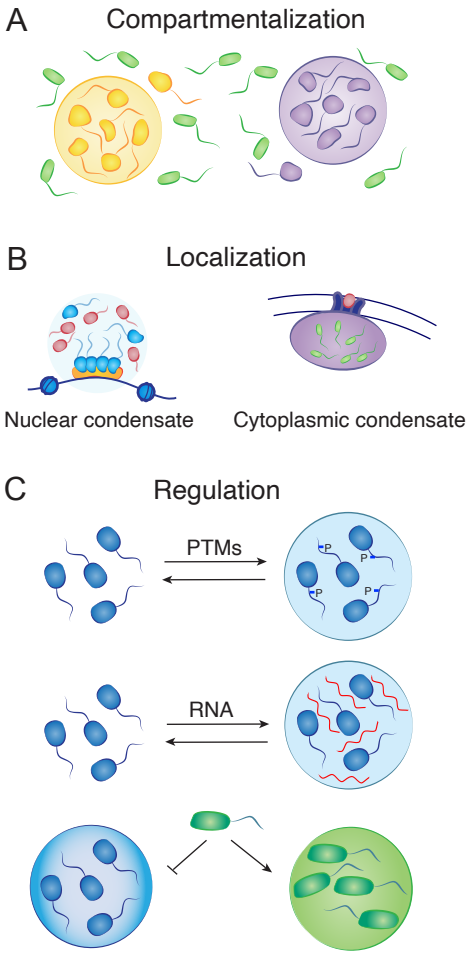

A
Compartmentalization
B
Localization
Nuclear condensate
Cytoplasmic condensate
C
Regulation
PTMs
P
P
P
P
RNA

Figure 4

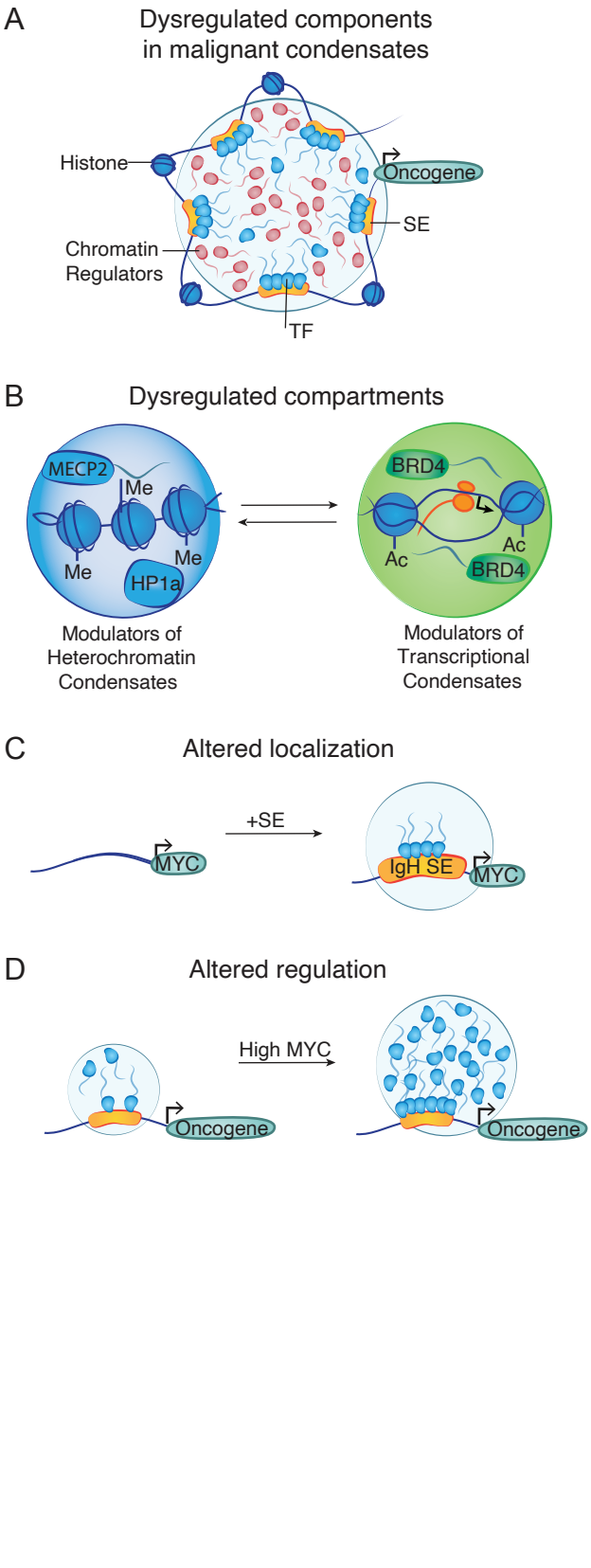

A
Dysregulated components
in malignant condensates
Histone
Oncogene
SE
Chromatin
Regulators
TF
B
Dysregulated compartments
MECP2
Me
Me
Me
HP1a
BRD4
Ac
Ac
BRD4
Modulators of
Heterochromatin
Condensates
Modulators of
Transcriptional
Condensates
C
Altered localization
+SE
MYC
IgH SE
MYC
D
Altered regulation
High MYC
Oncogene
Oncogene

Figure 5

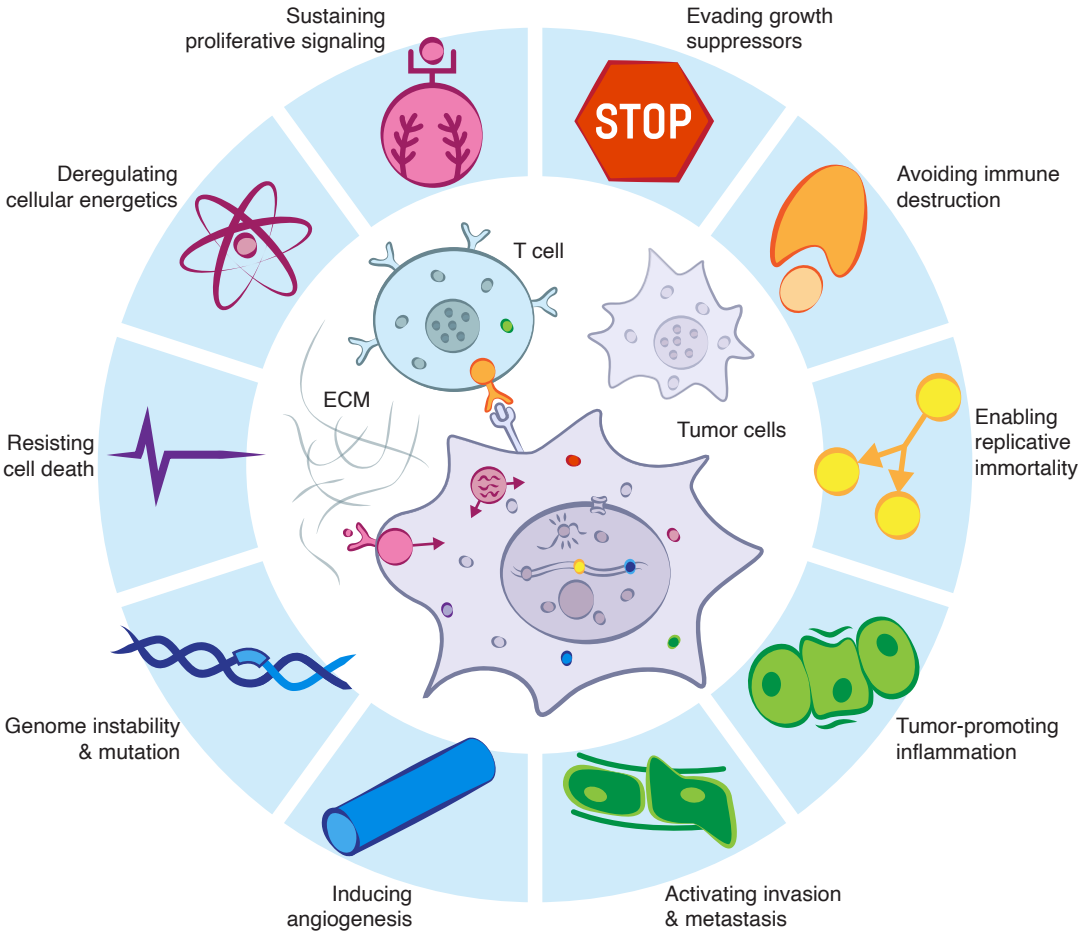
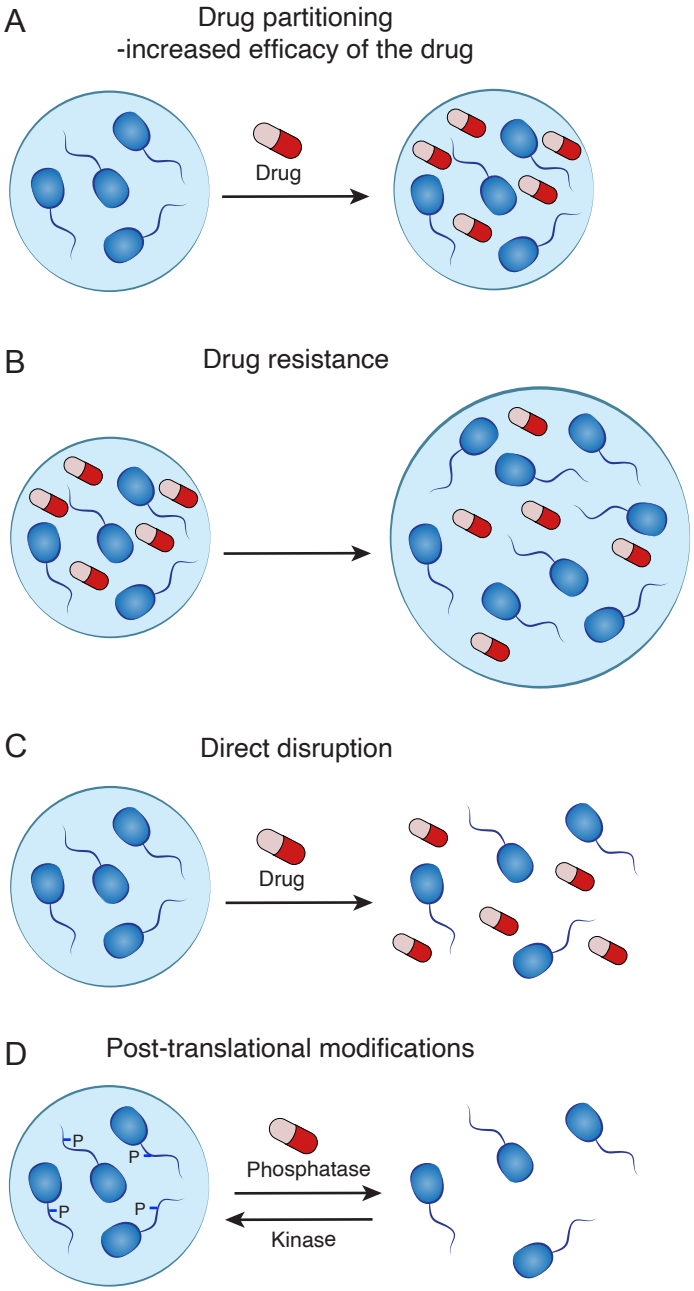

Sustaining proliferative signaling
Evading growth suppressors
STOP
Deregulating cellular energetics
Avoiding immune destruction
T cell
ECM
Tumor cells
Resisting cell death
Enabling replicative immortality
Genome instability & mutation
Tumor-promoting inflammation
Inducing angiogenesis
Activating invasion & metastasis

Figure 6


A
Drug partitioning
-increased efficacy of the drug
Drug
B
Drug resistance
C
Direct disruption
Drug
D
Post-translational modifications
P
P
P
P
Phosphatase
Kinase