A Unified Model: Chromatin-Bound Multicomponent Condensates

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In cells, highly coordinated multivalent interactions give rise to discrete functional assemblies—commonly referred to as biomolecular condensates—that compartmentalize the molecular components required for specific biological reactions. These condensates are increasingly recognized as organizational entities with central roles in normal cellular regulation and in the pathogenesis of human cancers. In a recent issue of *Cell*, Datar and colleagues investigated the condensation of NPM1c, a common gene mutation in acute myeloid leukemias (AML). They demonstrated the necessity and sufficiency of NPM1c in forming nuclear condensates termed coordinating bodies (C-body), which show copartitioning of a suite of transcriptional coactivators such as NUP98, KMT2A/MLL1, menin, and XPO1/CRM1. While C-bodies are necessary for driving NPM1c-mutant AMLs, blockade of the copartitioned components within C-bodies, such as the XPO1/CRM1 or menin interaction by inhibitors, significantly alters the condensate composition and functionality. Likewise, a systematic deletion study of various regions within NPM1c pointed to a role for the coordinated multivalent interaction in establishing the functional condensates, as previously reported in studies of the Wilms tumor-causing ENL mutants and AML-causing NUP98 oncofusions. Comixing of C-bodies and condensates formed by the oncofusion of NUP98 or KMT2A/MLL1 in cells suggested they are biophysically indistinguishable, indicative of a shared pathogenic mechanism. Altogether, recent studies of multiple genetic drivers in human cancers have revealed a type of chromatin-bound multicomponent onco-condensate, which may motivate the development of onco-condensate disruptors that could potentially be used as broad treatments for cancer.

Increasing evidence suggests that the emergence of aberrant biomolecular condensates via phase separation plays a critical role in the development of human cancers. Mutations of nucleophosmin (*NPM1*), most commonly a recurrent four-base-pair insertion in the C-terminal exon of one allele, generate a frameshift mutant protein (NPM1c) and represent the most frequent somatic lesion in adult acute myeloid leukemias (AML). NPM1c eliminates the conserved tryptophan residues (W288 and W290 or W290 alone) that constitute the nucleolar localization signal while simultaneously creating a novel leucine-rich nuclear export signal (NES), thereby driving aberrant redistribution of NPM1c in the cytosol and nucleoplasm. Previously, Wang and colleagues (1) demonstrated that NPM1c forms nucleoplasmic condensates, which recruit transcriptional (co) activators, such as RNA polymerase II (Pol II), Eleven-Nineteen-Leukemia protein (ENL; also known as MLLT1), and the complex of lysine methyltransferase 2A (KMT2A; also known as MLL1) and menin, due to heterotypic interactions. How exactly the NPM1c mislocalization and its condensation are related to leukemic transformation largely remains a mystery. In recent work, Datar and colleagues (2) aimed to dissect the underlying mechanism. Using a degron fused to endogenous NPM1c in AML cells and its ectopic expression in nonhematologic cells, they demonstrated the necessity and sufficiency of NPM1c in forming the nucleoplasmic condensates termed coordinating bodies (C-body), which exhibit significant copartitioning of exportin-1 (XPO1; also known as CRM1), nucleoporin 98 (NUP98), KMT2A/MLL1, and menin. Employing elegant microscopy methods, Datar and colleagues quantified NPM1c's partition coefficient (K^{tr}), which measures the strength of protein "transfer" between different cellular compartments, and revealed highly biased partitioning of NPM1c to condensates (with a K^{tr} value of 18 ± 2). DNA fluorescence *in situ* hybridization (FISH) of HOXA9, a leukemic proto-oncogene, together with immunostaining of C-body–containing components, revealed their frequent association with HOXA9 chromatin. Using a reconstitution system in which exogenous NPM1c was reintroduced into AML cells after degradation of endogenous NPM1c, the authors further showed that full-length NPM1c and mutants lacking the so-called A3 or B2 domains (which are dispensable for C-body formation) restored condensate assembly and differentiation arrest in the absence of endogenous NPM1c. In contrast, NPM1c mutants lacking regions essential for C-body formation failed to rescue either phenotype (2). Essentially, C-bodies are a type of chromatin-bound multicomponent onco-condensate (3), resembling what was previously reported for the Wilms tumor-causing ENL mutants (4) and various AML-causing NUP98 oncofusions (5–9).

Furthermore, the authors conducted a set of manipulation experiments to reveal the molecular basis underlying C-body formation and function (2). First, blockade of the copartitioned component within condensates, such as targeting the XPO1/CRM1 interaction by an inhibitor (eltanexor and selinexor) or disruption of the menin–KMT2A interaction by a menin inhibitor (VTP50469 and MI-503), significantly altered C-body stability and composition. An XPO1/CRM1 inhibitor dissolved C-bodies, suggesting that the XPO1/CRM1–NPM1c interaction is necessary for C-body formation. On the other hand, the menin inhibitor showed a more specific effect—it

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evicted menin, but not other tested factors (such as XPO1/CRM1, KMT2A/MLL1, and NUP98), from C-bodies while leaving the patterns of nuclear puncta largely intact; meanwhile, the menin inhibitor decreased leukemic oncogene expression and caused myeloid differentiation. Additionally, a more recent study suggests that targeted degradation of wild-type NUP98 also led to transcriptional repression of NPM1c target genes (10). These data agree with an earlier study of NUP98 oncofusion, showing that depletion of WDR5, an integral component of the KMT2A/MLL1–menin complex, or BRD4, an activator of RNA Pol II, suppressed oncogene expression and inhibited AML growth without having an apparent effect on condensation by NUP98 oncofusions (6). These observations strengthen the notion that oncoprotein condensation and cofactor partitioning are two separate events, a coordinated process that leads to the formation of functional onco-condensates and the cancerous transformation of cells (6). In parallel, Datar and colleagues (2) conducted overexpression and systematic domain deletion studies of NPM1c to correlate C-body formation and properties with AML biology. Nonphysiologically high expression of NPM1c in the NPM1c-positive AML cells produced larger C-bodies with reduced nuclear periphery enrichment, indicative of heterotypic destabilization, a phenomenon in which stoichiometric imbalance in one component of multicomponent condensates alters condensate composition, size, and/or function (2). Interestingly, those cells overexpressing NPM1c exhibited reduced growth compared with controls; likewise, there was a negative correlation between heterotypic destabilization caused by the NPM1c domain deletion mutants and leukemic transformation (2). These observations are reminiscent of the previously reported large but nonfunctional condensates formed by oncoproteins [such as mutant ENL (4) or NUP98 oncofusions (6)] at high concentrations, which lost heterotypic partitioning, most likely due to an increase in homotypic interactions. Although onco-condensates are causal for oncogenesis, their appropriate composition and states are equally important for their function in cancer.

Although the above findings establish C-bodies as the primary driver of leukemogenesis and a dominant role for heterotypic interactions in NPM1c onco-condensates (2), several outstanding questions remain. First, both wild-type NPM1 and NPM1c undergo condensation, and the simple addition of NES to wild-type NPM1 cannot recapitulate NPM1c's functions, such as C-body formation and leukemic transformation (2). Interestingly, NPM1's C-terminus normally has RNA-binding capacity, which is mutated to an XPO1/CRM1-binding NES in NPM1c. How exactly a small change in NPM1's C-terminus confers functional separation will need to be addressed by future studies. In-cell comixing studies of NPM1c and oncofusions of KMT2A/MLL1 or NUP98 indicate that the formed onco-condensates are biophysically indistinguishable (2). How the composition and chemico-physiologic states of these onco-condensates are determined still remains unknown. Wild-type NUP98 has long been known to be a highly mobile protein, with a minor fraction shuttling between nuclear pore complexes and the nucleoplasm, in which it forms so-called Glycine-Leucine-Phenylalanine-Glycine (GLFG) bodies to engage and activate chromatin. Fusing NUP98's phenylalanine-glycine (FG) repeats with a chromatin-associated factor drives the formation of condensates in the nucleus (5–9). Additionally, NUP98's FG repeats were shown to be both necessary and sufficient for recruiting a suite of coactivators, including KMT2/MLL complexes (KMT2A/MLL1, KMT2B/MLL2, WDR5, menin, and RBBP5), XPOs, SWI/SNF complexes, and p300, many of which, NPM1c copartitions to the onco-condensates, whereas NUP98's fusion partner provides a chromatin-targeting specificity mechanism (6). Identifying the molecular grammar underlying heterotypic associations among various biomolecules in the onco-condensates (oncoproteins, cofactors, DNA, histones, and/or RNA) is warranted in future investigations. Given the known poor toxicity profile of XPO1/CRM1 inhibitors, the above-outlined studies of multiple genetic drivers in cancers may elucidate the shared and targetable vulnerabilities to small molecules capable of modulating condensates' composition, size, and/or functionality.

Authors' Disclosures

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