

GENE EXPRESSION

Concentrating on intrinsic disorder

Many eukaryotic proteins contain intrinsically disordered regions (IDRs), which serve as flexible platforms for protein–protein interactions and can phase-separate into liquid-like condensates. Understanding of the properties and functionality of IDR-based interactions is still in its infancy. Three independent studies published in *Science* indicate that dynamic IDR–IDR interactions can concentrate transcription regulators on DNA to establish a transcription-competent compartment. Another study, reported in *Cell*, provides a comprehensive description of the molecular interactions that underlie the propensity of IDR-containing proteins to phase-separate.

Sabari et al. studied the role of IDRs in regulating super-enhancers (SEs) — large clusters of enhancers that drive robust expression of cell identity genes and are characterized by a high concentration of transcription regulators. They observed that two SE-associated transcription co-activators, bromodomain-containing protein 4 (BRD4) and Mediator of RNA polymerase II transcription subunit 1 (MED1), formed distinct puncta in nuclei of murine embryonic stem cells (ESCs), which often colocalized at SEs. These puncta showed high protein turnover, akin to the dynamics of liquid-like condensates. Furthermore, IDRs from BRD4 and MED1 formed phase-separated condensates in vitro and in cells after optogenetically induced aggregation. Importantly, MED1–IDR condensates were capable of sequestering BRD4 and the largest subunit of RNA polymerase II (Pol II), and inhibited transcription in nuclear extracts. Furthermore, formation of BRD4 and MED1-containing puncta was required for Pol II enrichment at SEs in ESCs.

The formation of dynamic clusters of the Mediator complex on SEs that colocalize with Pol II was visualized

by Cho et al. using live cell super-resolution and lattice light sheet microscopy. Thus, IDRs can drive the condensation of transcription co-activators at SEs, which facilitates the recruitment and concentration of other components of the transcription machinery. Based on the in vitro properties of these IDRs and their dynamics in cells, it was proposed that the capacity of IDRs to undergo phase separation is the driving force for protein condensation at SEs.

Chong et al. investigated the cellular dynamics of transcription factor-derived IDRs, which were targeted to endogenous or synthetic arrays of repetitive DNA. These IDRs formed nuclear puncta and recruited more IDRs through IDR–IDR interactions. These interactions were specific (not all IDRs could interact with each other) and dynamic. When highly expressed, IDRs formed puncta in the nucleoplasm independently of DNA; in these nucleoplasmic puncta, IDR–IDR interaction dynamics were even greater. Thus, repetitive DNA arrays promote the local concentration of DNA-targeted IDRs, such as those of transcription factors, thereby establishing IDR hubs that stabilize IDR–IDR interactions and facilitate further protein recruitment. Importantly, these hubs could recruit Pol II and were shown to be required for transcription factor function in gene expression. As IDR hubs consistently formed without noticeable phase separation, further studies are needed to clarify the function of phase separation in gene expression in vivo.

Inter-IDR interactions and condensate or hub formation were influenced by the amino acid composition of IDRs, raising the question of how the primary sequence of IDR-containing proteins



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“dynamic IDR–IDR interactions can concentrate transcription regulators”

controls their behaviour. This question was addressed by Wang et al., who investigated the properties of 22 IDR-containing proteins of the FUS family. They found that only three of these proteins were capable of phase separation in vitro under physiologically relevant conditions. Electrostatic interactions between Tyr (in IDRs) and Arg (in RNA-binding domains) were the key drivers of phase separation. Inter-IDR Tyr–Tyr interactions could also promote phase separation, but only at higher protein concentrations. Other residues determined the properties of condensates, including fluidity (Gly) and hardening (Ser and Gln).

In future, it will be important to further dissect the role of discrete protein regions and amino acids in regulating IDR-containing protein interactions. It will also be interesting to establish how specificity is achieved in these very dynamic interactions, how they control protein compartmentalization in different cellular contexts and how phase separation contributes to these processes in vivo.

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ORIGINAL ARTICLES Sabari, B. R. et al. Coactivator condensation at super-enhancers links phase separation and gene control. *Science*. <https://doi.org/10.1126/science.aar3958> (2018) | Cho, W.-K. et al. Mediator and RNA polymerase II clusters associate in transcription-dependent condensates. *Science*. <https://doi.org/10.1126/science.aar4199> (2018) | Chong, S. et al. Imaging dynamic and selective low-complexity domain interactions that control gene transcription. *Science*. <https://doi.org/10.1126/science.aar2555> (2018) | Wang, J. et al. A molecular grammar governing the driving forces for phase separation of prion-like RNA binding proteins. *Cell* <https://doi.org/10.1016/j.cell.2018.06.006> (2018)