MEDICINE

Drug modulation by nuclear condensates

Concentration of antineoplastic agents into spatial compartments influences activity

By **Aaron D. Viny**[1,2] *and* **Ross L. Levine**[1,2]

Many mysteries remain about the eukaryotic nucleus. In the past decade, much has been discovered anew about the three-dimensional (3D) organization of the nucleus and the dynamic interactions therein that influence cellular function. Studies have uncovered the critical roles that topologic structure, histone modifications, and DNA modifications play in regulating transcription. By contrast, the understanding of interactions among proteins, RNA, and chromatin in macromolecular assemblies is less developed. These condensates are the molecular basis for discrete nuclear spatial organization of active and repressive chromatin as well as distinct nuclear structures such as the nucleolus (*1, 2*). On page 1386 of this issue, Klein *et al.* (*3*) begin to dissect the functional relevance of nuclear condensates in regulating the distribution and activity of fluorescent-labeled antineoplastic agents with specific nuclear localization profiles. This finding could have wide-ranging implications for the understanding of pharmacologic mechanisms and has substantive consequences for therapeutic development, drug delivery, and target engagement.

Recent technologies have allowed for appreciation of hierarchical 3D structures within the nucleus that have both known and unknown functional importance. Most widely accepted is the principle of spatial separation of chromatin into regions of active transcription (euchromatin). These regions share the property of deoxyribonuclease (DNase) or transposase accessibility and the presence of transcriptional coactivators, including the mediator (MED) complex. These genomic regions are spatially separate from regions of transcriptional inactivity (heterochromatin), densely packed histone-bound chromatin, often demarcated by repressive histone methylation marks.

Beyond euchromatin and heterochromatin, other segregated nuclear subcompartments have been described as self-organizing condensates. Through careful assessment of nuclear condensates (*4, 5*), Klein *et al.* observed that fluorescent-labeled small molecules had distinct and specific spatial aggregation in different nuclear compartments. Fluorescent-labeled cisplatin, a chemotherapy drug that damages and cross-links DNA, was observed to aggregate in mediator of RNA polymerase II transcription subunit 1 (MED1) transcriptional condensates while diffusing freely through heterochromatin protein 1 (HP1)–demarcated heterochromatin. Upon locus-specific assessment of cisplatin-induced DNA damage (platination) across the genome, only the DNA contained in MED1 condensates had high amounts of cisplatin incorporation. This finding suggests specificity of the pharmacologic effect of cisplatin to a distinct type of condensate. Additionally, the differential effect on platinum incorporation was lost with bromodomain-containing protein 4 (BRD4) inhibition, which disrupts MED1 condensates.

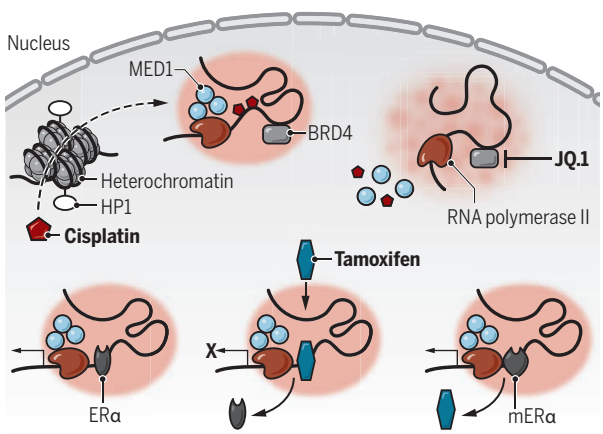
The authors also assessed the localization of tamoxifen and found that this targeted endocrine chemotherapy aggregated in MED1 condensates, competing with and evicting its target, estrogen receptor α (ERα), from these intranuclear structures. In human breast cancer cells, they found that ERα interacts with the *MYC* locus in MED1 condensates; this association was abrogated by tamoxifen and condensate accumulation. Notably, patient-derived ERα mutations that induce tamoxifen resistance led to their retention in MED1 condensates, rendering tamoxifen unable to outcompete oncogenic ERα.

Klein *et al.* demonstrate that a subset of small-molecule therapeutics can have differential enrichment in nuclear compartments (see the figure). Moreover, functional studies have demonstrated that redistribution of high-density regions of histone 3 lysine 27 acetylation (H3K27ac), consistent with transcription-activating super-enhancer function, within condensates may contribute to platinum resistance in human ovarian cancer cell lines (*6*). These two observations suggest an important, dynamic link between transcriptional units and epigenetic marks in nuclear condensates with pharmacologic agents possessing condensate-specific proclivities. These studies further suggest that the modulation of condensate structure and function has critical roles in gene regulation and therapeutic response. This raises the question of whether the localization and efficacy of cisplatin and of other small-molecule therapeutics are driven by transcriptional and epigenetic regulation, by the structure of nuclear condensates, or by these two dynamic processes acting in concert.

Undoubtedly, there remain technical limitations to the ability to assess and elucidate the relationship between nuclear structure and specific perturbations, particularly in dynamic contexts, including malignant transformation and the response to specific therapies. As a cell responds to intracellular and extracellular signals, transcription factor activity is influenced by both chromatin conformation and other dynamic factors that have a critical role in these same biologic processes. Notably, a recent description of genetic alterations in transcription factors was shown to affect

Pharmacophore-specific condensates

Cisplatin and tamoxifen aggregate in transcriptional condensates, affecting their pharmacokinetics. Cisplatin freely diffuses through HP1-labeled heterochromatin and accumulates in MED1 condensates. The BRD4 inhibitor JQ.1 abrogates MED1 condensates and attenuates drug-induced platination. Tamoxifen displaces ERα from target genes, but mutations that induce tamoxifen resistance (mERα) shift affinity as tamoxifen is evicted from transcriptional condensates.



BRD4, bromodomain-containing protein 4; ERα, estrogen receptor α; HP1, heterochromatin protein 1; MED1, mediator of RNA polymerase II transcription subunit 1.

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spatial localization to transcriptional condensates (*7*). Indeed, transcription-directed compartmentalization may have a critical role in regulating condensates, an observation best illustrated through the effects of herpes simplex virus type I in altering nuclear organization through highly accessible viral DNA binding sites and sequestration of RNA polymerase II (*8*).

Consistent with this hypothesis, intrinsically disordered regions within transcription factors can contribute to altered nuclear localization in human disease, as has been shown in syndactyly (fused fingers) driven by an intrinsically disordered region repeat expansion in homeobox protein 13 (HOXD13) (*7*). As was shown by Klein *et al.* with respect to pharmacophore-specific condensates, fluorescence recovery after photobleaching (FRAP)–based techniques were used to elucidate altered condensate formation in HOXD13 expansion syndactyly. Although FRAP cannot fully distinguish liquid diffusion from high-affinity protein structures (*9*), the relative contribution of liquid-liquid phase separation versus protein structured "hubs" remains an exciting and controversial question with respect to nuclear condensate formation and function.

These recent studies have dissected the inner workings of the nucleus, which are as beautiful and fascinating as much as they are still beyond complete understanding with respect to regulatory function and purpose. Enormous potential lies in the ability to manipulate these characteristics for therapeutic intervention. It is anticipated that further research will soon reveal the mechanistic importance of nuclear phase separation in cellular function, and the molecular consequences of linking spatial compartmentalization with nuclear function. ■

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ECOLOGY

Using information theory to decode network coevolution

Communication clashes shape the coevolution of insect-plant ecosystems

By **Ricard Solé**

Walking through a forest, you spot a colorful butterfly larva crawling and munching on a leaf—nothing unusual, just one scene in a calm ecological play. And yet, a massive "arms race" rages between plants and their herbivores (*1*, *2*), spurred by information and misinformation transfer. Chemical signals play the role of communicators in a channel that joins each pair of interacting partners. The mechanisms that drive coevolution of these chemically mediated webs have been an active area of research, but a satisfactory theory has yet to be established. On page 1377 of this issue, Zu *et al.* (*3*) describe a new application of information theory to coevolutionary dynamics in animal-plant networks.

Many scholars have explored the role of information in ecology and evolution (*4*) since the 1950s, in the wake of Claude Shannon's groundbreaking theory of information and communication (*5*). But the actual function of information, particularly in an evolutionary context, often has been obscured by insufficient data and the lack of a proper mapping of the links between information and fitness (*6*).

Zu *et al.* made use of plants' secondary metabolism (which forms metabolites not involved in plant growth or development) to couple two bipartite networks, namely the animal-plant (AP) one (i.e., who eats what) and the plant–volatile organic compounds (PV) one [i.e., what volatile organic compounds (VOCs) plants generate]. The authors gathered data from a tropical dry forest; insect larvae were collected from leaves, and trophic interactions were confirmed in the laboratory. The VOC repertoire was retrieved from leaves in the field with a method that characterizes the chemical profile around each leaf.

However, the way the authors built a communication channel between the AP and PV networks departed from Shannon's approach in a substantial way. The classical theory considers a sender and a receiver trying to communicate using a given code sent through a noisy channel (Morse code in the old telegraph system would be one example). For each signal sent, there is a probability that it will be misunderstood by the receiver. Not surprisingly, a great deal of standard information theory deals with finding ways of optimizing communication efficiency. However, in an ecological system in which interactions are highly asymmetric (one species eats the other), the needs at the ends of the (coevolving) communication channel are in clear conflict: Insects need to faithfully identify what leaves are edible, and plants need to avoid being identified as edible.

The aim of Zu *et al.* was to connect information-level descriptions of the two networks through a simple coevolutionary model that successfully solves the problem of defining fitness values for both plants and insects. The rules of the model simulate genetic mutations that influence pairwise interactions within the two bipartite networks. In the simulation, a given PV pair was chosen at random. With a certain probability, the connection between the plant and the chemical signal was added (if there was no link) or removed (if there was one), thus increasing or decreasing the VOC repertoire, respectively. A fitness value, F_P, was then computed using one of Shannon's entropic measures, which weights the uncertainty associated with chemical recognition by animals. If the new fitness value, F'_P, is larger than the original (before the PV choice), the change is accepted, and the VOC repertoire is expanded.

This feature of Zu *et al.*'s coevolutionary model is particularly notable, as communication networks usually are intended to increase channel efficiency through noise reduction (maximizing information transfer between sender and receiver). In their model, however, changes in a plant's VOC repertoire expanded the chemical diversity of volatiles that favor the confusion of the herbivores or, in Shannon's theory, that increase the herbivores' uncertainty about what plant choices they can make.

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