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Protein Droplets Help Organize Fly Brain Cell Development

A Q&A with brain development and fruit fly expert Minoree Kohwi

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NEW YORK — *Brain cells come in an extraordinary variety of shapes and play diverse roles, such as helping the body move and receiving information about the world from the senses. The nearly 90 billion neurons, a key type of brain cell, in the adult human brain arise from a small group of cells known as neural progenitors. Remarkably, they all do so using the same collection of genes: our genome.*

Our entire genome is six feet long when stretched out. This long strand of DNA must somehow fit into the nucleus, a compartment inside our cells about a tenth the width of a human hair. How does the way in which this DNA packs and folds into the nucleus help neural progenitor cells generate the brain's complexity?

By analyzing fruit fly embryos, Minoree Kohwi, PhD, a principal investigator at Columbia's Zuckerman Institute, is now one step closer to solving this mystery. In a study published on June 14 in Nature Communications, *Dr. Kohwi and her colleagues show that a protein in neural progenitor cells forms microscopic liquid-like beads inside the nucleus, a bit like the droplets in a lava lamp. The droplet-forming properties of these proteins help to organize DNA-folding in neural progenitor cells.*

We sat down with Dr. Kohwi, also an assistant professor of neuroscience at Columbia's Vagelos College of Physicians and Surgeons, to talk about these new insights into how the genome is organized and how that organization can change over development to give rise to different cell types. Such research, she said, could one day shed light on how brain disorders arise, and potentially inform treatments.

Why is genome organization important for brain development?

One of the fundamental questions in brain development in both insects and humans is how you start with a limited pool of neural progenitors and end up with the diversity of cell types we see in the brain. These cells are each made in specific places and times to achieve the kind of organization needed for brain function. Additionally, different types of cells have to be made in correct relative quantities to, for instance, balance excitatory

and inhibitory activity. Learning more about how neural diversity arises can help us better understand how some neurodevelopmental diseases emerge and perhaps give us insights into how we can repair the brain after injury or disease.

What is truly amazing about all this complexity in the brain is that it comes from the same template, a person's genome. How is that achieved? That's the big question we're trying to address. We're looking at this question from the perspective of nuclear architecture, how our DNA is folded and packaged in the nucleus to decipher the genomic instructions and control gene activity.

Think of the paper fortune tellers you may have played with growing up. It's just one piece of paper, but depending on how you open it, different facets of the origami gadget become visible. The genome kind of works that way, with its "facets" corresponding to different genes. We think that in neural progenitors, the way the genome is folded determines what genes can turn or off in its daughter neurons. Over time, neural progenitors change the folding of their genomes, which contributes to their ability to generate diverse cell types.

What discovery did you make regarding genome organization in developing brain cells?

We found that a protein named Dan, short for Distal antenna, can both bind to DNA and also coalesce into liquid-like condensates inside the nucleus, a bit like how oil droplets coalesce and separate from water.

In the nucleus, Dan strongly binds all over the genome. We imagine it acting like a bungee cord that can bring different parts of the genome together in the nucleus, possibly to orchestrate the activity of multiple genes or stabilize a particular genome structure.

What makes the liquid nature of these condensates important?

Just as the insides of our bodies are organized into organs, we've long known that the insides of cells are organized into compartments, called organelles, that are enclosed by membranes. The nucleus is one such organelle. But within the nucleus, there aren't additional smaller organelles to help organize its contents. It's been a big question as to how the DNA and proteins inside the nucleus are organized in a way that controls which genes can turn on or off.

An emerging idea is that some nuclear proteins may assemble in ways that help organize nuclear contents, such as by forming liquid condensates. These liquid condensates act like membraneless organelles that help bring order into the interior of the nucleus. Such proteins might facilitate or restrict which specific molecules can interact in these liquid condensates or can access a target gene, for example.

What role did you find Dan plays in the brain?

Dan is abundant in neural progenitor cells, but then it goes away temporarily. This disappearance coincides with a change in the three-dimensional folding of the neural progenitor's genome. Maintaining Dan expression in the cell blocks this reorganization. We found that not only does Dan form liquid-like condensates, but it also is required in neural progenitor genome organization.

With our data, we envision that Dan might help stabilize a folded genome configuration. The temporary loss of Dan expression then allows for a change in this genome configuration. Some set of genes might be stored away, and a different set of genes might become activatable. Then, when Dan is re-expressed in the progenitor, it could stabilize that new configuration. These are hypotheses we are testing right now.

What more would you like to learn about the Dan protein?

We're working on follow-up studies to vary the protein's DNA-binding and condensate-forming properties to see how they affect the organization of the genome. We want to understand how this impacts the genes that are turned on and off in the neurons developing from progenitor cells.

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The paper, "Dan forms condensates in neuroblasts and regulates nuclear architecture and progenitor competence in vivo," was published online in *Nature Communications* on June 14, 2024.

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