Proteins—and labs—coming together to prevent Rett syndrome

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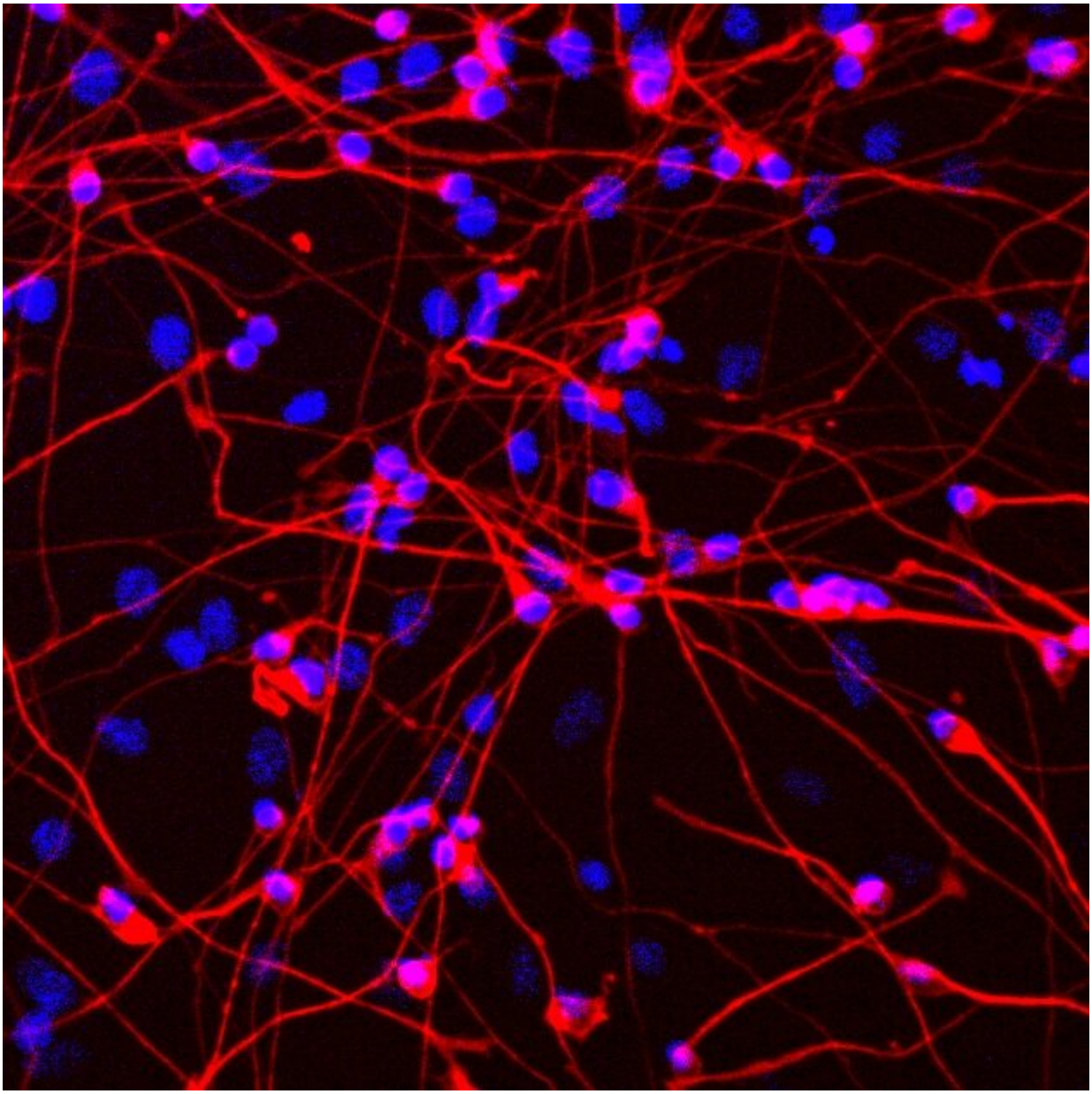

Immunofluorescence microscopy of MeCP2 neurons derived from mouse ESCs
Credit: Charles Li

New discoveries about the disruption of condensates in the neurodevelopmental disorder Rett syndrome provide insights into how cells compartmentalize chromosomes as well as new potential paths for therapies.

Scientists have, for many years, conceptualized the cell as a relatively free-flowing space, where—apart from the organization provided by specific cellular structures—molecules float freely, somehow ultimately ending up in the right place at the right time. In recent years, however, scientists have discovered that cells have much more spatial organization than previously thought thanks to a mechanism called phase separation, which occurs in cells when certain molecules form large droplet-like structures that separate what's inside of the droplet from the rest of the cell. The droplets, called condensates, help sequester and concentrate molecules in specific locations, and appear to increase the efficiency of certain cellular functions.

Whitehead Institute Member Richard Young, also a professor of biology at Massachusetts Institute of Technology (MIT), has been exploring the previously unknown role that condensates play in gathering the molecules needed for gene transcription—the process by which DNA is read into RNA. In order to better understand when and how cells use phase separation, Charles Li, a graduate student in Young's lab, set out to identify more proteins that can form condensates. That search led him to MeCP2, a protein associated with the severe neurodevelopmental disorder Rett syndrome, studied by Young's colleague at Whitehead Institute, Founding Member Rudolf Jaenisch, who is also a professor of biology at MIT. No cure for Rett syndrome currently exists, and

Jaenisch's lab has been investigating the biology of the disorder in the hopes of discovering a medical therapy that can rescue neurons affected by Rett syndrome.

With the discovery of MeCP2's condensate forming ability, Young and Jaenisch saw the opportunity for a promising collaboration between their labs. Led by co-first authors Li and Eliot Coffey, another graduate student in Young's lab, the two labs investigated MeCP2 and whether the disruption of its condensate-forming ability contributes to Rett syndrome. During these investigations, the researchers also uncovered how cells may use condensates to help organize the active and inactive parts of chromosomes. Their findings, published in the journal *Nature* on June 22, report on these insights and suggest new paths for developing therapies for Rett syndrome.

Phase separation and Rett syndrome

Proteins that form condensates often contain intrinsically disordered regions (IDRs), long spaghetti-like strands that transiently stick together to form a dynamic mesh. Research has historically focused on the structured regions of proteins, which bind very specifically to other molecules, while IDRs have largely been overlooked. In this case, MeCP2's large IDRs were exactly what drew Li to it.

"What was striking to me was that this protein has been studied for decades, and so much function has been ascribed to the protein as a whole, yet it only has one structured domain with a recognized function, the DNA binding domain. Beyond that, the entire protein is disordered, and how its parts function was largely unknown," Li says.

The researchers found that MeCP2 used its IDRs to glom together and form condensates. Then they tested many of the mutations in the MECP2 gene that are associated with Rett syndrome and found that they

all disrupt MeCP2's ability to form condensates. Their findings suggest that therapies targeting condensates associated with the protein, rather than the protein itself, may be promising in the hunt for a Rett syndrome treatment.

"MeCP2 and Rett syndrome have been studied intensely for many years in many labs and yet not a single therapy has been developed. When the project began, I was immediately fascinated by the idea that we might find a new disease mechanism that could help us finally understand how Rett syndrome arises and how it could be treated," Coffey says.

"Rick [Young] has shown that condensates play key roles in maintaining normal cellular function, and our latest collaboration illuminates how their disruption may drive diseases such as Rett syndrome," Jaenisch says. "I hope the insights we have gained will prove useful both in our continued search for a treatment for Rett syndrome and more broadly in research on condensates and disease."

Compartmentalizing chromosomes

The researchers' investigation into MeCP2's condensate forming behavior also shed light on how chromosomes are organized into regions of active and inactive genes. When MeCP2 is functioning normally, it helps to maintain heterochromatin, the roughly half of our chromosomes where genes are "turned off," unable to be read into RNA or further processed to make proteins. MeCP2 binds to sequences of DNA marked with a certain type of regulatory tag that is typically found in heterochromatin. This helps crowd MeCP2 to the threshold concentration needed to form heterochromatin condensates. These condensates, in turn, help to sequester the molecules needed to maintain it apart from euchromatin, the half of our chromosomes filled with active genes. Different proteins form condensates near euchromatin, concentrating the molecular machinery needed to transcribe active genes

there.

Since condensates form when proteins with large spaghetti-like IDRs stick together, one might expect that any protein containing IDRs could interact with any other IDR-containing protein to form droplets, and that is what the researchers have often seen. However, what they observed with MeCP2, which is associated with heterochromatin, is that key condensate-forming proteins associated with euchromatin refused to mix.

It's important for the health of the cell that the genes in heterochromatin not be inadvertently turned on. The researchers reason that discrete euchromatin and heterochromatin condensates may play a key role in ensuring that transcriptional machinery localizes to euchromatin only, while repressive machinery—like MeCP2—localizes to heterochromatin. The researchers are excited to turn their attention to how proteins are able to join condensates selectively, and when and where else in the cell they do so.

"There's a chemical grammar waiting to be deciphered that explains this difference in the ability of some proteins to move into one condensate versus another," Young says. "Discovering that grammar can help us understand how cells maintain the crucial balance between the active and silent halves of our genome, and it could help us understand how to treat disorders such as Rett syndrome."

More information: MeCP2 links heterochromatin condensates and neurodevelopmental disease, *Nature* (2020). DOI: 10.1038/s41586-020-2574-4

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