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Emergent properties of model membraneless organelles

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Timothy Nott did his PhD on molecular structure at the National Institute for Medical Research in London under the supervision of Dr. Smerdon. He graduated in 2009 and moved to Toronto to study the principles of how cells are internally compartmentalised in the group of Professor Pawson. He started as Postdoctoral Research Associate in 2014 (Professor Baldwin) at the university of Oxford before becoming a Sir Henry Dale fellow in 2016 in the department of biochemistry (University of Oxford). Timothy Nott is interested in compartmentalisation via Liquid-liquid phase separation in cells.

Career advice

• Find yourself a mentor. If you get lost in a research project or are conflicted about a career decision, a mentor who can give you the long view will be invaluable.
• Be proactive. Talk to scientists outside your immediate lab, institute, or field of expertise.
• Keep your eyes open and be prepared to act quickly. You never know where a good career/project/collaboration opportunity will come from or what form it will take.

Abstract

Condensation of cellular material into phase-separated liquid-like droplets has emerged as a fundamental new organising principle in cell biology. The dynamic and membraneless compartments formed in this way are predominantly associated with processing nucleic acids and are indispensable for cellular function. Surprisingly, we know little about the solvent environment inside these and other cellular bodies, yet it is likely to have a significant influence on the biochemical reactions that take place within them.

One important class of enzymes that are biochemically active inside membraneless organelles are DNA and RNA helicases, which remodel the structures of nucleic acids. In addition to ATP-dependent catalytic domains, several helicases possess intrinsically disordered regions that readily undergo liquid-liquid phase separation in cells and in vitro. We have recently found that model membraneless organelles reconstituted from only the disordered tails of the DEADbox helicase Ddx4 display emergent biochemical properties. Among these are the ability to selectively absorb RNAs based on their structure, and the destabilisation of nucleic acid duplexes. We hypothesise that in the context of a membraneless organelle, these properties could complement the catalytic activity of the helicase domain.

Here we show that the emergent biochemical properties of membraneless organelles formed from only the disordered tails of DEADbox RNA helicases can be tuned by their amino acid sequence, and subtle changes to their surrounding environment. These results suggest novel ways in which cells could modulate the intrinsic properties of membraneless organelle interiors to achieve specific biochemical outcomes.

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