Liquid-liquid phase separation-based membraneless organelles, the guardian bubbles of protein life.

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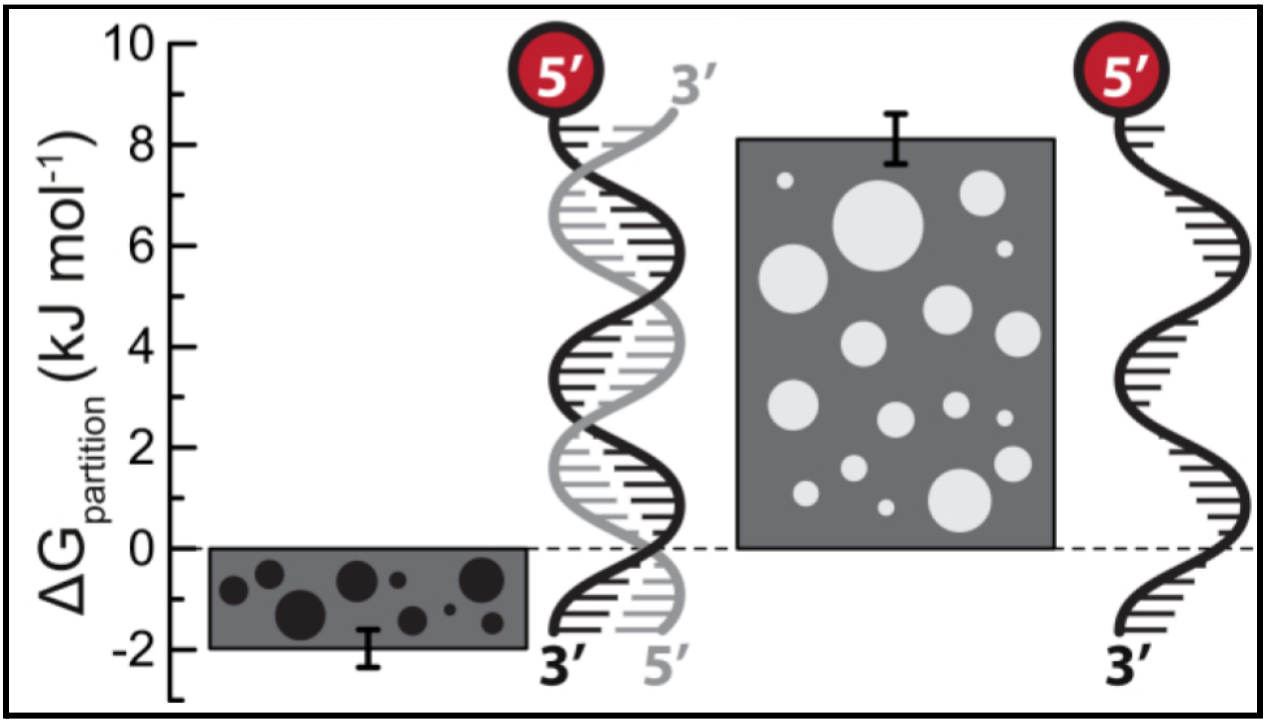

Figure 1. Single stranded DNA is protected within LLPS droplets but not double stranded DNA. Source: Nott *et al.* 2012 (1).

Liquid-liquid phase separation (LLPS) of proteins in aqueous buffers is a process of single phase liquid transition into a visible double phase system in which the proteins form a separate droplet within the aqueous buffer droplet. Interestingly, Nott *et al.* showed that the LLPS can further lead to the formation of membraneless organelles in response to some external environmental factors using Ddx4 protein (DEAD box containing RNA helicase) which is a disordered protein. Nott *et al*, explained that the proteins that are capable of LLPS have intrinsic disorderedness that in turn depends on different factors such as temperature, pH, salt concentration in the buffer (tonicity) and arginine methylation. For example, Nott *et al.* showed that the Ddx4 forms LLPS droplets between 22℃ to 32℃. And they interestingly talk about the formation of liquid condensates with the single strand DNA rather than double strand DNA due to the cation-pi interactions that appear to drive self-association, as observed in the context of folded proteins mediating interactions with single-stranded nucleic acids. This is because the single stranded DNA molecules

are more prone to the formation of hydrogen bonds or electrostatic interactions while the double stranded DNA molecules are almost neutral in this context. This not only proves that the protein LLPS droplets act as guardians of the proteins but also guard the associated single stranded molecules of DNA that could be involved in active transcription or replication processes. Especially in cases like starvation or dehydration conditions where the cell has to protect the most critical components by shutting down all other machineries. One can further take advantage of these LLPS enclosing the genetic material towards various applications in future.

Currently, we are repurposing these protein-LLPS droplets along with RNA molecules for anti-cancer therapeutics by leveraging the capability of these LLPS droplets to form membraneless organelles. All the biochemical and biophysical data from this study will be published in the future issues of TCABSE-J.

References

1. Nott TJ, Petsalaki E, Farber P, et al. Phase transition of a disordered nuage protein generates environmentally responsive membr -aneless organelles. *Mol Cell*. 2015;57(5):936-947. doi:10.1016/j.molcel.2015.01.013

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