Cell signaling and virus restriction via phase separation in the cytoplasm

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***Short Abstract* — Phase separation is a common and widely studied physical phenomenon: water freezes, oil and water phase separate, etc. There is now experimental data suggesting that a number of proteins undergo a phase-separation-like phenomenon inside the cytoplasm of cells, and that this phase separation is crucial to the biological function of the protein. Examples include the protein Dishevelled that needs to phase separate to perform its role in the Wnt signalling pathway, and TRIM5□, a protein that forms "droplets" that coat HIV capsids and hence restricts retroviral infection. Quantitative modeling suggests possible roles that phase separation can play in cell biology, such as exploiting the inherently sharp onset of phase separation to produce a switch-like response to a stimulus.**

***Keywords* — Phase separation, Wnt signalling, Dishevelled, TRIM5□, virus restriction**

I. Introduction and Experimental Motivation

A number of proteins appear to phase separate inside cells, in the sense that they spontaneously form domains of high concentration in dynamic equilibrium with the remainder of the cytoplasm (in which the concentration of the protein is much lower). These domains contain thousands or more of molecules of these proteins. Examples include Dishevelled and TRIM5□. Dishevelled is a protein in the Wnt signaling protein. FRAP experiments show that the high-concentration domains are in dynamic equilibrium with the remainder of the cytoplasm [1]. Dishevelled's ability to phase separate is required for its biological function [1,2]. Another example is TRIM5□. This protein also appears to phase separate [3]. The TRIM5□ domains are transported along microtubules and when they collide with HIV capsids they coat them [4]. TRIM5□ targets the HIV capsids for destruction by proteasomes in order to restrict viral infection.

II. Modelling

Even for the best studied system: Dishevelled, little is known about how phase separation enables the proteins to perform their biological function and why phase separation is sufficiently useful that natural selection has selected for it. I want to use simple models to address both the how and why questions.

Phase transitions are inherently phenomenon with sharp onsets. Water flips from the liquid to the solid state as a threshold temperature (0C) is crossed. I will consider quantitative models to see how the switch-like nature of phase transitions can be harnessed to produce efficient switches inside cells [5,6]. The Wnt pathway needs to produce switch-like responses to external stimuli.

For the TRIM5□ system quantitative modeling shows that the phase separated droplets transported along microtubules provide an efficient way of capturing HIV capsids. We can also compare binding of a phase-separated domain to a capsid, to binding of a single monomeric protein to a capsid. The domain can use the information that a capsid has a surface with of order 1000 copies of a protein, while a single protein cannot. Thus the domain is inherently more efficient, but needs to be transported as its diffusion is slow. Also, a much lower affinity between TRIM5□ and the HIV capsid protein is required than if it were monomeric. This much weaker affinity will ease the evolution of the required highly *specific* interaction: TRIM5□ must bind to viruses but not to other structures in the cell such as microtubules, organelles.

III. Conclusion

In summary: Recent experimental work has shown that cells are exploiting a well studied physical phenomenon, namely phase separation. We now wish to understand how cells are using this phenomenon. Quantitative modeling suggests that the cooperative nature of phase transitions may be useful for the efficient performance of a number of cell biological functions.

References

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