iCase Project / AY 2023 -2024

Phase transitions underlying viral replication: the role of biomolecular condensates in segmented RNA viral genome assembly

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Department/Institute: Biochemistry

Industrial Partner: Transition Bio

Research area: Biochemistry, biophysics of biomolecular condensates

Project outline:

There is an urgent need for new drugs to combat pathogenic viruses that threaten human, animal, and plant health. Most existing antivirals inhibit virus attachment/entry or target key enzymes, and new antiviral targets are needed to develop novel treatments and counter antiviral resistance. A key process in the replication cycle of many viruses is the formation of dynamic organelles called viral factories. Multiple lines of evidence suggest that viral factories may form via liquid-liquid phase separation (LLPS), including those that support replication of a vast range of important animal viruses, including influenza viruses, reo- and rotaviruses. Targeting LLPS is thus an emerging paradigm that may underlie the discovery of novel, broad-spectrum antivirals. This project will focus on dissecting the physicochemical properties of viral RNA-binding proteins that form complex biomolecular condensates to understand how they nucleate viral factories and support viral replication. This will lead to the identification of new therapeutic targets. Central to this proposal will be mass spectrometry (MS)-based proteomics methods combined with machine learning approaches and advanced microscopy and microfluidics techniques that will be used to bridge the gap between in vitro and in cellulo studies of viral factory formation. The insights gained from the work will underlie our search for compounds-modulators of LLPS that could be used for future antiviral therapies.

This project aims to quantitatively describe the formation of these condensates, we will examine the observed phase transitions of binary and tertiary mixtures of recombinantly produced viral proteins, as well as viral RNAs in vitro using the recently developed high throughput microfluidics platform PhaseScan. These findings will lead us to define a new model of viral replicative condensate formation that addresses protein-specific attributes (posttranslational modifications, conformation), and their highly selective RNA composition (partitioning of cognate viral transcripts and exclusion of non-viral RNAs).

The partitioning of small molecule compounds into these biomolecular condensates will be screened in collaboration with the Cambridge Proteomics Centre, to determine the degree of the partitioning of such molecules into the condensates. Successful hits will be then tested in vitro (PhaseScan) and in vivo (virus replication assays) to determine their potency in disrupting phase separation and viral replication.

BBSRC DTP main strategic theme: Understanding the rules of life