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Learning the RNA Jigsaw Rules from Viruses with Multi-segmented Genomes

A crucial step in viral replication is the formation of specialised organelles known as viral factories, or viroplasms. These cytoplasmic granules supporting viral replication are thought to be formed through phase separation (PS) of viral proteins and RNAs. We have shown that rotavirus viroplasms are ribonucleoprotein (RNP) granules, originating from the PS of non-structural proteins that orchestrate viroplasm formation, and accumulate eleven distinct types of viral RNA transcripts that will form the complete eleven-segmented rotavirus genome.

We have developed an in vitro system that mimics the behaviour of these viroplasmic condensates, capable of incorporating both single-stranded and double-stranded RNAs, as well as the viral RNA-dependent RNA polymerase. Using high-throughput analytical microfluidics, machine learning techniques, and microscopy, we explore phase transitions and maturation of viroplasms aiming to uncover their role in rotavirus replication, and the assembly of its eleven-segmented RNA genome. Our work sheds light on the mechanisms, by which viral factories selectively accumulate viral transcripts required for segmented genome packaging. We propose that these processes are required for the stoichiometric assembly and replication of the segmented viral RNA genome, highlighting the emergent properties of condensates in supporting viral replication.