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PAPER OF THE MONTH • AUGUST 2022



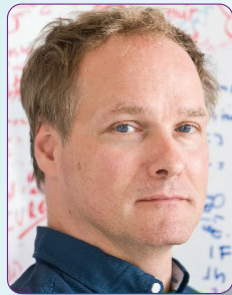
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 Cell Reports

Scaffolding viral protein NC nucleates phase separation of the HIV-1 biomolecular condensate

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Recent investigations have refocused attention on the study of membraneless organelles generated by biomolecular condensates (BMCs). BMCs are implicated in the control and compartmentalization of a growing number of cellular functions in both nuclear and cytoplasmic compartments. BMCs appear to be fundamental to the replication cycles of several viruses but remain to be functionally characterized.

Previously, we demonstrated that pan-retroviral nucleocapsid (NC) proteins phase separated into condensates regulating virus assembly. In the present publication, we discover that intrinsically disordered human immunodeficiency virus-type 1 (HIV-1) core proteins co-condense with the viral genomic RNA (vRNA) to assemble as BMCs attaining a geometry characteristic of viral reverse transcription complexes. We explore the predisposition, mechanisms, and pharmacologic sensitivity of HIV-1 core BMCs in living cells. HIV-1 vRNA-interacting NC condensates were found to be scaffolds onto which client capsid, reverse transcriptase, and integrase condensates assemble. HIV-1 core BMCs exhibit fundamental characteristics of BMCs and are drug-sensitive. Lastly, we find evidence that HIV-1 protease-mediated maturation of structural Gag and Gag-Pol precursor proteins in cells yields abundant and visible HIV-1 BMCs.

Our findings demonstrate that upon virus maturation by the viral protease, resulting disordered viral protein elements phase separate and coexist as multi-component protein- and vRNA-enriched BMCs, providing a fresh lens with which to examine the nature of infecting viruses and viral cores during ingress.