Development of drugs targeting Respiratory Syncytial Virus inclusion body condensates

Biomolecular condensates have emerged as an important subcellular organizing principle. Replication of many viruses, including human respiratory syncytial virus (RSV), occurs in virus-induced compartments called inclusion bodies (IBs) or viroplasm. IBs of negative-strand RNA viruses were recently shown to be biomolecular condensates that form through phase separation. Here we report that the steroidal alkaloid cyclopamine and its chemical analogue A3E inhibit RSV replication by disorganizing and hardening IB condensates. The actions of cyclopamine and A3E were blocked by a point mutation in the RSV transcription factor M2-1. IB disorganization occurred within minutes, which suggests that these molecules directly act on the liquid properties of the IBs. A3E and cyclopamine inhibit RSV in the lungs of infected mice and are condensate-targeting drug-like small molecules that have in vivo activity. Our data show that condensate-hardening drugs may enable the pharmacological modulation of not only many previously undruggable targets in viral replication but also transcription factors at cancer-driving super-enhancers.

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