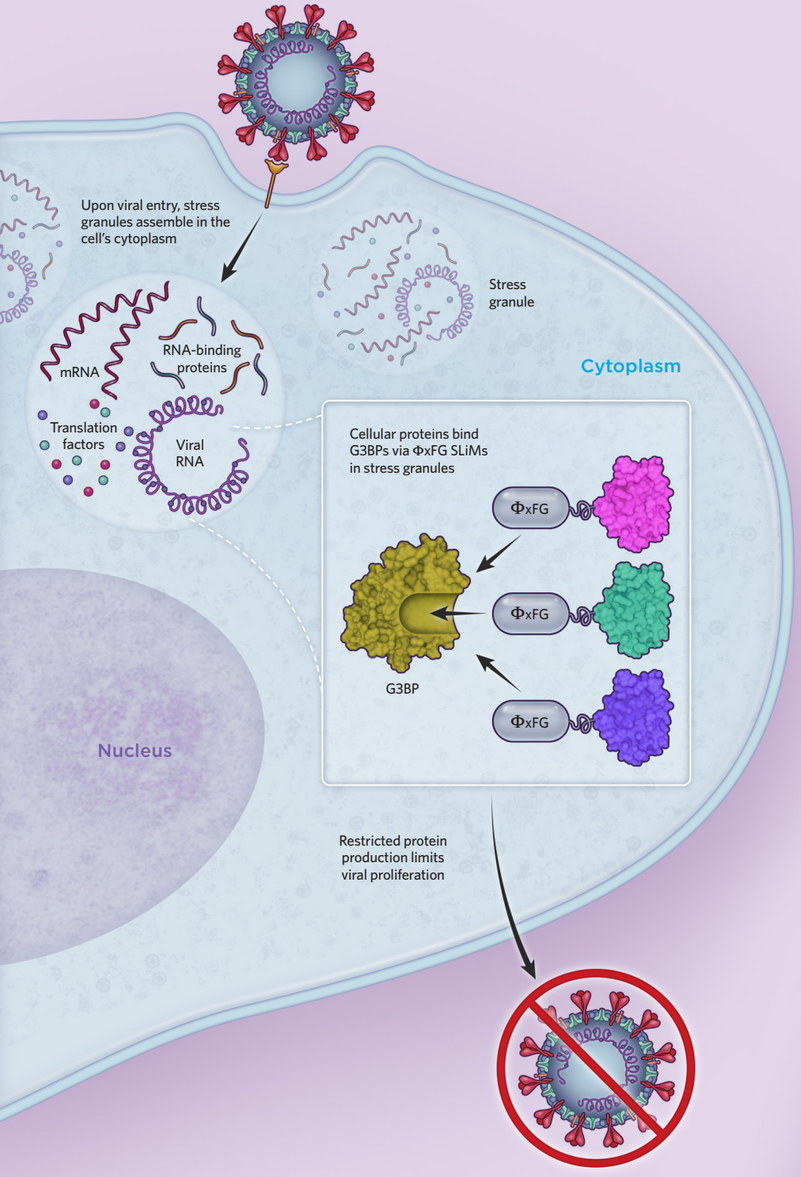
SLiMS IN SARS-COV-2 INFECTION

SARS-CoV-2 appears to take advantage of the host stress granule machinery deployed in response to viral infection to favor its proliferation. Specifically, our work shows that its nucleocapsid (N) protein, responsible for encapsulating viral RNA and coordinating replication and other functions, contains a SLiM that competes with cellular proteins in binding with stress granule–forming proteins, namely G3BP1 and G3BP2 (G3BPs). In doing so, the virus effectively promotes its proliferation while dampening the cell's antiviral defenses. Targeting these SLiM-mediated protein interactions may one day prove to be a feasible antiviral therapy approach.

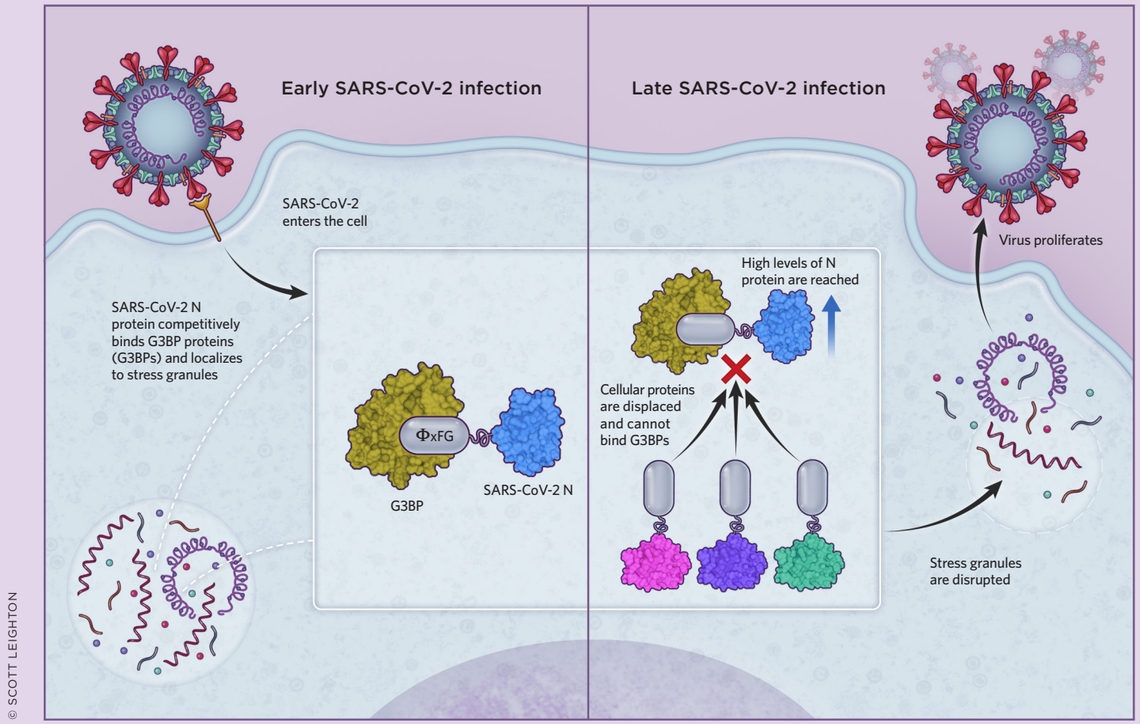


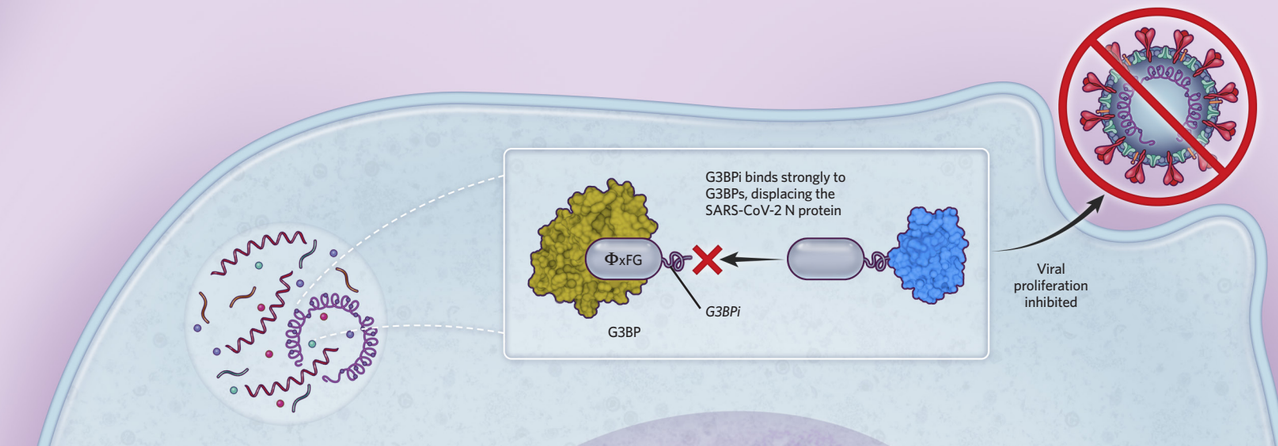
NORMAL STRESS RESPONSE

In response to viral infection or other stressors, cells form stress granules, membraneless organelles that contain host mRNA, viral RNA, translation factors, and RNA-binding proteins. These include G3BPs, which bind to other stress granule proteins via an ΦxFG SLiM, where Φ represents a hydrophobic amino acid, x represents any residue, and F and G represent phenylalanine and glycine, respectively. This response causes cells to limit their energy use and restrict protein production. Because viruses need the cellular machinery to produce their viral proteins and proliferate, the stress response can hamper this, with stress granules often associated with an antiviral role.

SARS-COV-2 INFECTION

In the case of SARS-CoV-2, we found in human cells that the N protein is able to bind G3BP proteins via an ΦxFG SLiM, possibly to localize viral replication to stress granules in early infection. As levels of the SARS-CoV-2 N protein increase in later infection stages, N effectively displaces all cellular proteins from G3BPs and disrupts cytoplasmic stress granules. This ultimately promotes viral proliferation and the dampening of antiviral defense mechanisms.





TARGETING STRESS GRANULE FORMATION

Based on these findings, we designed a peptide inhibitor containing ΦxFG-like SLiMs that bound strongly to G3BPs, preventing the binding of SARS-CoV-2 N protein in human cells. This peptide (G3BPi) inhibited viral proliferation in a monkey cell line commonly used in SARS-CoV-2 studies, though the specific downstream mechanisms remain to be elucidated.