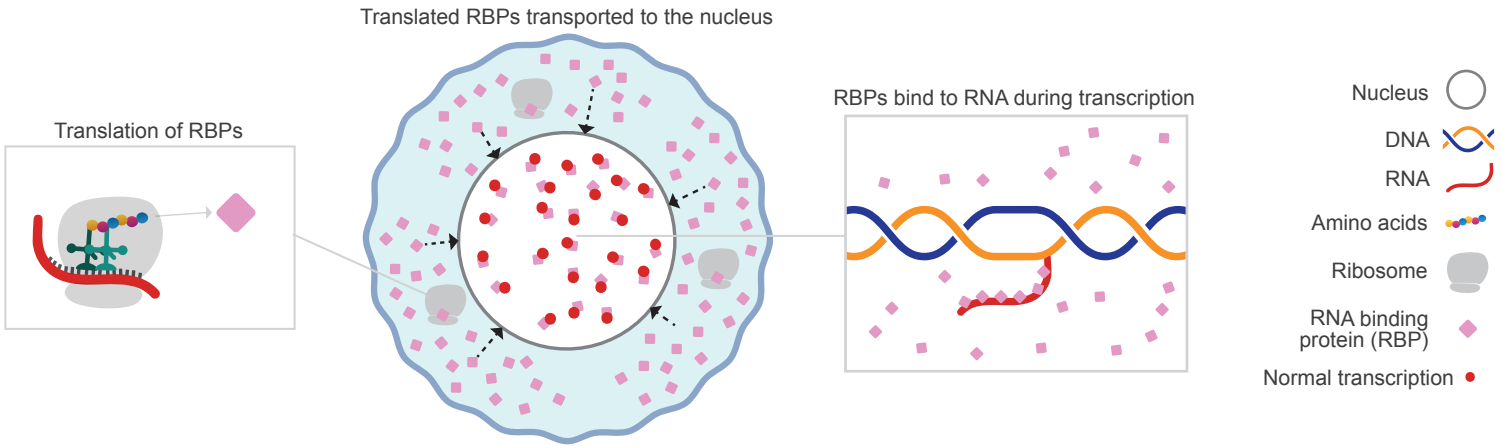
Proposed mechanism of SARS-CoV-2 severe infection

The onset of COVID19 can be extremely severe, with rapid infection of the lung and other organs. In many individuals the immune response is insufficient to prevent or inactivate these infections. We propose a molecular mechanism that may explain how the virus disrupts normal cellular processes (Step 1), causing it to rapid multiply and produce systemic infection:

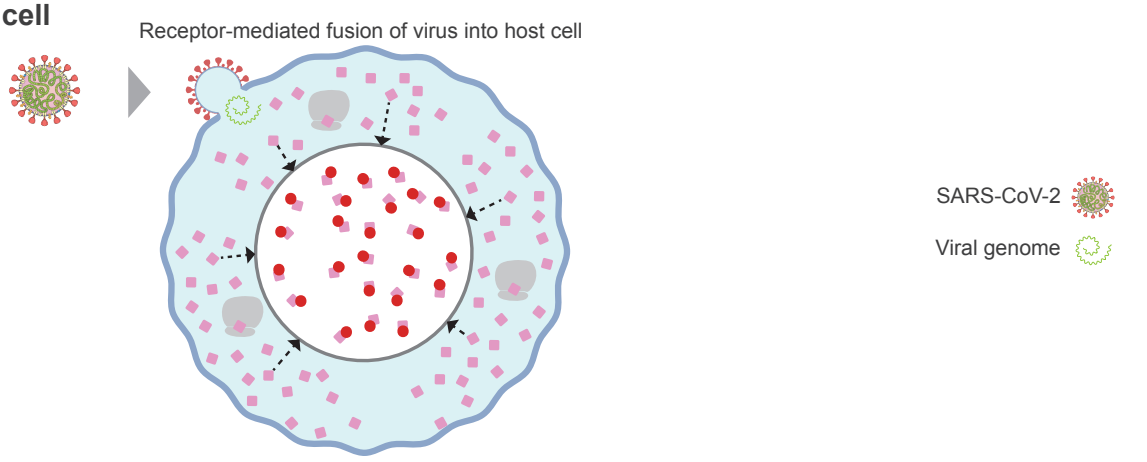
- SARS-CoV-2 replicating (+ strand) and coding (- strand) viral RNA depletes host RNA-binding proteins that ordinarily protect host chromosomes (Steps 2, 3 and 4).
- This damages chromosomes to a point where the repair response is overwhelmed (Step 5),
- Activating programmed cell death (apoptosis), killing the infected cells (Step 6),
- Releasing many viral particles, infecting neighboring cells and other tissues (Step 7). Loss of too many lung cells can cause oxygen deprivation of other organs, causing them to fail.

Evidence supporting this mechanism is presented in the accompanying article:
Rogan et al. A proposed mechanism for molecular pathogenesis of severe RNA-viral pulmonary infections. F1000Research, submitted.

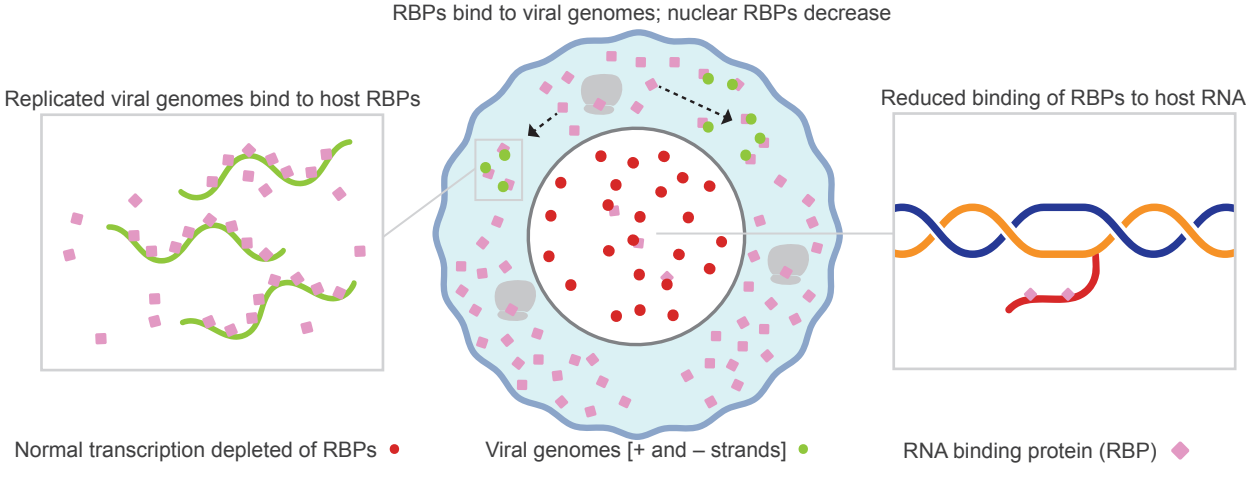
1. Normal transcription and RBP nuclear transport in uninfected cell



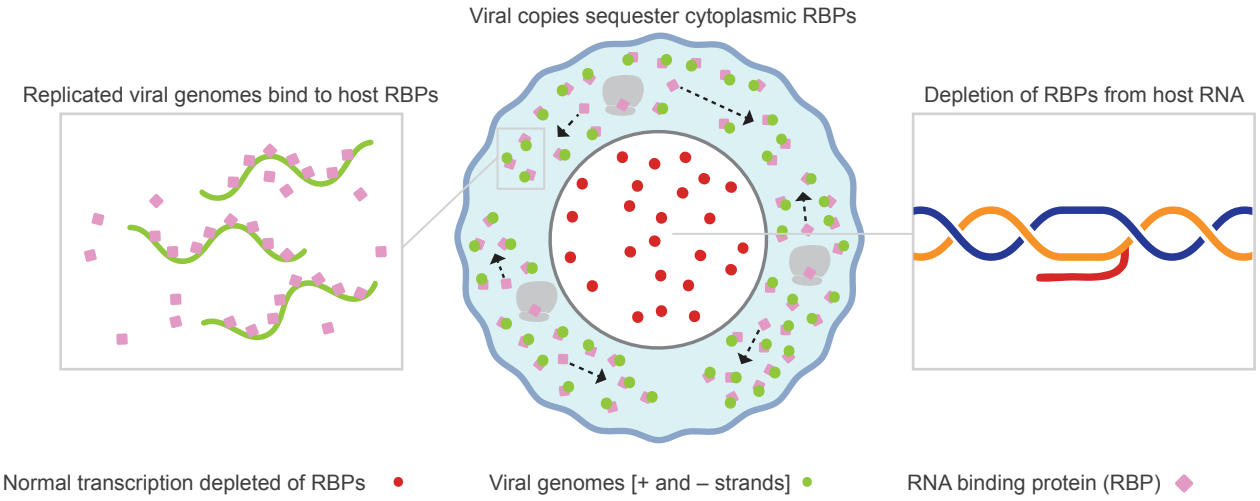
2. SARS-CoV-2 infects host cell



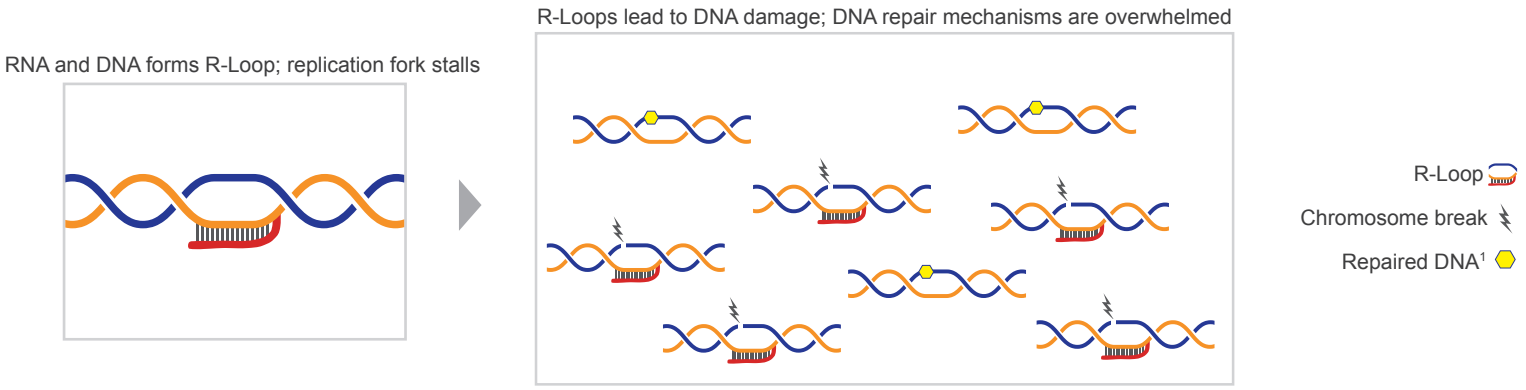
3. Replicated viral genomes bind RBPs in host cell



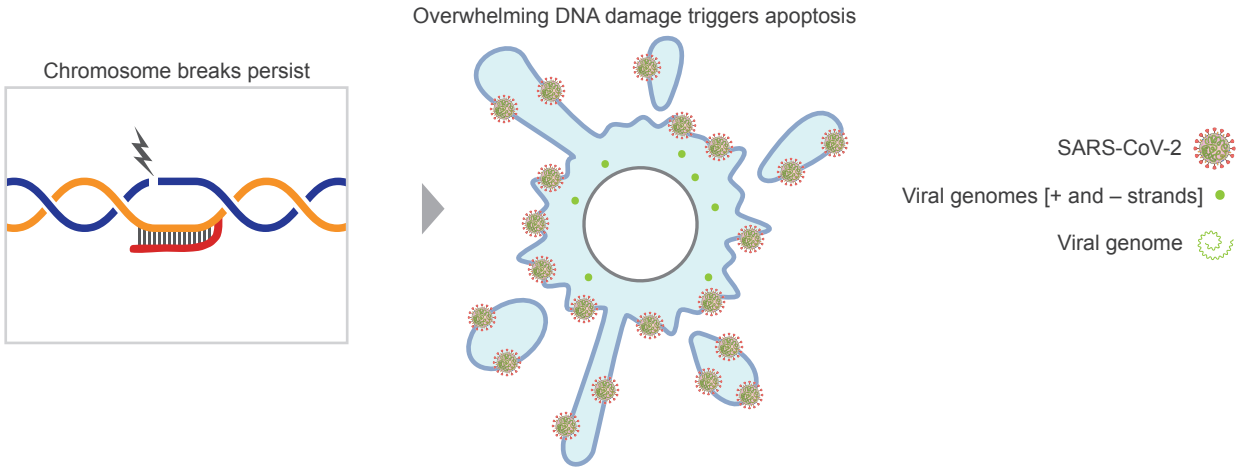
4. Abundant viral genomes prevent RBPs from entering nucleus and binding RNA



5. RNA:DNA hybrids form R-Loops which overwhelms host repair mechanisms

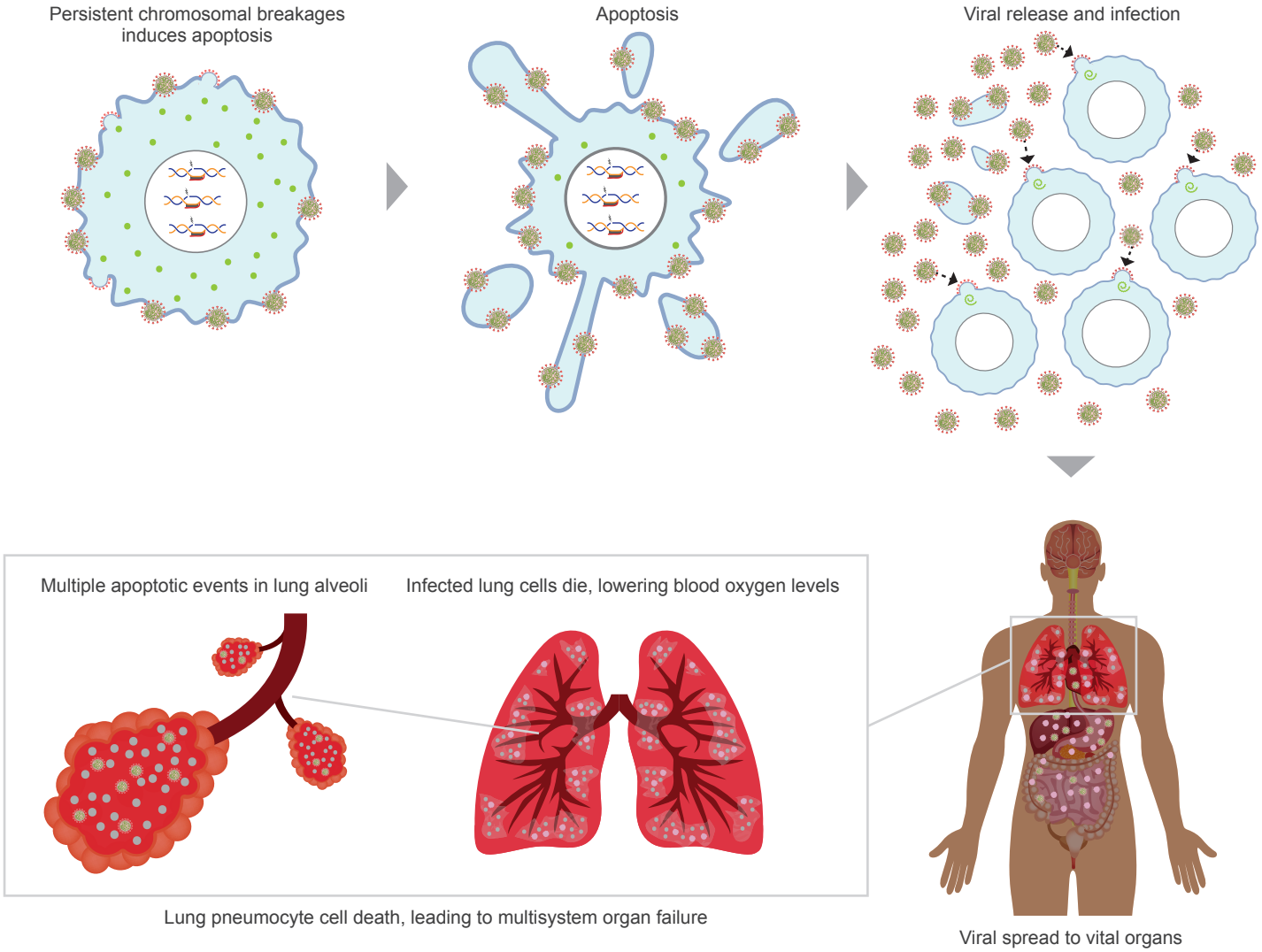


6. Persistent chromosome breaks initiate apoptosis



1. RNAse H, helicases and the Fanconi anemia complex (including BRCA1/2)

7. Apoptosis causes high multiplicity of infection



SARS-CoV-2 Viral genomes [+ and – strands] Viral genome Apoptotic events and infection Dead tissues due to apoptosis

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