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SUPPLEMENTARY INFORMATION

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Mechano-genomic regulation of coronaviruses and its interplay with ageing

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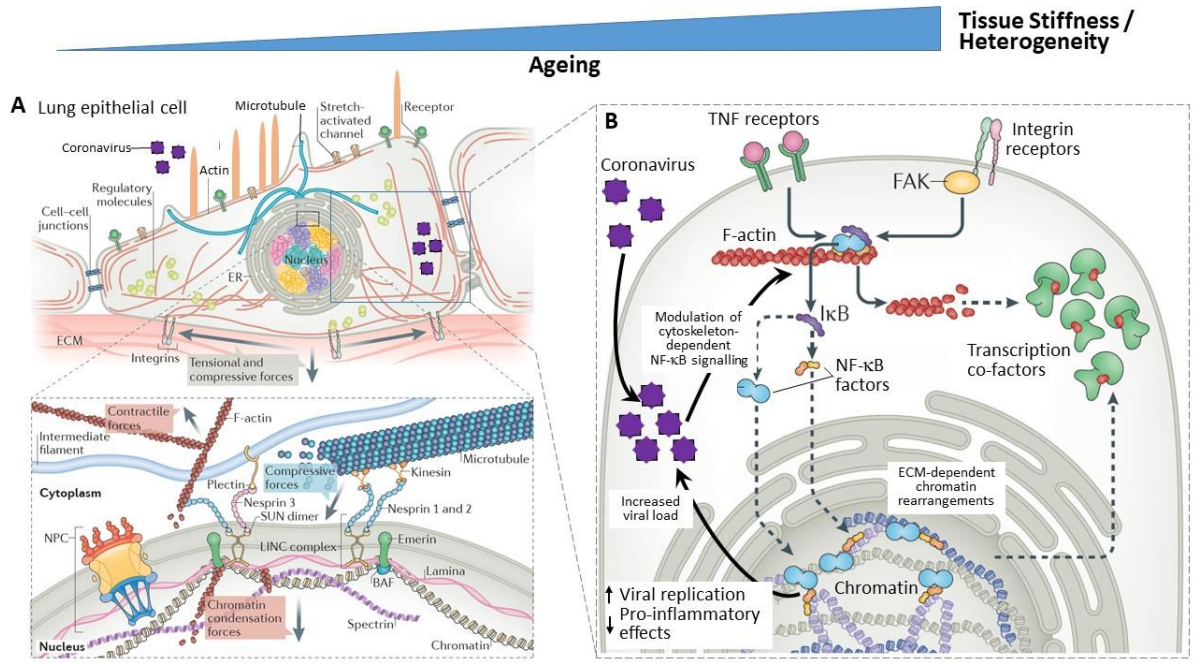
Supplementary Figure 1. Increased replication of coronaviruses via mechano-genomic regulation of NF-κB signalling



There is some evidence accumulated over the years that viral infection can predispose to tissue fibrosis, thereby changing the mechanical environment of the tissue (see for example here: https://www.ncbi.nlm.nih.gov/pubmed/19014649). We now propose the converse interaction between cell/tissue mechanics and viral infection that could be particularly relevant in the context of infection with respiratory viruses, such as coronaviruses, and lung tissue mechanical changes associated with ageing. Ageing is associated with increased heterogeneity of lung epithelial cells and increased lung tissue stiffness that could lead to changes in the mechanical state of cells of the aged lung epithelium. Cells in tissues extensively interact with their microenvironment and sense microenvironmental changes through various receptors, which initiate signalling pathways that transduce the signal to the nucleus. Changes of the extracellular matrix (ECM), including mechanical alterations such as stiffness, are transduced to the nucleus generally through the cytoskeleton networks of actin and microtubules as well as by regulatory molecules. These signals modulate the three-dimensional organization of chromosomes in the nucleus to regulate gene expression programs (see figure part **A**). Our hypothesis is that coronaviruses take advantage of the cytoskeleton-dependent NF-κB signalling to the nucleus to upregulate genes that promote virus replication and propagation, while dampening the pro-inflammatory effects of this signalling. We conjecture that such mechano-genomic regulation is ageing-dependent; namely, depending on the tissue stiffness — which increases with ageing — specific gene neighborhoods and transcription hotspots are formed in the genome, thus supporting the differential expression of various target genes including NF-κB targets (in this case skewing the target gene expression towards virus-promoting signals) (see figure part **B**). We envision that such a mechano-genomic perspective combined with imaging, sequencing, and machine learning in ageing lung organoid models infected by coronavirus could lead to new avenues for the screening of anti-viral drugs and their combinations as well as other therapeutic interventions. Figure adapted from Uhler, C., & Shivashankar, G. V. (2017). Regulation of genome organization and gene expression by nuclear mechanotransduction. *Nature Reviews Molecular Cell Biology*, **18**(12), 717-727.