

Multi-organ Proteomic Landscape of COVID-19 Autopsies

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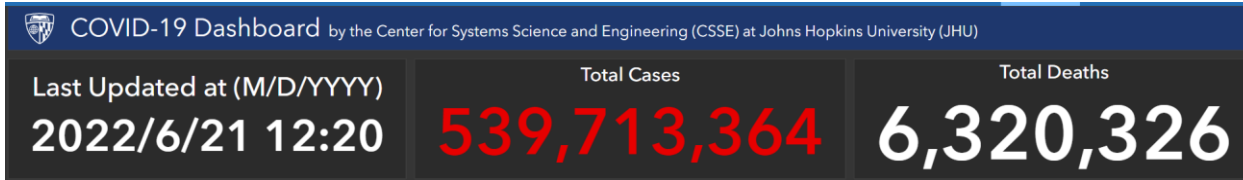
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CHAPTER 1

Background

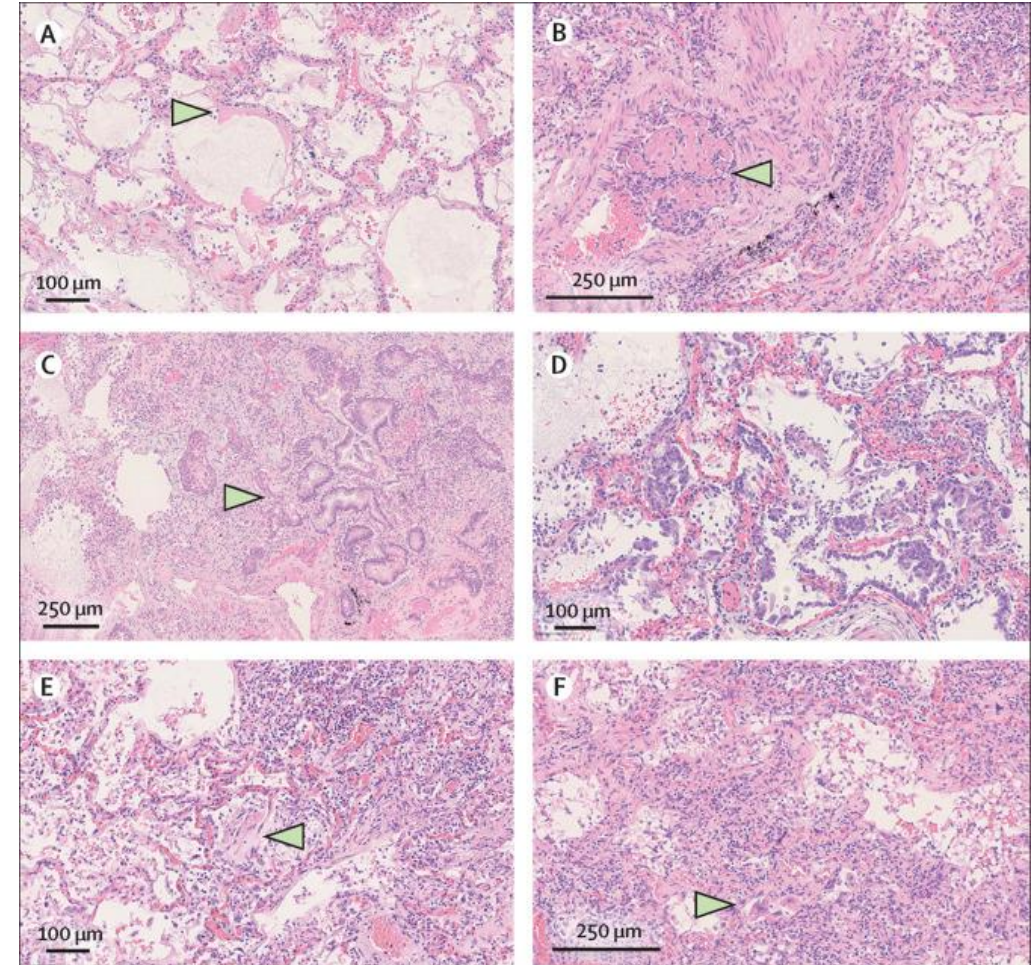
The ongoing COVID-19 pandemic



- 17% of COVID-19 patients could develop as Acute respiratory distress syndrome (ARDS);
- 65% of these ARDS patients died due to multi-organ dysfunction.

The features of multiorgan failure

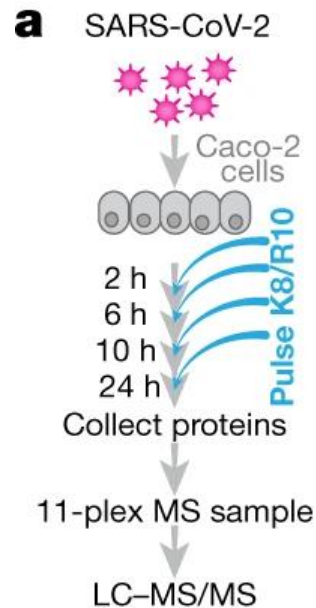
- Laboratory findings
AST, ALT, BUN, D-dimer, LDH, CK...
- Imaging findings
CT-scan...
- Morphological characterization of autopsies

Luca *et al.* The lancet infectious diseases. 2020

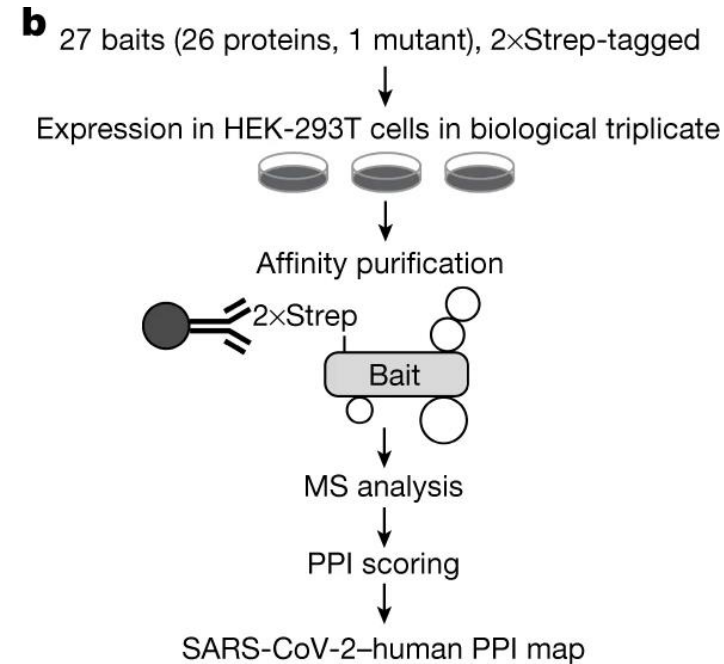
Mechanistic studies

In vitro SARS-CoV-2 infected cell line models

- Proteomics
- Global Phosphorylation Landscape



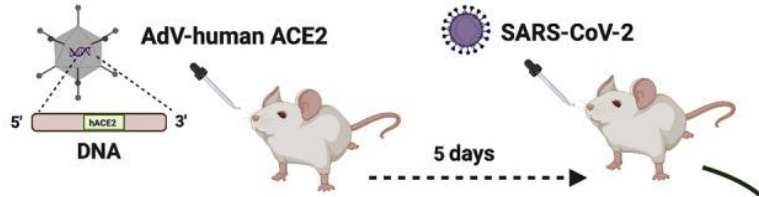
- A SARS-CoV-2 protein interaction map



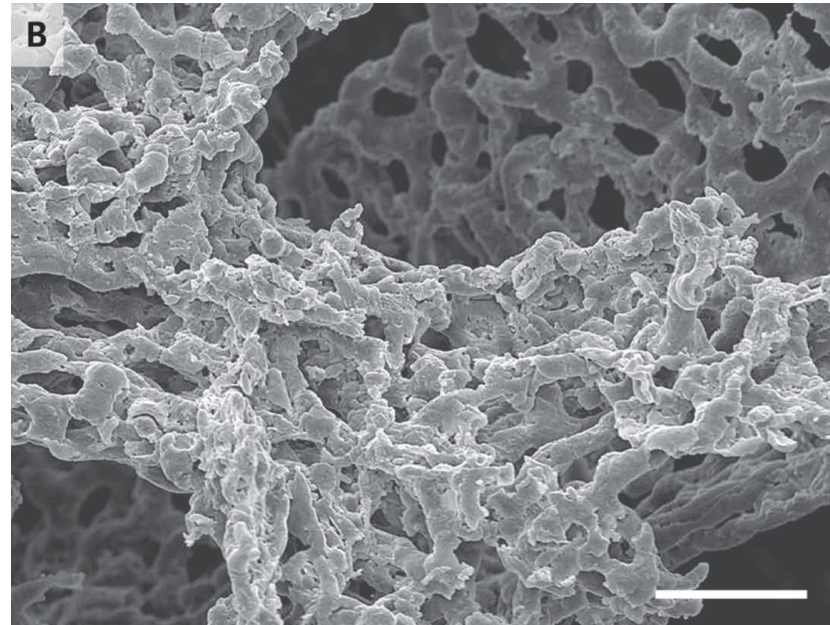
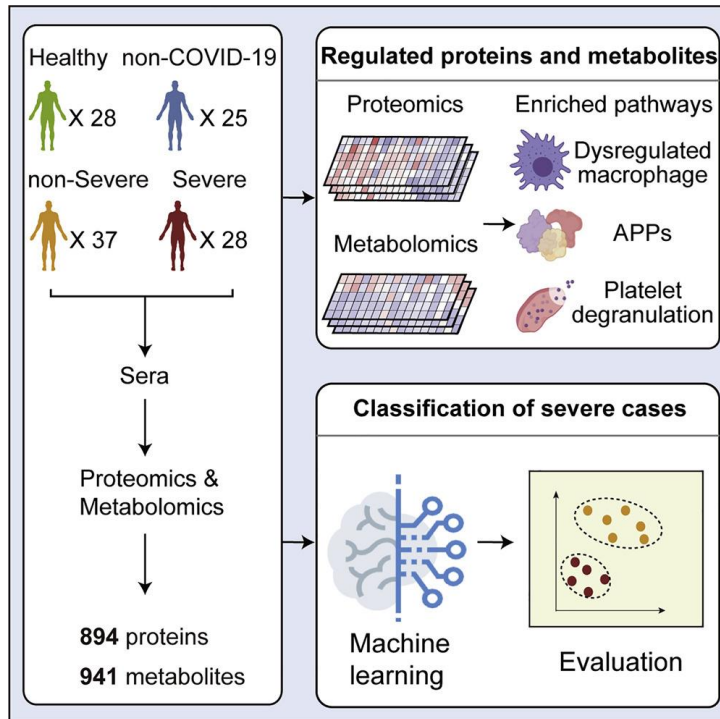
- New insights into virus-perturbed biochemical processes of COVID-19
- Potential therapies

Mechanistic studies

- In vivo* • SARS-CoV-2 infected mouse / rhesus macaque models



- Few studies have characterized **host responses at the molecular level from clinical specimens.**

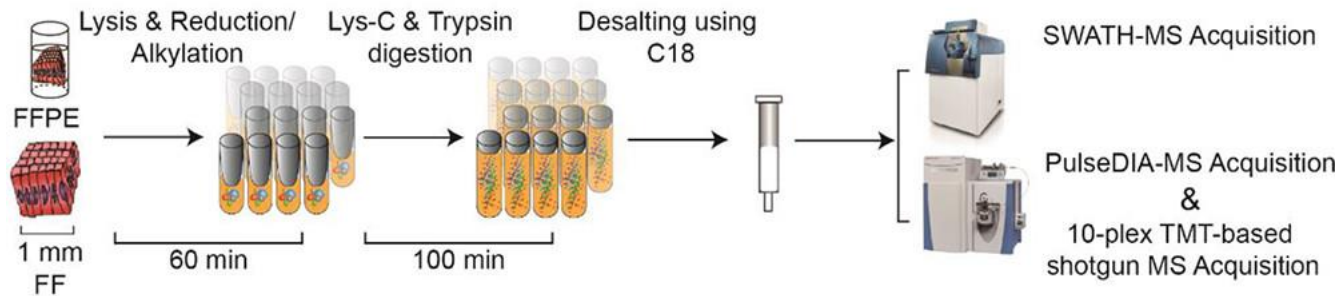


Lung transcriptome of seven COVID-19 autopsies

Bao et al., 2020; Hassan et al., 2020; Jiang et al., 2020; Chandrashekar et al., 2020; Deng et al., 2020; Messner et al., 2020; Shen et al., 2020a; Ackermann et al., 2020

Proteome

- **Effective and high-throughput** analysis of formalin-fixed tissue samples by latest advances of proteomics technologies

3 Hours from Tissue to Peptides (the accelerated PCT method)

- Proteins measured by mass spectrometry were much more stable than transcripts

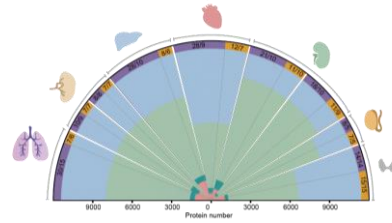
The molecular pathology of multi-organ injuries in COVID-19 patients remains unclear, preventing effective therapeutics development.

Our objectives

- To depict the multi-organ proteomic landscape of COVID-19 autopsies
- To uncover dysregulated proteins and biological processes between COVID-19 and non-COVID-19 groups
- To offer potential therapeutic clues

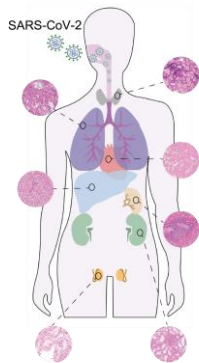
CHAPTER 2

Study Design



Sample collection

COVID-19 vs. non-COVID-19



Multiorgan proteome landscape



Data interpretation

① Dysregulated proteins

- Receptors
- TFs
- Cytokines
- Pathological changes associated factors (coagulation, fibrosis, angiogenesis)

③ Unique molecular characteristics in each organs

- Lung
- Testis

② Dysregulated pathways

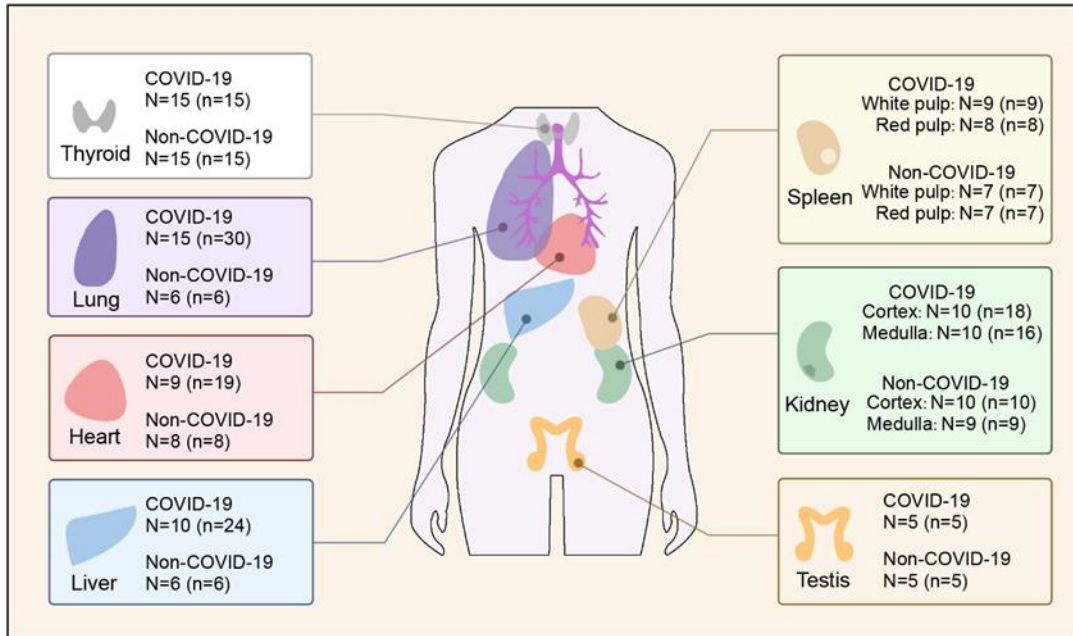
- Virus replicate
- Metabolism (fatty acids, glucose)
- Immunity

④ Systemic immunity state, metabolism and pathological changes

CHAPTER 3

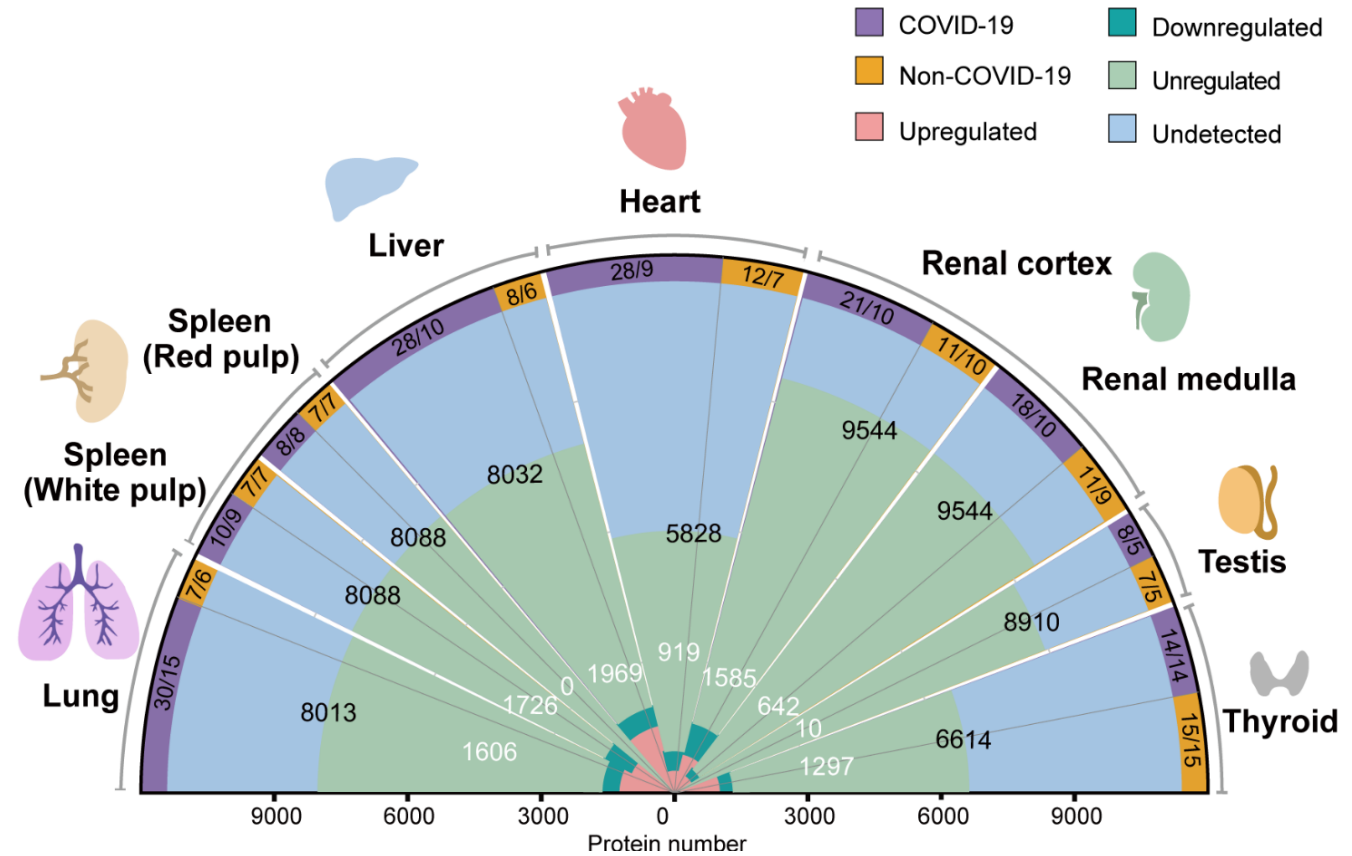
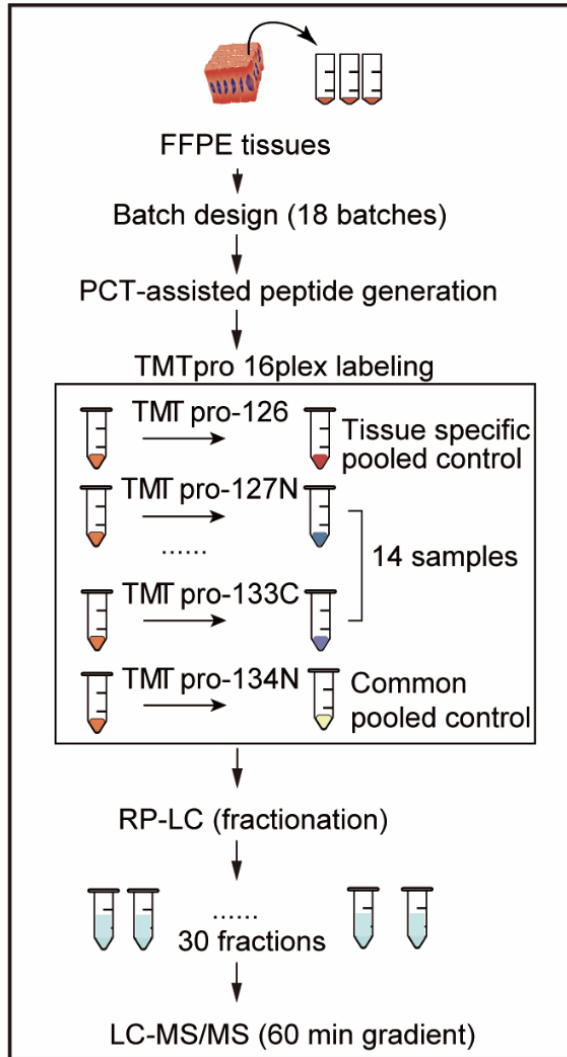
Results

144 autopsy tissue samples from 19 COVID-19 patients;
74 control samples from 56 non-COVID-19 cases.



Confounder effects between COVID-19 and non-COVID-19 groups

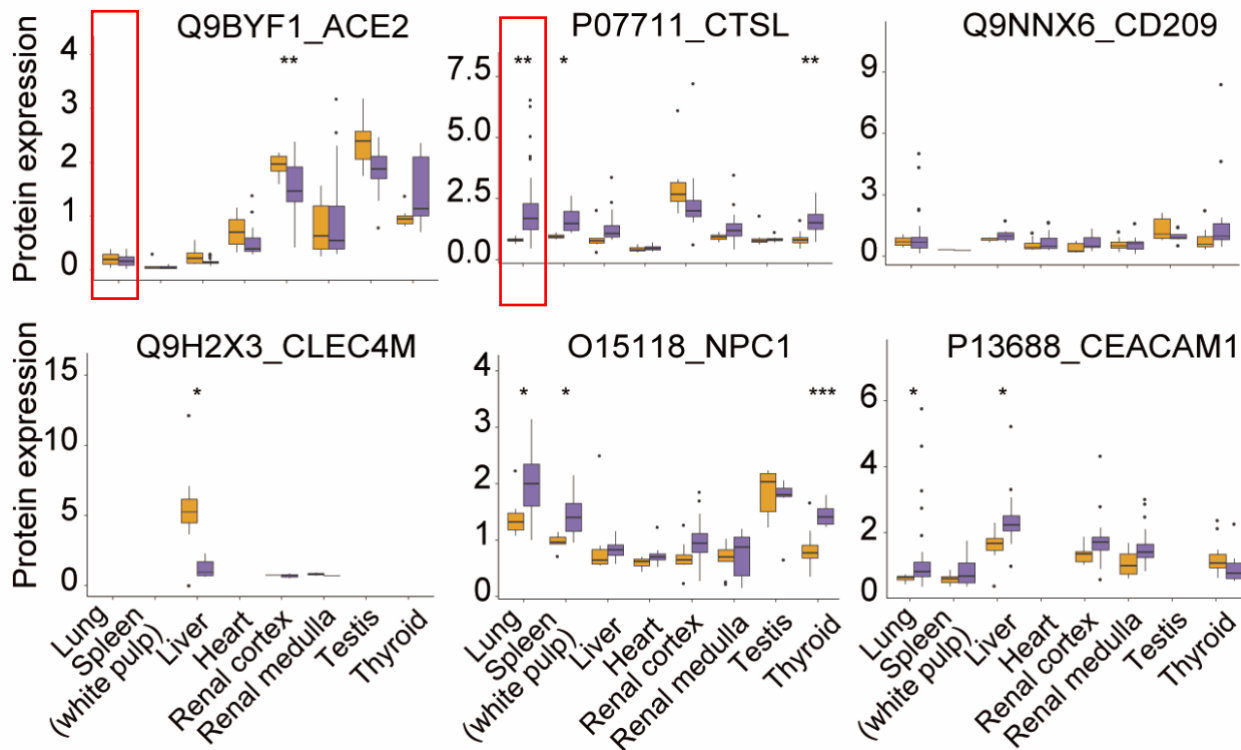
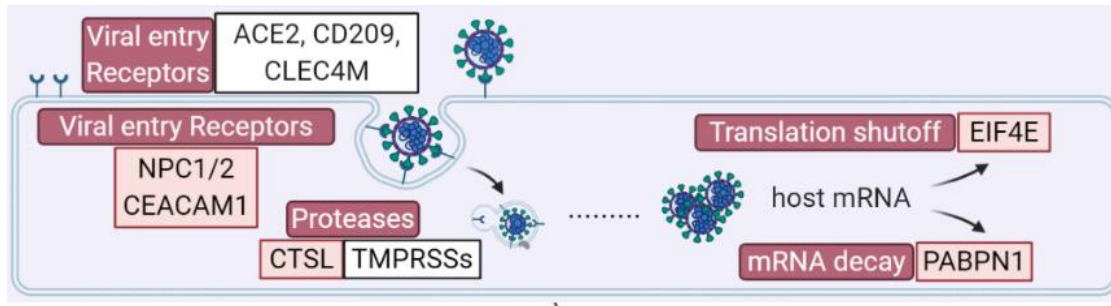
P (Fisher's exact test)	Gender	Smoking history	Hypertension	Diabetes	Coronary heart disease
Lung	0.613	0.0526	1	1	0.526
Spleen (white pulp)	1	1	0.0885	1	0.213
Spleen (red pulp)	1	1	0.2	1	0.2
Liver	0.307	1	0.234	1	0.25
Heart	0.131	1	0.62	1	0.206
Renal cortex	0.65	0.582	1	1	0.211
Renal medulla	1	0.582	0.656	1	0.211
Testis	1	0.429	1	1	1
Thyroid	1	1	0.264	1	0.33



- **11,394** proteins quantified;
- **5336** dysregulated proteins characterized from the seven types of organs between COVID-19 and control groups

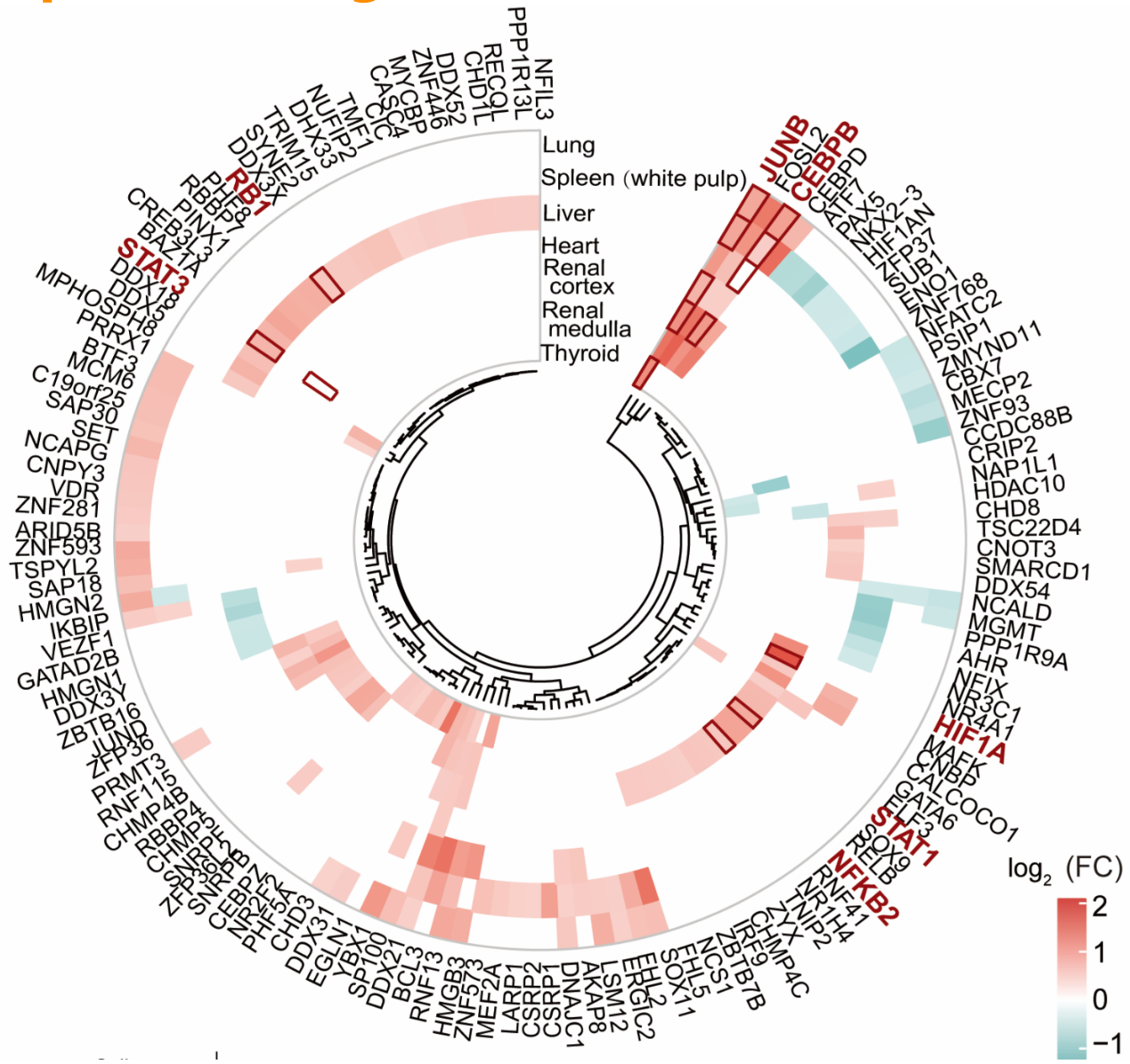
CTSL, rather than ACE2, was upregulated in lungs

Receptors and proteases

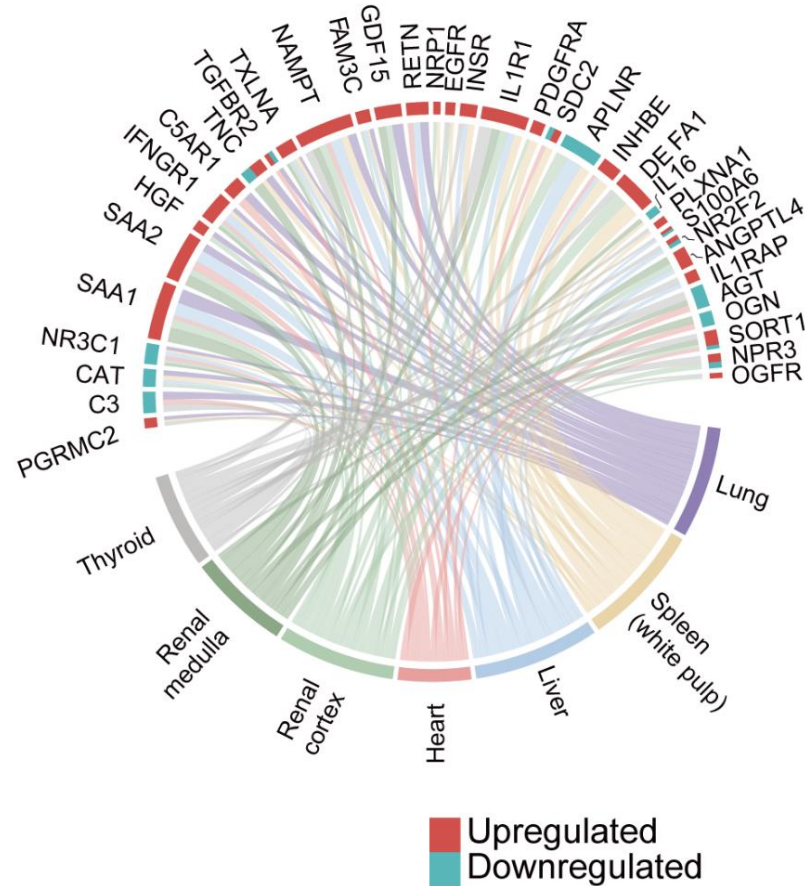


- CTSL, the serine protease of SARS-CoV-2 in the endosomal pathway, was significantly upregulated in the lung

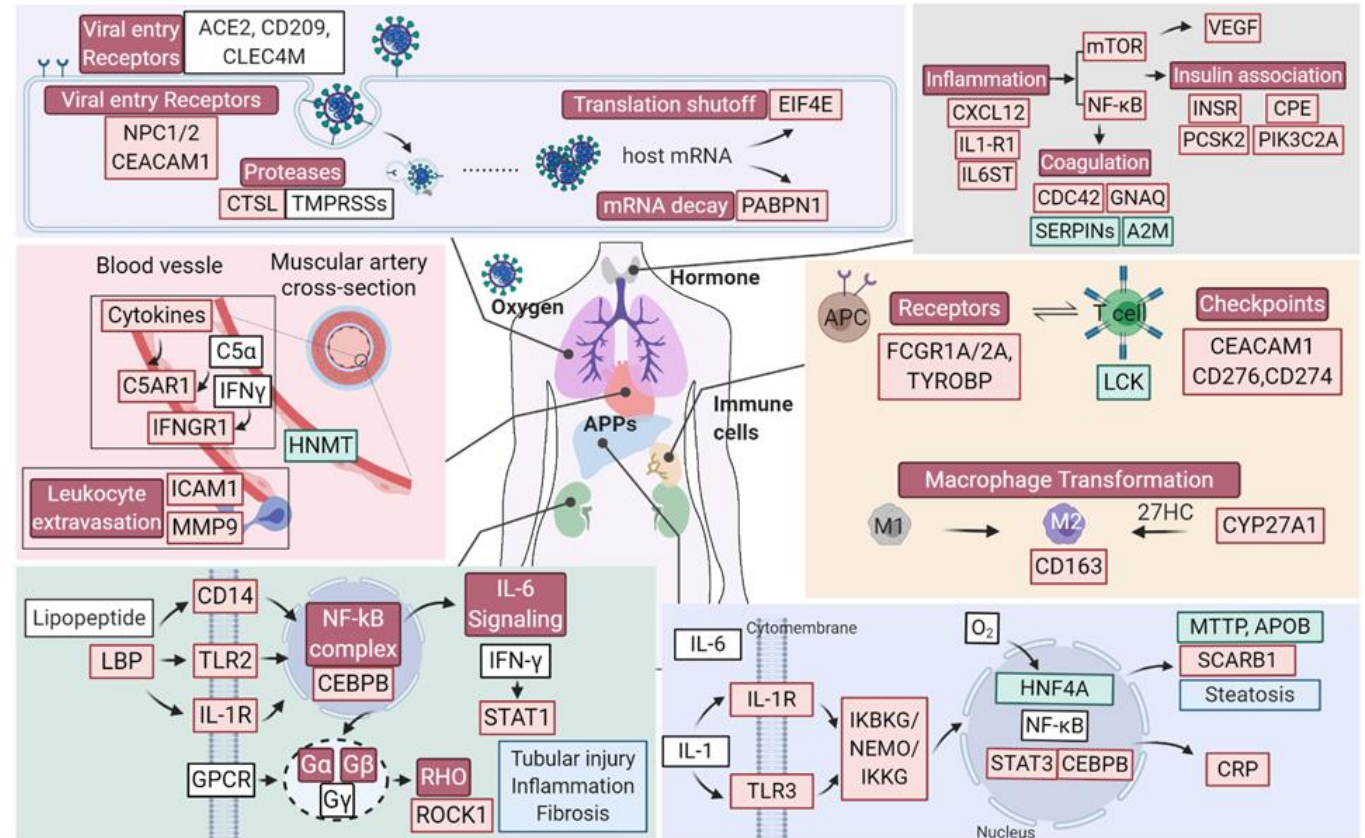
Upstream regulators



- 395 out of 1117 quantified TFs were altered in at least one tissue type
- Ten of these dysregulated TFs showed the same regulatory trend as the predicted activation state by their downstream proteins
 - Inflammatory responses
 - tissue injuries
 - hypoxia



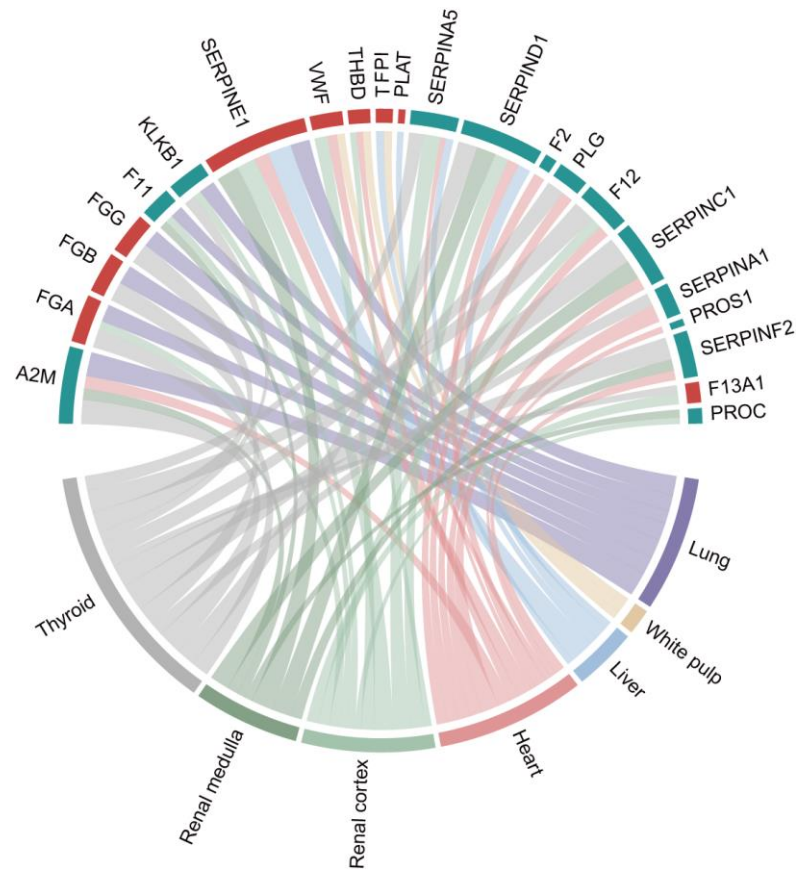
112 out of 242 quantified cytokines were significantly dysregulated



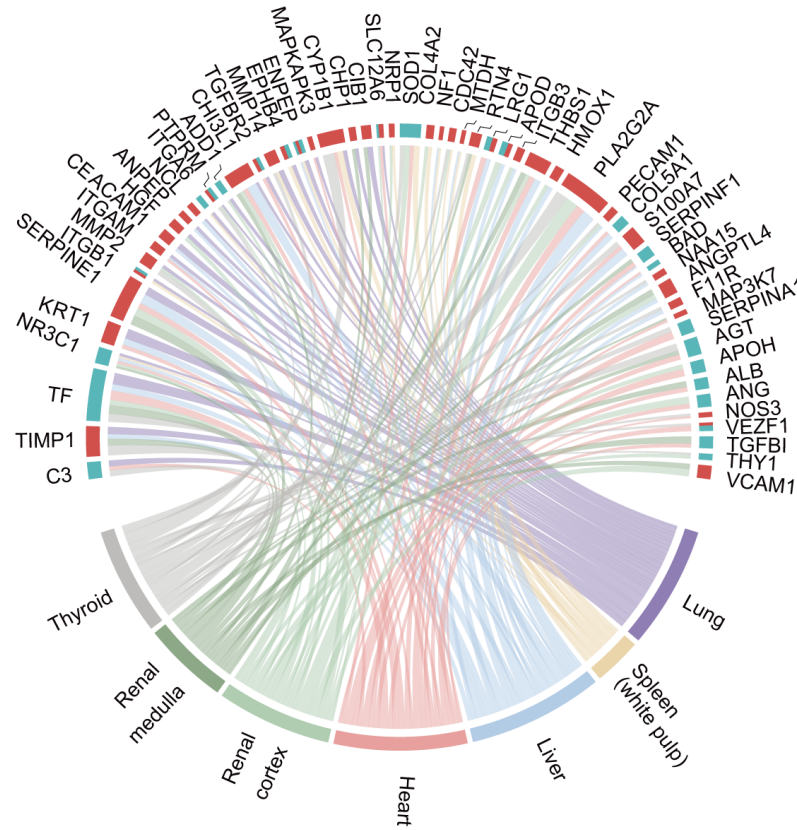
- Suppression of adaptive immunity in the lung and spleen of the COVID-19 patients
- Hyperinflammation in other organs:
 - activation of NF-κB signaling
 - acute phase response
 - ...

Multi-organ coagulation, angiogenesis and fibrosis

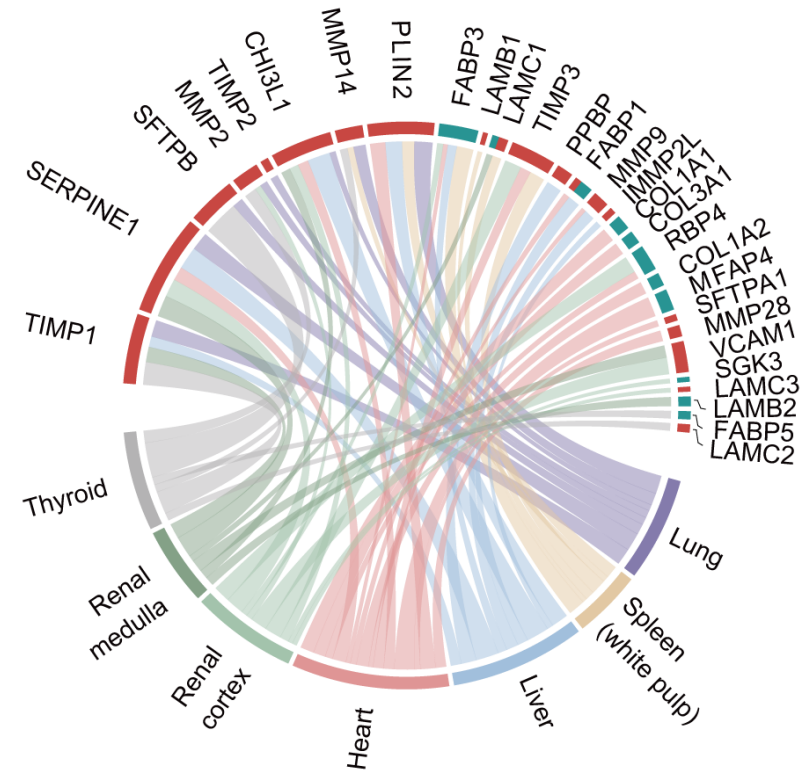
Coagulation



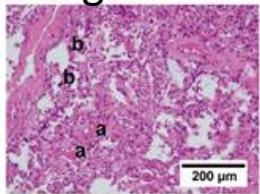
A total of 139 angiogenesis-related proteins



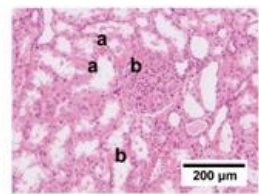
29 potential fibrosis markers



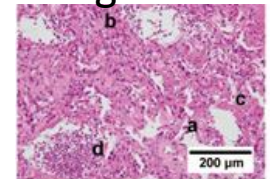
Lung



Renal cortex



Lung



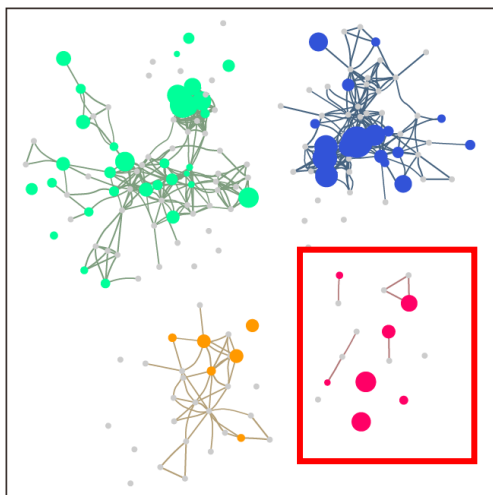
Four stage of fibrosis

■ Initiation

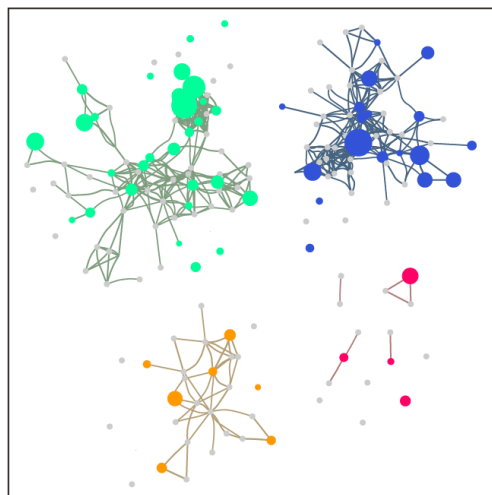
■ Inflammation

■ Proliferation

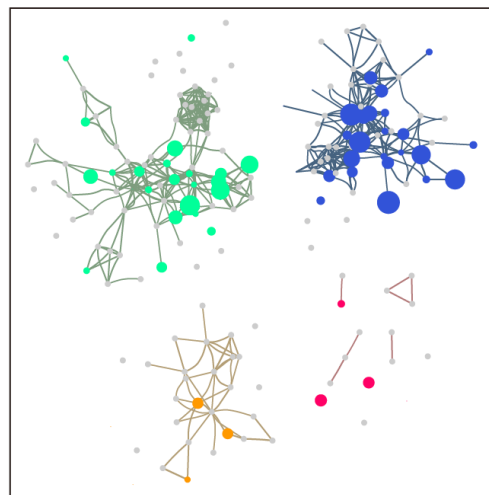
■ Modification



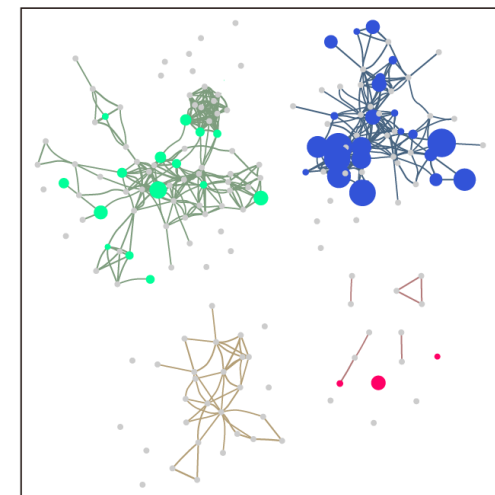
Lung



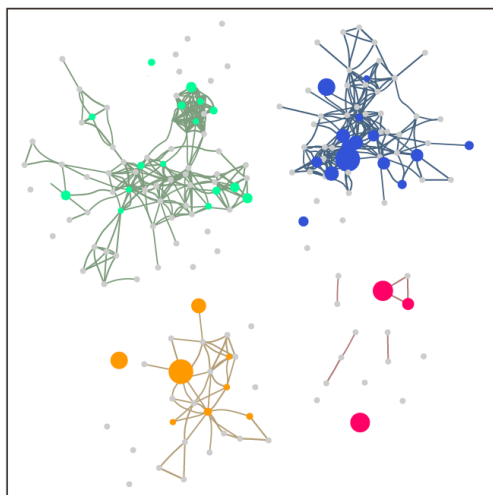
Spleen



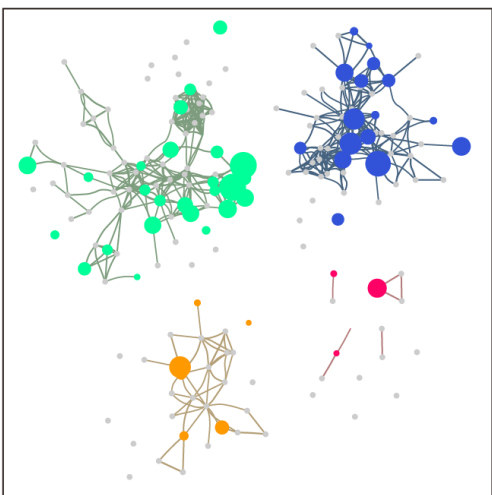
Renal cortex



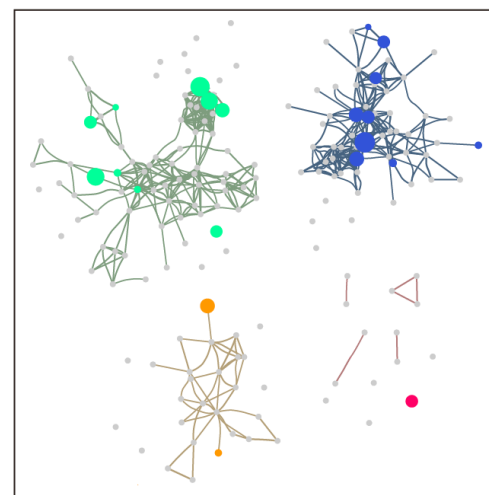
Thyroid



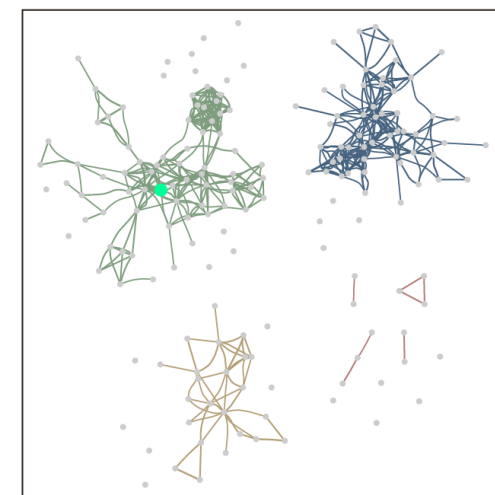
Heart



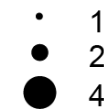
Liver



Renal medulla

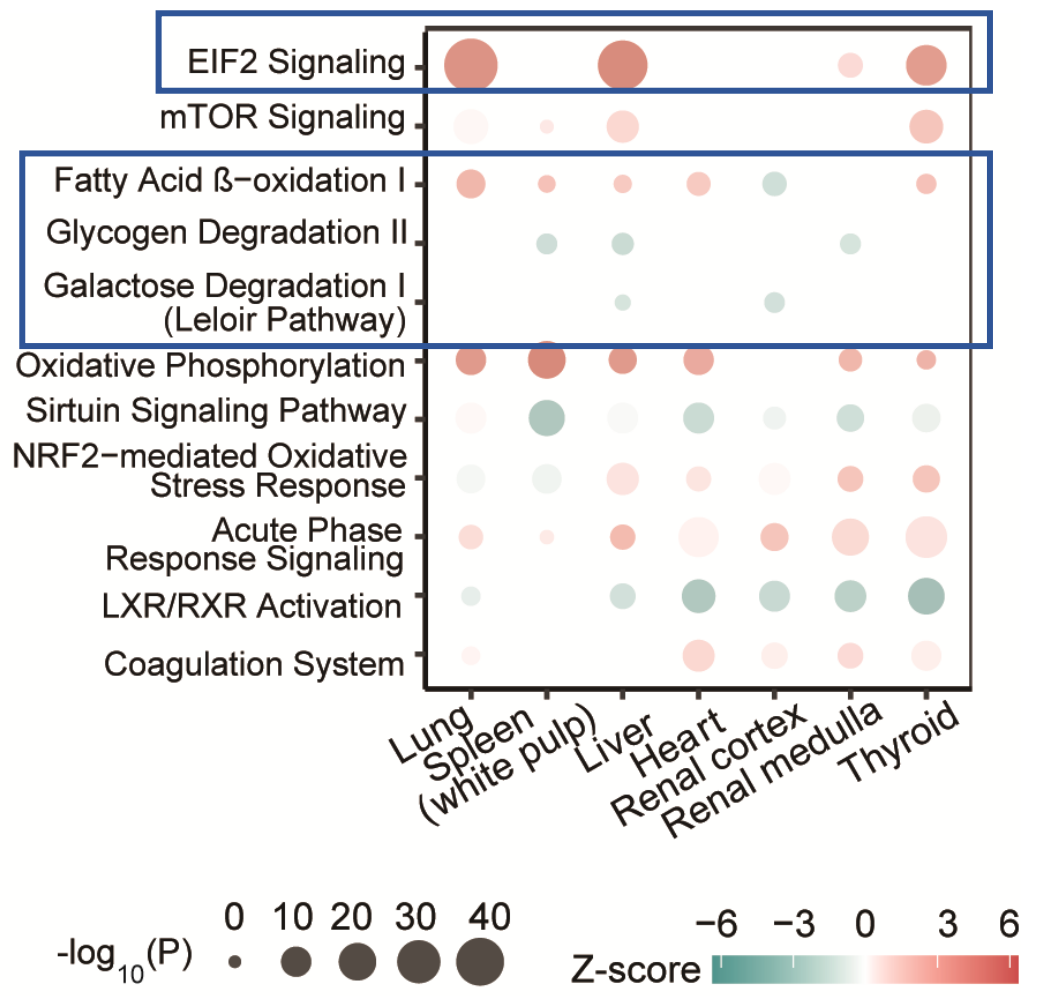


Testis

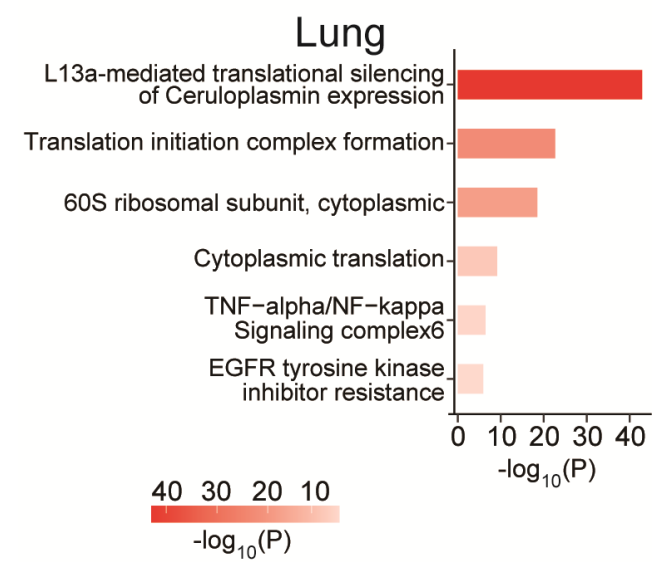
 $|\log_2(FC)|$ 

Dysregulated protein translation, glucose and fatty acid metabolism

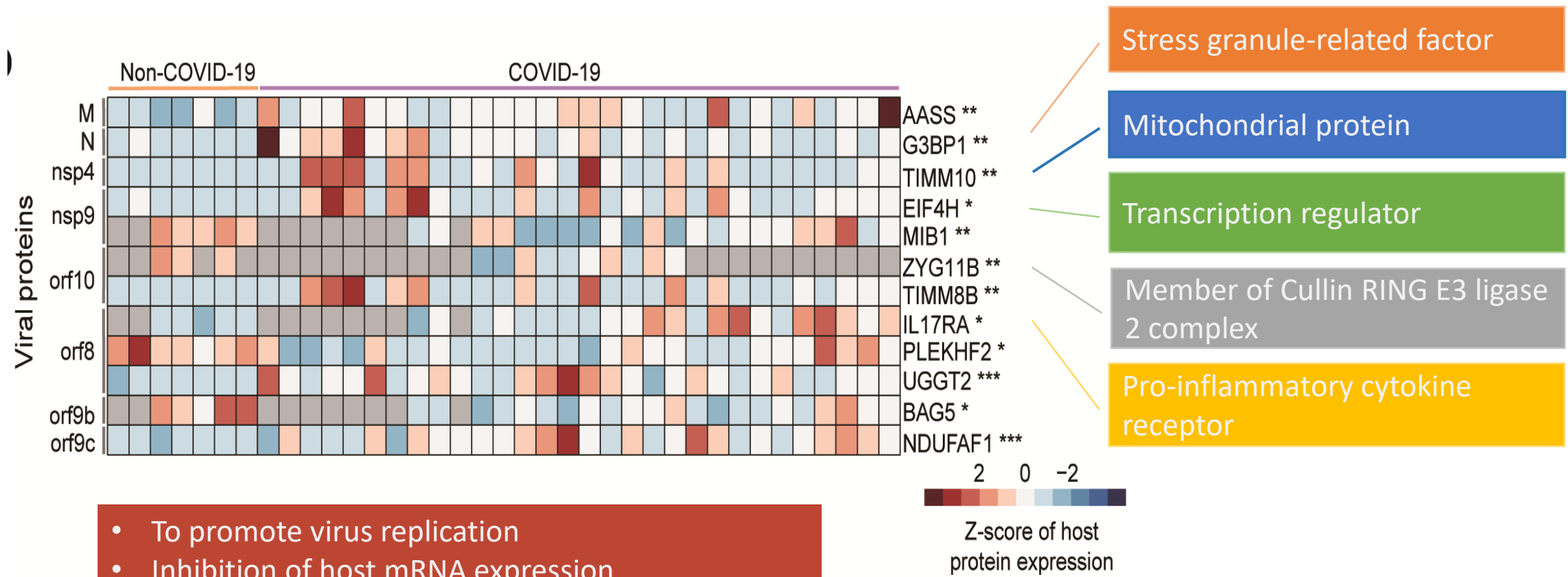
Pathway enrichment analysis for each tissue type using IPA



mRNA translation associated dysregulated proteins specific to the lung

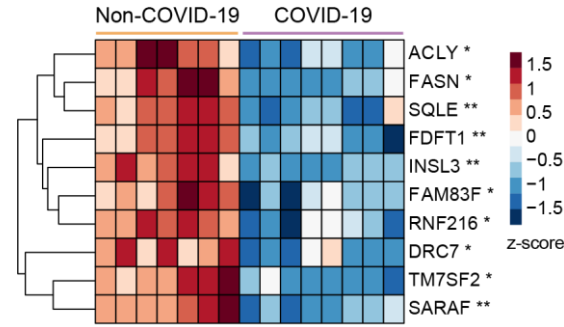


Virus-host interacting proteins in the lung

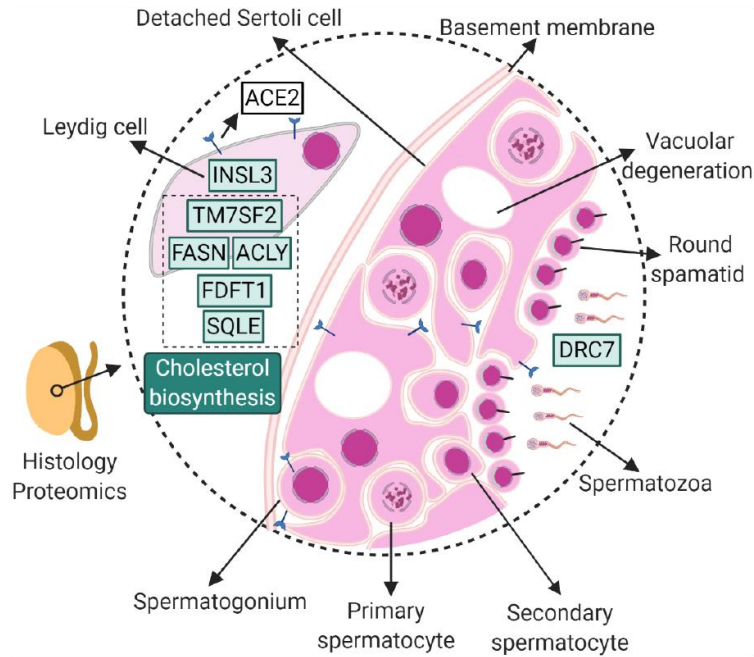


- To promote virus replication
- Inhibition of host mRNA expression
- Delivery of virus DNA
- Elevation of collagen and pulmonary fibrosis
- Degrade virus restriction factors

- Downregulated cholesterol biosynthesis

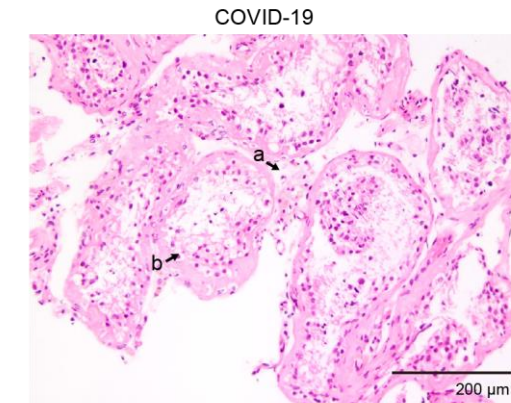
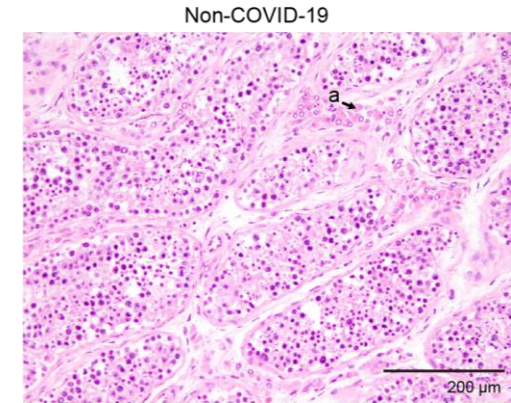


- Impaired Leydig cell functions or a reduced Leydig cell population



- Impaired sperm mobility

Histological examination revealed a reduction of Leydig cells



- 11,394 proteins were quantified, while 5336 proteins were dysregulated in COVID-19 organs
- Elevated CTSL in the COVID-19 lung tissue
- Evidence for multi-organ hyperinflammatory angiogenesis, coagulation and fibrosis in COVID-19 patients
- Reduced Leydig cells in the COVID-19 testis

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