

# Postmortem Tissue Proteomics Reveals the Pathogenesis of Multiorgan Injuries of COVID-19

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# Abstract

Multiorgan injuries are a major complication of severe COVID-19; however, its pathogenesis is barely understood. Herein, we profiled the host responses to SARS-CoV-2 infection by performing quantitative proteomics of COVID-19 postmortem samples, and provided a comprehensive proteome map covering the protein alterations in eight different organs/tissues. Our results revealed that lung underwent the most abundant protein alterations mainly enriched in immune-/inflammation-related or morphology-related processes, while surprisingly, other organs/tissues exhibited significant protein alterations mainly enriched in processes related with organ movement, respiration, and metabolism. These results indicate that the major cause of lung injury was excessive inflammatory response, and subsequent intravascular thrombosis and pulmonary architecture/function destruction, while other organs/tissues were mainly injured by hypoxia and functional impairment. Therefore, our findings demonstrate the significant pathophysiological alternations of host proteins/pathways associated with multiorgan injuries of COVID-19, which provides invaluable knowledge about COVID-19-associated host responses and sheds light on the pathogenesis of COVID-19.

## Introduction

Coronavirus Disease 2019 (COVID-19) is caused by a novel strain of coronavirus that was initially named as 2019 novel coronavirus (2019-nCoV) and later as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is the third coronavirus to cause severe respiratory disease in humans besides SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV). Since its emergence from late 2019, the outbreak of SARS-CoV-2 has caused around 6 million confirmed human infections and 360,000 deaths worldwide as reported by the World Health Organization (WHO) <sup>1</sup> and resulted in tremendous impacts on global health, social and economics, making COVID-19 a global pandemic and the worst public health crisis once a century. About 20% COVID-19 patients have been reported to develop severe or critical conditions <sup>2</sup>, and the mortality rate of critically ill cases can reach over 60% <sup>3</sup>. The main targets of SARS-CoV-2 are human low respiratory tract and lung, while many other organs, including liver, heart, intestine, kidney, central nervous system and muscle have been also found to be injured<sup>4-6</sup>. Among the broad symptoms of COVID-19, fever, pneumonia, respiratory failure, acute respiratory distress syndrome (ARDS), and sepsis are frequently observed complications, which are usually associated with pathophysiological changes such as alveolar macrophage activation, lymphopenia, cytokine release syndrome, thrombosis and intravascular coagulation in severe COVID-19 patients<sup>7-13</sup>. However, despite of extensive efforts made by global scientific community to study this emerging coronavirus disease, the molecular mechanisms underlying its pathogenesis, particularly the pathogenesis of COVID-19-associated multiorgan injuries, are still barely understood, which represents a major obstacle to fully understand and find out effective ways to combat against this deadly coronavirus disease.

Postmortem examination provides the most direct and reliable evidence of the pathophysiological changes in organs/tissues of disease victims, thereby representing an invaluable opportunity to understand the pathogenesis of COVID-19-associated multiorgan injuries. In the current study, we profiled

the host responses to fatal SARS- CoV-2 infection by performing quantitative proteomics of COVID-19 postmortem samples. Our study generates a comprehensive proteome map covering the protein alterations in eight different organs or tissues, including lung, liver, intestine, kidney, spleen, brain, heart, and muscle, from three deceased COVID-19 victims. Therefore, our study reveals that COVID-19 is able to cause significant pathophysiological changes in the aspect of host proteins and pathways in multiple human tissues or organs. More importantly, the injuries in lungs are caused by direct effects of SARS-CoV-2 infection-led excessive pro-inflammatory responses, and subsequent intravascular thrombosis and pulmonary architecture/function destruction, probably leading to a systemic hypoxia; while unlike in lungs, the damages in other organs/tissues are more indirect effects such as hypoxia and functional impairment. These different host protein responses contribute to the pathogenesis of COVID-19-associated multiorgan injuries.

## Results

### The experimental procedure of this study

Postmortem tissue samples were collected during the autopsy of 3 patients who were deceased from respiratory failure caused by SARS-CoV-2 infection at Wuhan Jinyintan Hospital (Fig. 1a). We collected the samples of lung and muscle from Patient 1, the samples of lung, heart, liver, spleen, kidney, intestine, brain and muscle from Patient 2, and the samples of lung, heart, liver, spleen, kidney, brain and muscle from Patient 3 (Fig. 1a). Besides, lung paracancerous tissue samples from two lung cancer patients were collected for comparison. For each tissue sample, total proteins were extracted and processed by trypsin, and the resulting peptides were subjected to tandem mass tag (TMT) labeling and analyzed by liquid chromatography with tandem mass spectrometry (LC-MS/MS) (Fig. 1b).

We analyzed the pathology of pulmonary autopsy specimens from patients 2 and 3. The main pathological change of the post-mortem lung tissues from two patients was diffuse alveolar damage (Fig. 1c) which is similar with that caused by SARS14. The histology was represented mainly by a widespread destruction of pulmonary architecture, with extensive fibromyxoid exudate, alveolar haemorrhage, formation of hyaline membranes, and interstitial thickening. In addition, the ultrastructure of these lung tissue samples under transmission electron microscopy revealed several virion-like particles in alveolar epithelial cells (Fig. 1d). These virion-like particles were approximately 80-120 nm in diameter, with spiky-like projections on the surface and typical electron lucent center, which display typical coronavirus morphology of SARS-CoV-2 virion<sup>15</sup>. Furthermore, the immunofluorescent staining assays were performed to detect the presence of SARS-CoV-2 nucleocapsid protein (NP) in lung tissue samples. As shown in Fig. 1e, green fluorescence of NP protein was observed, showing the presence of SARS-CoV-2 antigens in the lung tissues of these patients.

### A protein atlas of eight COVID-19 postmortem tissue types

From the LC-MS/MS analysis, we obtained 49,815 non-redundant peptides, with a number ranged from 36,046 to 37,855 peptides in 3 lung, 2 kidney, 2 liver, 1 intestine, 2 brain, 2 heart, 3 muscle and 2 spleen

samples of COVID-19 postmortem tissues, as well as 2 normal lung samples (Fig. 2a). These peptides were mapped to their corresponding protein sequences, and we used the reporter ion MS2 module of the MaxQuant software package for protein quantification<sup>16</sup>. From the results, we observed that 5346 human proteins were quantified in at least one sample (Table S1), with protein numbers ranged from 4776 to 5000 (Fig. 2b). Furthermore, we evaluated the quality of the proteomic data by checking the original MS/MS data, and found that the average spectral counts of all peptides were 2.66, with 29,618 peptides (59.5%) matched by  $\geq 2$  spectral counts (Fig. 2c). Thus, our results indicate that the proteomic profiling is highly reliable at the peptide level. Both human and SARS-CoV-2 protein sequences were included for database search, while no viral proteins were detected in any tissue samples, probably due to the background of large amount of host proteins. To eliminate the sample loading difference, a z-score plus median centering method was used to individually normalize the proteomic data for each sample, and the normalized protein expression (*NPE*) value was determined for each protein (Fig. 2d, Table S2). Using *NPE* values of proteins, a principal component analysis (PCA) revealed that different COVID-19 postmortem tissue types could be roughly separated (Fig. 2e). Moreover, we used an entropy-based method<sup>17,18</sup> to identify 226 potential tissue-specific proteins (TSPs), including 158 TSPs in brain and 68 TSPs in other tissues, respectively (Fig. 2f, Table S3). This result is consistent with the existing knowledge, since brain is one of the most specialized organs in the human body. Thus, it's not surprised that brain has most potential TSPs.

Next, a hierarchical clustering was conducted for all proteins in the eight tissue types, and the result was visualized by a software package named Heatmap Illustrator (HemI)<sup>19</sup>. Obviously, different tissue types had distinct molecular signatures, and potential TSPs can be directly recognized from the heatmap (Fig. 2g). Based on the annotations of GeneCards (<https://www.genecards.org/>)<sup>20</sup>, a comprehensive database for human genes, several TSPs were picked out and shown for each tissue sample (Fig. 2g and Fig. S1-S2). For example, UMOD/uromodulin, a known kidney-specific protein<sup>21</sup>, exhibited much higher expressions in two kidney samples than other tissues (Fig. 2h). Also, S100A8 and its partner S100A9, the Ca<sup>2+</sup> binding proteins that play important roles in regulating pro-inflammatory response<sup>22</sup>, are only highly expressed in lung samples (Fig. 2h and Fig. S1). In addition, NRG1/Neurogranin, a critical regulator in neurodevelopment and cognition<sup>23,24</sup>, exhibited higher expressions only in two brain samples. Taken together, our proteomic profiling revealed a landscape of differential protein expressions in COVID-19 postmortem tissue types.

### **Proteomic alterations reveal that human tissues are differentially affected in response to COVID-19**

To probe the protein changes upon SARS-CoV-2 infection, we downloaded the proteomic datasets of six normal human tissues from the Human Proteome Map (HPM)<sup>25</sup>, with a number of quantified proteins ranged from 12,007 to 16,868 (Fig. 3a). Compared to HPM, > 96.0% of proteins quantified in this study were also covered by HPM, indicating the high quality of our proteomic profiling (Fig. 3b). To enable an unbiased comparison between COVID-19 and normal samples, the same z-score plus median centering method was used to individually normalize each dataset (Fig. 3c).

To identify differentially expressed proteins (DEPs), we used a tool named Model-based Analysis of Proteomic data (MAP) to analyze each pair of COVID-19 and normal tissues<sup>26</sup>. Muscle and spleen samples were not analyzed due to the lack of the corresponding normal tissues data in HPM. In contrast with conventional statistical methods, MAP did not estimate technical and systematic errors from technical replicates. Based on a hypothesis that technical and systematic errors might be approximately identical for quantified proteins within a small window, the standard normal distribution was adopted to model the proteomic data and directly calculate a  $p$ -value for each protein. In total, we identified 2604, 611, 212, 173, 51 and 42 potential DEPs in lung, kidney, liver, intestine, brain and heart tissue samples, respectively (Fig. 3d, Table S4, adjusted  $p$ -value < 0.05). In particular, we revealed numerous alterations of host proteins in different organ that may contribute to the pathogenesis of COVID-19. For example, the protein levels of APC, AKT1 and S100A8/A9 were significantly elevated in postmortem lung tissues (Fig. S3). Among them, S100A8 and S100A9 are acute phase proteins whose alterations are usually in response to inflammation, infection and injury, and can promote inflammatory cytokines release and immune cell migration<sup>22</sup>. Besides, APC can increase T lymphocyte activation through nuclear factor of activated T cells<sup>27</sup>, AKT1 is essential for microvascular permeability and leukocyte recruitment and extravasation during acute inflammation<sup>28</sup>, and RNF14 is a transcriptional co-activator involved in immune response and mitochondrial function<sup>29</sup>. Interestingly, we found that a number of TSPs such as S100A8/9, UMOD and NRG1 were also DEPs in the same tissue types, and all these proteins were significantly up-regulated in COVID-19 postmortem tissues. In addition, we found that many important proteins were down-regulated in different postmortem tissues. For example, ALB and HBB, two fundamental proteins in plasma, were significantly down-regulated in all the six tissue types, especially in liver and kidney (Fig. 3d).

The count of potential DEPs across the six postmortem tissue types demonstrated that lung tissues harbored the greatest number of DEPs (70.5%, 2604/3693), following with kidney (16.5%), liver (5.7%), intestine (4.7%), brain (1.4%) and heart (1.1%) (Fig. 3E). In particular, overlaps were less observed through a comparison of different tissues, and 583 DEPs in lung were mutually shared by other tissues (Fig. 3f) and 57 DEPs were shared by at least four tissues (Fig. 3f and Fig. S4). Taken together, our results indicate that lungs presented the most significantly protein alterations in response to COVID-19 in all the tissues examined, implying that lung represents the major organ for SARS-CoV-2-host interactions, while other tissues are also affected by COVID-19.

### **Fundamental biological processes are distinctly impacted in different tissues of COVID-19 patients**

To identify biological processes up- or down-regulated in the six COVID-19 postmortem tissue types, we used a tool named Gene Set Enrichment Analysis (GSEA), which was developed based on the Kolmogorov–Smirnov test<sup>30</sup>. No statistically over-represented processes were detected in postmortem kidney, intestine and heart samples, whereas 16, 3 and 15 enriched processes were identified from lung, liver and brain of COVID-19 tissues, respectively (Fig. 4a, Table S5). In postmortem lung tissues, up-regulated processes were mainly focused on immune response- and inflammation- related process, such as humoral immune response (GO:0006959), complement activation (GO:0006956), and B cell mediated

immunity (GO:0019724), which were not significantly elevated in other tissue types (Fig. 4b and Fig. S5). On the other hand, the cell morphology maintenance-related pathways, such as establishment endothelial barrier, were only found to be downregulated in lung tissues (Fig. S5), supporting the hypothesis that lung is the potentially major virus-host battlefields of COVID-19. Three metabolism-related processes were up-regulated in liver, and a number of neuron-specific processes were enriched in brain (Fig 4b), indicating that organ-specific functions were altered upon SARS-CoV-2 infection. Top 10 mostly changed DEPs were separately shown for three processes including humoral immune response (GO:0006959) and complement activation (GO:0006956) in postmortem lung as well as nicotinamide adenine dinucleotide (NADH) metabolic process in postmortem kidney (Fig. 4c).

In particular, we observed that many fundamental processes involved in organ movement, respiration and metabolism were dramatically down-regulated in the six postmortem tissue types, with a number ranged from 6 (heart) to 72 (kidney) (Fig. 4a). In total, there were 15 basic processes, such as actin filament-based movement (GO:0030048), NADH metabolic process (GO:0006734) and glucose catabolic process (GO:0006007), were significantly down-regulated in  $\geq 4$  tissue types (Fig. 4d and Table S5). Based on these results, it could be proposed that brain and heart were less affected by COVID-19 in the aspects of the numbers of DEPs and altered processes, whereas in addition to lung, kidney and liver also significantly affected (Fig. 3e and 4a). Taken together, these results indicate that the responses of distinct tissues in response to COVID-19 are different in critically ill conditions.

### **A COVID-19-associated protein-protein interaction network**

We sought to map the protein-protein interactions between SARS-CoV-2-encoded proteins and DEPs by using a published interactome data of SARS-CoV-2 proteins 31. We obtained 110 known virus-host protein-protein interactions (PPIs) between 23 viral proteins and 110 interacting DEPs differentially regulated in postmortem lung tissues (Table S6). Other lung DEPs were also included for modeling an integrative virus-host molecular network. As shown in Fig. 5, these interacting DEPs were classified into 6 groups according to their functions, including immune response, metabolic process, transcription/translation, cell signaling/development, transport, and cytoskeleton organization, which are participate in almost all the major biological functions in host. Moreover, Gene Ontology (GO) analysis showed that these DEPs were generally involved in several immune response-related processes, including Rab protein signal transduction, blood coagulation and neutrophil degranulation (Fig. S6 and Table S7), which are consistent with the previous findings that cytokine storm, alveolar macrophage activation, intravascular coagulation and microthrombosis are frequently presented in severe COVID-19 cases<sup>13,32</sup>. Together, these results suggest that SARS-CoV-2-encoded proteins might directly affected the functions of the interacting host proteins in infected lungs.

## **Discussion**

In this study, we provide the postmortem tissue proteomic datasets that provides the most direct and reliable evidence of the pathophysiological changes of human bodies in response to SARS-CoV-2

infections, and uncovers that SARS-CoV-2 infection affected different set of host processes in different organs or tissues, which probably contribute to the pathogenesis of COVID-19-associated multiorgan injuries.

One of the key findings obtained here is that proteins and pathways are differently altered in distinct human tissues or organs in response to COVID-19. We found that the immune- and inflammation-related pathways, such as humoral immune response, complement activation, B-cell mediated immunity, acute phase response and cytolysis, were upregulated only in lungs in all the tissues examined, showing that excessive immune response and inflammation were extensively occurred in lungs. Consistently, our histopathological examinations also showed that interstitial mononuclear/macrophage cell infiltration and inflammation were presented in lung tissues. On the other hand, cell morphology maintenance-related pathways were downregulated in lungs. These result indicate that the microscopic structure of alveolar cells and lungs were severely damaged, consistent with the postmortem pathological and histopathological observations in the current study and by others that extensive fibromyxoid exudation, alveolar haemorrhage and thrombosis were found in lungs<sup>33,34</sup>. Therefore, we conclude that the excessive inflammation in lungs of severe COVID-19 cases increases vascular permeability and activates coagulation cascades, resulting in vascular thrombosis and probably a systemic hypoxia, and also causes a widespread destruction of pulmonary architecture and functions. Our findings are in accordance with previous clinical and autopsy observations that severe or critical ill COVID-19 patients are frequently associated with massive intravascular thrombus, hypoxemia, and ARDS<sup>3,5,7-11,33-35</sup>, which are pathophysiologically associated with cytokine storm, alveolar macrophage activation, intravascular coagulation and microthrombosis<sup>12,13,32</sup>.

On the other hand, unlike the host protein responses in lungs, our study revealed that the differentially expressed proteins in tissues of liver, kidney, intestine, brain, and heart are mainly present in pathways involved in organ movement, respiration, and metabolism. For example, some shared altered pathways, including muscle filament sliding and contraction, cellular respiration, NADH metabolic process, hydrogen peroxide metabolic process, and glucose catabolic process, were found to be significantly downregulated in kidney, liver, intestine, and brain. These result indicate that these tissues were affected by hypoxia and their functions and morphology were dramatically impaired, which are consistent with the previous clinical data that multiorgan failure are frequently observed complications in severe COVID-19 cases<sup>3,8-10</sup>. Surprisingly, based on our proteomic data, very few immune- or inflammation- related pathways were found to be significantly altered in other organs/tissues, indicating that the leading cause of multiorgan injuries in non-lung organs/tissues is hypoxia but not excessive. Thus, we propose that lung is the center of the virus-host battlefields of COVID-19, and the excessive inflammatory responses to SARS-CoV-2 infection in lungs result in the thrombosis and destruction of pulmonary architecture and functions, leading to hypoxia of multiple organs in the whole body and subsequent disease aggravation.

Furthermore, our work also reveals numerous alterations of host proteins in different organs that may contribute to the pathogenesis of COVID-19. It would be intriguing to speculate that some of the significantly altered proteins and related pathways could be promising therapeutic targets for COVID-19.

For instance, S100A8 and S100A9, which are acute-phase proteins and damage-associated molecular patterns (DAMPs) and can promote pro-inflammatory cytokine release and immune cell migration<sup>22</sup>, were significantly elevated in lungs. Interestingly, S100A8/A9 inhibitors, quinoline-3-carboxamide compounds, have shown promising outcomes in treating inflammatory diseases with good safety records in clinical trials. Besides, given that hypoxia could be a major cause of multiorgan injuries, some clinically approved anticoagulants might have potential to ameliorate severe conditions of COVID-19 associated with intravascular coagulation, hypoxia, and inflammation. Therefore, S100A8/A9 and probably other COVID-19-altered host proteins and pathways uncovered here should be further exploited for their potential as therapeutic targets.

Omics studies under the pathophysiological conditions caused by viral infections are powerful weapons to explore the pathogenesis of viral infectious diseases, establish animal models as well as develop potential clinical treatments. After the outbreak of COVID-19, both direct RNA sequencing (DRS)-based transcriptomic and LC-MS/MS-based proteomic, metabolomic or lipidomic profilings were conducted for analyzing SARS-CoV-2 and/or host samples<sup>36-39</sup>. Recently, using a human cell culture model permissive for SARS-CoV-2 infection, Bojkova et al. quantified 6,382 proteins from SARS-CoV-2-infected Caco-2 cells and identified many significantly altered cellular pathways upon SARS-CoV-2 infection<sup>37</sup>. In addition, Gordon et al. generated a SARS-CoV-2-encoded protein interactome using affinity-purification mass spectrometry (AP-MS)<sup>31</sup>. In this study, using this interactome data, we generated 110 known virus-host PPIs between 22 viral proteins of SARS-CoV-2 and 110 interacting DEPs in lung tissues, suggesting that these viral proteins directly affect the expressions and/or functions of these interacting host proteins. Therefore, it would be intriguing to integrate the omics data to generate a more comprehensive picture of the pathogenicity of SARS-CoV-2 and the pathogenesis of COVID-19.

In summary, this postmortem proteomic study reveals that SARS-CoV-2 infection is associated with extensive virus-host interactions and causes significant host responses in multiple organs, which contribute to multiorgan injuries. This work provides an invaluable proteome map and resource for the research community to better understand COVID-19-associated host responses, sheds light on the pathogenesis of COVID-19, and provides hints of potential therapeutic strategies.

## Declarations

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### Author contributions:

Q.Y., D.W., J.Z. and T.S. performed experiments with the help of C.H., R.C., M.H., J.X., Q.Y., R.L., Y.B., X.Y., J.M., Y.W., Y.H., X.Z. Y.R. and S.P.; W.N., Y.X., and Y.Q.

analyzed the proteomics data with the help of D.W., J.Z. and T.S.; Y.Q., D.W., W.N., J.Z., T.S, D.-Y.Z., Y.X., Y.S. and X.Z. performed the experimental design and data interpretation; X.Z, Y.X., D.-Y.Z. and Y.S. analyzed the data and wrote the paper; X.Z., Y.Q., Y.S. and D.-Y.Z. designed and supervised the overall study.

### Competing interests

The authors declare no conflicts of interest.

### Informed consent

All work performed in this study was approved by the Wuhan Jinyintan Hospital Ethics Committee (No. KY-2020-15.01) and the written informed consent was waived.

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## Supplementary Materials

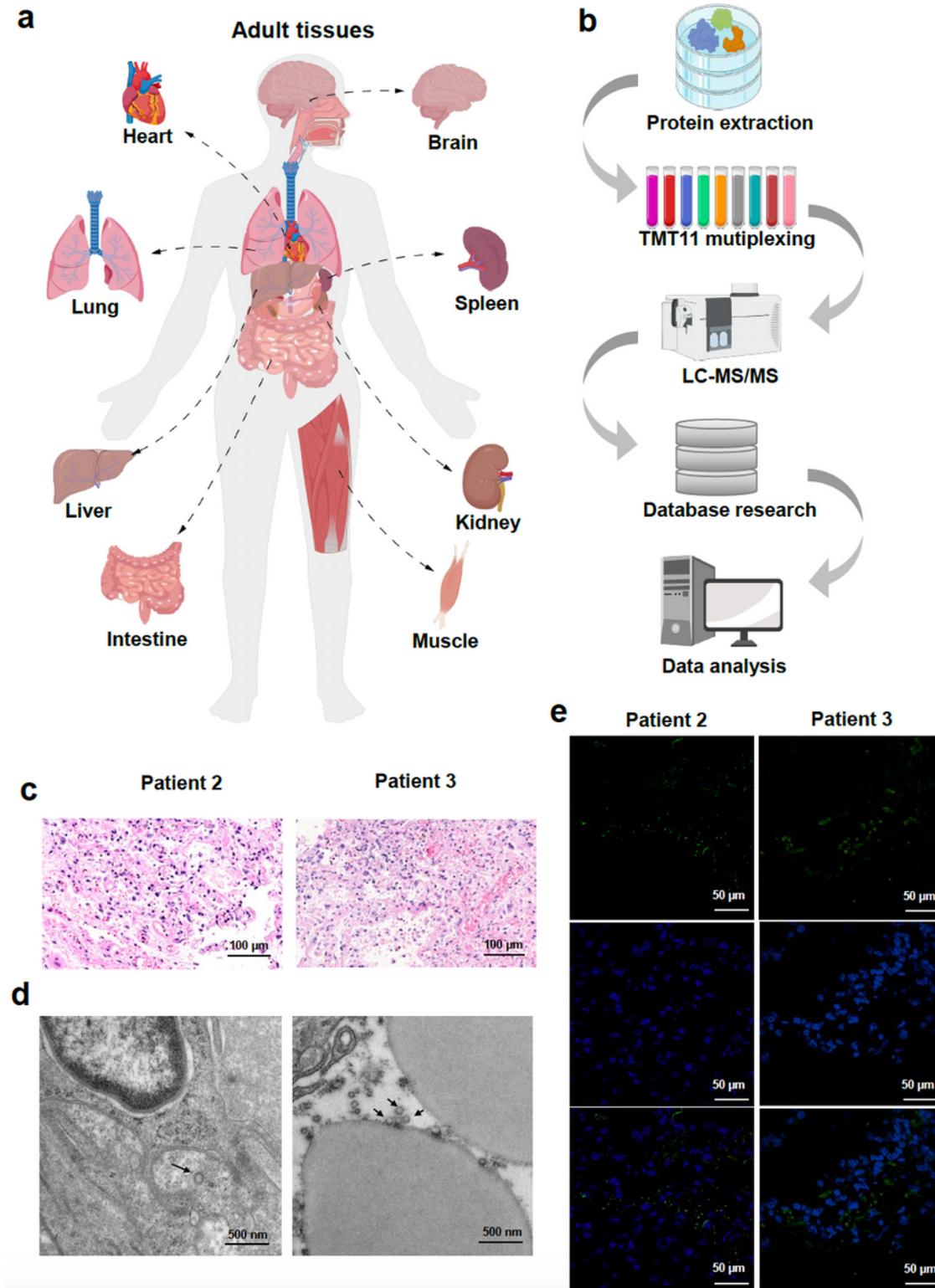
Materials and Methods

Fig. S1-S6

Table S1-S7

References

# Figures



**Figure 1**

Study design and patients. a, Overview of postmortem tissue samples that were analyzed to generate a draft map of COVID-19 patient's proteome are shown. b, The workflow of tissue samples preparation. c, Pathological changes of lung tissue in two patients with COVID-19. The tissues were fixed with

paraformaldehyde and stained with the hematoxylin an eosin (HE). d, SARS-CoV-2-like particles (black arrowed) observed by electron microscopy in lung tissues (left, original magnification 9600 $\times$ ; right, original magnification 7800 $\times$ ). e, SARS-CoV-2 nucleocapsid (NP) protein (green) and DAPI (blue) detected by immunofluorescence staining.

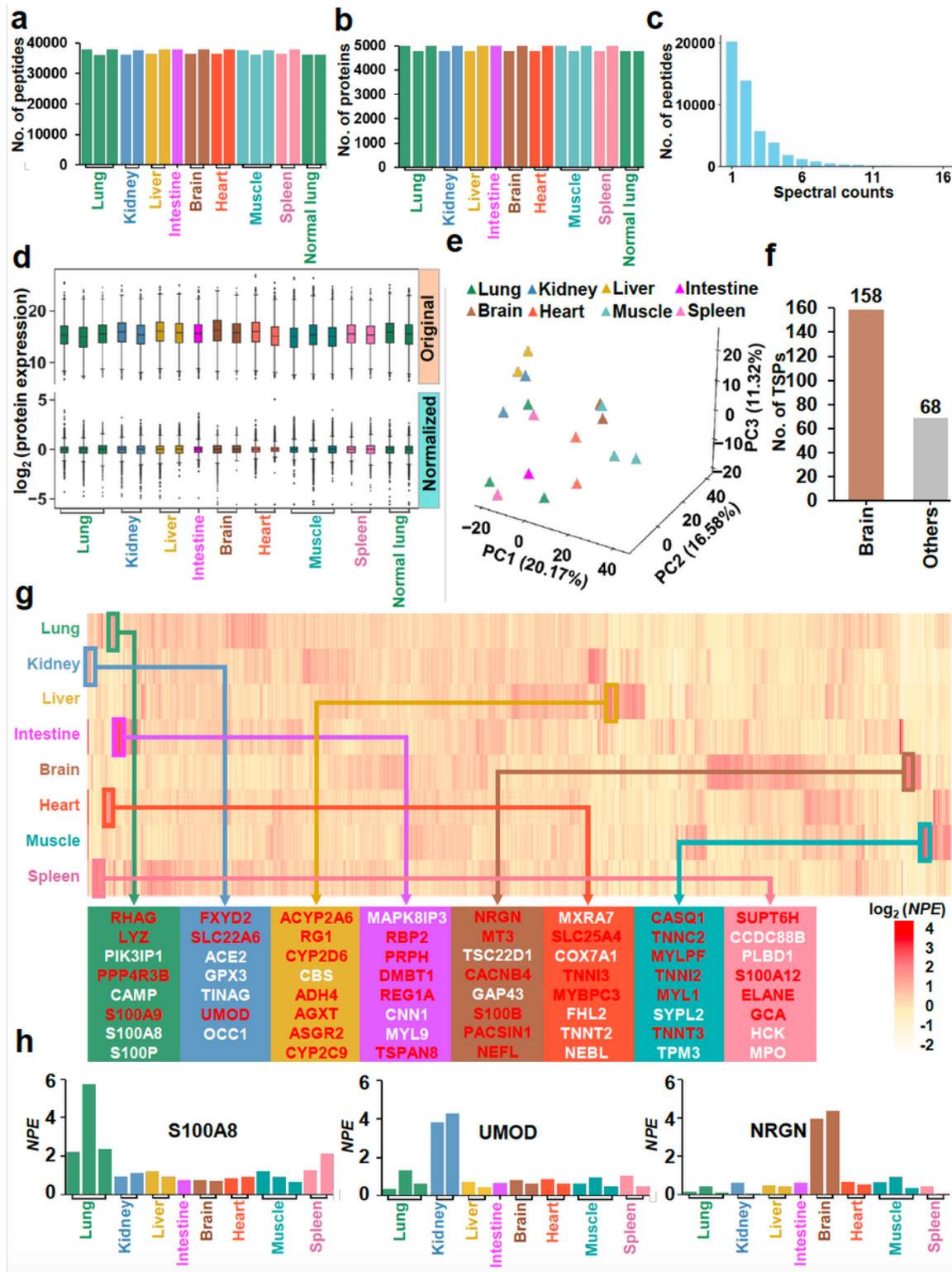


Figure 2

Proteomic profiling of eight types of COVID-19 postmortem tissues. a-b, The distribution of numbers of quantified (a) peptides and (b) proteins in the 17 postmortem and 2 normal lung tissues. c, The distribution of MS/MS spectral counts of quantified peptides. d, Normalization of the proteomic data using the z-score plus median centering method. e, PCA analysis of the proteomic data with NPE values. f, An entropy-based prediction of potential TSPs (entropy < 2.5). g, A heatmap of protein expressions in the eight types of postmortem tissues, after a hierarchical clustering. Selected proteins in boxes include well-characterized (red) and potential (white) TSPs. h, The expression profile of several TSPs in the eight types of tissues.

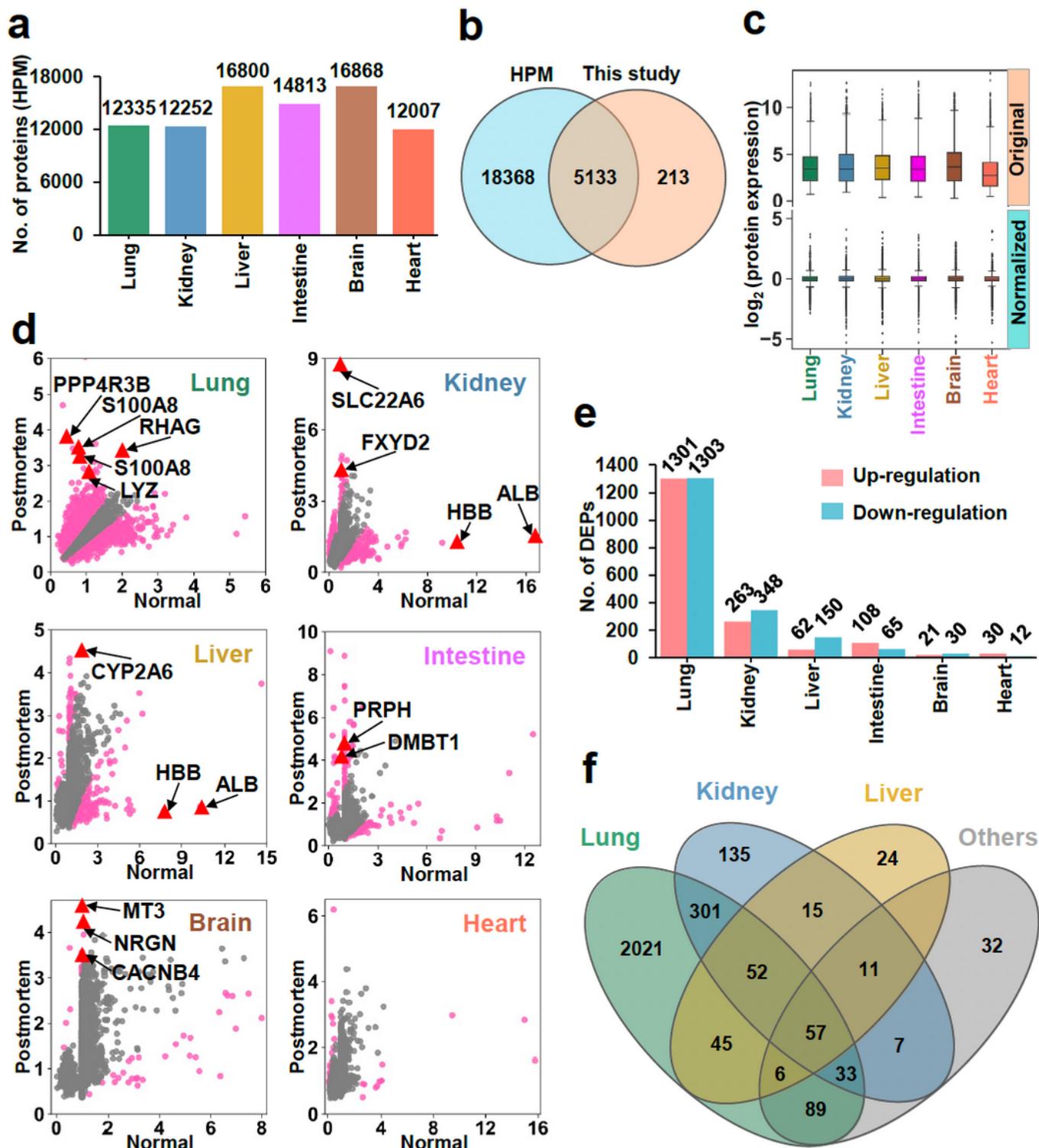
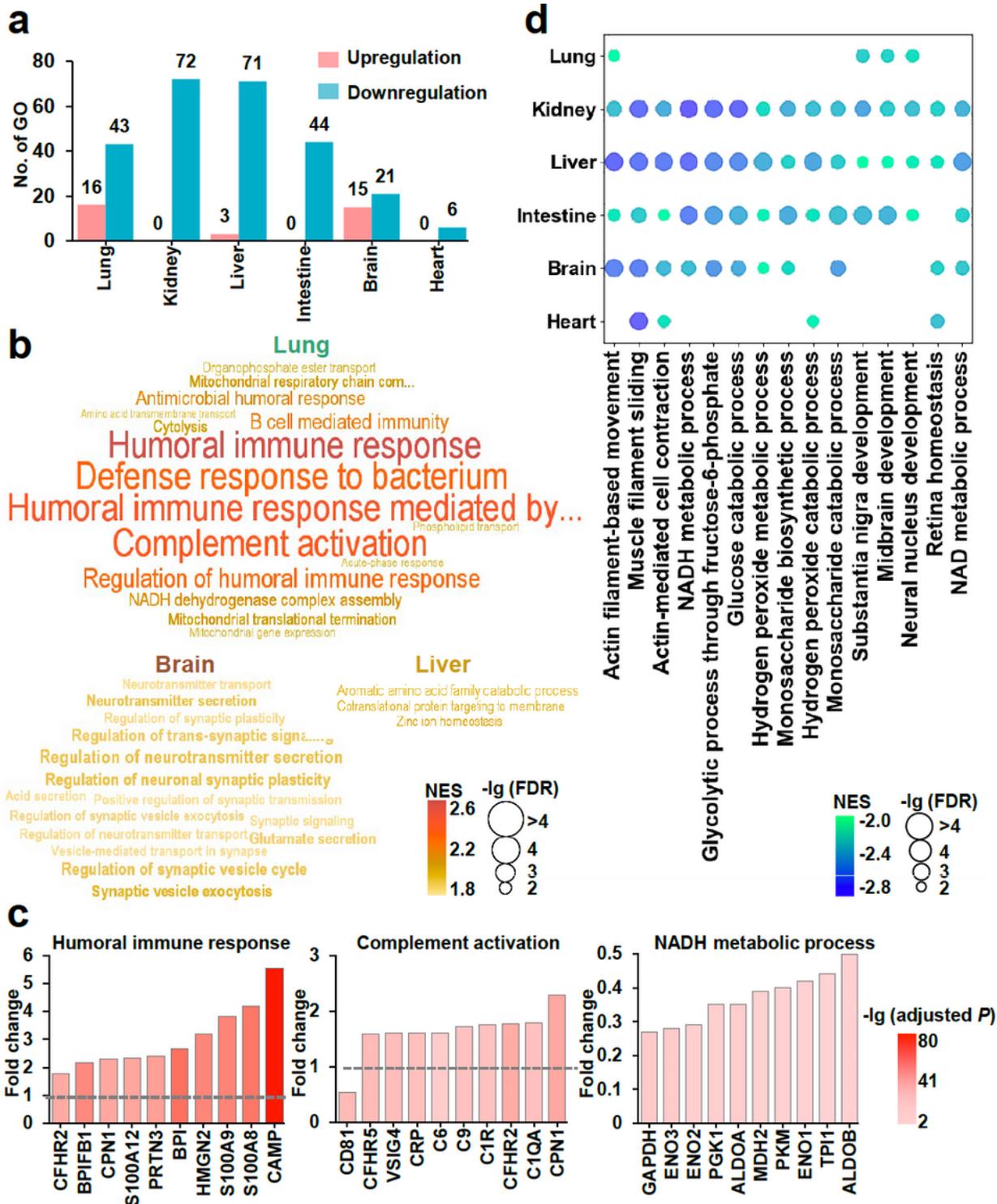


Figure 3

A comparison of the proteomic data in postmortem tissues against normal tissues. a, The distribution of numbers of quantified proteins for six tissues obtained from HPM. b, The overlap of quantified proteins in HPM and this study. c, The z-score plus median centering normalization of the HPM proteomic data. d, MAP-based identification of potential DEPs in each type of postmortem tissues. Arrows indicate the DEPs

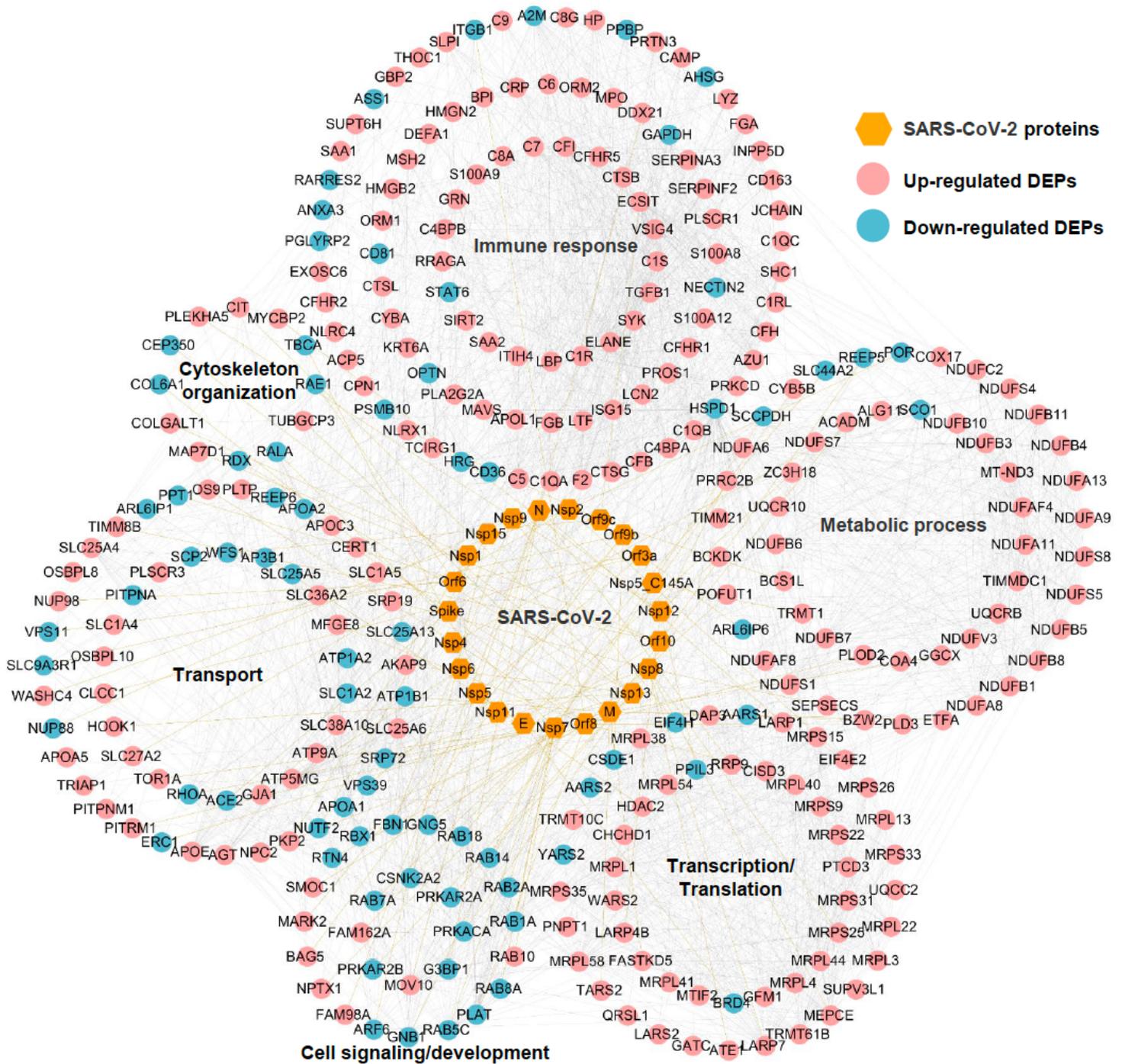
in each tissues also shown as TEPs. e, The distribution of numbers of up- and down-regulated DEPs in the six types of postmortem tissues. f, The overlap of DEPs in different postmortem tissues.



**Figure 4**

Differentially regulated biological processes in COVID-19 postmortem tissues. a, The distribution of numbers of significantly up- or down-regulated GO biological processes detected by GSEA (FDR q-val < 0.01) in the six types of postmortem tissues. b, Visualization of up-regulated processes in postmortem

lung, liver and brain, using a word cloud illustrator WocEA 40. c, Down-regulated processes in  $\geq 4$  postmortem tissue types. d, Top 10 mostly changed DEPs in three differentially regulated processes.



**Figure 5**

A virus-host protein interaction network. In the network, the 308 up- (pink) and down-regulated (cyan) DEPs in postmortem lung tissues were classified into 6 groups based on their major functions. The PPIs between the 23 SARS-CoV-2 proteins (orange) were shown in yellow links, whereas PPIs between host proteins were shown in grey links.

## Supplementary Files

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- [Supplementarytables17.xlsx](#)
- [SupplementaryMaterials.pdf](#)