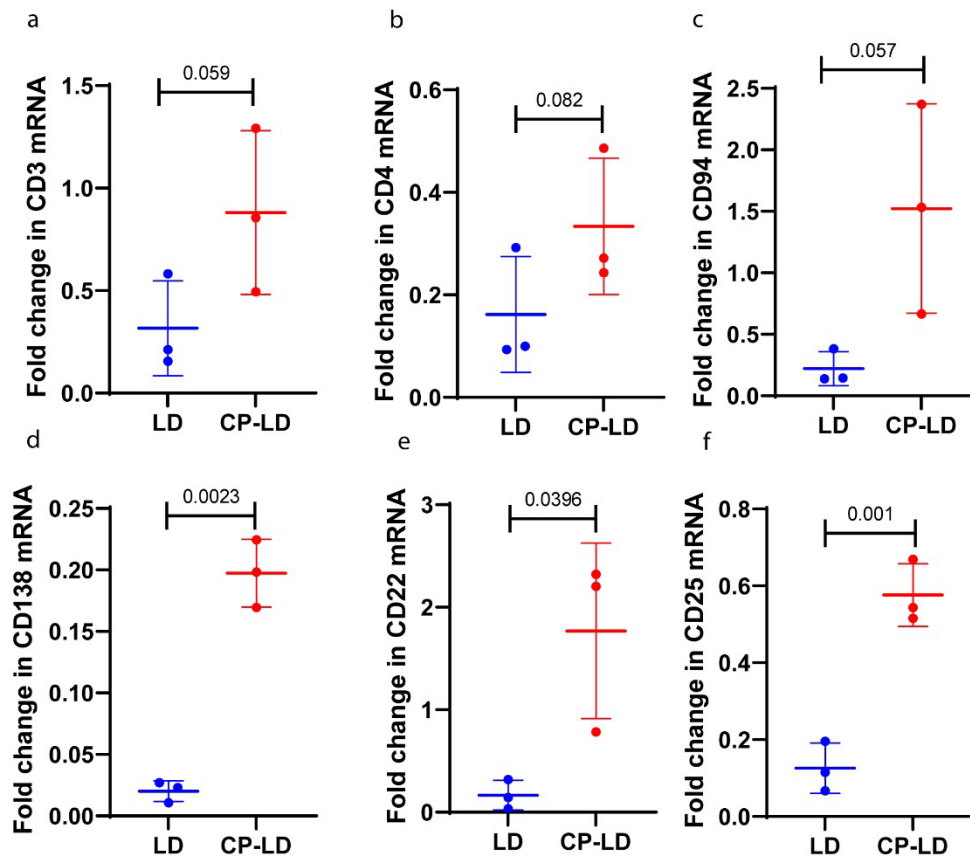


**Figure S1. Histopathology of the trachea in SARS-CoV-2 infected hamsters.**

Histopathological analysis of trachea (4, 7 and 16 dpi., n=3 per time point) revealed squamous metaplasia of tracheal epithelial cells (**a, d**) and accumulation of mucinous exudates and macrophages and neutrophils in the tracheal lumen (**g, j**) in LD infected hamsters at 7 dpi.

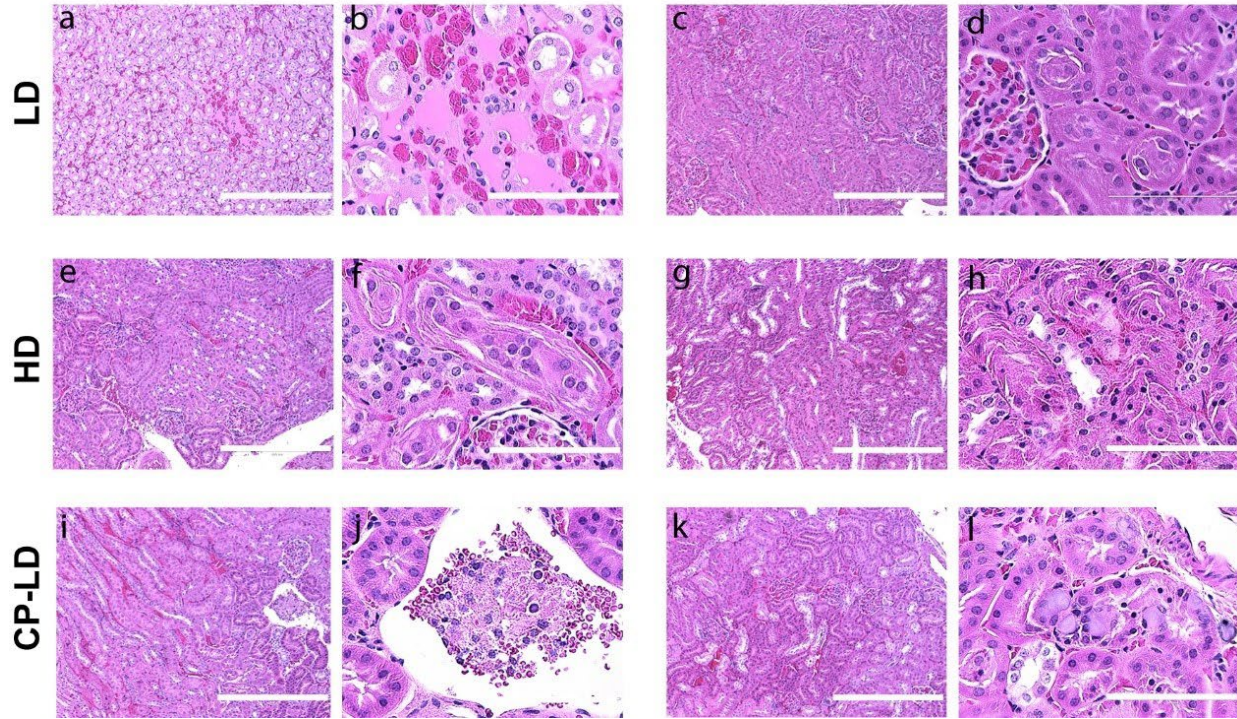
Epithelial metaplasia (**b, h, k**) and mucosal detachment (**b, e**) in HD infected hamsters on 4 and 7 d.p.i. Severe stratified squamous metaplasia (**c, f**) at 4 dpi and detachment of epithelial cells (**i, l**) on 16 d.p.i. in the cyclophosphamide treated LD infected hamsters. The images **a-c, g-i** are 100x and **d-f, j-l** are 400x magnifications. Scale bar represents 100  $\mu$ m (**d-f, j-l**) or 400  $\mu$ m (**a-c, g-i**).

**LD**-low dose; **HD**-high dose; **CP-LD**-cyclophosphamide treated (immunosuppressed) and low dose infected groups.

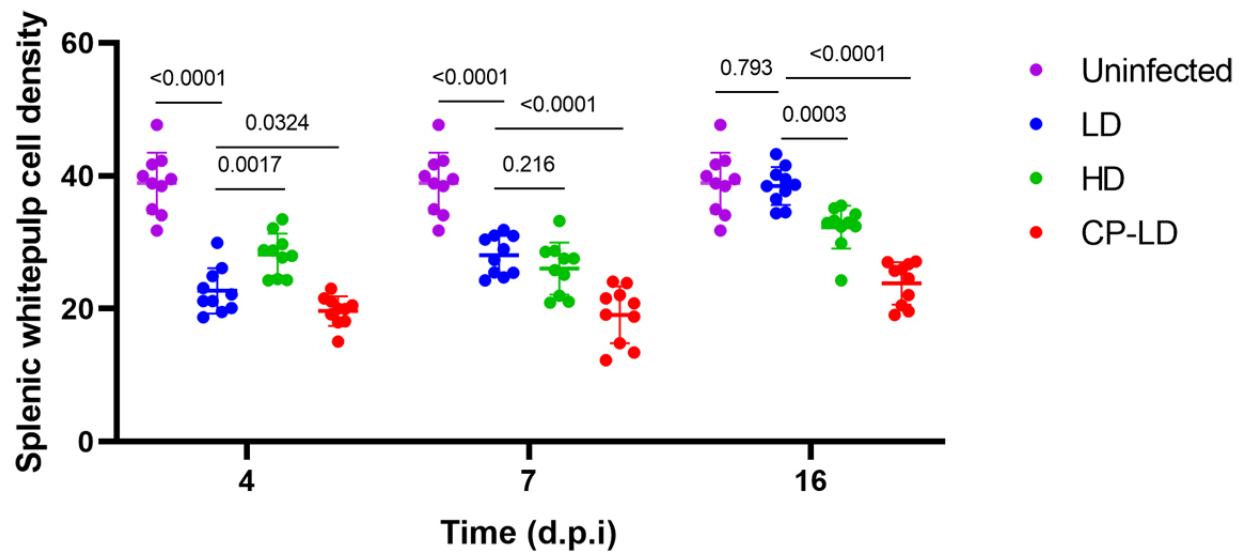


**Figure S2: qPCR analysis of B and T cell lineage markers in LD and CP-LD infected hamster lungs.** The level of T cell markers CD3, CD4, CD94 expression in the lungs was not significantly different between LD and CP-LD infected animals at 7 dpi (**a**, **b**, **c**), whereas expression of plasma cell marker CD138 (**d**), B cell marker CD22 (**e**) and Treg marker CD25 (**f**) was significantly down-regulated in LD, compared to CP-LD infected hamster lungs. The values are normalized with GAPDH/b-actin transcripts and represent the fold change in expression compared to uninfected hamsters. Statistical analysis was performed by two-sided Welch's t-test. Data represent mean ± sd (**a-f**). The blue, green, and red indicate LD, HD, and CP-LD infected hamsters, respectively, and each dot represents an individual hamster data (**a-f**). **LD**-low dose; **CP-LD**-cyclophosphamide treated (immunosuppressed) and low dose infected groups.





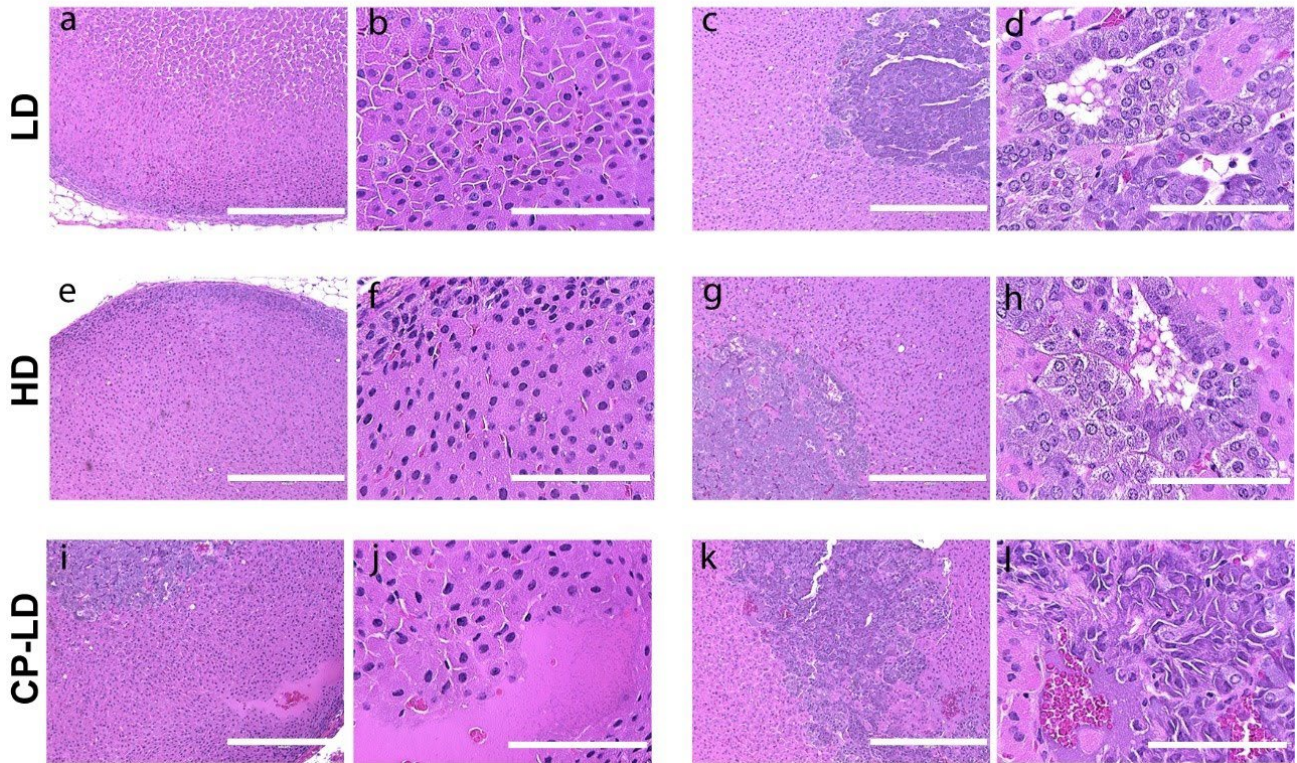
**Figure S3. Histopathology of the adrenal gland in SARS-CoV-2 infected hamsters.** A section of the adrenal cortex showing degenerated cells with pyknotic nuclei (**a, b**) on 4 dpi. and liquefaction necrosis in the medulla (**c, d**) on day 7 dpi. Hyperplasia/hypertrophy of adrenal cortex (**e, f**) and mild degeneration in the cortical cells (**f**) and liquefaction necrosis in the medullary chords (**g, h**) on 7 dpi. In CP-LD infected hamsters, severe degeneration and liquefaction necrosis in the cortex is seen as eosinophilic necrotic material (**i, j**) on 4 dpi and chromatolysis and necrosis of chromaffin cells in the medulla (**k, l**) on 7 dpi were observed. The images **a, e, i, c, g, k** are 100x and **b, f, j, d, h, l** are 400x magnifications. Scale bar represents 100  $\mu\text{m}$  (**b, f, j, d, h, l**) or 400  $\mu\text{m}$  (**a, e, i, c, g, k**). **LD**-low dose; **HD**-high dose; **CP-LD**-cyclophosphamide treated (immunosuppressed) and low dose infected groups.



**Figure S4. White pulp content in the spleen of SARS-CoV-2 infected hamsters.**

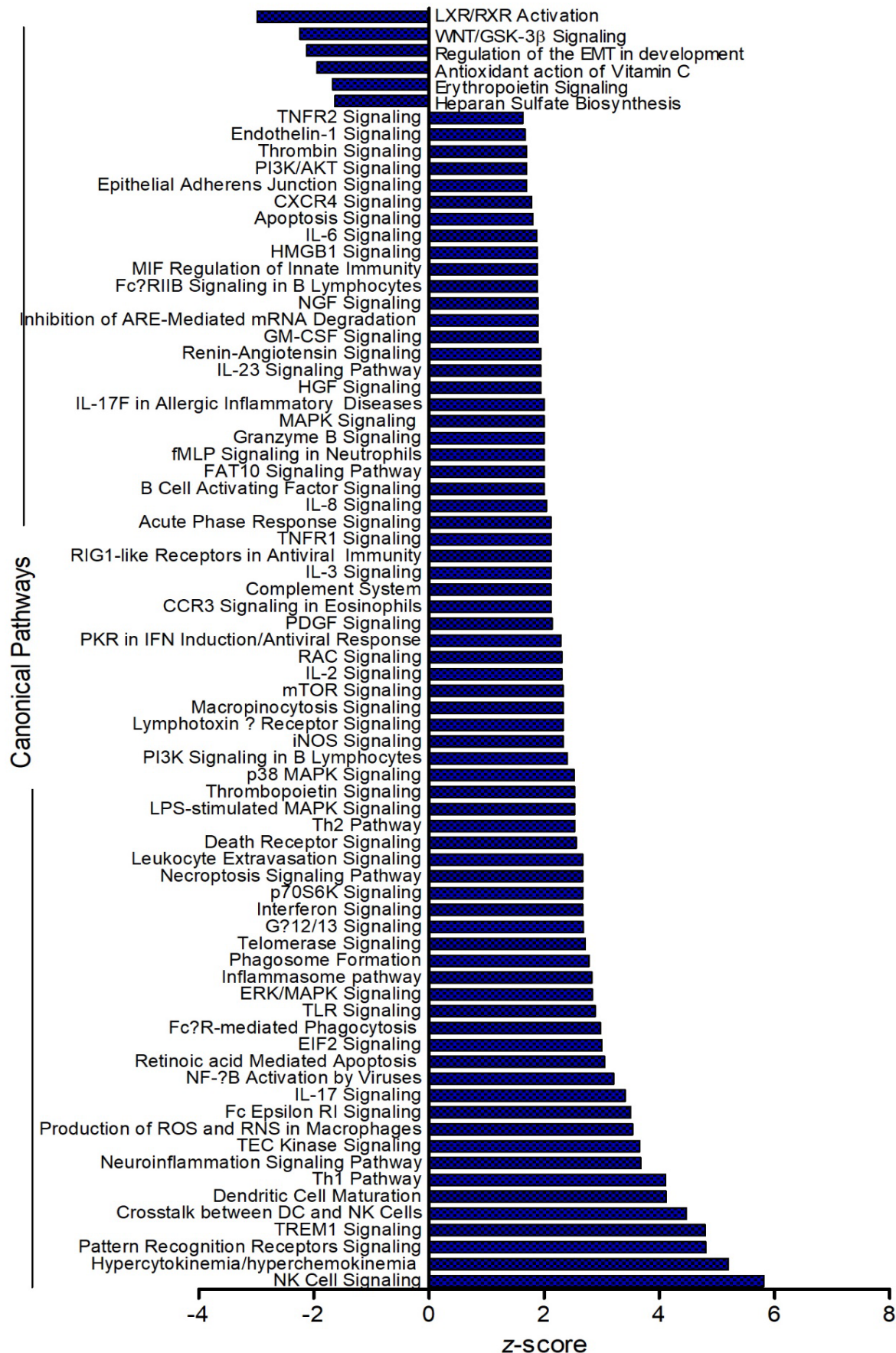
Histopathological analysis at 4, 7 and 16 dpi revealed differential white pulp density in the spleen upon SARS-CoV-2 infection. **LD**-low dose; **HD**-high dose; **CP-LD**-cyclophosphamide treated (immunosuppressed) and low dose infected groups.





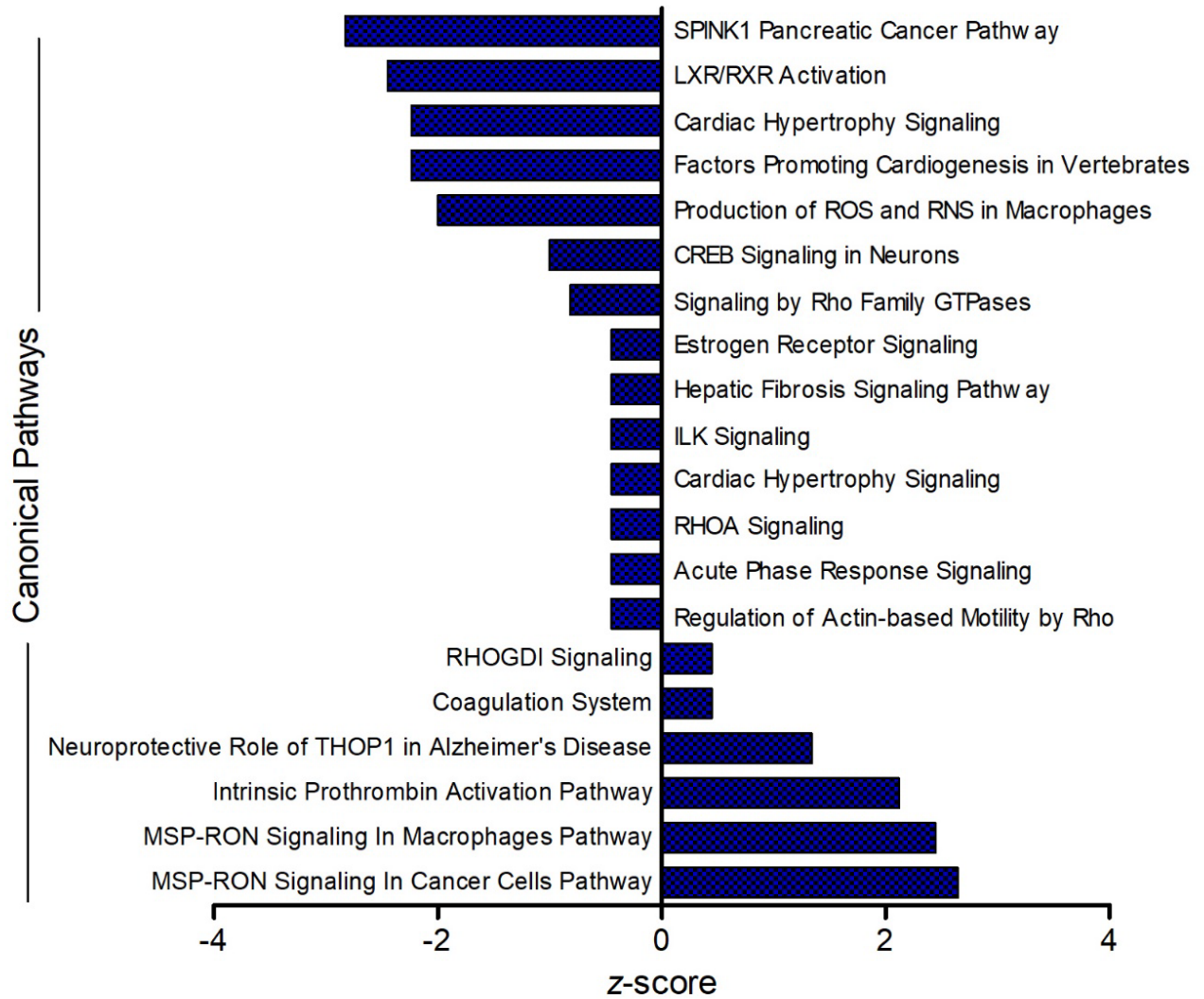
**Figure S5. Acute renal tubular necrosis in SARS-CoV-2 infected hamsters.**

Histopathological analysis of kidney (4, 7 and 16 dpi. n=3 per time point) revealed that the severe necrosis of renal tubules with karyolysis and accumulation of eosinophilic material in the tubular lumen (**a, b**) and tubular degeneration and mild infiltration of lymphocytes in the interstitium (**c, d**) following LD infection (4 d.p.i). HD infected hamsters' kidneys showed severe acute tubular necrosis of proximal convoluted tubules with pyknosis and loss of brush border into the lumen (**e, f, g, h**) on 4-16 dpi. Glomerular corpuscular necrosis and detachment from the arterioles (**i, j**) and basophilic ground-glass bodies in the cells of proximal convoluted tubules, pyknosis, and margination of the nucleus (**k, l**) in CP-LD infected hamsters on 16 dpi. The images **a, e, i, c, g, k** are 100x and **b, f, j, d, h, l** are 400x magnifications. Scale bar represents 100  $\mu\text{m}$  (**b, f, j, d, h, l**) or 400  $\mu\text{m}$  (**a, e, i, c, g, k**). LD-low dose; HD-high dose; CP-LD-cyclophosphamide treated (immunosuppressed) and low dose infected groups.



**Figure S6. Top canonical pathways operative in immunocompetent hamster lungs infected with low-dose SARS-CoV-2 at 4 days post-infection.** Pathways with positive z-score values are upregulated/activated, and those with negative z-score values are downregulated/suppressed.

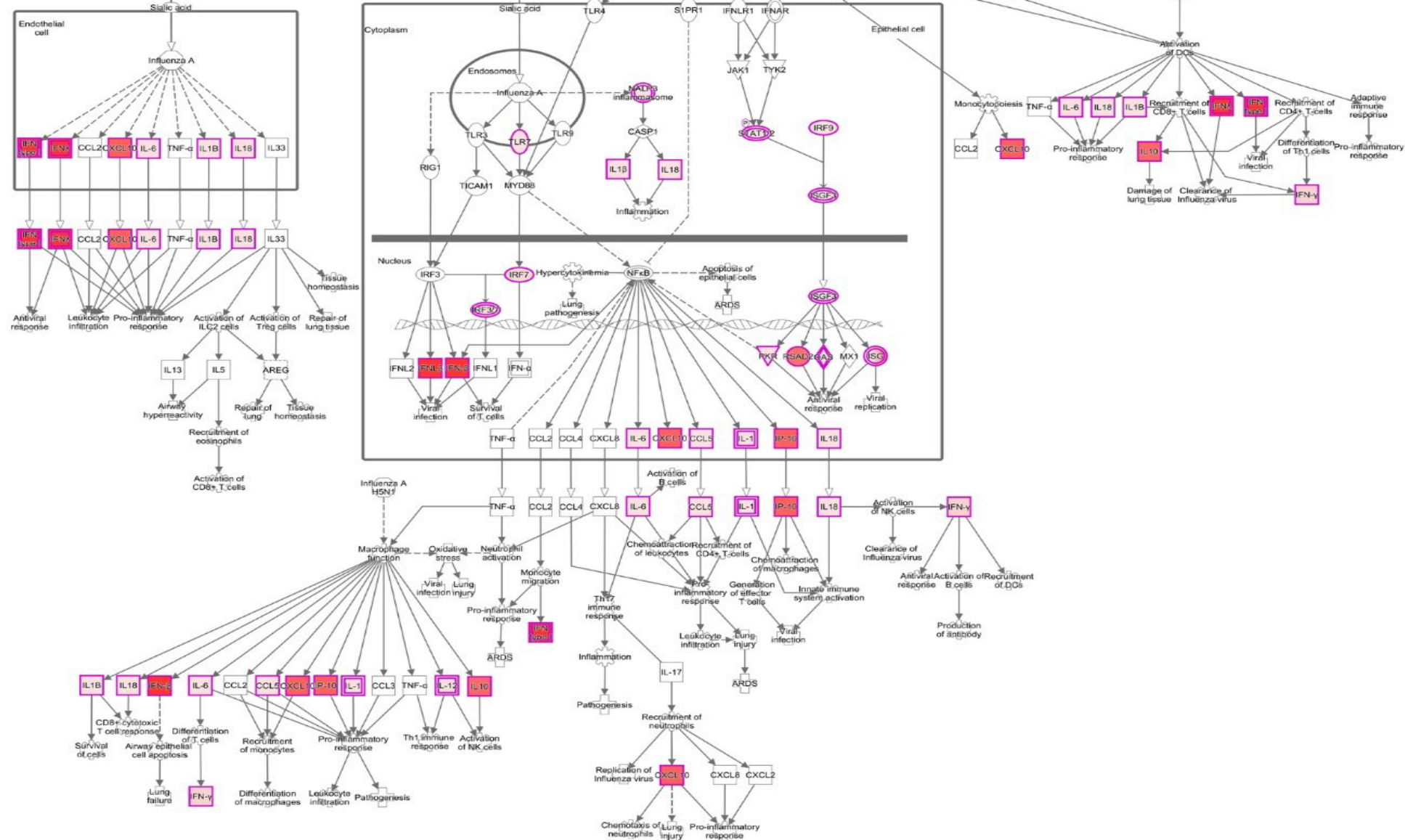




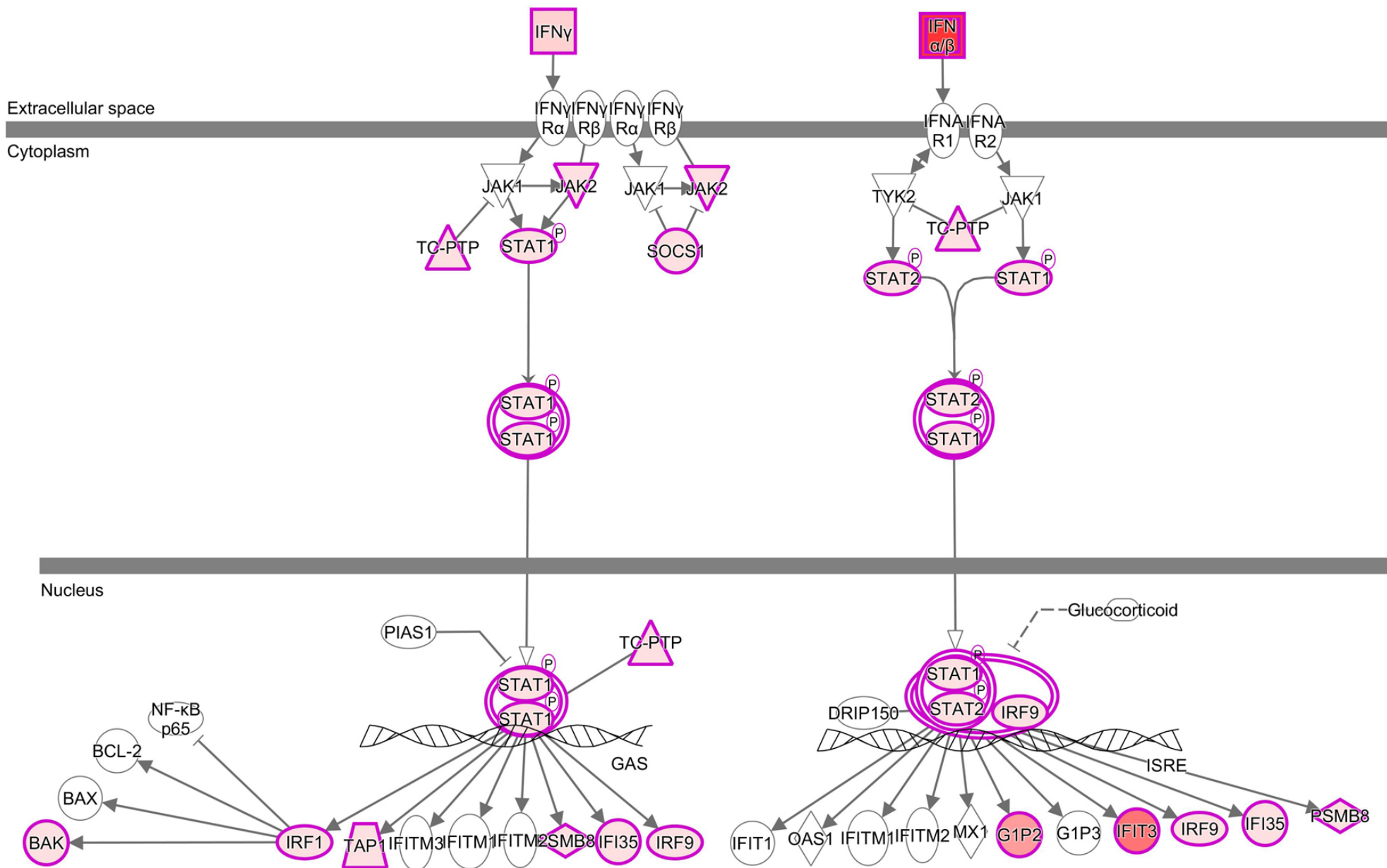
**Figure S7. Top canonical pathways operative in immunocompetent hamster lungs infected with low-dose SARS-CoV-2 at 16 days post-infection.** Pathways with positive z-score values are upregulated/activated, and those with negative z-score values are downregulated/suppressed.



Diagram illustrating the signaling pathway of Influenza A virus in an endothelial cell. Salicylic acid is shown at the top, leading to Influenza A. Influenza A then triggers a cascade of cytokines: IL-1, IL-2, CCL2, CXCL10, IL-6, TNF- $\alpha$ , IL1B, IL18, and IL33. The cytokines IL-1, IL-2, IL-6, IL1B, and IL18 are highlighted in pink boxes, while CCL2, CXCL10, TNF- $\alpha$ , and IL33 are in white boxes.

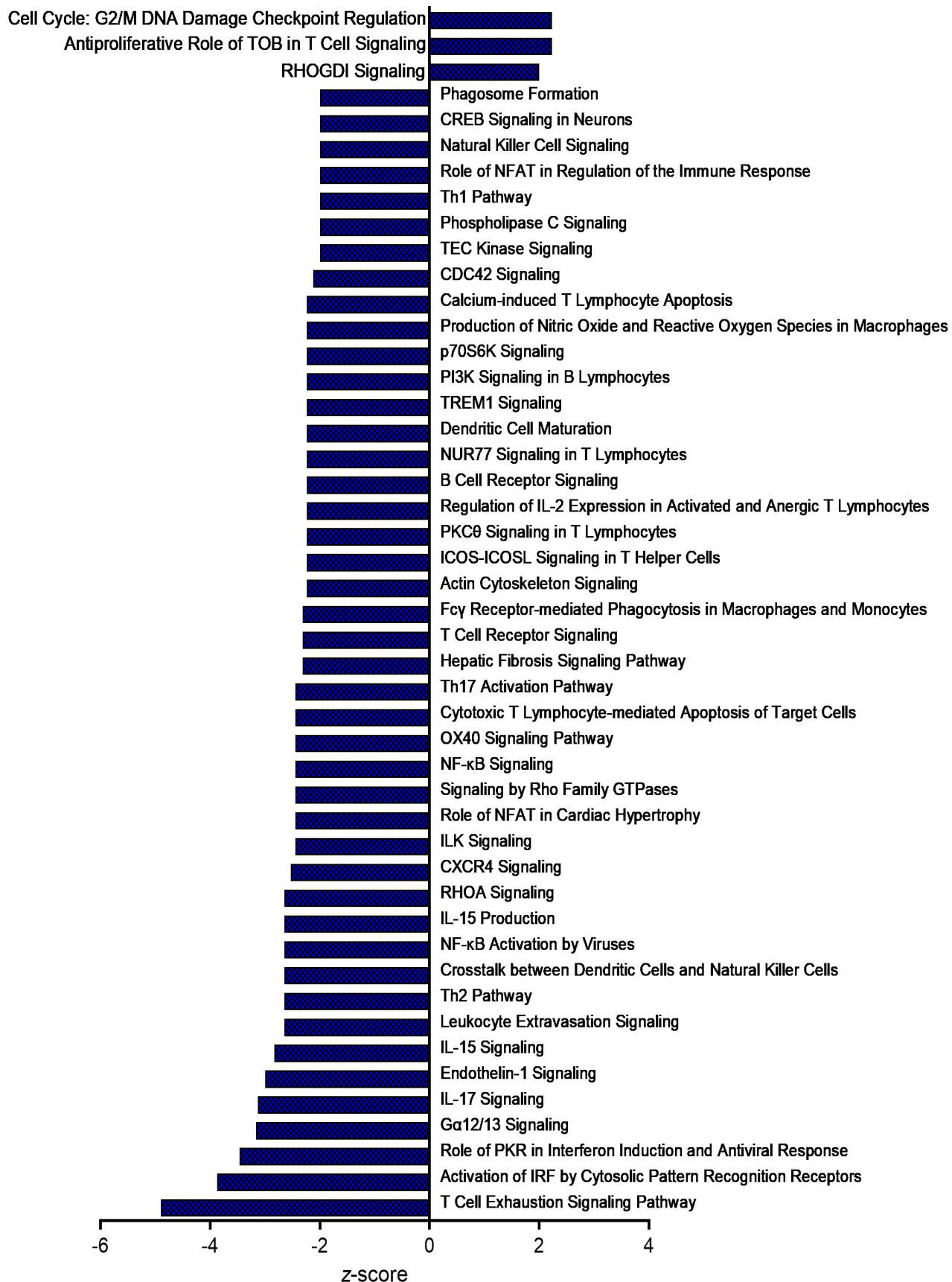


**Figure S8. Canonical hypercytokinemia/hyperchemokineemia pathway map.** Network genes and their interactions are shown with superimposed data from immunocompetent hamster lungs infected with low-dose SARS-CoV-2 at 4 dpi. Red color indicates upregulation, with the intensity of color proportional to the expression level (i.e., darker the color, stronger the expression).





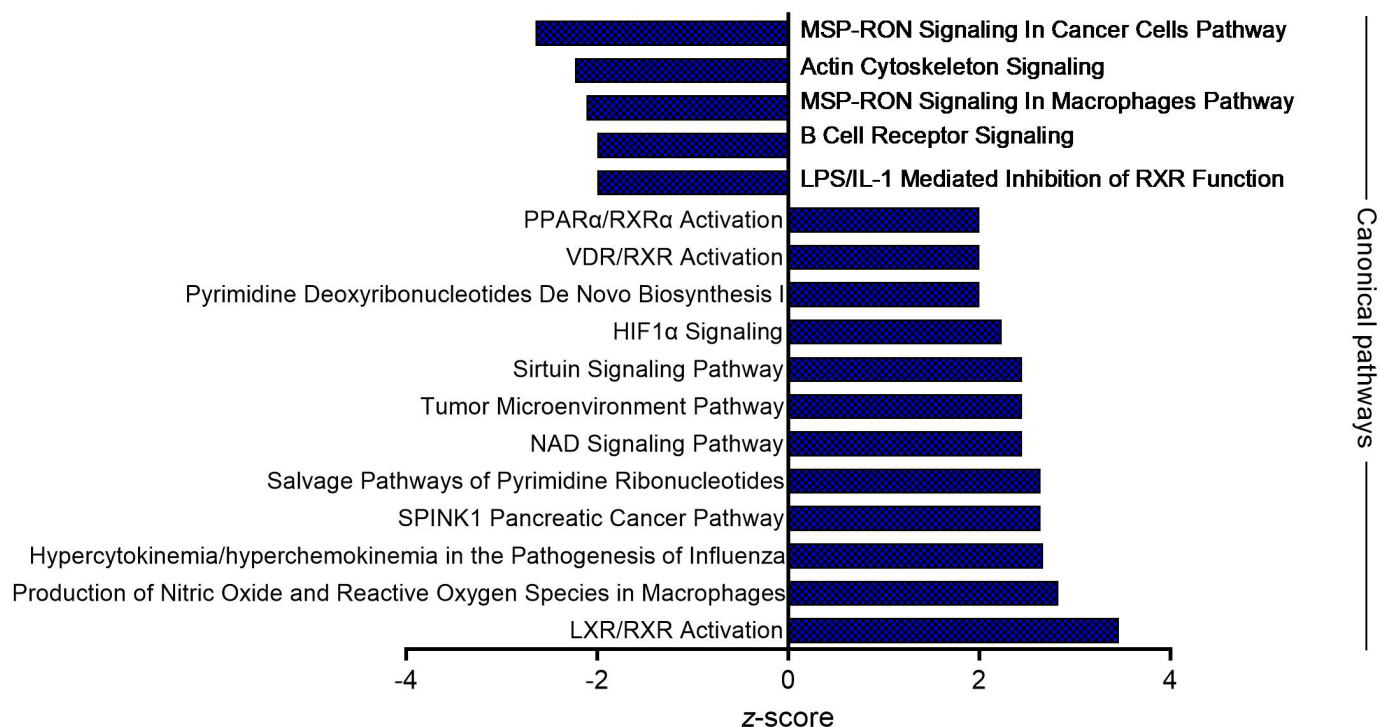
**Figure S9. Canonical interferon signaling pathway map.** Network genes and their interactions are shown with superimposed data from immunocompetent hamster lungs infected with low-dose SARS-CoV-2 at 4 dpi. Red color indicates upregulation, with the intensity of color proportional to the expression level (i.e., darker the color, stronger the expression).



Canonical pathways

**Figure S10. Top canonical pathways operative in immunocompromised hamster lungs infected with low-dose SARS-CoV-2 at 4 days post-infection.** Pathways with positive z-score values are upregulated/activated, and those with negative z-score values are downregulated/suppressed.





**Figure S11. Top canonical pathways operative in immunocompromised hamster lungs infected with low-dose SARS-CoV-2 at 16 days post-infection.** Pathways with positive z-score values are upregulated/activated and those with negative z-score values are downregulated/suppressed.

**Table S1.** Differentially regulated biological functions at 4dpi versus uninfected hamster lungs

<i>Categories</i>	<i>Diseases or Functions Annotation</i>	<i>p-value</i>	<i>z-score</i>	<i># Molecules</i>
Antimicrobial activities of host cells	Antimicrobial response	1.74E-34	5.136	120
Cell Death and Survival	Cytotoxicity	5.04E-24	5.514	81
	Cytolysis	1.43E-24	2.991	90
Cell-mediated Immune Response	T cell development	3.02E-47	5.186	187
	Differentiation of T lymphocytes	6.43E-38	5.12	139
	T cell homeostasis	8.58E-51	5.283	195
	T cell migration	3.84E-34	5.073	111
Cell-To-Cell Signaling and Interaction	Immune response of myeloid cells	2.82E-24	5.513	77
	Response of antigen presenting cells	1.11E-26	5.295	82
	Binding of myeloid cells	3.78E-22	4.156	74
Cellular Growth, Proliferation and Movement	Stimulation of cells	1.12E-26	3.876	103
	Stimulation of lymphatic system cells	9.23E-25	3.409	62
	Stimulation of leukocytes	8.31E-25	4.241	70
	Stimulation of mononuclear leukocytes	5.29E-25	3.65	63
	Stimulation of lymphocytes	1.51E-25	3.487	61
	Stimulation of T lymphocytes	8.42E-23	3.316	53
	Recruitment of blood cells	1.8E-40	5.174	130
	Recruitment of cells	1.25E-40	4.998	137
	Recruitment of myeloid cells	7.77E-33	4.314	105
	Recruitment of leukocytes	2.36E-40	5.192	128
	Recruitment of granulocytes	1.05E-24	4.268	79
	Recruitment of phagocytes	3.33E-32	4.36	99
	Recruitment of neutrophils	6.83E-24	3.993	71
	Interaction of leukocytes	6.06E-34	6.442	131
	Binding of leukocytes	7.64E-34	6.415	130
	Interaction of mononuclear leukocytes	1.56E-23	4.975	75
	Binding of lymphocytes	9.18E-23	4.496	63
	Interaction of phagocytes	2.21E-24	4.483	77
	Activation of myeloid cells	3.02E-25	4.178	109
	Response of lymphocytes	1.6E-28	2.621	82
	Adhesion of immune cells	3.59E-32	6.276	121
	Activation of mononuclear leukocytes	3.18E-51	4.954	186
	Activation of lymphocytes	2.52E-51	4.9	181

	Activation of T lymphocytes	1.09E-45	4.555	149
	Activation of antigen presenting cells	1.74E-28	3.86	110
Inflammatory Response	Immune response of leukocytes	5.24E-41	6.073	130
	Immune response of phagocytes	1.8E-29	6.007	90
	Response of phagocytes	4.06E-31	6.004	97
	Immune response of antigen presenting cells	8.26E-26	5.226	77
	Degranulation of myeloid cells	2.78E-24	3.715	127
	Degranulation of leukocytes	1.07E-28	3.556	140
	Degranulation of phagocytes	2.44E-24	3.308	126
	Inflammatory response	1.14E-63	6.031	279
	Cell-mediated response	2.04E-31	3.697	85
	Antibody response	3.85E-23	3.625	62
	Innate immune response	1.47E-23	3.581	80
	Degranulation	3.13E-35	3.572	171
Cellular Development	Differentiation of progenitor cells	4.52E-22	3.248	129
	Proliferation of blood cells	5.84E-67	3.852	294
	Development of progenitor cells	9.63E-23	2.914	99
	Differentiation of mononuclear leukocytes	3.4E-56	6.076	239
	Development of mononuclear leukocytes	2.37E-56	5.85	239
	Differentiation of antigen presenting cells	1.49E-23	4.623	77
	Differentiation of phagocytes	3.91E-24	4.441	91
	Development of phagocytes	4.49E-22	3.759	83
	Development of hematopoietic progenitor cells	3.01E-22	2.944	94
	Proliferation of B lymphocytes	1.13E-23	4.06	94
	Proliferation of mononuclear leukocytes	2.45E-62	4.27	259
	Proliferation of immune cells	5.7E-66	4.229	274
	Proliferation of lymphocytes	3.98E-60	4.155	253
	Expansion of T lymphocytes	6.37E-32	3.308	74
	Cell proliferation of T lymphocytes	2.89E-56	3.12	217
	Expansion of mononuclear leukocytes	2.12E-32	2.918	83
	Expansion of lymphocytes	4.17E-31	2.838	80
	Expansion of leukocytes	7.59E-33	2.739	87
	Expansion of lymphoid cells	1.72E-31	2.679	81



Cellular Function and Maintenance	Cellular homeostasis	1.65E-52	5.611	425
	Function of leukocytes	1.35E-76	3.069	208
	Function of mononuclear leukocytes	5.35E-52	2.533	133
	Function of lymphocytes	1.32E-51	2.471	132
	Function of T lymphocytes	1.28E-43	2.021	109
Free Radical Scavenging	Synthesis of reactive oxygen species	4.55E-24	5.031	142
	Metabolism of reactive oxygen species	2.73E-24	4.901	148
Humoral Immune Response, Protein Synthesis	Quantity of IgG	9.45E-34	2.944	89
Immunological Disease	Hypersensitive reaction	3.59E-34	3.937	143
	Immunodeficiency	2.17E-27	-3.252	105
Organismal Survival	Organismal survival	3.17E-56	-2.157	560
	Morbidity or mortality	3.7E-59	-2.177	572

**Table S2.** Differentially regulated biological functions at 16dpi versus uninfected hamster lungs

Categories	Diseases or Functions Annotation	p-value	z-score	# Molecules
Cellular Movement	Cellular infiltration by myeloid cells	6.41E-06	3.241	14
	Cellular infiltration by phagocytes	2.23E-06	2.935	14
	Cellular infiltration by leukocytes	1.24E-09	2.882	22
	Cellular infiltration	2.22E-09	2.871	23
	Cellular infiltration by granulocytes	7.28E-05	2.573	10
	Infiltration by neutrophils	0.00035	2.76	8
Hematological System Development and Function	Quantity of macrophages	0.0004	2.532	9
Organismal Injury and Abnormalities	Edema	0.00045	2.747	12
Organismal Survival and Cell Death	Survival of organism	1.51E-07	-3.324	27
	Organismal death	1.41E-08	2.554	58
	Necrosis of muscle	0.000143	2.204	12
	Lung injury	1.06E-06	2.007	12
	Cell death of muscle cells	0.00045	2.033	11
Lipid Metabolism, Small Molecule Biochemistry	Fatty acid metabolism	3.54E-09	-2.253	25
	Transport of lipid	0.000118	-2.381	10
	Export of molecule	0.000937	-2.401	10
	Transport of molecule	0.00097	-2.613	32
Cardiovascular Disease and Abnormalities	Failure of heart	7.23E-07	2.63	14
	Degeneration of heart	2.16E-09	2.599	8
	Congestive heart failure	1.75E-05	2.236	8

**Table S3.** Differentially regulated biological functions in immunosuppressed SARS-CoV-2 infected hamster lungs at 4dpi

<b>Categories</b>	<b>Diseases or Functions Annotation</b>	<b>p-value</b>	<b>z-score</b>	<b># Molecules</b>
Organismal survival	Cell survival	1.15E-17	-5.865	86
	Cell viability	2.72E-16	-6.371	81
	Cell viability of leukocytes	1.59E-24	-4.592	38
	Cell viability of lymphocytes	8.23E-20	-4.07	29
Cell Morphology	Polarization of helper T lymphocytes	4.25E-13	-2.753	11
	Polarization of lymphocytes	9.9E-15	-2.495	16
	Polarization of mononuclear leukocytes	1.33E-15	-2.645	17
	Polarization of Th1 cells	6.44E-13	-2.385	8
Cell Signaling and Molecular Transport	Flux of Ca <sup>2+</sup>	2.37E-16	-2.614	32
	Mobilization of Ca <sup>2+</sup>	2.1E-17	-2.439	34
Cell-mediated Immune Response	Differentiation of effector T lymphocytes	2.47E-11	-2.056	9
	Differentiation of T lymphocytes	5.24E-28	-2.383	50
	Proliferation of thymocytes	1.91E-14	-2.802	17
	T cell development	5.05E-42	-4.257	73
	T cell homeostasis	1.93E-44	-4.457	76
	T cell migration	4.32E-20	-2.333	36
Cell-To-Cell Signaling and Interaction	Interaction of lymphocytes	1.83E-16	-3.367	25
	Interaction of T lymphocytes	2.17E-14	-3.125	21
	Activation of lymphocytes	2.35E-42	-3.338	70
	Activation of mononuclear leukocytes	5.82E-42	-3.428	71
	Activation of natural killer cells	2.65E-12	-3.611	18
	Activation of T lymphocytes	2.23E-32	-3.199	54
Cellular Growth and Development	Maturation of blood cells	2.92E-14	-2.455	27
	Maturation of cells	2.73E-12	-2.898	34
	Proliferation of blood cells	6.93E-54	-2.429	104
	Proliferation of progenitor cells	5.63E-13	-3.388	31
	Development of B lymphocytes	1.54E-13	-2.097	20
	Proliferation of hematopoietic progenitor cells	3.24E-15	-3.216	29
	Dendropoiesis	1.9E-13	-2.81	20
	Development of antigen presenting cells	1.21E-12	-2.142	22
	Differentiation of antigen presenting cells	5.42E-16	-2.836	27
	Hematopoiesis of mononuclear leukocytes	1.87E-53	-4.181	94

	Hematopoiesis of phagocytes	1.19E-14	-2.075	25
	Leukopoiesis	3.98E-54	-4.343	101
	Development of hematopoietic progenitor cells	5.94E-17	-2.266	33
	Proliferation of immune cells	1.83E-56	-2.465	102
	Proliferation of lymphocytes	1.9E-57	-2.301	100
	Proliferation of mononuclear leukocytes	7.64E-58	-2.464	101
	Maturation of lymphocytes	3.47E-16	-3.003	21
Cellular Function and Maintenance	Cellular homeostasis	9.2E-31	-4.633	111
	Ion homeostasis of cells	2.36E-12	-2.464	40
	Lymphocyte homeostasis	5.57E-45	-4.653	78
	Function of helper T lymphocytes	4.76E-20	-2	20
Cellular Movement and Immune Cell Trafficking	Cell movement of leukocytes	1.43E-26	-2.927	71
	Cell movement of lymphocytes	7.35E-24	-2.731	48
	Cell movement of mononuclear leukocytes	4.22E-23	-2.673	51
Hematological System Development and Function	Quantity of B lymphocytes	5.47E-33	-2.303	54
	Quantity of CD4+ T-lymphocytes	4.67E-30	-2.354	41
	Quantity of lymphocytes	6.31E-49	-3.894	92
	Quantity of regulatory T lymphocytes	6.4E-13	-2.507	19
	Quantity of T lymphocytes	2.05E-38	-3.039	71
	Quantity of leukocytes	9.58E-51	-3.909	105
	Quantity of mononuclear leukocytes	3.42E-48	-3.771	93
Inflammatory Response	Cell-mediated response	1.1E-17	-2.29	28
	Inflammatory response	2.56E-18	-2.386	59
Cell Death and Survival	Apoptosis	3.45E-22	2.226	126
	Apoptosis of blood cells	7.07E-32	2.173	60
	Apoptosis of leukocytes	2.17E-31	2.224	57
	Apoptosis of lymphatic system cells	2.57E-28	3.066	49
	Apoptosis of lymphocytes	3.78E-28	2.963	47
	Apoptosis of mononuclear leukocytes	2.54E-29	2.895	49
	Cell death of lymphatic system cells	1.62E-33	2.698	57
	Cell death of lymphocytes	1.35E-34	2.549	56
	Cell death of mononuclear leukocytes	7.78E-36	2.464	58

	Morbidity or mortality	5.4E-15	5.817	107
	Organismal death	4.91E-14	5.658	104



**Table S4.** Differentially regulated biological functions in immunosuppressed SARS-CoV-2 infected hamster lungs at 16dpi

Categories	Diseases or Functions Annotation	p-value	z-score	# Molecules
Antimicrobial and Inflammatory Response	Antimicrobial response	3.65E-18	2.177	40
Cellular Movement and Cellular immunity	Cell movement	8.33E-13	2.825	118
	Migration of cells	1.66E-12	2.626	109
	Migration of mononuclear leukocytes	4.73E-10	2.138	33
	T cell migration	2.47E-09	2.223	26
	Cell movement of T lymphocytes	1.01E-07	2.119	22
	Movement of CD4+ T-lymphocytes	5.62E-07	2.295	11
Cellular Function and Maintenance	Ion homeostasis of cells	7.37E-07	2.131	35
Humoral Immune Response	Quantity of lymphoid tissue	4.37E-10	-2.022	31
	Quantity of B lymphocytes	1.56E-12	-2.696	35
	Quantity of marginal-zone B lymphocytes	1.86E-07	-2.06	12
	Quantity of IgG3	1.85E-09	-2.125	13
	Quantity of IgG2b	4.97E-08	-2.234	11
Lipid Metabolism and Molecular Transport	Transport of lipid	4.58E-12	3.482	27
	Transport of fatty acid	6.46E-08	2.762	11
	Flux of lipid	9.23E-08	2.519	15
	Transport of steroid	2.75E-07	2.199	16
	Efflux of lipid	3.47E-07	2.359	14
	Efflux of cholesterol	6.07E-07	2.003	13
	Fatty acid metabolism	9.78E-12	2.871	45
	Transport of carboxylic acid	3.18E-07	2.915	13
	Transport of molecule	1.67E-06	3.905	72
	Protein-protein	6.99E-08	-2.578	18
Organismal Injury and Abnormalities	Fibrosis	6.92E-14	-2.792	57
	Morbidity or mortality	9.64E-12	-3.901	118
	Organismal survival	4.96E-11	-3.853	115
	Thrombus formation	1.63E-09	-2.375	22

**Table S5.** List of primers used for hamster and SARS-CoV-2 genes in the present study

Gene target	Name of the primer	Sequence 5'-3'	Product size
1 IL1B	Ham_IL1b_F1	AAAGCCTTGACCTGAGCTATC	110
	Ham_IL1b_R1	CTTCTCCACAGCCACAATGA	
2 TNFA	Ham_TNFA_F1	GGTTTACTCCCAGGTTCTCTTC	112
	Ham_TNFA_R1	GGACAGGAGGTTGACGTTAT	
3 IFNG	Ham_IFNg_F1	GCTATGTCTGGCTGCTACTG	99
	Ham_IFNg_R1	CCCTCCATTACGACATCTAAG	
4 CCL2	Ham_CCL2_F1	CTGGACCAGAGTCAAGCTAAAT	110
	Ham_CCL2_R1	GGAAAGGCAGTAGTAGACACATTA	
5 MIP1A	Ham_MIP1a_F1	CCTCCTGCTGCTTCTTCTATG	118
	Ham_MIP1a_R1	TGCCGGTTTCTCTTGGTTAG	
6 IL10	Ham_IL10_F1	AGCGCTGTCATCGATTTCTC	90
	Ham_IL10_R1	CGCCTTTCTCTTGGAGCTTAT	
7 IL4	Ham_IL4_F1	GAAGAACTCCACGGAGAAAGAC	80
	Ham_IL4_R1	GGGTCACCTCATGTTGGAAATA	
8 IL6	Ham_IL6_F1	GACTTCCATCCACTTGTCTTCT	104
	Ham_IL6_R1	TTGGGAGTAGTGTCTCTGT	
9 IL7	Ham_IL7_F1	ACACAGATGCTGGTGAAGT	97
	Ham_IL7_R1	TCTCTCTCAGTAGCCTCTTTAGG	
10 CCL5	Ham_CCL5_F1	TGCTTTGACTACCTCTCCTTTAC	109
	Ham_CCL5_R1	GGTTCCTTCGGGTGACAAA	
11 ACTN	Ham_b-actin_F1	CCCAGAGCAAGAGAGGTATTC	90
	Ham_b-actin_R1	GGTGCCAGATCTTCTCCATATC	
12 GAPDH	Ham_GAPDH_F1	AGAACGGGAAGCTTGTCATC	113
	Ham_GAPDH_R1	GCCAGTAGACTCCACAACATAC	
13 SARS-CoV-2-N	SARS-CoV-2 N_F1	GTGATGCTGCTCTTGCTTTG	97
	SARS-CoV-2 N_R1	GTGACAGTTTGGCCTTGTTG	