

# Lung epithelial response to SARS-CoV2 and diabetes

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## Abstract

In SARS-CoV2 infections causing coronavirus disease-2019 (COVID-19) metabolic co-morbidities portend worse disease outcomes. We aimed at understanding the pathogenetic mechanisms underlying this phenomenon that may differentiate SARS-CoV2 infection from few other respiratory viruses that caused more limited pandemics in the recent past. A meta-analysis, of publicly available gene expression studies on human lung epithelial cells (HLEC) infected with different respiratory viruses, revealed both shared and exclusive transcriptional regulations. In addition, a few key metabolic pathways were found to be exclusively enriched in SARS-CoV2 infection. Systemic metabolic disorders are known to cause similar dysregulations in HLECs, which possibly underlie the predisposition of diabetic individuals to chronic lung diseases. We further performed an integrated analysis of the transcriptome from SARS-CoV2-infected HLECs, COVID-19 bronchoalveolar lavage and autopsied lung transcriptome as well as lung transcriptome from preclinical models of diet-induced obesity, revealing significant overlaps among these key pathways in these discreet contexts. This led us to hypothesize that with underlying metabolic co-morbidities this metabolic dysregulation of the HLECs on SARS-CoV2 infection is aggravated promoting widespread disruption of lung epithelial integrity, driving the worse prognosis. We envisage that any therapeutic agent that can target these key featured pathways, viz. metformin, should be of interest in SARS-CoV2 infection and warrants further studies.

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SARS-CoV2, is a newly emerged strain of coronavirus responsible for causing the coronavirus disease-2019 pandemic (COVID-19), wreaking havoc worldwide. This virus belongs to the genus Betacoronavirus whose other members—severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) are known for two previous outbreaks. Although, SARS and MERS caused deadly pneumonia with mortality rates of 10% and 36% respectively<sup>1</sup>, much higher as compared to 2.3% for SARS-CoV2 infections<sup>2</sup>, the overall number of deaths from SARS-CoV2 far outweighs the previous outbreaks. At genome level, SARS-CoV2 is more similar to a bat SARs-CoV showing 96% genome identity than that of SARS and MERS sharing about 79% and 50% of genome identity respectively<sup>3,4</sup>. Two of the significant predictors of severity and death in patients affected by SARS, MERS and pandemic influenza are diabetes and uncontrolled glycemia<sup>5-7</sup>. Interestingly, majority of deaths in the SARS-CoV2 infection have occurred in patients suffering from metabolic co-morbidities and indeed metabolic co-morbidities have been reported to portend worse disease outcomes in multiple studies carried out in different geographical locations,

with completely different ethnic populations.<sup>8-10</sup> But, the reason for this often-fatal role of metabolic comorbidities, more apparent in the case of SARS-CoV2 infection, is not yet mechanistically clear. We aimed at understanding the pathogenetic mechanisms underlying this prognostic implication of metabolic disorders in COVID-19 that may differentiate SARS-CoV2 infection from few other respiratory viruses that caused more limited pandemics in the recent past.

In order to do so, we undertook a meta-analysis of three publicly available gene expression studies (RNA-sequencing as well as microarray data) done on human lung epithelial cells (HLECs) (either A549 or Calu-3 cells) infected with different respiratory viruses, viz. SARS-CoV2, Respiratory Syncytial Virus or RSV, H1N1 Influenza, SARS and H3N2 Influenza<sup>11-13</sup>. The HLEC transcriptome on infection with these viruses revealed transcriptional signatures shared between the different viruses as well as transcriptional regulations exclusive to each of the viruses, as expected (Figure 1A). SARS-CoV2 was found to drive differential regulation of maximum number of genes among the datasets analyzed. Further analysis of the significantly regulated gene expressions revealed the key enriched pathways that are differentially regulated among these viruses (Figure 1B, C; Supplemental information). In Figure 1B and C, we represented pathways, among those enriched, which have role in cellular metabolic regulation and for which the nature of regulation of the pathway could be ascertained and excluded pathways that are related to diseases of no apparent relevance. Amongst these, modulation of a few key metabolic pathways (viz. AMPK signaling pathway, HIF1 $\alpha$ signaling pathway, mitophagy, AGE-RAGE signaling pathway, pentose phosphate pathway etc.) as well as the cellular senescence pathway and lysosome mediated degradation pathway were found to be exclusive to SARS-CoV2 infection (Figure 1B,C). The AGE-RAGE signaling pathway and cellular senescence pathway were upregulated (Figure 1B), whereas the AMPK signaling pathway, HIF1 $\alpha$  signaling pathway, mitophagy, pentose phosphate pathway and the lysosome pathway were all downregulated (Figure 1C). Interestingly, dysregulation of most of these metabolic pathways (upregulation of AGE-RAGE signaling and downregulation of AMPK signaling pathway, HIF1 $\alpha$  signaling pathway, mitophagy as well as the pentose phosphate pathway) have all been previously implicated in systemic disease pathogenesis observed in insulin resistance, Type 2 diabetes and its associated complications<sup>14-18</sup>.

Type 2 diabetes mellitus (T2DM) and obesity are two of the major co-morbidities portending worse prognostic outcomes in Covid-19 patients<sup>8-10</sup>. Interestingly, previous reports have established the increased association of asthma and chronic obstructive pulmonary disease(COPD) with these metabolic disorders<sup>19</sup>. Infact, these diseases associated with increased systemic metabolic disorder, are known to cause metabolic dysregulations in HLECs, which possibly underlie the predisposition of diabetic individuals towards asthma and COPD<sup>20,21</sup>. In order to compare the transcriptomic signature of SARS-CoV2 infected lung and diabetic lung, we performed an integrated analysis of the HLEC transcriptome in response to SARS-CoV2 infection as well as a COVID-19 bronchoalveolar lavage<sup>22</sup>and autopsied lung transcriptome<sup>23</sup> with lung transcriptome from two different datasets of preclinical rodent models of diet-induced obesity<sup>24,25</sup> (Figure 2A). Interestingly, we found significant overlaps in how some of these key pathways are transcriptionally regulated in lung in these two distinct clinical contexts of SARS-CoV2 infection and metabolic disorder (Figure 2B). In Figure 1D, selection of pathways were based on whether 1) pathway enrichment and the nature of regulation are shared between at least two datasets, 2) are not enriched in any of the other 4 virus datasets (RSV, SARS, H1N1 and H3N2), 3) are related to cellular metabolic regulation, 4) are represented in either Figure 1B or 1C and 5) are not primarily linked to diseases of no apparent relevance. Thus, the similarity in the dysregulation of pathways in HLECs/lung upon SARS-CoV2 infection and metabolic disorders was apparent.

Our meta-analysis led us to hypothesize that with underlying metabolic co-morbidities, e.g. T2DM, this already present metabolic dysregulation of the HLECs is further aggravated upon SARS-CoV2 infection leading to faster and more widespread disruption of epithelial integrity and pulmonary damage, leading to worse disease outcomes. This provides a possible explanation for the distinction observed in the characteristics of the population subgroups worst affected by SARS-CoV2 and the other above-mentioned viruses including viruses belonging to the same family, such as SARS.

We envisage that any therapeutic agent that can target these key featured pathways, as shown in Figure 2B,

should be of interest in SARS-CoV2 infection. This also points to a hitherto untapped potential for use of the widely used anti-diabetic drug metformin in COVID-19, which is an established modulator of most of these dysregulated pathways<sup>26-30</sup>. Indeed, metformin has been reported to inhibit AGEs, thus downregulating the AGE-RAGE signaling pathway associated with diabetes complications<sup>26</sup>. Metformin also enhances mitophagy in patients with Type 2 diabetes<sup>27</sup>. This anti-diabetic drug has also been reported to maintain cellular integrity by hindering cellular senescence<sup>28</sup>. The role of metformin in upregulation of the AMPK signaling pathway is one of its most well-established mechanisms of action involved in treating diabetes, reported in multiple studies<sup>29</sup>. Metformin has also been reported to modulate fatty acid metabolism<sup>30</sup>.

In addition to its projected effect on maintenance of lung epithelial integrity through these metabolic pathways in the epithelial cells, metformin has also been shown to boost CD8<sup>+</sup> T cell memory though metabolic reprogramming, an effect which will also add to its potential therapeutic action in COVID-19<sup>31,32</sup>. In a preclinical model on pulmonary effects of air pollution it was also shown that metformin can attenuate the production of the proinflammatory cytokine IL-6 from alveolar macrophages<sup>33</sup>, which is also a critical component of the hyperimmune response in COVID-19<sup>34</sup>. Moreover, vascular thromboembolism has been shown to be a unique feature in a number of COVID-19 patients in different studies<sup>35,36</sup> and metformin has been shown to have an antithrombotic effect through inhibition of platelet activation and maintenance of endothelial integrity<sup>37,38</sup>. Thus, metformin, due to its multifaceted pharmacodynamics, is well poised for acting as a therapeutic agent in SARS-CoV2 infections. But for ascertaining the therapeutic potential of metformin, mechanistic studies in the context of SARS-CoV2 infection, as well as comprehensive clinical trials in COVID-19 patients with or without metabolic co-morbidities, are warranted.

## Methods

### Datasets used in this study

Datasets used in the meta-analysis: SARS-Cov-2 (Calu-3)- Calu-3 cells either mock-infected (control) or infected with SARS-CoV-2 (strain USA-WA1/2020), (MOI 2), were collected after 24 hours of treatment (control-3, infected-3) and subjected to RNA-seq as described in GSE147507.RSV (A549) - A549 cells either mock-infected (control) or infected with RSV (strain A2), (MOI 15), were collected after 24 hours of treatment (control-2, infected-2) and subjected to RNA-seq as described in GSE147507.H1N1 (A549) - A549 cells either mock-infected (control) or infected with H1N1 (strain A/Puerto Rico/8/1934), (MOI 5), were collected after 9 hours of treatment (control-2, infected-2) and subjected to RNA-seq as described in GSE147507.SARS (Calu-3)- Calu-3 subclone 2B4 cells either mock-infected (control) or infected with SARS-CoV, (MOI 0.1), were collected after 24 hours of treatment (control-3, infected-3) and subjected to microarray as described in GSE17400.H3N2 (Calu-3) – Calu-3 cells either uninfected (control) or infected with H3N2, were collected after 24 hours of treatment (control-2, infected-3) and subjected to microarray as described in GSE19580.SARS-Cov-2 (A549)-A549 cells either mock-infected (control) or infected with SARS-CoV-2 (strain USA-WA1/2020), (MOI 0.2), were collected after 24 hours of treatment (control-3, infected-3) and subjected to RNA-seq as described in GSE147507.

The data sets used for the integrated analysis: SARS-Cov-2 (Calu-3); SARS-Cov-2 (A549), as described in previous section; Covid patient BALF- RNA-seq was performed on peripheral blood mononuclear cells (PBMCs) from 3 Covid-2019 patients and bronchoalveolar lavage fluid (BALF) from 2 of the Covid-2019 patients as described in GSA id PRJCA002326.Covid-19 lung (Autopsy)- RNA-seq was performed on a total of 15 lung sections from 5 Covid-2019 patients and 5 lung sections used as negative control as described in GSE150316. Diet induced obesity and diabetes (DIOD) rodent lung 1- RNA-seq was performed on lung tissue obtained from 3 C57BL/6J mice fed with 60% High Fat Diet (obese mice) as well as 3 mice fed with 10% Low Fat Diet (lean control) as described in GSE123938. Diet induced obesity and diabetes (DIOD) rodent lung 2- RNA-seq was performed on lung tissue obtained from 4 C57BL/6 mice fed with 40% High Fat Diet (obese mice) as well as 4 mice fed with 12% Low Fat Diet (lean control) as described in GSE3963412.

### RNA-seq data analysis

For the RNA-seq datasets (GSE147507, GSE123938, GSE3963412), count data was uploaded in online MeV

software and normalised using the DESeq tool, while for GSE150316, DESeq normalised data was already available. Differential expression of genes between control and target groups was analysed using the Limma pipeline. The output provided by the Limma contained a list of statistically differentially expressed genes ( $p<=0.05$ ). This list of genes was uploaded in the online Network Analyst software and the output containing the list of significantly enriched pathways ( $p<=0.05$ ) was downloaded (the list of pathways for each dataset is given below), along with the list of genes implicated in each pathway. Furthermore, for each of the enriched pathways we carefully looked into the expression patterns of each member genes and based upon the directionality of the key enzymes, regulatory proteins, neighbouring genes and published studies, the upregulation/downregulation of the respective pathway was deciphered.

For the GSA id PRJCA002326 dataset, since only raw read data was available, Thefastq reads were mapped to hg38 using STAR (v2.27.2b) to create the sample-wise bam files. The bam files were then processed using Rsamtools, Rsubread and Genomic Alignments R packages to create the count table. The count data was subsequently analysed using the MeV software and NetworkAnalyst software as described above.

### Microarray data analysis

For the microarray datasets (GSE17400, GSE19580), the data was analysed using the online Geo2R tool (default options) to determine the differential expression of genes between control and the target set and the output file containing a list of differentially expressed genes was downloaded. Amongst these genes, only those whose regulation was significant (adj.  $p<=0.05$ ) were uploaded in the NetworkAnalyst software and downstream analysis was done in an identical manner to that in the RNA-seq data analysis.

### Author Contributions:

Concept and design: Ganguly, Paul, Raychaudhuri. Analysis of transcriptome data: Raychaudhuri, Lahiri, Paul. Drafting of the manuscript: Ganguly, Paul. Critical revision of the manuscript for important intellectual content: Raychaudhuri, Ray. Statistical analysis: Raychaudhuri, Lahiri, Paul.

Supervision: Ganguly, Paul.

### Conflict of Interest Disclosures:

None to be reported.

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### Figure legend

**Figure 1. Dysregulation in lung epithelial metabolic pathways in SARS-CoV2 infection. 1A)** Heatmap depicting the number of shared as well as exclusive significantly regulated genes, in the indicated cell lines in response to infection with indicated viruses. The diagonal of the heatmap represents the genes exclusively regulated only in the indicated datasets. (Detail about dataset is described in supplementary

**data). 1B,C)** Circos plots depicting the upregulated (**B**) and downregulated (**C**) enriched pathways that are exclusive to or shared among the indicated datasets. Datasets are the same as described in the legend of Fig 1A. **1D)** Table shows the abbreviations and their corresponding pathway designations.

**Figure 2. Shared enrichment of metabolic pathways between SARS-CoV2-infected and diabetic lung.** **2A)** Integrated analysis of the HLEC transcriptome in response to SARS-CoV2 infection as well as a COVID-19 bronchoalveolar lavage (BAL) and autopsied lung transcriptome along with lung transcriptome from two different datasets of preclinical rodent models of diet-induced obesity and diabetes (DIOD lung) was performed. **2B)** Heatmap depicting the upregulation (value 1) or downregulation (value -1) of selected pathways in the indicated datasets. The heatmap was generated using the CIMMINER software and unsupervised clustering using the correlation algorithm and average linkage cluster method.

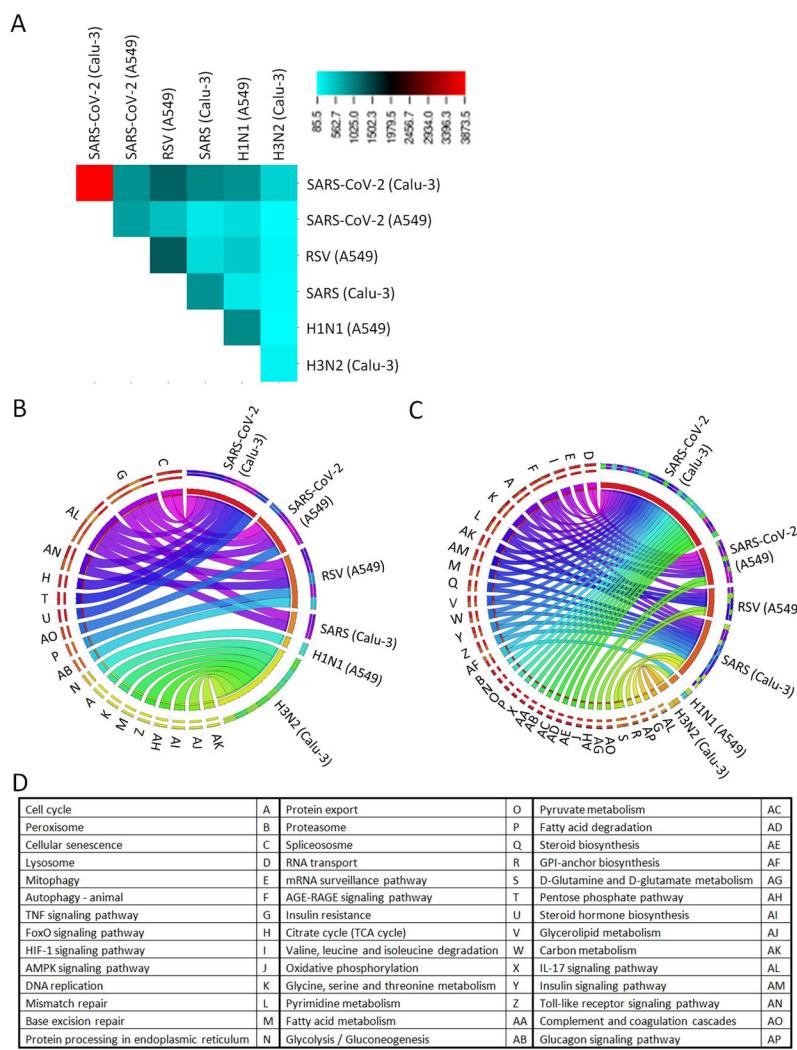


Figure 1

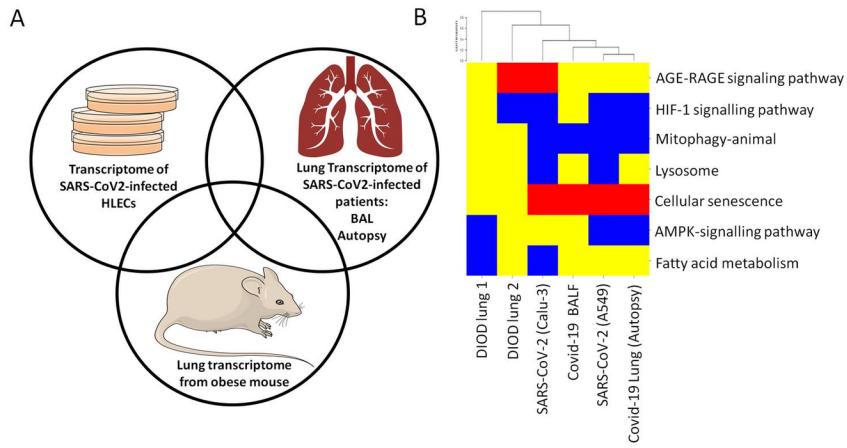


Figure 2

## Supplemental Information

### List of significantly enriched pathways

SARS-CoV-2 (Calu-3)- GSE147507

Pathway	Total	Expected	Expected	Hits	Hits
TNF signaling pathway	110	42.9	80	80	5.09E
Non-alcoholic fatty liver disease (NAFLD)	149	58.1	99	99	7.23E
Metabolic pathways	1430	558	670	670	1.40E
Herpes simplex infection	492	192	261	261	4.63E
Pancreatic cancer	75	29.2	57	57	6.33E
HTLV-I infection	219	85.4	130	130	5.07E
Hepatitis C	155	60.4	98	98	6.30E
Epstein-Barr virus infection	201	78.4	120	120	1.46E
Cell cycle	124	48.3	81	81	2.06E
Colorectal cancer	86	33.5	60	60	6.08E
DNA replication	36	14	31	31	6.79E
Hepatitis B	163	63.5	98	98	2.87E
Apoptosis	136	53	84	84	5.10E
Chronic myeloid leukemia	76	29.6	52	52	1.73E
Influenza A	167	65.1	96	96	7.79E
Huntington's disease	193	75.2	108	108	1.00E
Small cell lung cancer	93	36.3	59	59	1.40E
Prostate cancer	97	37.8	61	61	1.44E
Parkinson's disease	142	55.4	83	83	1.72E
AGE-RAGE signaling pathway in diabetic complications	100	39	62	62	2.38E
Endometrial cancer	58	22.6	40	40	3.38E
Non-small cell lung cancer	66	25.7	44	44	4.53E
Kaposi's sarcoma-associated herpesvirus infection	186	72.5	102	102	6.78E
Measles	138	53.8	79	79	9.06E

Pathway	Total	Expected	Expected	Hits	Hits
Platinum drug resistance	73	28.5	47	47	9.16E
Alzheimer's disease	171	66.7	94	94	1.35E
Endocrine resistance	98	38.2	59	59	1.55E
Pathways in cancer	530	207	252	252	2.01E
Glioma	75	29.2	47	47	2.62E
Valine, leucine and isoleucine degradation	48	18.7	33	33	2.71E
Tuberculosis	179	69.8	96	96	4.15E
Ubiquitin mediated proteolysis	137	53.4	76	76	5.89E
Oxidative phosphorylation	133	51.8	74	74	6.44E
Base excision repair	33	12.9	24	24	8.52E
Endocytosis	244	95.1	124	124	9.11E
Autophagy - animal	128	49.9	71	71	0.000
p53 signaling pathway	72	28.1	44	44	0.000
Glyoxylate and dicarboxylate metabolism	30	11.7	22	22	0.000
Mismatch repair	23	8.97	18	18	0.000
EGFR tyrosine kinase inhibitor resistance	79	30.8	47	47	0.000
Neurotrophin signaling pathway	119	46.4	66	66	0.000
Legionellosis	55	21.4	35	35	0.000
B cell receptor signaling pathway	71	27.7	43	43	0.000
FoxOsignaling pathway	132	51.5	72	72	0.000
NOD-like receptor signaling pathway	178	69.4	93	93	0.000
Fluid shear stress and atherosclerosis	139	54.2	75	75	0.0002
Chagas disease (American trypanosomiasis)	103	40.2	58	58	0.0002
Progesterone-mediated oocyte maturation	99	38.6	56	56	0.0002
IL-17 signaling pathway	93	36.3	53	53	0.0003
ErbBsignaling pathway	85	33.1	49	49	0.0003
Protein processing in endoplasmic reticulum	165	64.3	86	86	0.0003
HIF-1 signaling pathway	100	39	56	56	0.0003
Mitophagy - animal	65	25.3	39	39	0.0004
Central carbon metabolism in cancer	65	25.3	39	39	0.0004
Carbon metabolism	116	45.2	63	63	0.0004
Pertussis	76	29.6	44	44	0.0004
Prolactin signaling pathway	70	27.3	41	41	0.0004
Osteoclast differentiation	128	49.9	68	68	0.0004
Toxoplasmosis	113	44	61	61	0.0004
mTORsignaling pathway	153	59.6	79	79	0.0005
Nucleotide excision repair	47	18.3	29	29	0.0013
Proteasome	45	17.5	28	28	0.0013
Melanoma	72	28.1	41	41	0.0014
NF-kappa B signaling pathway	100	39	54	54	0.0015
Epithelial cell signaling in Helicobacter pylori infection	68	26.5	39	39	0.0015
Acute myeloid leukemia	66	25.7	38	38	0.0016
Viral carcinogenesis	201	78.4	99	99	0.0017
Breast cancer	147	57.3	75	75	0.0018
Citrate cycle (TCA cycle)	30	11.7	20	20	0.0019
Vibrio cholerae infection	50	19.5	30	30	0.0020
Lysosome	123	47.9	64	64	0.0020
Notch signaling pathway	48	18.7	29	29	0.0020
Hippo signaling pathway	154	60	77	77	0.0032
Tight junction	170	66.3	84	84	0.0032

Pathway	Total	Expected	Expected	Hits	Hits
Bladder cancer	41	16	25	25	0.0038
Apoptosis - multiple species	33	12.9	21	21	0.0038
Thyroid cancer	37	14.4	23	23	0.0038
Longevity regulating pathway - multiple species	62	24.2	35	35	0.0038
Biosynthesis of amino acids	75	29.2	41	41	0.0040
Renal cell carcinoma	69	26.9	38	38	0.0040
Toll-like receptor signaling pathway	104	40.5	54	54	0.0040
Glycosaminoglycan biosynthesis - chondroitin sulfate / dermatan sulfate	20	7.8	14	14	0.0040
Estrogen signaling pathway	138	53.8	69	69	0.0051
Terpenoid backbone biosynthesis	22	8.58	15	15	0.0052
Glycine, serine and threonine metabolism	40	15.6	24	24	0.0052
Spliceosome	134	52.2	67	67	0.0052
Oocyte meiosis	125	48.7	63	63	0.0053
VEGF signaling pathway	59	23	33	33	0.0053
Adherens junction	72	28.1	39	39	0.0061
Pyrimidine metabolism	57	22.2	32	32	0.0062
Proteoglycans in cancer	201	78.4	96	96	0.0063
Pathogenic Escherichia coli infection	55	21.4	31	31	0.0063
MAPK signaling pathway	295	115	136	136	0.0066
Fatty acid metabolism	53	20.7	30	30	0.0068
Fc gamma R-mediated phagocytosis	91	35.5	47	47	0.0091
N-Glycan biosynthesis	50	19.5	28	28	0.0107
Cellular senescence	160	62.4	77	77	0.0109
Fatty acid degradation	44	17.2	25	25	0.0122
Glycolysis / Gluconeogenesis	68	26.5	36	36	0.0132
Fc epsilon RI signaling pathway	68	26.5	36	36	0.0132
Alanine, aspartate and glutamate metabolism	36	14	21	21	0.0144
Signaling pathways regulating pluripotency of stem cells	139	54.2	67	67	0.0161
2-Oxocarboxylic acid metabolism	18	7.02	12	12	0.0163
One carbon pool by folate	20	7.8	13	13	0.0163
Pyruvate metabolism	39	15.2	22	22	0.0202
Amino sugar and nucleotide sugar metabolism	48	18.7	26	26	0.0231
Antifolate resistance	31	12.1	18	18	0.0243
GnRH signaling pathway	93	36.3	46	46	0.0249
Wnt signaling pathway	158	61.6	74	74	0.0250
Insulin signaling pathway	137	53.4	65	65	0.0250
Regulation of lipolysis in adipocytes	55	21.4	29	29	0.0262
Glycosylphosphatidylinositol (GPI)-anchor biosynthesis	25	9.75	15	15	0.0263
Tryptophan metabolism	42	16.4	23	23	0.0271
Protein export	23	8.97	14	14	0.0275
Longevity regulating pathway	89	34.7	44	44	0.0281
Steroid biosynthesis	19	7.41	12	12	0.0284
Sphingolipid signaling pathway	119	46.4	57	57	0.0284
Insulin resistance	108	42.1	52	52	0.0319
Peroxisome	83	32.4	41	41	0.0337
Inositol phosphate metabolism	74	28.8	37	37	0.0349

SARS-CoV-2 (A549)- GSE147507

Pathway	Total	Expected	Hits	P.Value	FDR
NOD-like receptor signaling pathway	178	16.9	33	0.000121	0.0318
Pertussis	76	7.21	18	2.00E-04	0.0318
Autophagy - animal	128	12.1	24	0.000836	0.0886
Leishmaniasis	74	7.02	16	0.00129	0.102
IL-17 signaling pathway	93	8.82	18	0.0025	0.134
Lysosome	123	11.7	22	0.00253	0.134
Amoebiasis	96	9.11	18	0.00358	0.163
Calcium signaling pathway	188	17.8	29	0.00573	0.228
TNF signaling pathway	110	10.4	19	0.00711	0.243
Influenza A	167	15.8	26	0.00764	0.243
Complement and coagulation cascades	79	7.49	14	0.0156	0.427
Phagosome	152	14.4	23	0.0161	0.427
Pentose phosphate pathway	30	2.85	7	0.0197	0.481
PI3K-Akt signaling pathway	354	33.6	45	0.0247	0.505
Staphylococcus aureus infection	68	6.45	12	0.0248	0.505
HIF-1 signaling pathway	100	9.49	16	0.0254	0.505
Apoptosis	136	12.9	20	0.0313	0.538
Legionellosis	55	5.22	10	0.0321	0.538
AMPK signaling pathway	120	11.4	18	0.0334	0.538
EGFR tyrosine kinase inhibitor resistance	79	7.49	13	0.0338	0.538
Measles	138	13.1	20	0.0358	0.539
Epstein-Barr virus infection	201	19.1	27	0.0398	0.539
Mitophagy - animal	65	6.17	11	0.0406	0.539
Endocrine resistance	98	9.3	15	0.0422	0.539
Cell cycle	124	11.8	18	0.0442	0.539
Cellular senescence	160	15.2	22	0.0478	0.539
DNA replication	36	3.42	7	0.0493	0.539

## RSV (A549)- GSE147507

Pathway	Total	Expected	Expected	Hits	P.Value	FDR
Influenza A	167	23	46	46	1.78E-06	0.000565
Epstein-Barr virus infection	201	27.7	50	50	1.51E-05	0.00229
Legionellosis	55	7.58	20	20	2.16E-05	0.00229
Kaposi's sarcoma-associated herpesvirus infection	186	25.7	46	46	3.85E-05	0.00279
Hepatitis C	155	21.4	40	40	4.38E-05	0.00279
Small cell lung cancer	93	12.8	27	27	9.07E-05	0.00481
Bladder cancer	41	5.65	15	15	0.000212	0.00877
Platinum drug resistance	73	10.1	22	22	0.000221	0.00877
Complement and coagulation cascades	79	10.9	23	23	0.000282	0.00996
TNF signaling pathway	110	15.2	29	29	0.000324	0.0103
Measles	138	19	34	34	0.000413	0.011
Chronic myeloid leukemia	76	10.5	22	22	0.000415	0.011
Chemokine signaling pathway	190	26.2	43	43	0.000556	0.0136
Pathways in cancer	530	73.1	99	99	0.000689	0.0156
Glioma	75	10.3	21	21	0.000902	0.0191
Apoptosis - multiple species	33	4.55	12	12	0.000964	0.0192
Non-small cell lung cancer	66	9.1	19	19	0.00108	0.0203
Apoptosis	136	18.8	32	32	0.00139	0.0245

Pathway	Total	Expected	Expected	Hits	P.Value	FDR
Rheumatoid arthritis	91	12.5	23	23	0.00237	0.0397
Type II diabetes mellitus	46	6.34	14	14	0.0027	0.041
Focal adhesion	199	27.4	42	42	0.00271	0.041
Melanoma	72	9.93	19	19	0.00328	0.0474
EGFR tyrosine kinase inhibitor resistance	79	10.9	20	20	0.00435	0.0601
ErbBsignaling pathway	85	11.7	21	21	0.0048	0.0636
Glyoxylate and dicarboxylate metabolism	30	4.14	10	10	0.00523	0.0659
Colorectal cancer	86	11.9	21	21	0.00555	0.0659
Prion diseases	35	4.83	11	11	0.00574	0.0659
Central carbon metabolism in cancer	65	8.96	17	17	0.0058	0.0659
p53 signaling pathway	72	9.93	18	18	0.00762	0.0835
Hepatitis B	163	22.5	34	34	0.00789	0.0837
Mismatch repair	23	3.17	8	8	0.00918	0.0941
Insulin signaling pathway	137	18.9	29	29	0.011	0.109
Viral myocarditis	59	8.14	15	15	0.0121	0.117
Prolactin signaling pathway	70	9.65	17	17	0.0126	0.117
IL-17 signaling pathway	93	12.8	21	21	0.0139	0.124
Carbon metabolism	116	16	25	25	0.014	0.124
Osteoclast differentiation	128	17.7	27	27	0.0145	0.124
Endocytosis	244	33.6	46	46	0.0153	0.128
Proteasome	45	6.21	12	12	0.0162	0.132
Glutathione metabolism	56	7.72	14	14	0.0174	0.136
NOD-like receptor signaling pathway	178	24.5	35	35	0.0175	0.136
Glycolysis / Gluconeogenesis	68	9.38	16	16	0.0204	0.154
D-Glutamine and D-glutamate metabolism	5	0.69	3	3	0.0211	0.156
Renal cell carcinoma	69	9.52	16	16	0.0232	0.168
Endocrine resistance	98	13.5	21	21	0.0244	0.172
PI3K-Akt signaling pathway	354	48.8	62	62	0.0253	0.175
Pertussis	76	10.5	17	17	0.0275	0.186
B cell receptor signaling pathway	71	9.79	16	16	0.0299	0.198
Platelet activation	124	17.1	25	25	0.0305	0.198
Vasopressin-regulated water reabsorption	44	6.07	11	11	0.033	0.21
Amoebiasis	96	13.2	20	20	0.0363	0.226
Viral carcinogenesis	201	27.7	37	37	0.0381	0.226
Regulation of actin cytoskeleton	214	29.5	39	39	0.039	0.226
Fc gamma R-mediated phagocytosis	91	12.5	19	19	0.0398	0.226
Hematopoietic cell lineage	97	13.4	20	20	0.04	0.226
Ferroptosis	40	5.52	10	10	0.0411	0.226
Fc epsilon RI signaling pathway	68	9.38	15	15	0.0413	0.226
Staphylococcus aureus infection	68	9.38	15	15	0.0413	0.226
Autophagy - animal	128	17.7	25	25	0.043	0.232
Toll-like receptor signaling pathway	104	14.3	21	21	0.044	0.233
Pancreatic cancer	75	10.3	16	16	0.0472	0.242
Tuberculosis	179	24.7	33	33	0.0472	0.242

## SARS (Calu-3)- GSE17400

Pathway	Total	Expected	Expected	Hits	P.Value	FDR
Cell cycle	124	16.3	40	40	2.18E-08	6.92E-06

Pathway	Total	Expected	Expected	Hits	P.Value	FDR
Oocyte meiosis	125	16.4	36	36	2.41E-06	0.000383
DNA replication	36	4.72	15	15	1.97E-05	0.00209
One carbon pool by folate	20	2.62	10	10	7.61E-05	0.00605
Mismatch repair	23	3.01	9	9	0.00161	0.102
Amphetamine addiction	68	8.91	18	18	0.00228	0.12
Neurotrophin signaling pathway	119	15.6	27	27	0.00265	0.12
Biosynthesis of amino acids	75	9.83	19	19	0.00301	0.12
Progesterone-mediated oocyte maturation	99	13	23	23	0.00388	0.125
Spliceosome	134	17.6	29	29	0.00393	0.125
Long-term potentiation	67	8.78	17	17	0.00479	0.133
Melanogenesis	101	13.2	23	23	0.00505	0.133
Pyrimidine metabolism	57	7.47	15	15	0.00545	0.133
RNA transport	165	21.6	33	33	0.00786	0.179
Legionellosis	55	7.21	14	14	0.00971	0.205
Dopaminergic synapse	131	17.2	27	27	0.0103	0.205
Amoebiasis	96	12.6	21	21	0.0115	0.206
Citrate cycle (TCA cycle)	30	3.93	9	9	0.0121	0.206
mRNA surveillance pathway	91	11.9	20	20	0.0127	0.206
Glucagon signaling pathway	103	13.5	22	22	0.013	0.206
TNF signaling pathway	110	14.4	23	23	0.0144	0.206
Alanine, aspartate and glutamate metabolism	36	4.72	10	10	0.0147	0.206
Renin secretion	69	9.04	16	16	0.0149	0.206
Nucleotide excision repair	47	6.16	12	12	0.0157	0.208
HTLV-I infection	219	28.7	40	40	0.0171	0.218
Gap junction	88	11.5	19	19	0.0179	0.219
Signaling pathways regulating pluripotency of stem cells	139	18.2	27	27	0.0218	0.251
Base excision repair	33	4.32	9	9	0.0227	0.251
2-Oxocarboxylic acid metabolism	18	2.36	6	6	0.0229	0.251
Circadian entrainment	97	12.7	20	20	0.0248	0.263
IL-17 signaling pathway	93	12.2	19	19	0.0308	0.303
GnRH signaling pathway	93	12.2	19	19	0.0308	0.303
Ubiquitin mediated proteolysis	137	18	26	26	0.0315	0.303
Kaposi's sarcoma-associated herpesvirus infection	186	24.4	33	33	0.041	0.351
Autophagy - animal	128	16.8	24	24	0.0427	0.351
Osteoclast differentiation	128	16.8	24	24	0.0427	0.351
Valine, leucine and isoleucine degradation	48	6.29	11	11	0.0428	0.351
Fanconi anemia pathway	54	7.08	12	12	0.0437	0.351
p53 signaling pathway	72	9.44	15	15	0.044	0.351
Chagas disease (American trypanosomiasis)	103	13.5	20	20	0.0442	0.351
EGFR tyrosine kinase inhibitor resistance	79	10.4	16	16	0.0482	0.37
Cocaine addiction	49	6.42	11	11	0.0489	0.37

## H1N1 (A549)- GSE147507

Pathway	Total	Expected	Hits	P.Value	FDR
Protein processing in endoplasmic reticulum	165	17.2	33	0.000163	0.0518
Legionellosis	55	5.74	14	0.00118	0.188
TGF-beta signaling pathway	92	9.6	17	0.0133	1
Cytokine-cytokine receptor interaction	294	30.7	42	0.0208	1

Pathway	Total	Expected	Hits	P.Value	FDR
Protein digestion and absorption	90	9.39	16	0.0227	1
Amino sugar and nucleotide sugar metabolism	48	5.01	10	0.024	1
mRNA surveillance pathway	91	9.49	16	0.0249	1
Selenocompound metabolism	17	1.77	5	0.026	1
Glycosylphosphatidylinositol (GPI)-anchor biosynthesis	25	2.61	6	0.0397	1
Endocytosis	244	25.5	34	0.0475	1

### H3N2 (Calu-3)-GSE19580

Pathway	Total	Expected	Expected	Hits	P.Value	FDR
DNA replication	36	1.51	12	12	1.24E-08	3.96E-06
Cell cycle	124	5.21	20	20	1.83E-07	2.91E-05
Pentose phosphate pathway	30	1.26	9	9	2.39E-06	0.000253
Epstein-Barr virus infection	201	8.44	22	22	3.36E-05	0.00267
Pentose and glucuronate interconversions	34	1.43	8	8	6.20E-05	0.00394
Hepatitis C	155	6.51	17	17	0.000257	0.0121
Biosynthesis of amino acids	75	3.15	11	11	0.000267	0.0121
Fructose and mannose metabolism	33	1.39	7	7	0.000359	0.0143
Hepatitis B	163	6.85	17	17	0.000467	0.0153
IL-17 signaling pathway	93	3.91	12	12	0.00048	0.0153
Carbon metabolism	116	4.87	13	13	0.0011	0.0319
Salmonella infection	86	3.61	10	10	0.00309	0.0798
Necroptosis	162	6.8	15	15	0.00326	0.0798
Pathways in cancer	530	22.3	35	35	0.0048	0.106
Kaposi's sarcoma-associated herpesvirus infection	186	7.81	16	16	0.005	0.106
TNF signaling pathway	110	4.62	11	11	0.0063	0.125
NOD-like receptor signaling pathway	178	7.48	15	15	0.00779	0.146
Glutathione metabolism	56	2.35	7	7	0.00855	0.147
Galactose metabolism	31	1.3	5	5	0.00876	0.147
Viral carcinogenesis	201	8.44	16	16	0.0103	0.16
HTLV-I infection	219	9.2	17	17	0.0106	0.16
Tight junction	170	7.14	14	14	0.0121	0.175
Measles	138	5.8	12	12	0.0131	0.181
Drug metabolism - other enzymes	79	3.32	8	8	0.0174	0.23
Inflammatory bowel disease (IBD)	65	2.73	7	7	0.0186	0.237
Folate biosynthesis	26	1.09	4	4	0.022	0.269
Fanconi anemia pathway	54	2.27	6	6	0.0249	0.283
Ascorbate and aldarate metabolism	27	1.13	4	4	0.025	0.283
Legionellosis	55	2.31	6	6	0.0269	0.283
Bladder cancer	41	1.72	5	5	0.0275	0.283
Apoptosis	136	5.71	11	11	0.0276	0.283
Chemokine signaling pathway	190	7.98	14	14	0.0288	0.286
Pyrimidine metabolism	57	2.39	6	6	0.0315	0.303
Th17 cell differentiation	107	4.49	9	9	0.0355	0.332
Pancreatic cancer	75	3.15	7	7	0.0374	0.339
Steroid hormone biosynthesis	60	2.52	6	6	0.0392	0.339
Alcoholism	180	7.56	13	13	0.0395	0.339
Small cell lung cancer	93	3.91	8	8	0.0411	0.342
Glycerolipid metabolism	61	2.56	6	6	0.042	0.342

Pathway	Total	Expected	Expected	Hits	P.Value	FDR
Base excision repair	33	1.39	4	4	0.0479	0.381
One carbon pool by folate	20	0.84	3	3	0.0493	0.382

### Covid patient BALF- GSA id PRJCA002326

Pathway	Total	Expected	Expected	Hits	P.Value	FDR
Alzheimer's disease	171	71	104	104	2.10E-07	5.03E-01
Oxidative phosphorylation	133	55.2	84	84	3.16E-07	5.03E-01
Parkinson's disease	142	58.9	88	88	5.66E-07	6.00E-01
Chemokine signaling pathway	190	78.9	105	105	7.50E-05	0.00596
Malaria	49	20.3	33	33	0.000221	0.0141
Dopaminergic synapse	131	54.4	74	74	0.000346	0.0173
Phagosome	152	63.1	84	84	0.000381	0.0173
Spliceosome	134	55.6	75	75	0.000463	0.0184
Non-alcoholic fatty liver disease (NAFLD)	149	61.8	82	82	0.00053	0.0187
Chagas disease (American trypanosomiasis)	103	42.7	59	59	0.000832	0.0265
Notch signaling pathway	48	19.9	31	31	0.00102	0.0295
Protein processing in endoplasmic reticulum	165	68.5	88	88	0.00129	0.0316
Salmonella infection	86	35.7	50	50	0.00129	0.0316
Platelet activation	124	51.5	68	68	0.00173	0.0387
Pathogenic Escherichia coli infection	55	22.8	34	34	0.00182	0.0387
Huntington's disease	193	80.1	100	100	0.00218	0.0434
Pathways in cancer	530	220	251	251	0.00274	0.051
Osteoclast differentiation	128	53.1	69	69	0.00289	0.051
Fc gamma R-mediated phagocytosis	91	37.8	51	51	0.00343	0.0575
Complement and coagulation cascades	79	32.8	45	45	0.00383	0.0609
Oxytocin signaling pathway	153	63.5	80	80	0.00423	0.064
Th1 and Th2 cell differentiation	92	38.2	51	51	0.00464	0.0671
Epithelial cell signaling in Helicobacter pylori infection	68	28.2	39	39	0.00586	0.0773
Hematopoietic cell lineage	97	40.3	53	53	0.00587	0.0773
Leukocyte transendothelial migration	112	46.5	60	60	0.00627	0.0773
Tight junction	170	70.6	87	87	0.00632	0.0773
Apoptosis	136	56.4	71	71	0.00711	0.0838
FoxOsignaling pathway	132	54.8	69	69	0.0076	0.0863
Mitophagy - animal	65	27	37	37	0.00845	0.0882
Shigellosis	65	27	37	37	0.00845	0.0882
Prion diseases	35	14.5	22	22	0.00867	0.0882
Primary immunodeficiency	37	15.4	23	23	0.00888	0.0882
Epstein-Barr virus infection	201	83.4	100	100	0.0102	0.0932
Pertussis	76	31.5	42	42	0.0104	0.0932
Focal adhesion	199	82.6	99	99	0.0105	0.0932
Calcium signaling pathway	188	78	94	94	0.0106	0.0932
Amphetamine addiction	68	28.2	38	38	0.0114	0.098
Vibrio cholerae infection	50	20.8	29	29	0.0134	0.112
Regulation of actin cytoskeleton	214	88.8	105	105	0.0141	0.113
Retrograde endocannabinoid signaling	148	61.4	75	75	0.0143	0.113
HTLV-I infection	219	90.9	107	107	0.0153	0.119
Kaposi's sarcoma-associated herpesvirus infection	186	77.2	92	92	0.016	0.119
Carbon metabolism	116	48.1	60	60	0.016	0.119

Pathway	Total	Expected	Expected	Hits	P.Value	FDR
Endocytosis	244	101	118	118	0.0164	0.119
Phosphatidylinositol signaling system	99	41.1	52	52	0.0168	0.119
Legionellosis	55	22.8	31	31	0.0182	0.126
Chronic myeloid leukemia	76	31.5	41	41	0.0187	0.126
Proteasome	45	18.7	26	26	0.0199	0.132
Hippo signaling pathway -multiple species	29	12	18	18	0.0203	0.132
Proteoglycans in cancer	201	83.4	98	98	0.021	0.134
Ribosome	153	63.5	76	76	0.0239	0.149
Cellular senescence	160	66.4	79	79	0.0255	0.156
B cell receptor signaling pathway	71	29.5	38	38	0.0267	0.16
2-Oxocarboxylic acid metabolism	18	7.47	12	12	0.0276	0.161
Circadian entrainment	97	40.3	50	50	0.0283	0.161
Long-term potentiation	67	27.8	36	36	0.0285	0.161
ECM-receptor interaction	82	34	43	43	0.0289	0.161
Basal cell carcinoma	63	26.1	34	34	0.0303	0.166
Autophagy - animal	128	53.1	64	64	0.0309	0.166
Apelin signaling pathway	137	56.9	68	68	0.0319	0.169
Cell adhesion molecules (CAMs)	146	60.6	72	72	0.0328	0.171
Adherens junction	72	29.9	38	38	0.0344	0.173
Arrhythmogenic right ventricular cardiomyopathy (ARVC)	72	29.9	38	38	0.0344	0.173
Natural killer cell mediated cytotoxicity	131	54.4	65	65	0.0356	0.177
Non-small cell lung cancer	66	27.4	35	35	0.0381	0.186
Glucagon signaling pathway	103	42.7	52	52	0.0398	0.188
Oocyte meiosis	125	51.9	62	62	0.0398	0.188
Cytokine-cytokine receptor interaction	294	122	137	137	0.0407	0.188
Hippo signaling pathway	154	63.9	75	75	0.0408	0.188
Endometrial cancer	58	24.1	31	31	0.0436	0.198
Fructose and mannose metabolism	33	13.7	19	19	0.0455	0.204
cGMP-PKG signaling pathway	166	68.9	80	80	0.0462	0.204
IL-17 signaling pathway	93	38.6	47	47	0.0479	0.209
Rheumatoid arthritis	91	37.8	46	46	0.0497	0.214

### Covid-19 Lung (Autopsy)- GSE150316

Pathway	Total	Expectd	Hits	P.Value	FDR
Cellular senescence	160	11.8	33	4.00E-08	1.27E-05
HTLV-I infection	219	16.1	38	4.51E-07	6.97E-05
FoxO signaling pathway	132	9.71	27	8.29E-07	6.97E-05
TNF signaling pathway	110	8.09	24	1.00E-06	6.97E-05
Chagas disease (American trypanosomiasis)	103	7.57	23	1.10E-06	6.97E-05
Kaposi's sarcoma-associated herpesvirus infection	186	13.7	33	1.57E-06	8.32E-05
Pathways in cancer	530	39	67	5.56E-06	0.000253
Renal cell carcinoma	69	5.07	17	6.86E-06	0.000273
Colorectal cancer	86	6.32	18	4.10E-05	0.00138
Complement and coagulation cascades	79	5.81	17	4.60E-05	0.00138
p53 signaling pathway	72	5.3	16	5.06E-05	0.00138
Apelin signaling pathway	137	10.1	24	5.19E-05	0.00138
Insulin resistance	108	7.94	20	9.79E-05	0.00239
MAPK signaling pathway	295	21.7	40	0.000105	0.00239

Pathway	Total	Expectd	Hits	P.Value	FDR
mTOR signaling pathway	153	11.3	25	0.000118	0.00239
IL-17 signaling pathway	93	6.84	18	0.00012	0.00239
Hepatitis B	163	12	26	0.000131	0.00245
cAMP signaling pathway	212	15.6	31	0.000161	0.00285
cGMP-PKG signaling pathway	166	12.2	26	0.000177	0.00297
Circadian rhythm	31	2.28	9	0.000274	0.00436
Oxytocin signaling pathway	153	11.3	24	0.000305	0.00451
AGE-RAGE signaling pathway in diabetic complications	100	7.35	18	0.000312	0.00451
Proteoglycans in cancer	201	14.8	29	0.000329	0.00455
Chronic myeloid leukemia	76	5.59	15	0.00035	0.00464
Sphingolipid signaling pathway	119	8.75	20	0.000382	0.00485
Breast cancer	147	10.8	23	0.00042	0.00514
B cell receptor signaling pathway	71	5.22	14	0.000553	0.00651
Prostate cancer	97	7.13	17	0.000627	0.00691
Melanoma	72	5.3	14	0.000641	0.00691
Platelet activation	124	9.12	20	0.000661	0.00691
Longevity regulating pathway	89	6.55	16	0.000673	0.00691
Mitophagy - animal	65	4.78	13	0.00075	0.00746
Ras signaling pathway	232	17.1	31	8.00E-04	0.00771
Rheumatoid arthritis	91	6.69	16	0.000866	0.008
Apoptosis	136	10	21	0.000881	0.008
Pancreatic cancer	75	5.52	14	0.00098	0.00842
Glioma	75	5.52	14	0.00098	0.00842
Neurotrophin signaling pathway	119	8.75	19	0.00101	0.00848
Small cell lung cancer	93	6.84	16	0.0011	0.00892
Pertussis	76	5.59	14	0.00112	0.00892
Epithelial cell signaling in Helicobacter pylori infection	68	5	13	0.00117	0.00907
Legionellosis	55	4.04	11	0.00188	0.014
Th17 cell differentiation	107	7.87	17	0.00194	0.014
Regulation of actin cytoskeleton	214	15.7	28	0.00194	0.014
Phosphatidylinositol signaling system	99	7.28	16	0.00217	0.015
Choline metabolism in cancer	99	7.28	16	0.00217	0.015
Rap1 signaling pathway	206	15.1	27	0.00226	0.0153
Insulin signaling pathway	137	10.1	20	0.00232	0.0154
Non-small cell lung cancer	66	4.85	12	0.00279	0.018
Focal adhesion	199	14.6	26	0.00283	0.018
Endometrial cancer	58	4.27	11	0.00293	0.0183
Chemokine signaling pathway	190	14	25	0.00308	0.0188
Prion diseases	35	2.57	8	0.00324	0.0195
ErbB signaling pathway	85	6.25	14	0.00336	0.0198
Salmonella infection	86	6.32	14	0.00376	0.0217
Adipocytokine signaling pathway	69	5.07	12	0.00408	0.023
Amoebiasis	96	7.06	15	0.00412	0.023
EGFR tyrosine kinase inhibitor resistance	79	5.81	13	0.00468	0.0256
Cytokine-cytokine receptor interaction	294	21.6	34	0.00532	0.0287
Wnt signaling pathway	158	11.6	21	0.00569	0.0297
Measles	138	10.1	19	0.00569	0.0297
HIF-1 signaling pathway	100	7.35	15	0.00607	0.0306
Inflammatory mediator regulation of TRP channels	100	7.35	15	0.00607	0.0306
Fluid shear stress and atherosclerosis	139	10.2	19	0.00615	0.0306

Pathway	Total	Expectd	Hits	P.Value	FDR
PI3K-Akt signaling pathway	354	26	39	0.00673	0.0329
Cholinergic synapse	112	8.24	16	0.00754	0.0362
GnRH signaling pathway	93	6.84	14	0.00764	0.0362
Vascular smooth muscle contraction	132	9.71	18	0.00774	0.0362
Glucagon signaling pathway	103	7.57	15	0.00799	0.0368
Malaria	49	3.6	9	0.00853	0.0387
Fc epsilon RI signaling pathway	68	5	11	0.0101	0.0448
Amphetamine addiction	68	5	11	0.0101	0.0448
Pantothenate and CoA biosynthesis	19	1.4	5	0.0103	0.045
Aldosterone synthesis and secretion	98	7.21	14	0.012	0.0505
Estrogen signaling pathway	138	10.1	18	0.0121	0.0505
Autophagy - animal	128	9.41	17	0.0122	0.0505
Osteoclast differentiation	128	9.41	17	0.0122	0.0505
Prolactin signaling pathway	70	5.15	11	0.0125	0.0511
Signaling pathways regulating pluripotency of stem cells	139	10.2	18	0.013	0.0522
Axon guidance	181	13.3	22	0.0132	0.0524
Longevity regulating pathway - multiple species	62	4.56	10	0.0142	0.0554
AMPK signaling pathway	120	8.83	16	0.0143	0.0554
T cell receptor signaling pathway	101	7.43	14	0.0154	0.0584
Melanogenesis	101	7.43	14	0.0154	0.0584
Thyroid cancer	37	2.72	7	0.0166	0.0623
Transcriptional misregulation in cancer	186	13.7	22	0.0177	0.0654
Leishmaniasis	74	5.44	11	0.0186	0.068
Adrenergic signaling in cardiomyocytes	145	10.7	18	0.0194	0.0694
Central carbon metabolism in cancer	65	4.78	10	0.0194	0.0694
Epstein-Barr virus infection	201	14.8	23	0.0222	0.0783
Phospholipase D signaling pathway	148	10.9	18	0.0234	0.0817
Hematopoietic cell lineage	97	7.13	13	0.0247	0.0855
Gap junction	88	6.47	12	0.0268	0.0917
Bladder cancer	41	3.02	7	0.0282	0.0955
Progesterone-mediated oocyte maturation	99	7.28	13	0.0287	0.0962
Dopaminergic synapse	131	9.63	16	0.0303	0.1
NF-kappa B signaling pathway	100	7.35	13	0.0309	0.101
Hippo signaling pathway	154	11.3	18	0.0332	0.108
Leukocyte transendothelial migration	112	8.24	14	0.0346	0.111
Fatty acid biosynthesis	18	1.32	4	0.0387	0.123
Platinum drug resistance	73	5.37	10	0.04	0.126
Toll-like receptor signaling pathway	104	7.65	13	0.0408	0.127
Thyroid hormone signaling pathway	116	8.53	14	0.0447	0.138
Non-alcoholic fatty liver disease (NAFLD)	149	11	17	0.046	0.14
Hypertrophic cardiomyopathy (HCM)	85	6.25	11	0.0461	0.14
Shigellosis	65	4.78	9	0.0471	0.141

## DIOD rodent lung 1- GSE123938

Pathway	Total	Expected	Hits	P.Value	FDR
Primary immunodeficiency	36	1.77	12	7.12E-08	2.24E-05
Hematopoietic cell lineage	95	4.66	15	5.34E-05	0.00838
Tryptophan metabolism	48	2.36	9	0.00046	0.0482

<b>Pathway</b>	<b>Total</b>	<b>Expected</b>	<b>Hits</b>	<b>P.Value</b>	<b>FDR</b>
Cytokine-cytokine receptor interaction	296	14.5	28	0.000622	0.0488
Morphine addiction	92	4.51	12	0.00171	0.107
Jak-STAT signaling pathway	165	8.1	17	0.00296	0.139
AMPK signaling pathway	126	6.18	14	0.00341	0.139
cAMPsignaling pathway	211	10.4	20	0.00354	0.139
Intestinal immune network for IgA production	43	2.11	7	0.00453	0.15
Wntsignaling pathway	160	7.85	16	0.0052	0.15
PI3K-Akt signaling pathway	358	17.6	29	0.00526	0.15
Rheumatoid arthritis	84	4.12	10	0.00777	0.203
Cholinergic synapse	113	5.54	12	0.00923	0.223
Th17 cell differentiation	102	5.01	11	0.0111	0.229
Aldosterone synthesis and secretion	102	5.01	11	0.0111	0.229
Neuroactive ligand-receptor interaction	348	17.1	27	0.012	0.229
GABAergic synapse	90	4.42	10	0.0124	0.229
Purine metabolism	136	6.67	13	0.0159	0.271
Amphetamine addiction	68	3.34	8	0.0176	0.271
HTLV-I infection	246	12.1	20	0.0181	0.271
Apelin signaling pathway	139	6.82	13	0.0188	0.271
Hedgehog signaling pathway	44	2.16	6	0.0196	0.271
Cell adhesion molecules (CAMs)	171	8.39	15	0.0207	0.271
Fatty acid metabolism	57	2.8	7	0.0207	0.271
Circadian entrainment	99	4.86	10	0.023	0.281
Calcium signaling pathway	189	9.27	16	0.0233	0.281
T cell receptor signaling pathway	101	4.96	10	0.026	0.295
Th1 and Th2 cell differentiation	87	4.27	9	0.0263	0.295
ABC transporters	48	2.36	6	0.0289	0.313
Dilated cardiomyopathy	90	4.42	9	0.0319	0.334
Dopaminergic synapse	135	6.62	12	0.0331	0.335
Focal adhesion	199	9.77	16	0.0353	0.346
Butanoate metabolism	27	1.32	4	0.041	0.379
Phototransduction	27	1.32	4	0.041	0.379
Selenocompound metabolism	17	0.834	3	0.0478	0.429

## DIOD rodent lung 2- GSE3963412

<b>Pathway</b>	<b>Total</b>	<b>Expected</b>	<b>Hits</b>	<b>P.Value</b>	<b>FDR</b>
Hematopoietic cell lineage	95	7.1	27	6.64E-10	1.46E-07
B cell receptor signaling pathway	72	5.38	23	9.83E-10	1.46E-07
Primary immunodeficiency	36	2.69	16	1.40E-09	1.46E-07
Protein processing in endoplasmic reticulum	163	12.2	30	3.07E-06	0.000241
T cell receptor signaling pathway	101	7.55	22	3.85E-06	0.000242
Calcium signaling pathway	189	14.1	30	6.11E-05	0.0032
NF-kappa B signaling pathway	109	8.14	20	0.000141	0.00607
Cell adhesion molecules (CAMs)	171	12.8	27	0.000155	0.00607
Epstein-Barr virus infection	230	17.2	33	2.00E-04	0.00696
Antigen processing and presentation	91	6.8	17	0.000351	0.011
Chemokine signaling pathway	200	14.9	29	0.000401	0.0114
AGE-RAGE signaling pathway in diabetic complications	101	7.55	18	0.000434	0.0114
Fc gamma R-mediated phagocytosis	87	6.5	16	0.000622	0.015

Pathway	Total	Expected	Hits	P.Value	FDR
Leukocyte transendothelial migration	115	8.59	19	0.000808	0.0181
Leishmaniasis	67	5.01	13	0.00118	0.0232
Jak-STAT signaling pathway	165	12.3	24	0.00118	0.0232
HIF-1 signaling pathway	105	7.85	17	0.00188	0.0347
EGFR tyrosine kinase inhibitor resistance	80	5.98	14	0.00219	0.0382
Toxoplasmosis	108	8.07	17	0.00256	0.0418
Natural killer cell mediated cytotoxicity	118	8.82	18	0.00277	0.0418
Non-small cell lung cancer	66	4.93	12	0.00319	0.0418
Legionellosis	58	4.33	11	0.00333	0.0418
Arginine and proline metabolism	50	3.74	10	0.00337	0.0418
ErbBsignaling pathway	84	6.28	14	0.00349	0.0418
Th17 cell differentiation	102	7.62	16	0.0035	0.0418
Focal adhesion	199	14.9	26	0.00355	0.0418
Pathways in cancer	535	40	57	0.00363	0.0418
Mucin type O-glycan biosynthesis	28	2.09	7	0.00372	0.0418
Intestinal immune network for IgA production	43	3.21	9	0.00387	0.0419
Cytokine-cytokine receptor interaction	296	22.1	35	0.00433	0.0453
Measles	144	10.8	20	0.00503	0.051
NOD-like receptor signaling pathway	206	15.4	26	0.00565	0.0539
Longevity regulating pathway - multiple species	62	4.63	11	0.00567	0.0539
GABAergic synapse	90	6.73	14	0.00658	0.0608
Pancreatic cancer	75	5.6	12	0.00917	0.0823
Glutamatergic synapse	114	8.52	16	0.0104	0.0899
Regulation of actin cytoskeleton	217	16.2	26	0.011	0.0899
Platinum drug resistance	77	5.75	12	0.0113	0.0899
Platelet activation	125	9.34	17	0.0114	0.0899
Prion diseases	34	2.54	7	0.0115	0.0899
Th1 and Th2 cell differentiation	87	6.5	13	0.012	0.0922
Rap1 signaling pathway	209	15.6	25	0.0127	0.0931
Glycosphingolipid biosynthesis - lacto and neolacto series	27	2.02	6	0.013	0.0931
Carbohydrate digestion and absorption	43	3.21	8	0.013	0.0931
Osteoclast differentiation	128	9.56	17	0.0142	0.0992
Axon guidance	180	13.5	22	0.0148	0.101
Protein digestion and absorption	90	6.73	13	0.0158	0.105
PI3K-Akt signaling pathway	358	26.8	38	0.017	0.111
MAPK signaling pathway	294	22	32	0.0196	0.126
Alanine, aspartate and glutamate metabolism	38	2.84	7	0.0208	0.13
Estrogensignaling pathway	134	10	17	0.0216	0.133
Sphingolipid metabolism	48	3.59	8	0.0245	0.148
Rassignaling pathway	233	17.4	26	0.0252	0.148
Amoebiasis	106	7.92	14	0.0257	0.148
Nicotine addiction	40	2.99	7	0.027	0.148
VEGF signaling pathway	58	4.33	9	0.027	0.148
Endometrial cancer	58	4.33	9	0.027	0.148
Glycosphingolipid biosynthesis - globo and isoglobo series	16	1.2	4	0.0273	0.148
Prostate cancer	97	7.25	13	0.0278	0.148
Renal cell carcinoma	68	5.08	10	0.0286	0.15
Inflammatory bowel disease (IBD)	59	4.41	9	0.0298	0.154
Fluid shear stress and atherosclerosis	143	10.7	17	0.0375	0.187
IL-17 signaling pathway	91	6.8	12	0.0376	0.187

Pathway	Total	Expected	Hits	P.Value	FDR
Small cell lung cancer	92	6.87	12	0.0404	0.196
Adherens junction	72	5.38	10	0.0405	0.196
Cholinergic synapse	113	8.44	14	0.0415	0.197
Chagas disease (American trypanosomiasis)	103	7.7	13	0.0426	0.198
Sphingolipid signaling pathway	124	9.27	15	0.0428	0.198
Thyroid hormone signaling pathway	115	8.59	14	0.047	0.213
Gastric acid secretion	74	5.53	10	0.0475	0.213
Phagosome	181	13.5	20	0.0497	0.22