Expanded View Figures

Figure EV1. Complementary clinical aspects and olfaction test in hamsters, infected or not by the SARS-CoV-2, with and without ivermectin treatment.

A Progression of body weight in male and female hamsters, mock-infected or SARS-CoV-2-infected, treated with saline or with 400 µg/kg ivermectin. Symbols indicate the median ± interquartile range.
B Curves represent the percentage of animals that did not find the hidden (buried) food.
C Curves represent the percentage of animals that did not find the visible (unburied) food.
D Summary of olfactory status.

Data information: Food finding assays were performed at 3 days post-infection. *n* = 6/group, except males CoV_saline and males CoV_ivermectin, where *n* = 12/group. The *P* value is indicated in bold when significant at a 0.05 threshold. Log-rank (Mantel–Cox) test (B, C) and Fisher's exact test (D). Data were obtained from three independent experiments for males and two independent experiments for females. The data for CoV_saline and CoV_ivermectin groups (B) are already presented in Fig 1B.
Source data are available online for this figure.

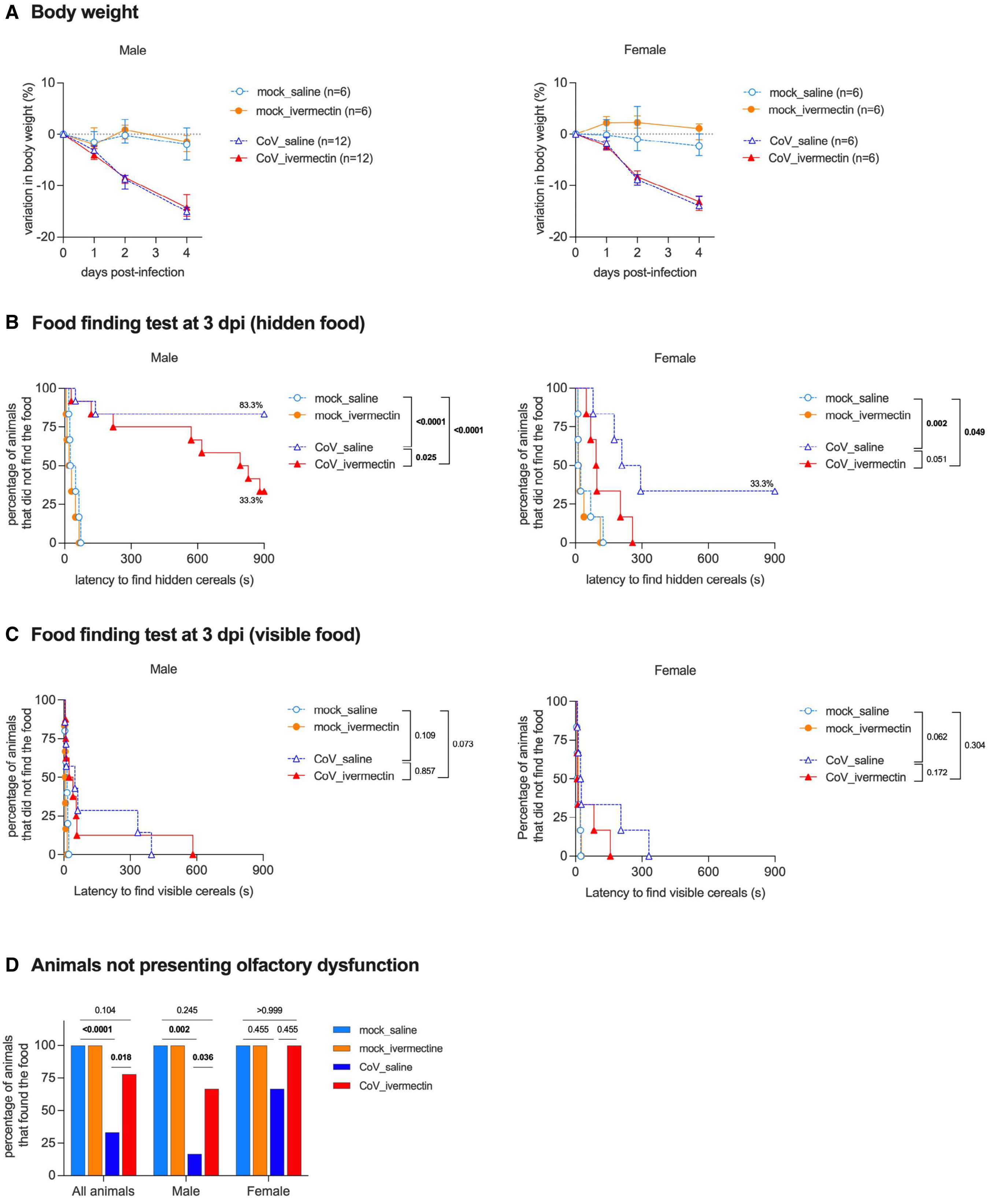

A Body weight
Male
Female
variation in body weight (%)
10
0
-10
-20
0 1 2 3 4
days post-infection
mock_saline (n=6)
mock_ivermectin (n=6)
CoV_saline (n=12)
CoV_ivermectin (n=12)
CoV_saline (n=6)
CoV_ivermectin (n=6)
B Food finding test at 3 dpi (hidden food)
percentage of animals that did not find the food
100
75
50
25
0
0 300 600 900
latency to find hidden cereals (s)
83.3%
33.3%
mock_saline
mock_ivermectin
CoV_saline
CoV_ivermectin
<0.0001
<0.0001
0.025
0.002
0.049
0.051
C Food finding test at 3 dpi (visible food)
Latency to find visible cereals (s)
Percentage of animals that did not find the food
0.109
0.073
0.857
0.062
0.304
0.172
D Animals not presenting olfactory dysfunction
percentage of animals that found the food
0.104
<0.0001
0.018
0.245
0.002
0.036
>0.999
0.455
0.455
All animals
Male
Female
mock_saline
mock_ivermectine
CoV_saline
CoV_ivermectin

Figure EV1.

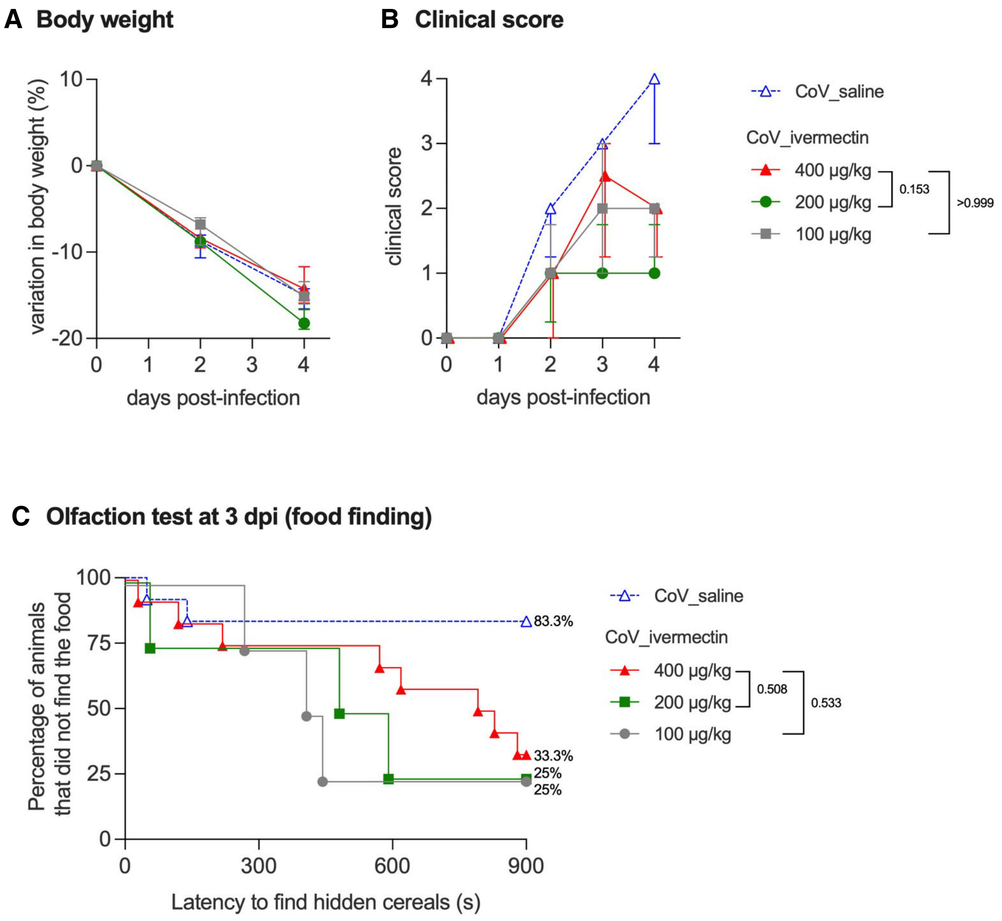


Figure EV2. Clinical aspects of SARS-CoV-2-infected male hamsters and treated with different doses of ivermectin.

A Progression of body weight in male hamsters, treated with saline or with 400, 200, or 100 µg/kg ivermectin. Symbols indicate the median ± interquartile range.

B Clinical score based on a cumulative 0–4 scale: ruffled fur; slow movements; apathy; and absence of exploration activity. Symbols indicate the median ± interquartile range.

C Olfaction deficit based on the buried food finding test. Curves represent the percentage of animals that did not find the buried food. Food finding assays were performed at 3 days post-infection.

Data information: *n* = 12/group (CoV_saline and CoV_ivermectin 400 µg/kg, as shown in Fig 1) or *n* = 4 (CoV_ivermectin 200 µg/kg and 100 µg/kg). The *P* value is indicated in bold when significant at a 0.05 threshold. Mann–Whitney test at 4 dpi (B) and log-rank (Mantel–Cox) test (C). The data for CoV_saline and CoV_ivermectin 400 µg/kg groups (B, C) are already presented in Fig 1B.
Source data are available online for this figure.

Figure EV3. Transcriptomic aspects in the lung of SARS-CoV-2-infected hamsters compared to mock-infected hamsters at 4 days post-infection.

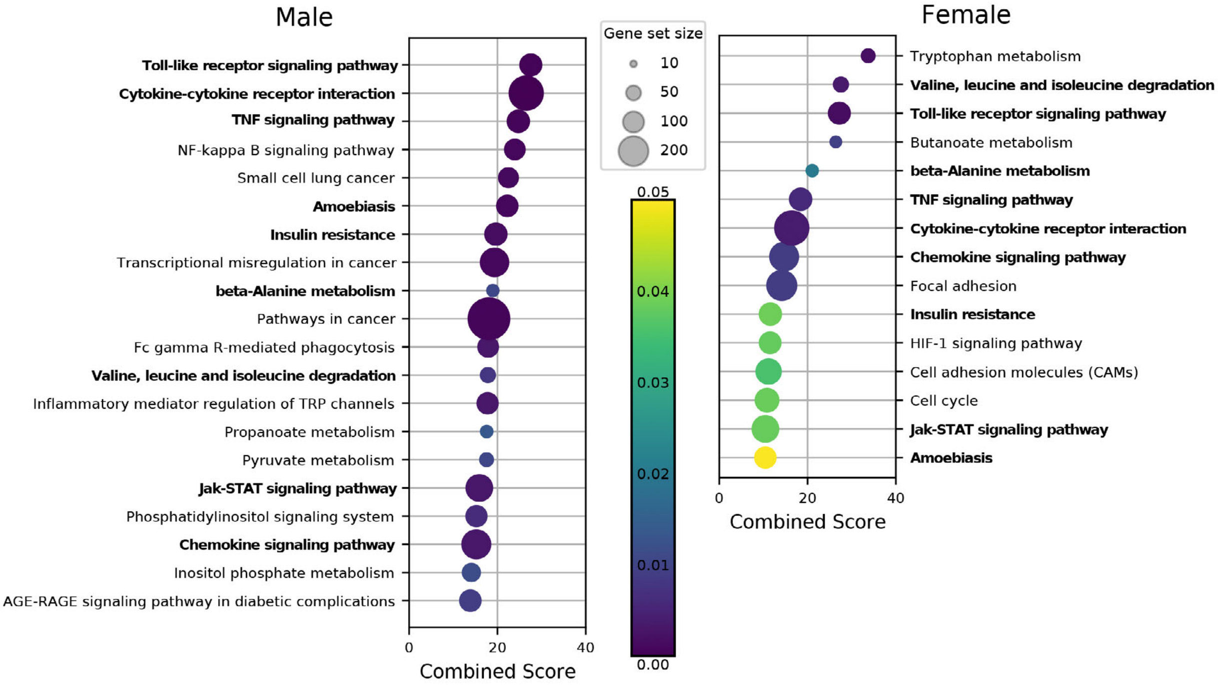
A KEGG enrichment.

B GO enrichment analysis.

Data information: Selected terms are based on the up- and downregulated genes between infected (CoV_saline) and mock-infected (mock_saline) samples. Only the 20 highest fold enrichments are plotted for the upregulated gene set. Circle sizes are proportional to the gene set size, which shows the total size of the gene set associated with GO terms. Circle color is proportional to the corrected *P*-values. Terms identified in both sexes are marked in bold. Complete analyses are listed in Dataset EV1.
Source data are available online for this figure.

▶

A **KEGG enrichment**



B **GO enrichment**

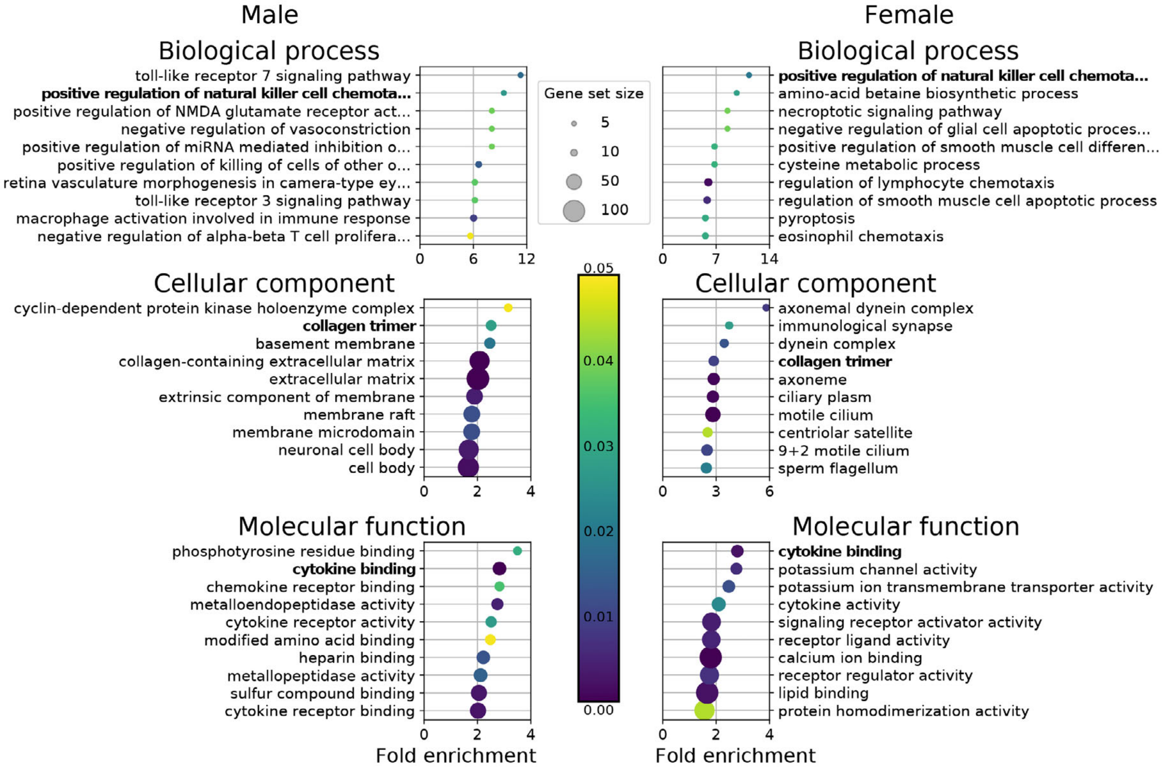


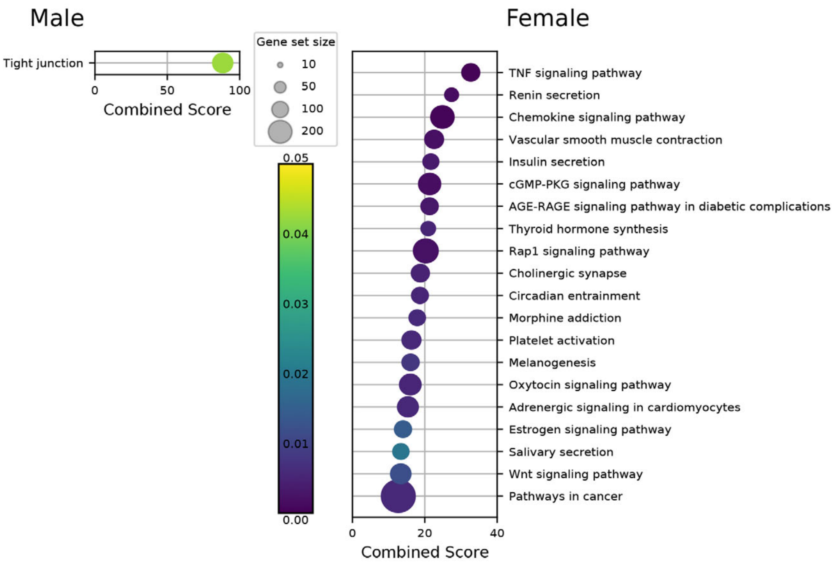
Figure EV3.

Figure EV4. Transcriptomic aspects in the lung of SARS-CoV-2-infected and ivermectin-treated hamsters compared to SARS-CoV-2-infected and saline-treated hamsters at 4 days post-infection.

A KEGG enrichment.
B GO enrichment analysis.

Data information: Selected terms are based on the up- and downregulated genes between IVM-treated (CoV_ivermectin) and saline-treated (CoV_saline) samples. Only the 20 highest fold enrichments are plotted for the upregulated gene set. Circle sizes are proportional to the gene set size, which shows the total size of the gene set associated with GO terms. Circle color is proportional to the corrected *P*-values. Complete analyses are listed in Dataset EV1.
Source data are available online for this figure.

A **KEGG enrichment**



B **GO enrichment**

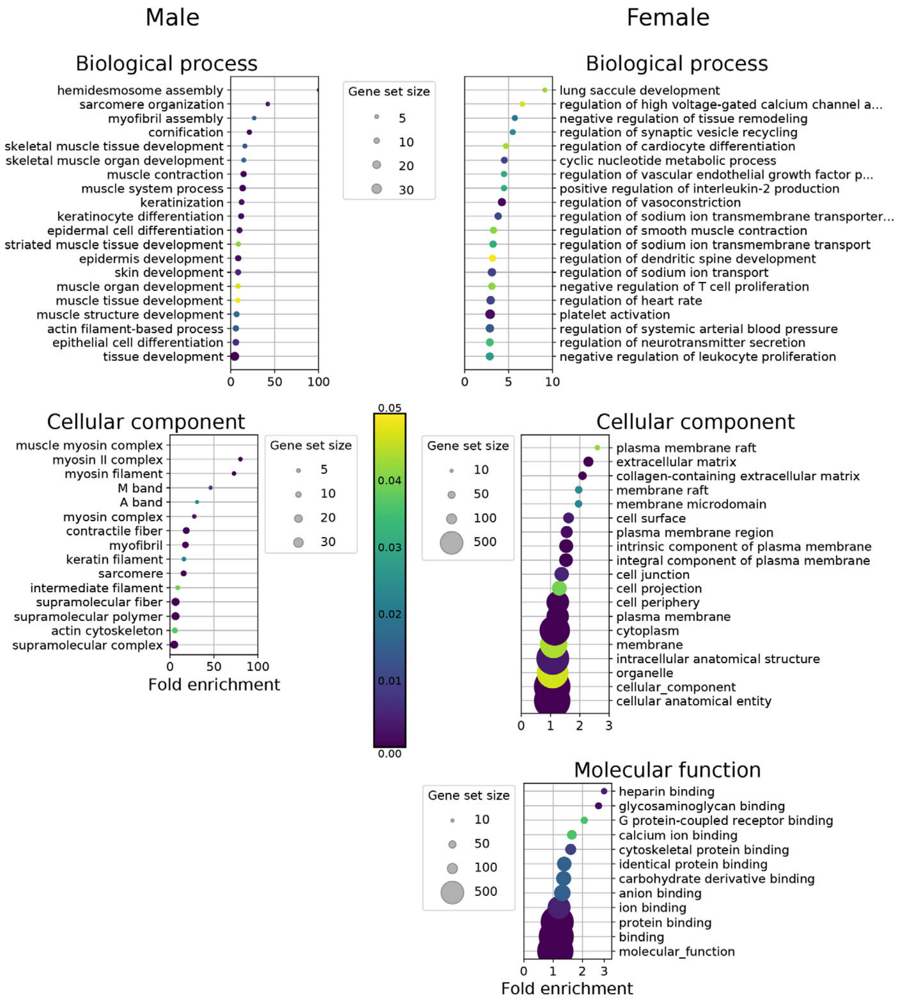


Figure EV4.

Figure EV5. Transcriptomic profile in the lung of SARS-CoV-2-infected hamsters with and without ivermectin treatment at 4 days post-infection.

A Heatmaps showing the differentially expressed genes according to the selected KEGG pathways, calculated in comparison with mock-infected hamsters. * indicates Benjamini–Hochberg-adjusted *P*-value<0.05 in the comparison between saline and ivermectin within the same sex. Color gradient represents the transcription $\log_2$ fold change comparing infected and mock-infected. Complete analyses are listed in Dataset EV1.

B Validation targets in the lung at 4 dpi. Horizontal lines indicate medians. The *P* value is indicated in bold when significant at a 0.05 threshold. Mann–Whitney test.

Data information: M: male hamsters and F: female hamsters. Data were obtained from two independent experiments for each sex.
Source data are available online for this figure.

▶

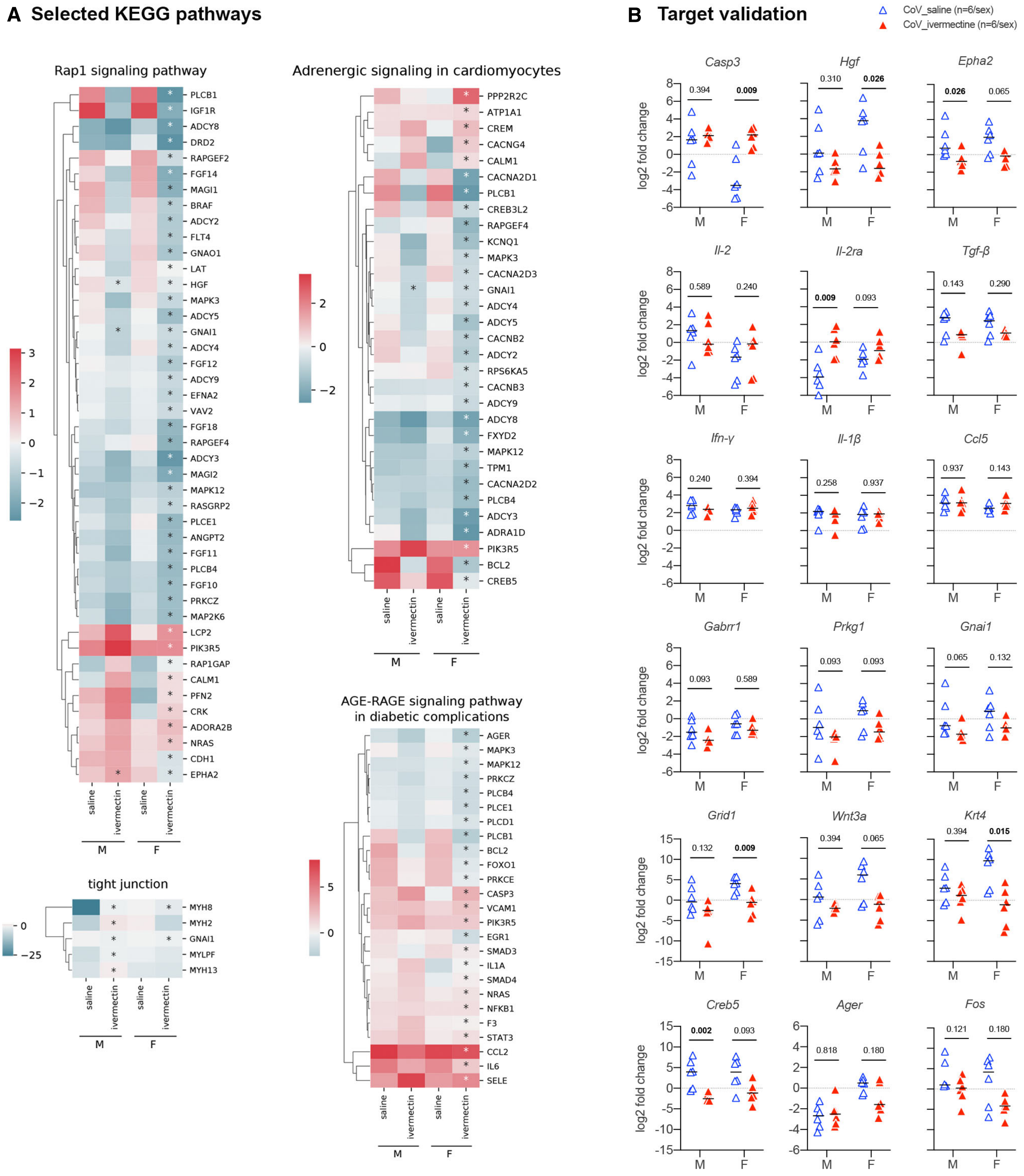

A Selected KEGG pathways
Rap1 signaling pathway
PLCB1
IGF1R
ADCY8
DRD2
RAPGEF2
FGF14
MAGI1
BRAF
ADCY2
FLT4
GNAO1
LAT
HGF
MAPK3
ADCY5
GNAI1
ADCY4
FGF12
ADCY9
EFNA2
VAV2
FGF18
RAPGEF4
ADCY3
MAGI2
MAPK12
RASGRP2
PLCE1
ANGPT2
FGF11
PLCB4
FGF10
PRKCZ
MAP2K6
LCP2
PIK3R5
RAP1GAP
CALM1
PFN2
CRK
ADORA2B
NRAS
CDH1
EPHA2
saline
ivermectin
saline
ivermectin
M
F
3
2
1
0
−1
−2
Adrenergic signaling in cardiomyocytes
PPP2R2C
ATP1A1
CREM
CACNG4
CALM1
CACNA2D1
PLCB1
CREB3L2
RAPGEF4
KCNQ1
MAPK3
CACNA2D3
GNAI1
ADCY4
ADCY5
CACNB2
ADCY2
RPS6KA5
CACNB3
ADCY9
ADCY8
FXYD2
MAPK12
TPM1
CACNA2D2
PLCB4
ADCY3
ADRA1D
PIK3R5
BCL2
CREB5
2
0
−2
saline
ivermectin
saline
ivermectin
M
F
tight junction
MYH8
MYH2
GNAI1
MYLPF
MYH13
0
−25
saline
ivermectin
saline
ivermectin
M
F
AGE-RAGE signaling pathway in diabetic complications
AGER
MAPK3
MAPK12
PRKCZ
PLCB4
PLCE1
PLCD1
PLCB1
BCL2
FOXO1
PRKCE
CASP3
VCAM1
PIK3R5
EGR1
SMAD3
IL1A
SMAD4
NRAS
NFKB1
F3
STAT3
CCL2
IL6
SELE
5
0
saline
ivermectin
saline
ivermectin
M
F
*
B Target validation
CoV_saline (n=6/sex)
CoV_ivermectine (n=6/sex)
log2 fold change
M
F
Casp3 0.394 0.009
Hgf 0.310 0.026
Epha2 0.026 0.065
Il-2 0.589 0.240
Il-2ra 0.009 0.093
Tgf-β 0.143 0.290
Ifn-γ 0.240 0.394
Il-1β 0.258 0.937
Ccl5 0.937 0.143
Gabrr1 0.093 0.589
Prkg1 0.093 0.093
Gnai1 0.065 0.132
Grid1 0.132 0.009
Wnt3a 0.394 0.065
Krt4 0.394 0.015
Creb5 0.002 0.093
Ager 0.818 0.180
Fos 0.121 0.180
8
6
4
2
0
-2
-4
-6
15
10
5
0
-5
-10
-15

Figure EV5.