Graphical Abstract

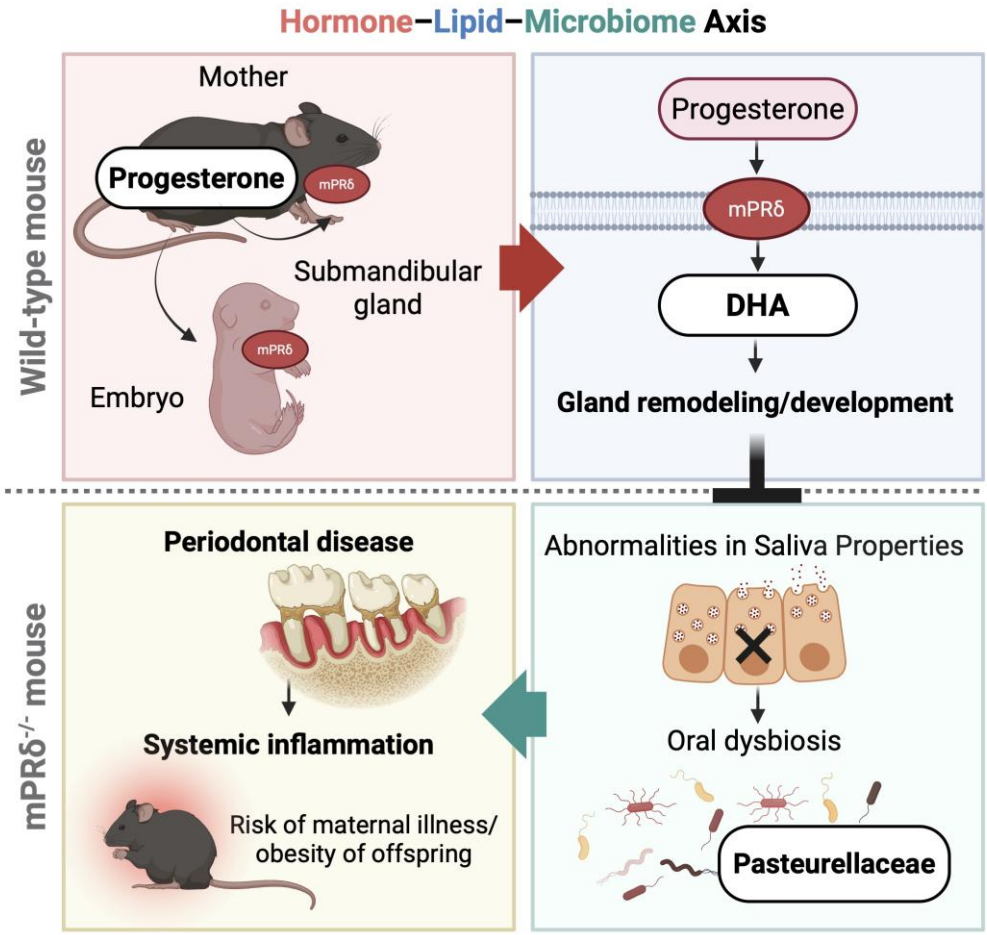


Fig. 1

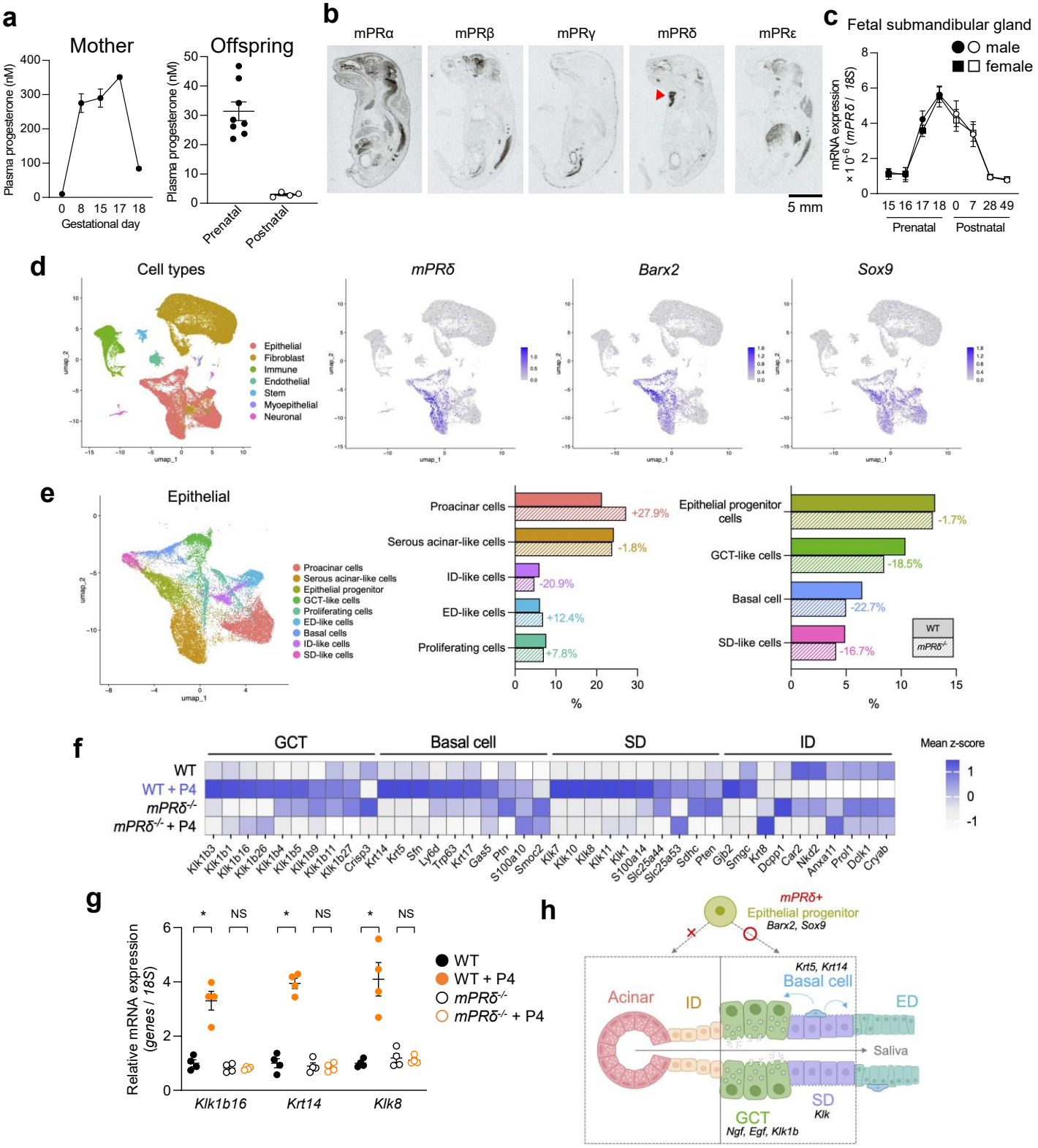

a
Mother
Offspring
Plasma progesterone (nM)
Gestational day
Prenatal
Postnatal
b
mPRα
mPRβ
mPRγ
mPRδ
mPRε
5 mm
c
Fetal submandibular gland
male
female
mRNA expression
Prenatal
Postnatal
d
Cell types
mPRδ
Barx2
Sox9
Epithelial
Fibroblast
Immune
Endothelial
Stem
Myoepithelial
Neuronal
e
Epithelial
Proacinar cells
Serous acinar-like cells
Epithelial progenitor
GCT-like cells
Proliferating cells
ED-like cells
Basal cells
ID-like cells
SD-like cells
+27.9%
-1.8%
-20.9%
+12.4%
+7.8%
-1.7%
-18.5%
-22.7%
-16.7%
WT
mPRδ-/-
%
f
GCT
Basal cell
SD
ID
WT
WT + P4
mPRδ-/-
mPRδ-/- + P4
Mean z-score
Klk1b3
Klk1b1
Klk1b16
Klk1b26
Klk1b4
Klk1b5
Klk1b9
Klk1b11
Klk1b27
Crisp3
Krt14
Krt5
Sfn
Ly6d
Trp63
Krt17
Gas5
Ptn
S100a10
Smoc2
Klk7
Klk10
Klk8
Klk11
Klk1
S100a14
Slc25a44
Slc25a53
Sdhc
Pten
Gjb2
Smgc
Krt8
Dcpp1
Car2
Nkd2
Anxa11
Prol1
Dclk1
Cryab
g
Relative mRNA expression (genes / 18S)
NS
WT
WT + P4
mPRδ-/-
mPRδ-/- + P4
Klk1b16
Krt14
Klk8
h
mPRδ+
Epithelial progenitor
Barx2, Sox9
Krt5, Krt14
Basal cell
Acinar
ID
ED
Saliva
SD
Klk
GCT
Ngf, Egf, Klk1b

Fig. 2

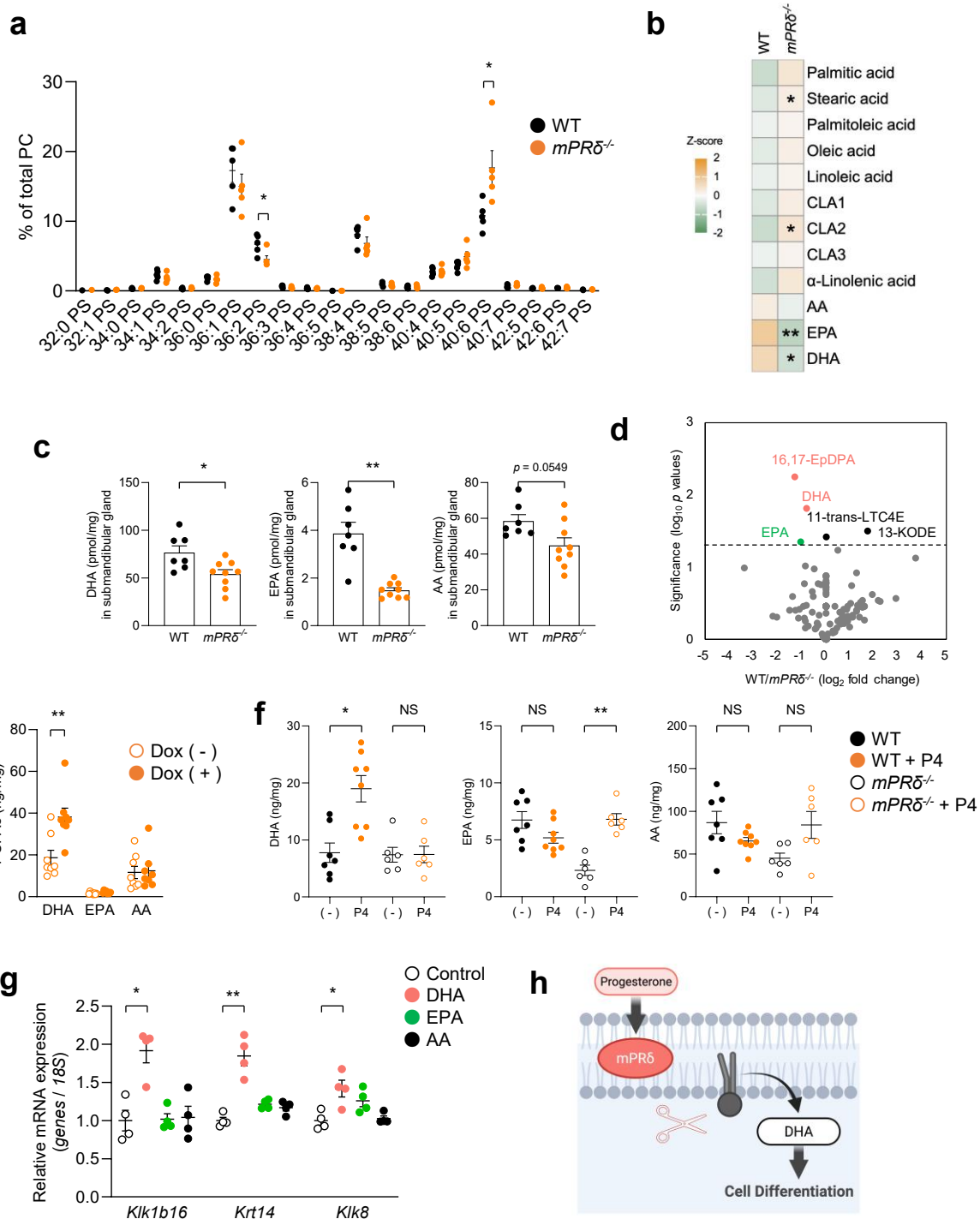

a
% of total PC
WT
mPRδ-/-
32:0 PS
32:1 PS
34:0 PS
34:1 PS
34:2 PS
36:0 PS
36:1 PS
36:2 PS
36:3 PS
36:4 PS
36:5 PS
38:4 PS
38:5 PS
38:6 PS
40:4 PS
40:5 PS
40:6 PS
40:7 PS
42:5 PS
42:6 PS
42:7 PS
b
Z-score
Palmitic acid
Stearic acid
Palmitoleic acid
Oleic acid
Linoleic acid
CLA1
CLA2
CLA3
α-Linolenic acid
AA
EPA
DHA
c
DHA (pmol/mg) in submandibular gland
EPA (pmol/mg) in submandibular gland
AA (pmol/mg) in submandibular gland
p = 0.0549
d
16,17-EpDPA
DHA
11-trans-LTC4E
EPA
13-KODE
Significance (log10 p values)
WT/mPRδ-/- (log2 fold change)
e
PUFAs (ng/mg)
Dox (-)
Dox (+)
DHA
EPA
AA
f
DHA (ng/mg)
EPA (ng/mg)
AA (ng/mg)
NS
WT
WT + P4
mPRδ-/-
mPRδ-/- + P4
g
Relative mRNA expression (genes / 18S)
Control
DHA
EPA
AA
Klk1b16
Krt14
Klk8
h
Progesterone
mPRδ
DHA
Cell Differentiation

Fig. 3

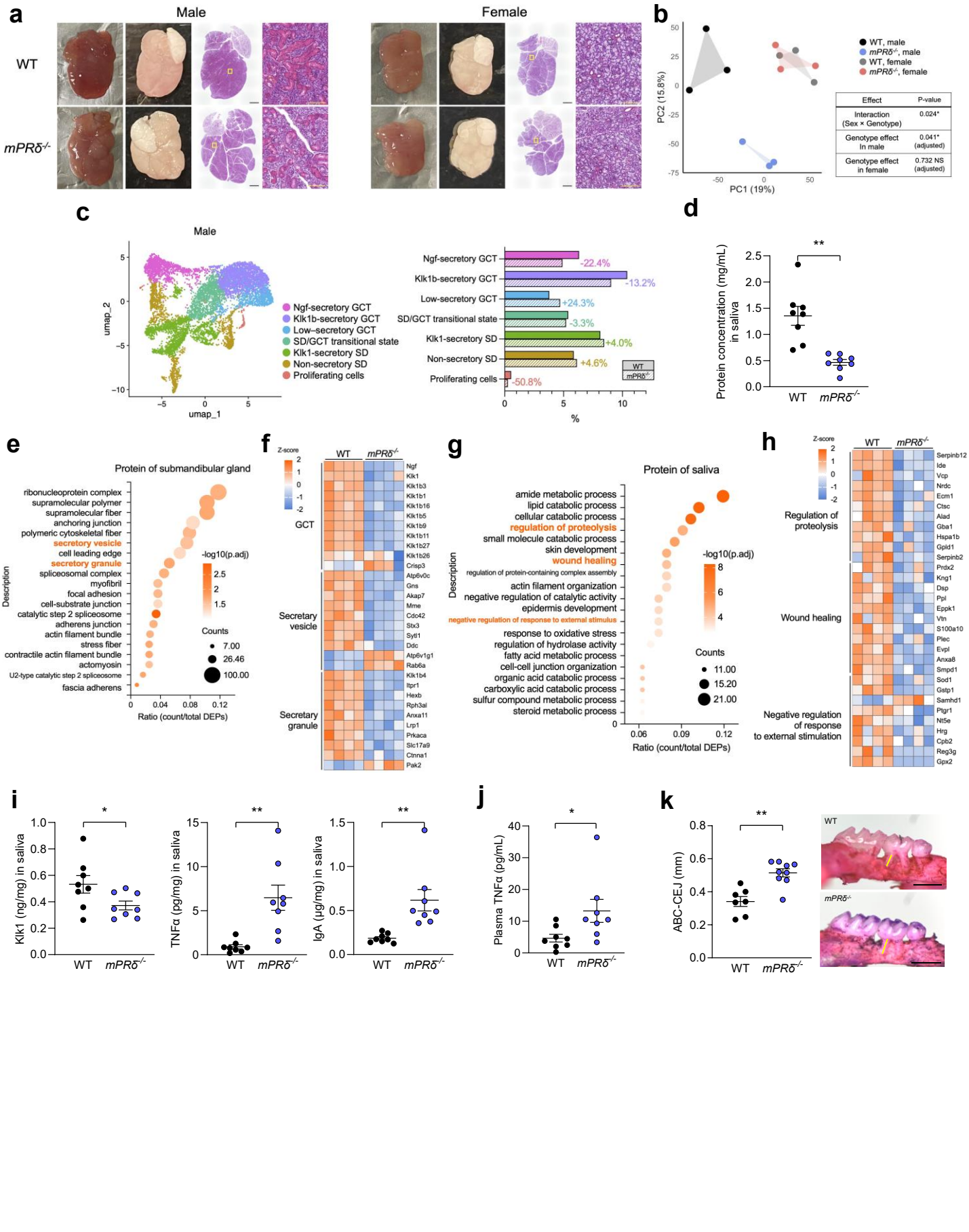
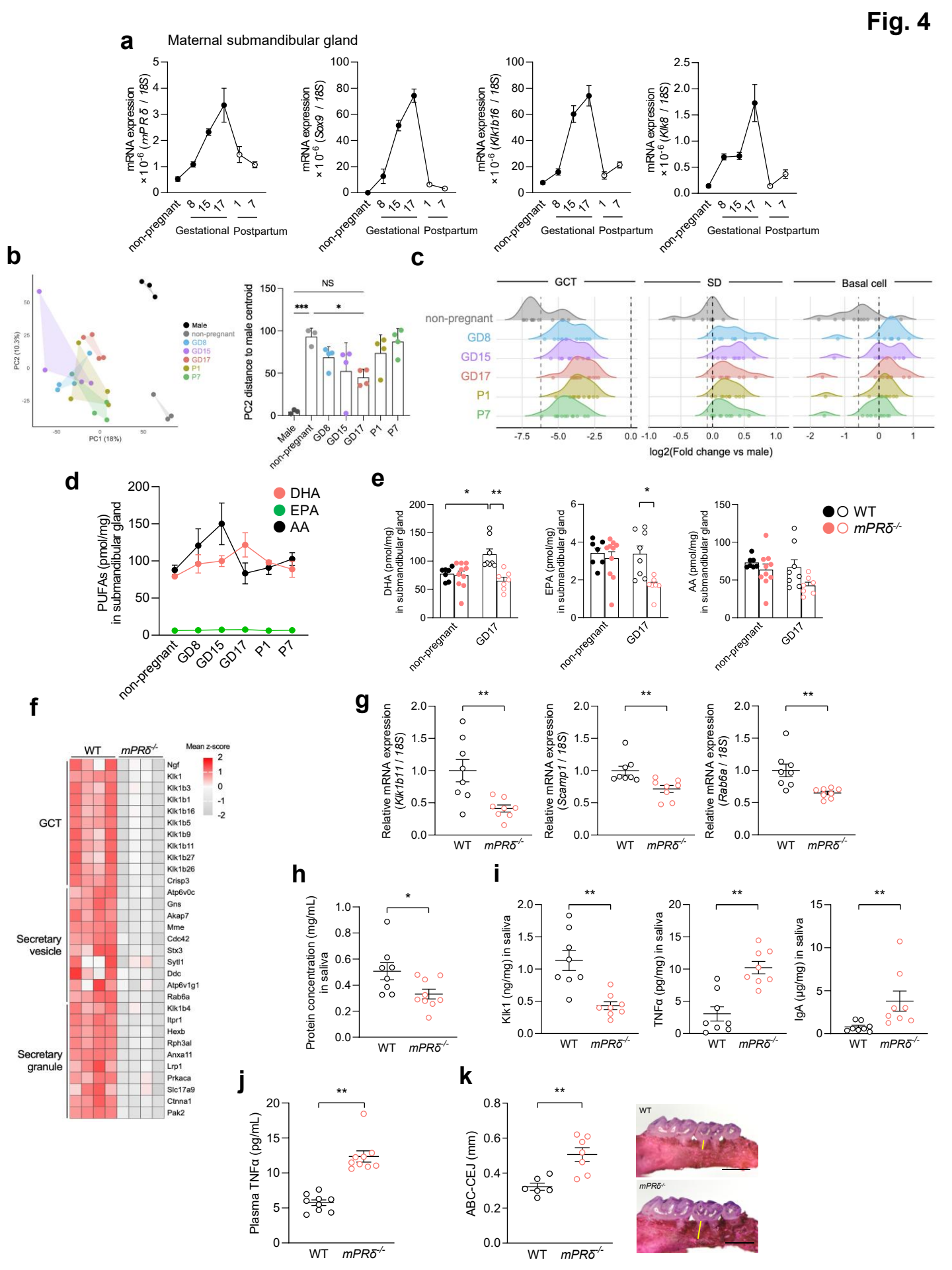
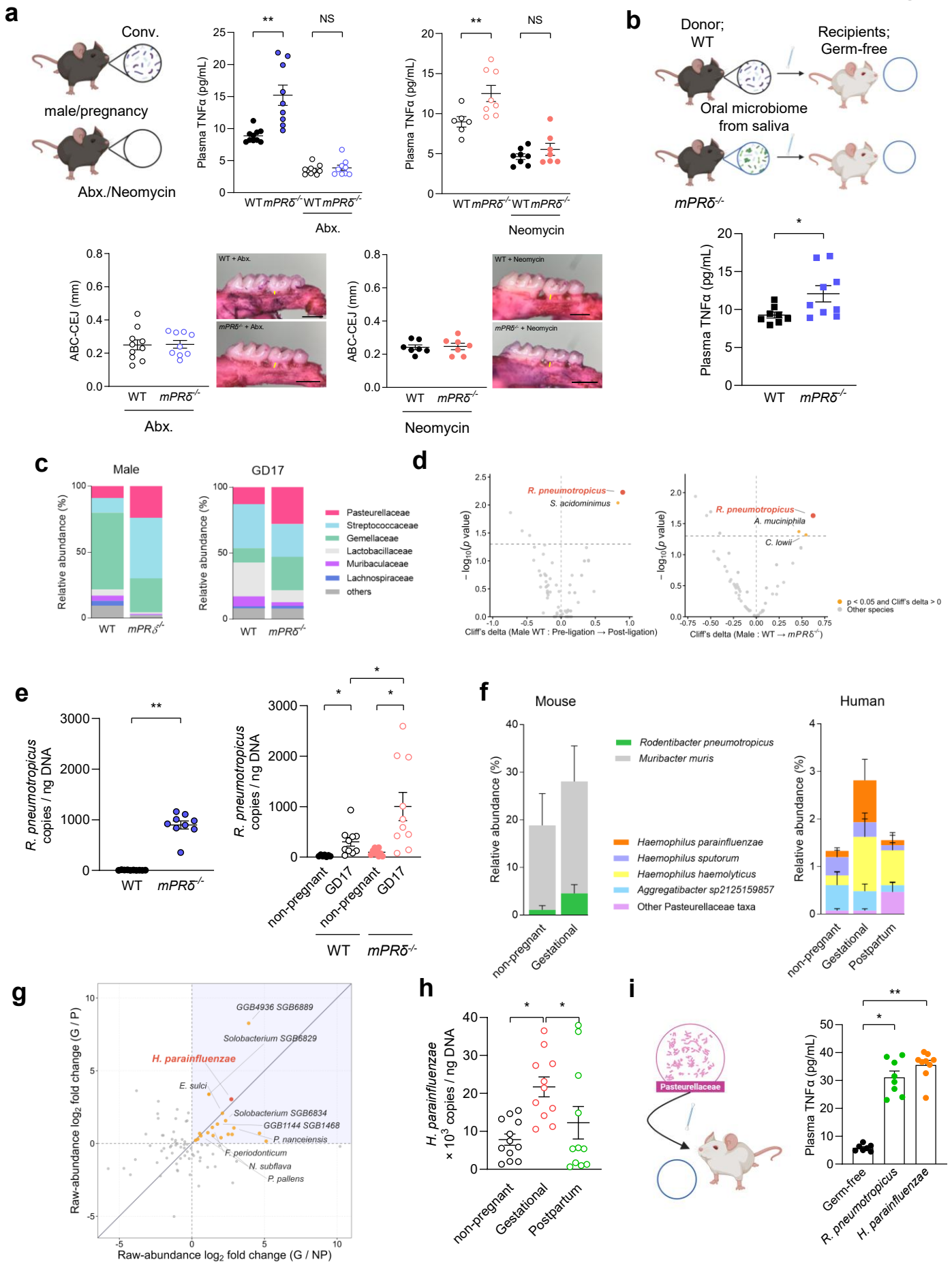
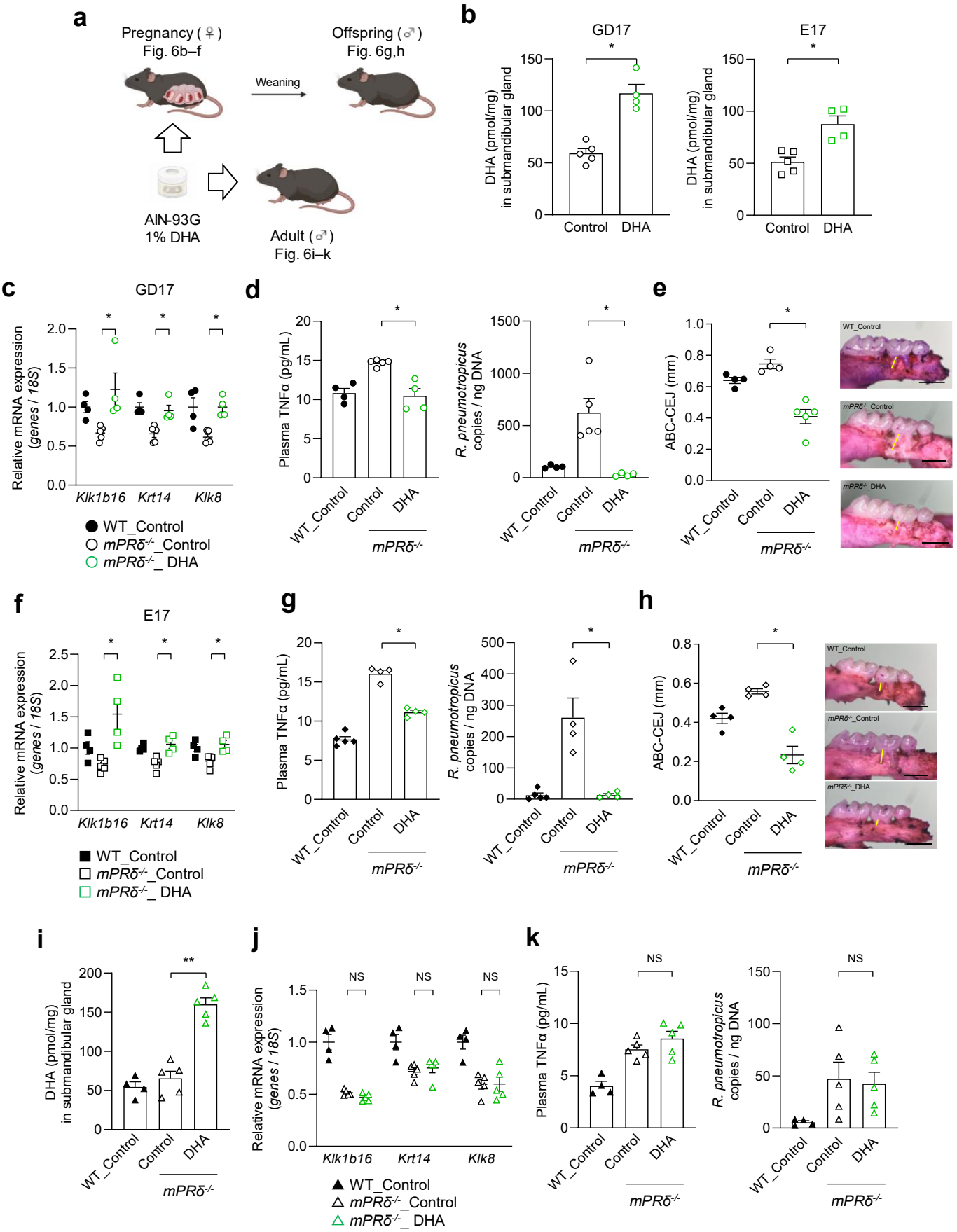

a
Male
Female
WT
mPRδ-/-
b
WT, male
mPRδ-/-, male
WT, female
mPRδ-/-, female
PC1 (19%)
PC2 (15.8%)
Effect | P-value
Interaction (Sex × Genotype) | 0.024*
Genotype effect In male | 0.041* (adjusted)
Genotype effect in female | 0.732 NS (adjusted)
c
Male
umap_1
umap_2
Ngf-secretory GCT
Klk1b-secretory GCT
Low-secretory GCT
SD/GCT transitional state
Klk1-secretory SD
Non-secretory SD
Proliferating cells
-22.4%
-13.2%
+24.3%
-3.3%
+4.0%
+4.6%
-50.8%
%
d
Protein concentration (mg/mL) in saliva
WT
mPRδ-/-
e
Protein of submandibular gland
Description
ribonucleoprotein complex
supramolecular polymer
supramolecular fiber
anchoring junction
polymeric cytoskeletal fiber
secretory vesicle
cell leading edge
secretory granule
spliceosomal complex
myofibril
focal adhesion
cell-substrate junction
catalytic step 2 spliceosome
adherens junction
actin filament bundle
stress fiber
contractile actin filament bundle
actomyosin
U2-type catalytic step 2 spliceosome
fascia adherens
-log10(p.adj)
Counts
Ratio (count/total DEPs)
f
Z-score
WT
mPRδ-/-
GCT
Secretary vesicle
Secretary granule
Ngf
Klk1
Klk1b3
Klk1b1
Klk1b16
Klk1b5
Klk1b9
Klk1b11
Klk1b27
Klk1b26
Crisp3
Atp6v0c
Gns
Akap7
Mme
Cdc42
Stx3
Syt11
Ddc
Atp6v1g1
Rab6a
Klk1b4
Itpr1
Hexb
Rph3al
Anxa11
Lrp1
Prkaca
Slc17a9
Ctnna1
Pak2
g
Protein of saliva
Description
amide metabolic process
lipid catabolic process
cellular catabolic process
regulation of proteolysis
small molecule catabolic process
skin development
wound healing
regulation of protein-containing complex assembly
actin filament organization
negative regulation of catalytic activity
epidermis development
negative regulation of response to external stimulus
response to oxidative stress
regulation of hydrolase activity
fatty acid metabolic process
cell-cell junction organization
organic acid catabolic process
carboxylic acid catabolic process
sulfur compound metabolic process
steroid metabolic process
-log10(p.adj)
Counts
Ratio (count/total DEPs)
h
Z-score
WT
mPRδ-/-
Regulation of proteolysis
Wound healing
Negative regulation of response to external stimulation
Serpinb12
Ide
Vcp
Nrdc
Ecm1
Ctsc
Alad
Gba1
Hspa1b
Gpld1
Serpinb2
Prdx2
Kng1
Dsp
Ppl
Eppk1
Vtn
S100a10
Plec
Evpl
Anxa8
Smpd1
Sod1
Gstp1
Samhd1
Ptgr1
Nt5e
Hrg
Cpb2
Reg3g
Gpx2
i
Klk1 (ng/mg) in saliva
TNFα (pg/mg) in saliva
IgA (μg/mg) in saliva
WT
mPRδ-/-
j
Plasma TNFα (pg/mL)
WT
mPRδ-/-
k
ABC-CEJ (mm)
WT
mPRδ-/-

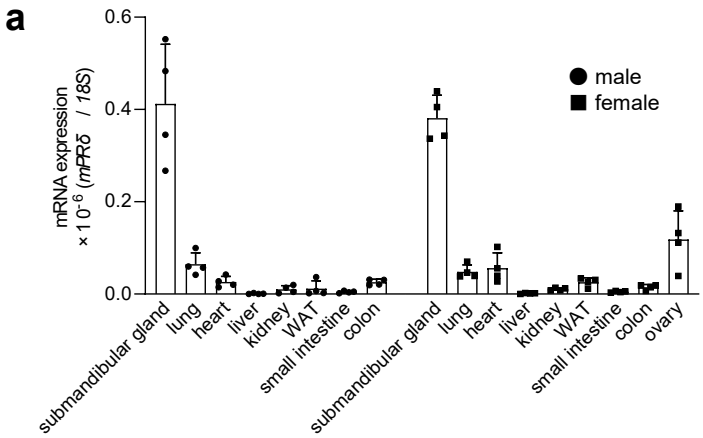
Fig. 4

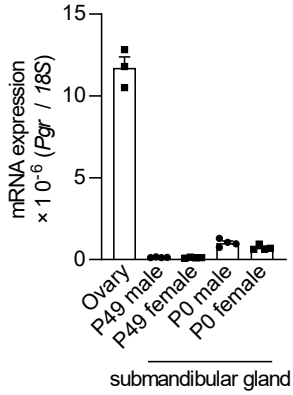

a
Maternal submandibular gland
mRNA expression × 10^-6 (mPRδ / 18S)
mRNA expression × 10^-6 (Sox9 / 18S)
mRNA expression × 10^-6 (Klk1b16 / 18S)
mRNA expression × 10^-6 (Klk8 / 18S)
non-pregnant
8
15
17
1
7
Gestational
Postpartum
b
PC2 (10.3%)
PC1 (18%)
Male
non-pregnant
GD8
GD15
GD17
P1
P7
PC2 distance to male centroid
NS
***
*
c
GCT
SD
Basal cell
log2(Fold change vs male)
d
PUFAs (pmol/mg) in submandibular gland
DHA
EPA
AA
e
DHA (pmol/mg) in submandibular gland
EPA (pmol/mg) in submandibular gland
AA (pmol/mg) in submandibular gland
WT
mPRδ-/-
f
Mean z-score
Ngf
Klk1
Klk1b3
Klk1b1
Klk1b16
Klk1b5
Klk1b9
Klk1b11
Klk1b27
Klk1b26
Crisp3
Atp6v0c
Gns
Akap7
Mme
Cdc42
Stx3
Sytl1
Ddc
Atp6v1g1
Rab6a
Klk1b4
Itpr1
Hexb
Rph3al
Anxa11
Lrp1
Prkaca
Slc17a9
Ctnna1
Pak2
GCT
Secretary vesicle
Secretary granule
g
Relative mRNA expression (Klk1b11 / 18S)
Relative mRNA expression (Scamp1 / 18S)
Relative mRNA expression (Rab6a / 18S)
h
Protein concentration (mg/mL) in saliva
i
Klk1 (ng/mg) in saliva
TNFα (pg/mg) in saliva
IgA (μg/mg) in saliva
j
Plasma TNFα (pg/mL)
k
ABC-CEJ (mm)

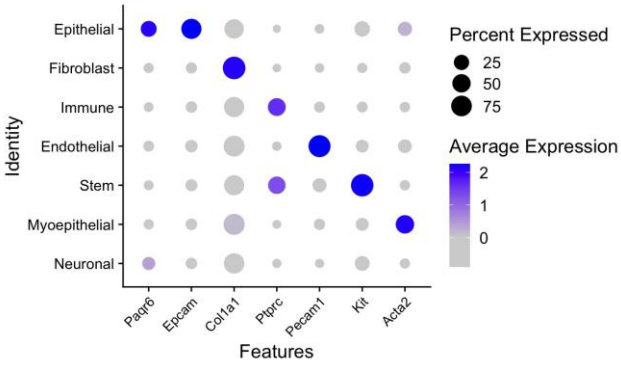

a
Conv.
male/pregnancy
Abx./Neomycin
Plasma TNFα (pg/mL)
**
NS
WT mPRδ-/- WT mPRδ-/-
Abx.
Neomycin
ABC-CEJ (mm)
WT + Abx.
mPRδ-/- + Abx.
WT + Neomycin
mPRδ-/- + Neomycin
WT
mPRδ-/-
b
Donor; WT
Recipients; Germ-free
Oral microbiome from saliva
mPRδ-/-
*
c
Male
GD17
Relative abundance (%)
Pasteurellaceae
Streptococcaceae
Gemellaceae
Lactobacillaceae
Muribaculaceae
Lachnospiraceae
others
d
R. pneumotropicus
S. acidominimus
A. muciniphila
C. lowii
− log10(p value)
Cliff's delta (Male WT : Pre-ligation → Post-ligation)
Cliff's delta (Male : WT → mPRδ-/-)
p < 0.05 and Cliff's delta > 0
Other species
e
R. pneumotropicus copies / ng DNA
non-pregnant
GD17
f
Mouse
Human
Rodentibacter pneumotropicus
Muribacter muris
Haemophilus parainfluenzae
Haemophilus sputorum
Haemophilus haemolyticus
Aggregatibacter sp2125159857
Other Pasteurellaceae taxa
Gestational
Postpartum
g
GGB4936 SGB6889
Solobacterium SGB6829
H. parainfluenzae
E. sulci
Solobacterium SGB6834
GGB1144 SGB1468
P. nanceiensis
F. periodonticum
N. subflava
P. pallens
Raw-abundance log2 fold change (G / P)
Raw-abundance log2 fold change (G / NP)
h
H. parainfluenzae × 10^3 copies / ng DNA
i
Pasteurellaceae
Germ-free
R. pneumotropicus
H. parainfluenzae

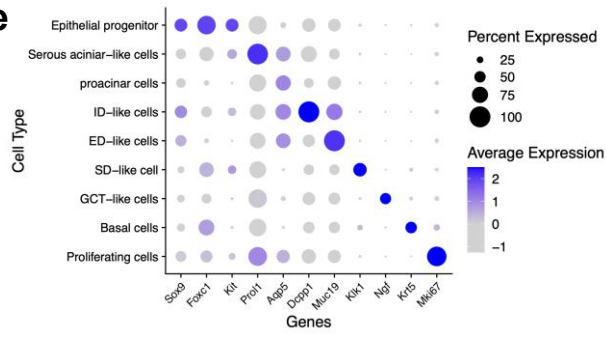

a
Pregnancy (♀)
Fig. 6b–f
Offspring (♂)
Fig. 6g,h
Weaning
AIN-93G
1% DHA
Adult (♂)
Fig. 6i–k
b
GD17
E17
DHA (pmol/mg) in submandibular gland
Control
DHA
c
GD17
Relative mRNA expression (genes / 18S)
Klk1b16
Krt14
Klk8
WT_Control
mPRδ-/-_Control
mPRδ-/-_ DHA
d
Plasma TNFα (pg/mL)
R. pneumotropicus copies / ng DNA
WT_Control
Control
DHA
mPRδ-/-
e
ABC-CEJ (mm)
WT_Control
mPRδ-/-_Control
mPRδ-/-_DHA
f
E17
g
h
i
DHA (pmol/mg) in submandibular gland
j
NS
k

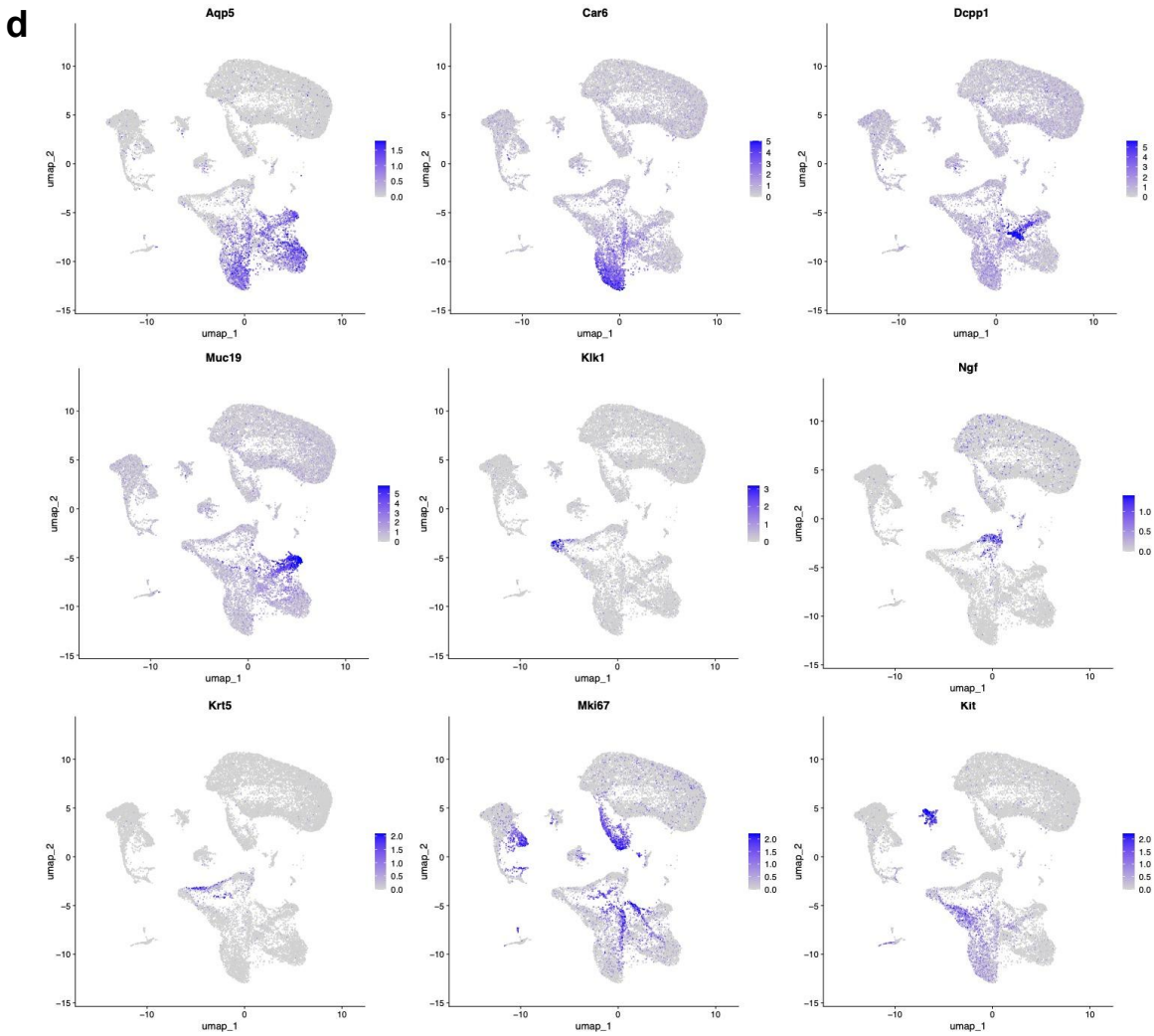
Extended Data Fig. 1



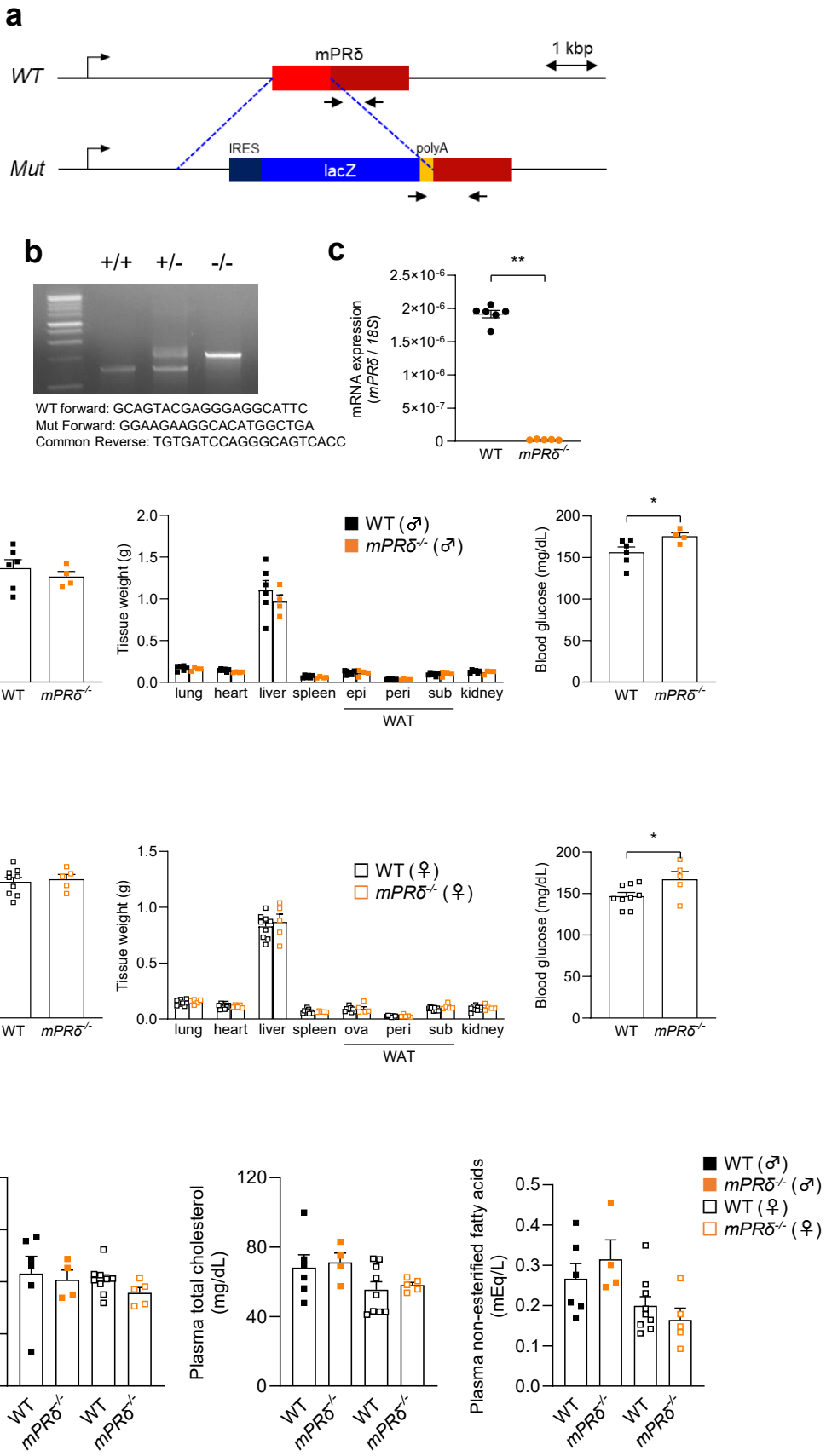




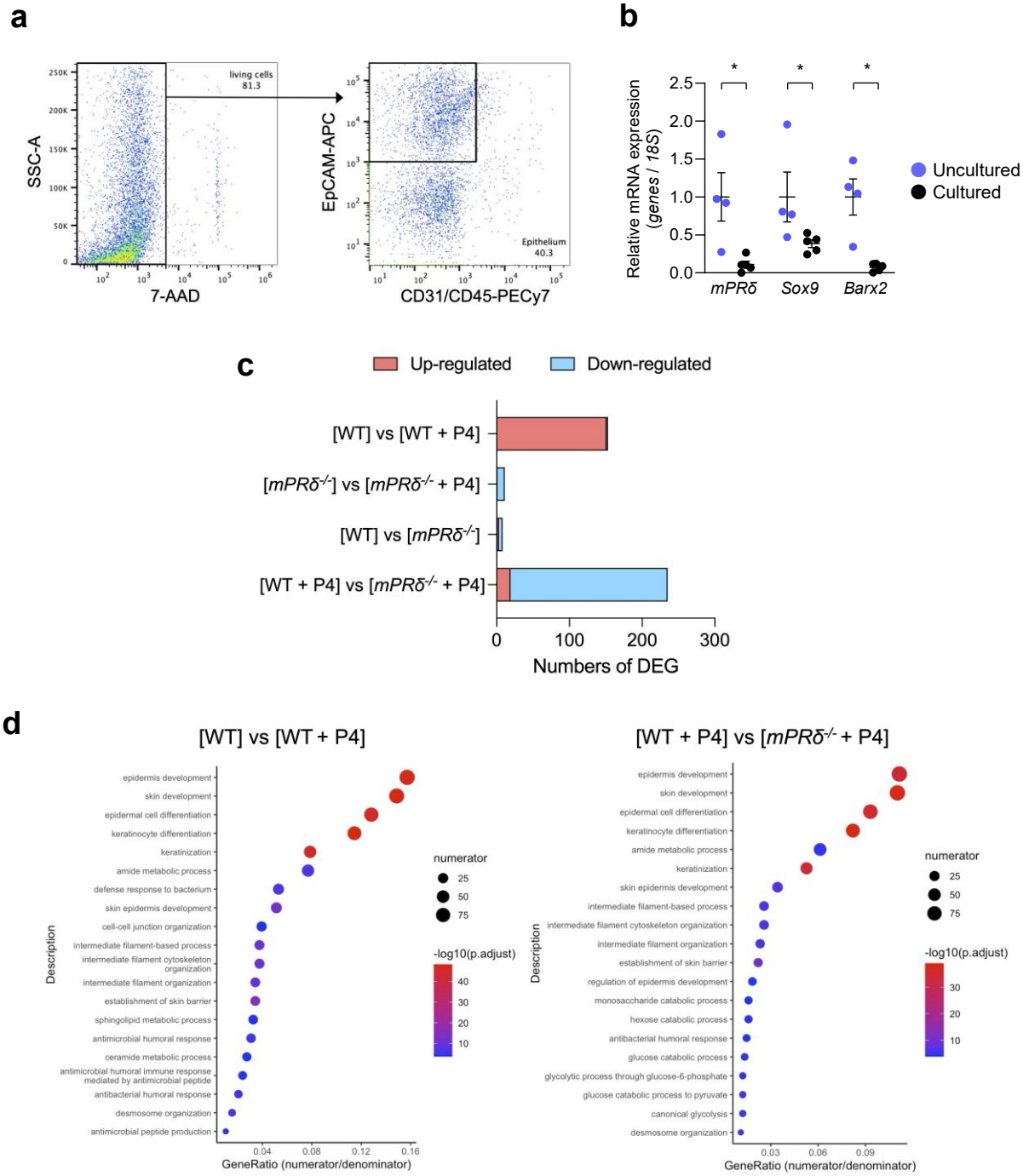




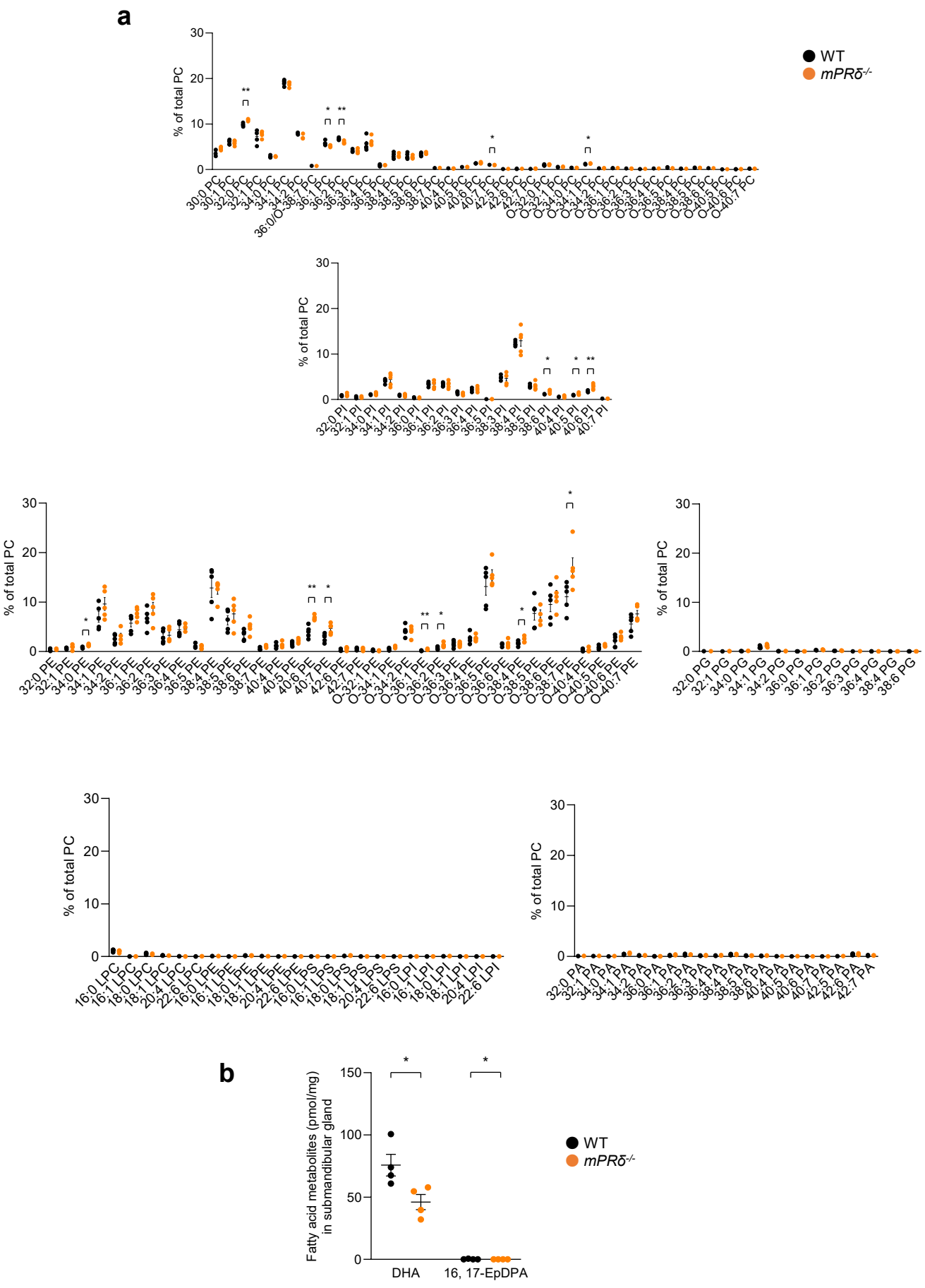
Extended Data Fig. 2

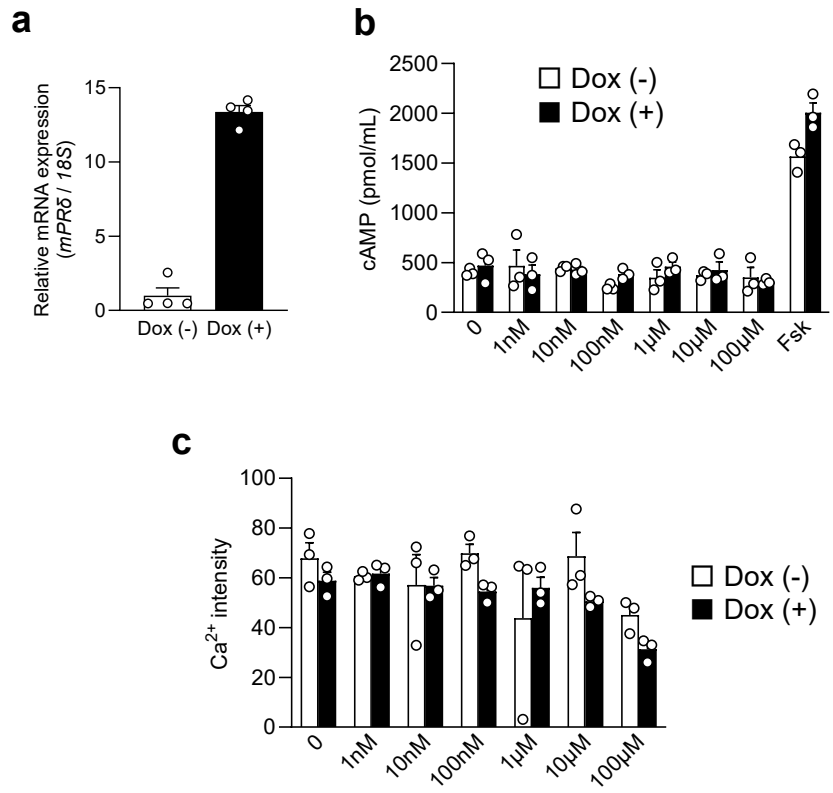


Extended Data Fig. 3

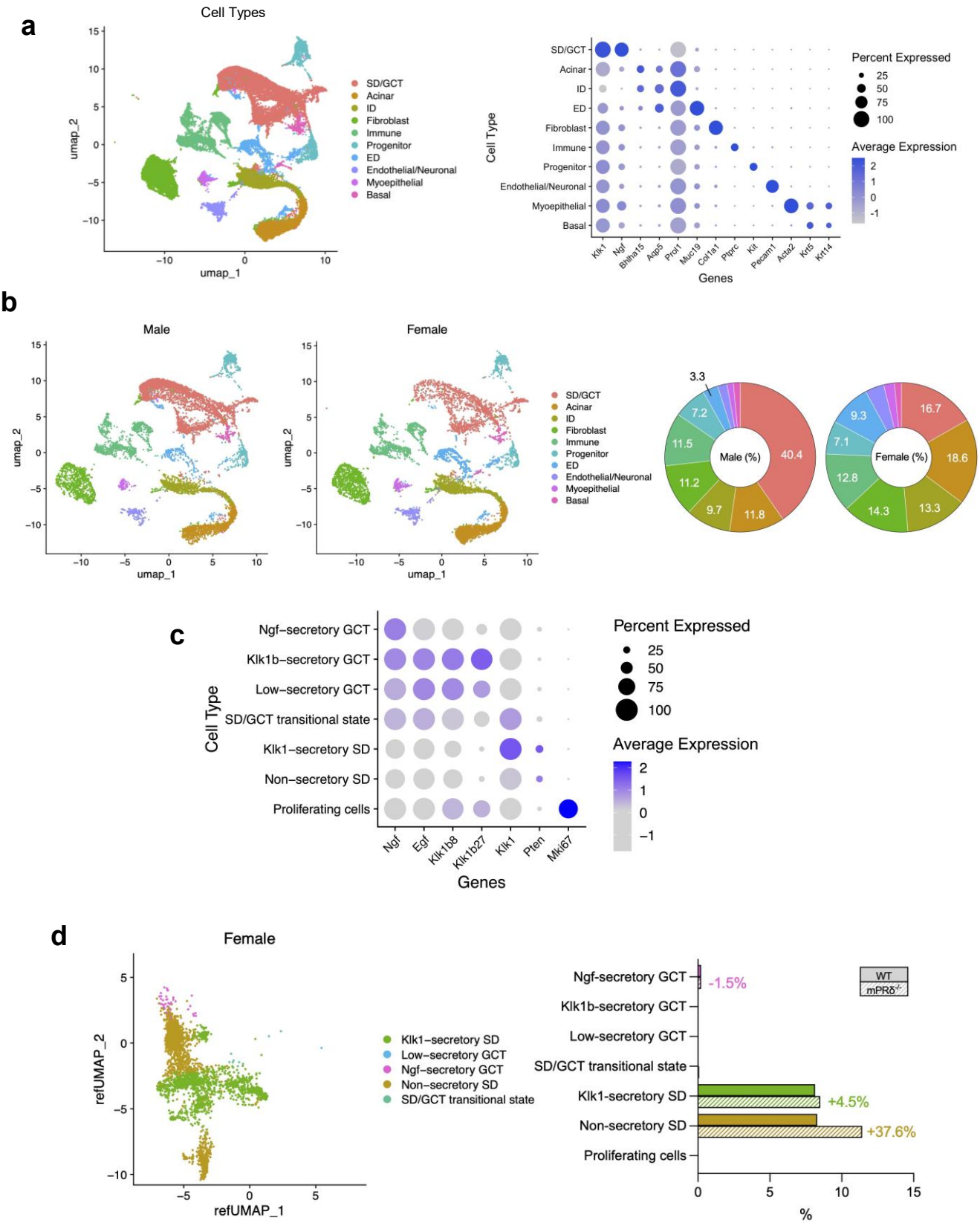


Extended Data Fig. 4

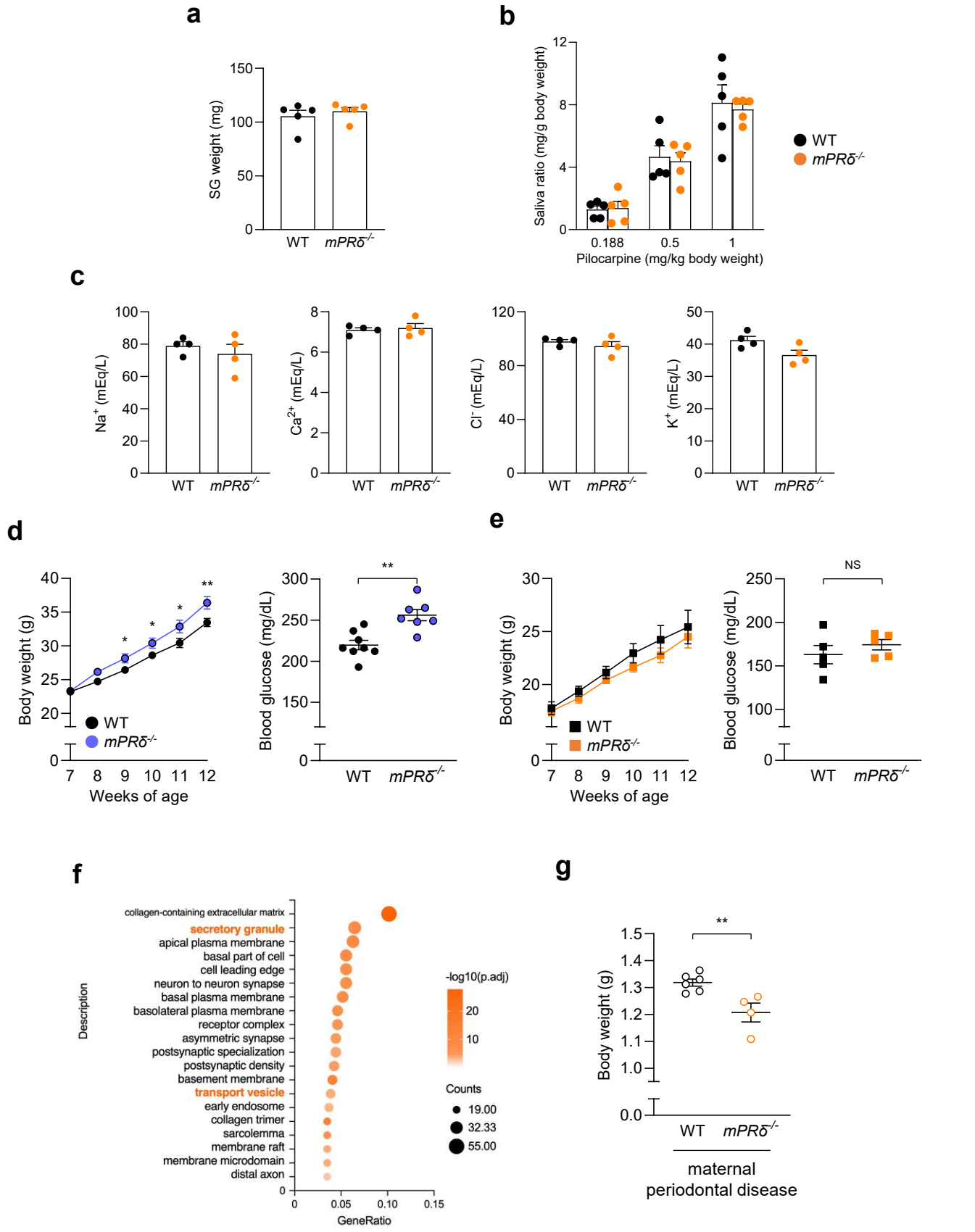



a
Relative mRNA expression
(mPR5 / 18S)
15
10
5
0
Dox (-)
Dox (+)
b
cAMP (pmol/mL)
2500
2000
1500
1000
500
0
Dox (-)
Dox (+)
0
1nM
10nM
100nM
1μM
10μM
100μM
Fsk
c
Ca2+ intensity
100
80
60
40
20
0
Dox (-)
Dox (+)
0
1nM
10nM
100nM
1μM
10μM
100μM

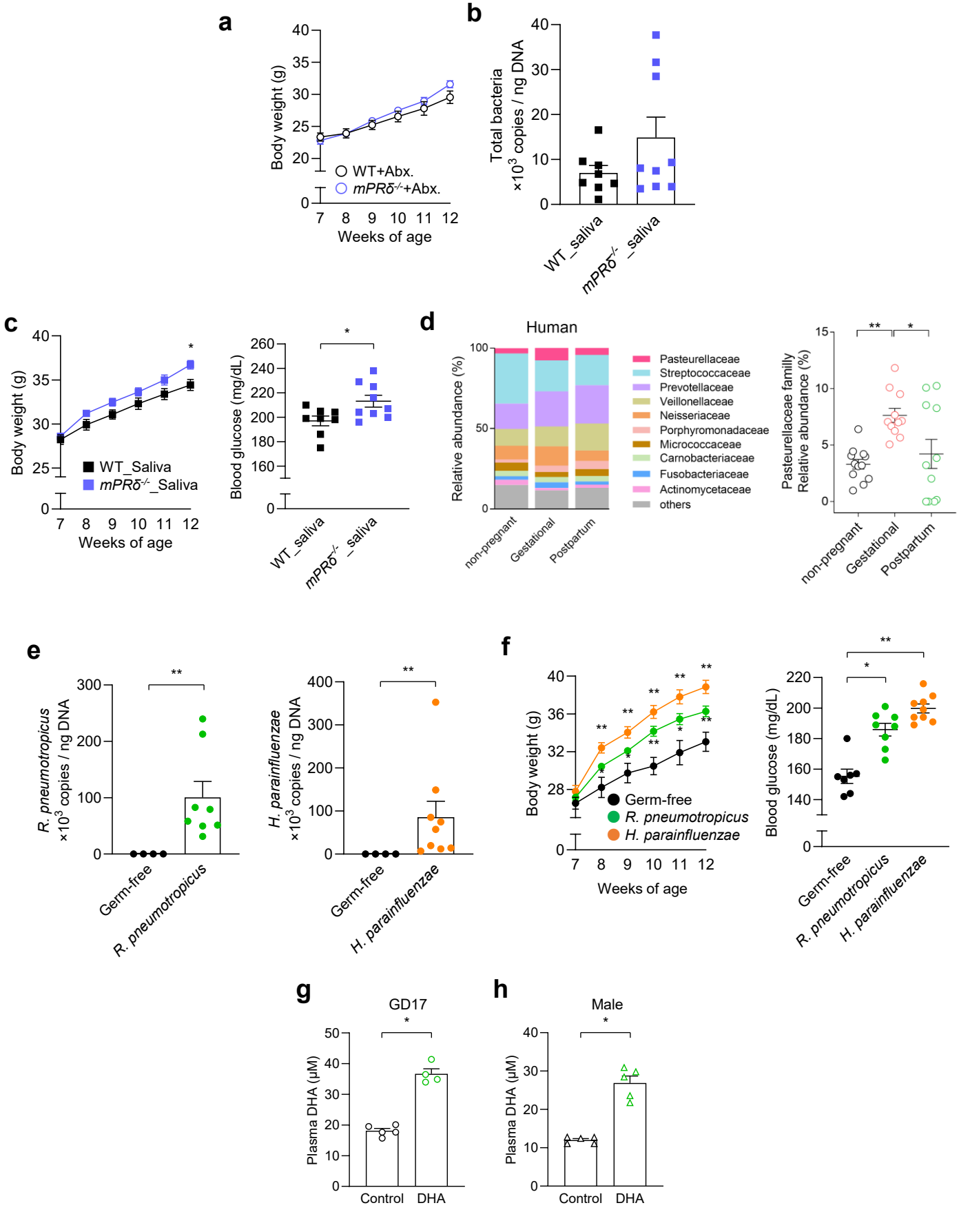
Extended Data Fig. 6



Extended Data Fig. 7



Extended Data Fig. 8



Supplementary Table. 1

Ingredient, g	AIN93G	AIN93G+DHA
Casein	200	198
L-Cystine	3	2.97
Corn Starch	397.486	393.51114
Maltodextrin	132	130.68
Sucrose	100	99
Cellulose, BW200	50	49.5
Soybean Oil	70	69.3
DHA	0	10
t-butylhydroquinone	0.014	0.01386
Mineral Mix S10022G	35	34.65
Vitamin Mix V10037	10	9.9
Choline Bitartrate	2.5	2.475
Total weight	1000	1000
Energy, kcal/g		
% Energy	4.0	4.0
Fat	16	18
Carbohydrate	64	62
Protein	20	20

Supplementary Table. 2

Target		Sequence
mPRδ	Forward	5′-TGCCTACCCCTTCTTGTTTG-3′
	Reverse	5′-TGGCTGCCAATATAGTC-3′
Klk1b16	Forward	5′-GAGAACTGTGCCAAAGCCTACC-3′
	Reverse	5′-GGTTCCTTGGAGAACACCATCAC-3′
Krt14	Forward	5′-GAAGAACCGCAAGGATGCTGAG-3′
	Reverse	5′-TGCAGCTCGATCTCCAGGTTCT-3′
Klk8	Forward	5′-TCCTGGTTGGAGACAGATGGGT-3′
	Reverse	5′-AGGATGCTGGATAGACTGAGCC-3′
Sox9	Forward	5′-CACACGTCAAGCGACCCATGAA-3′
	Reverse	5′-TCTTCTCGCTCTCGTTCAGCAG-3′
Pgr	Forward	5′-CGACGTGGAGGGAGCTTTCT-3′
	Reverse	5′-CCTGGGTGGTGACAGTCCTT-3′
Barx2	Forward	5′-AGAAGTCGCACCATCTTCAC-3′
	Reverse	5′-GGGCCAAGTCCAACCTGTCT-3′
Scamp1	Forward	5′-AGCCAACAGAGGAACATCCAGC-3′
	Reverse	5′-CTCACGACGATCCAACTCTGCA-3′
Rab6a	Forward	5′-GGAAAGACGTCCTTGATCACCC-3′
	Reverse	5′-CTCTTGACCTGCTGTGTCCCAT-3′
18S rRNA	Forward	5′-ACGCTGAGCCAGTCAGTGTA-3′
	Reverse	5′-CTTAGAGGGACAAGTGGCG-3′

Supplementary Table. 3

Target		Sequence
Total bacteria	Forward	5′-ACTCCTACGGGAGGCAGCAGT-3′
	Reverse	5′-ATTACCGCGGCTGCTGGC-3′
Rodentibacter pneumotropicus	Forward	5′-ACGGGTGAGTAATGCTTGGG-3′
	Reverse	5′-ACGCCCCCTTTTGTCCTTAG-3′
Haemophilus parainfluenzae	Forward	5′-GCACGCAGGCGGTGACTTAA-3′
	Reverse	5′-TCCTGTTTGCTCCCCACGCT-3′