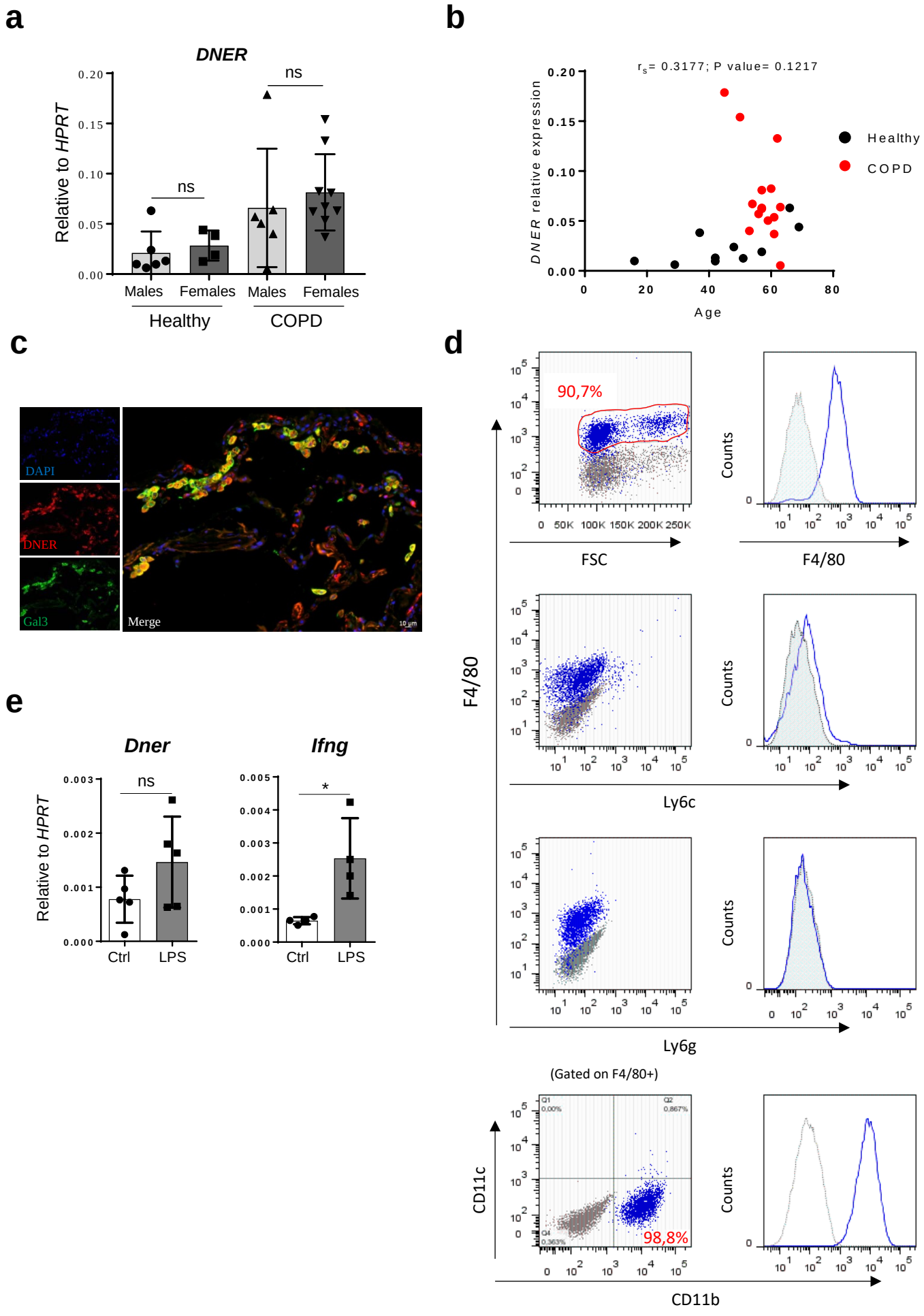
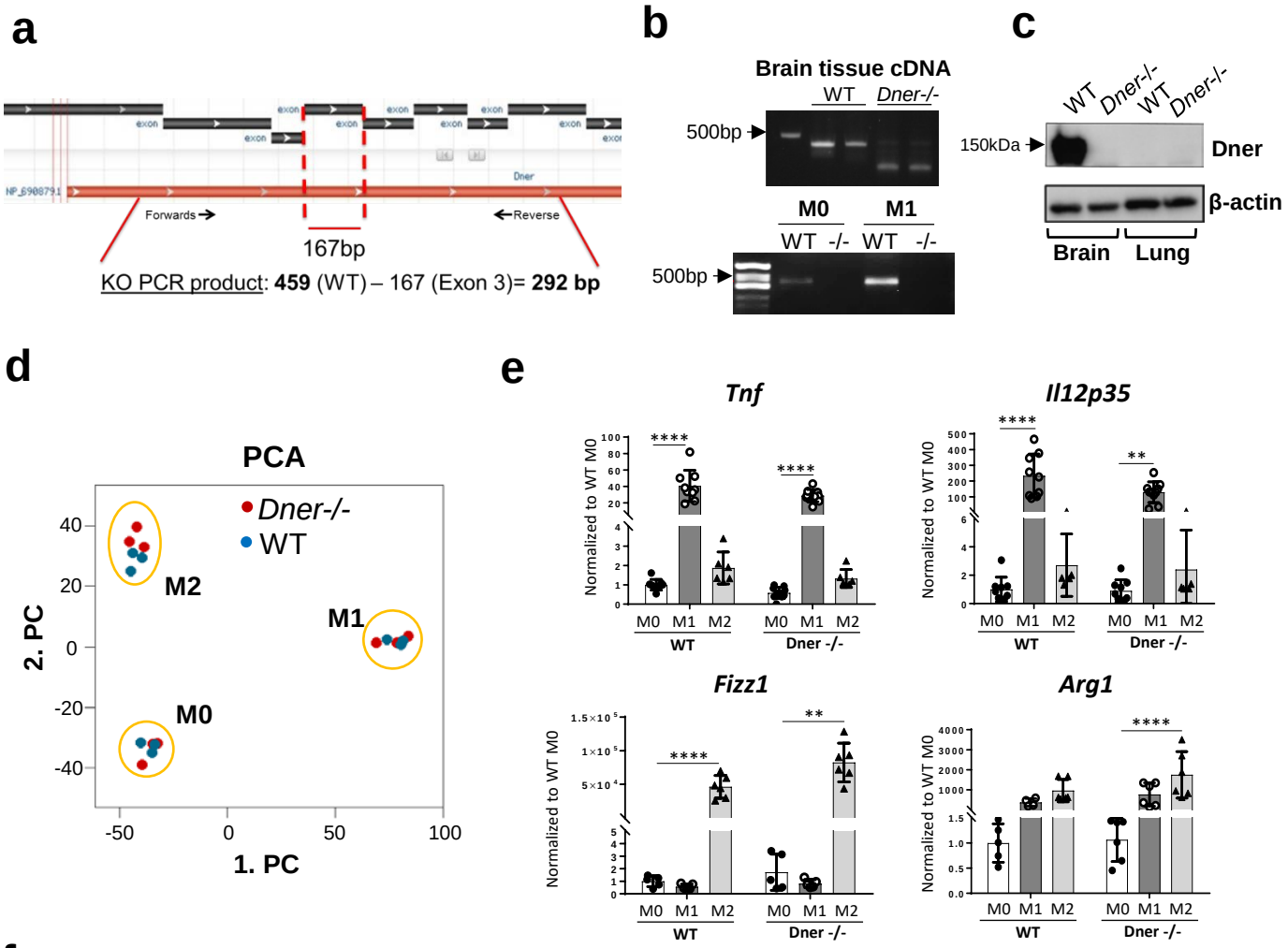
Supplementary Figure 1



Supplementary Figure 2

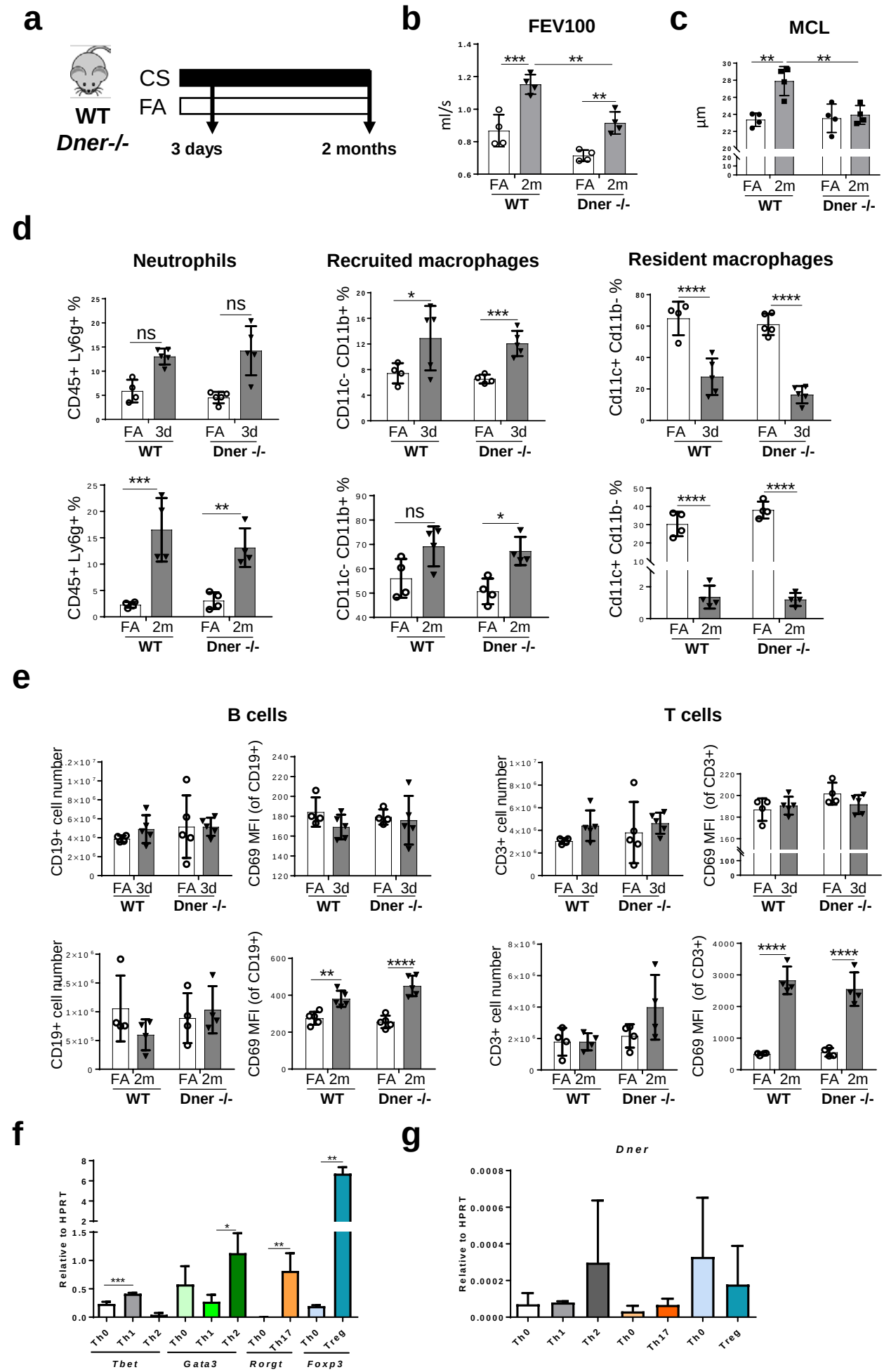


f

Enriched genes in IFNγ signalling dataset (from Fig 2F)

GENE SYMBOL	RANK METRIC SCORE	RUNNING ES	CORE ENRICHMENT
IFNGR1	0,555793166	0,016395938	Yes
SUMO1	0,555555582	0,06843433	Yes
FCGR1A	0,548780501	0,11730901	Yes
OAS2	0,476190478	0,14225388	Yes
PTAFR	0,454545468	0,17979813	Yes
PTPN1	0,384615391	0,18147604	Yes
GBP5	0,33427763	0,18348804	Yes
OAS1	0,317919075	0,20190263	Yes
PRKCD	0,306122452	0,22340244	Yes
JAK2	0,294117659	0,24346457	Yes
SOCS3	0,292035401	0,2672922	Yes
IFNGR2	0,276280522	0,28188163	Yes
VCAM1	0,255033553	0,28695264	Yes

Supplementary Figure 3



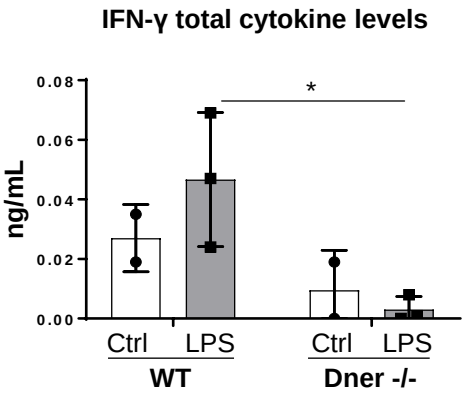
Supplementary Figure 4

a

Enriched genes of Notch1 pathway in WT M1 (Fig. 4e)

GENE SYMBOL	RANK METRIC SCORE	RUNNING ES	CORE ENRICHMENT
HDAC3	1.296296239	0.1251865	Yes
CREBBP	0.814317822	0.19795468	Yes
HIF1A	0.518518507	0.20764284	Yes
null	0.483870953	0.24362169	Yes
HDAC2	0.47356829	0.28676453	Yes
TLE4	0.434964508	0.3138684	Yes
MYC	0.333333343	0.2899674	Yes
NCOR1	0.32764855	0.3188046	Yes
TLE2	0.3125	0.33849412	Yes
SNW1	0.263157904	0.32508263	Yes
HDAC1	0.257731944	0.3445112	Yes
HDAC10	0.2360515	0.3449183	Yes
TBL1X	0.217391297	0.3469396	Yes

b

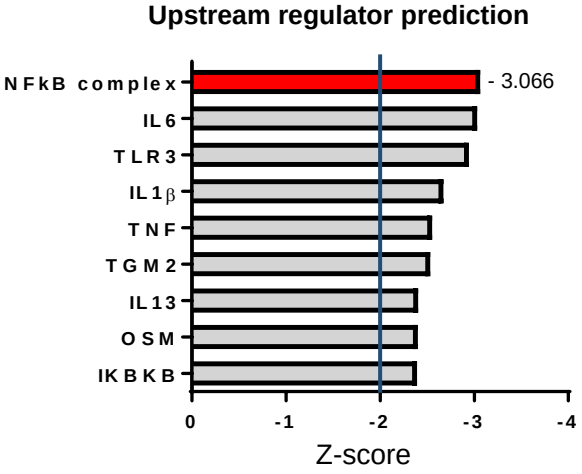


c

Enriched genes of NFkB pathway in WT M1 (Fig. 5c)

GENE SYMBOL	RANK METRIC SCORE	RUNNING ES	CORE ENRICHMENT
HDAC3	1.296296239	0.20311034	Yes
FOXP3	0.555555582	0.2531114	Yes
RELA	0.543243885	0.33511746	Yes
HDAC2	0.47356829	0.38970152	Yes
RPS3	0.428571433	0.43746465	Yes
COMMD7	0.373134315	0.46795464	Yes
ANXA4	0.263157904	0.43196097	Yes
HDAC1	0.257731944	0.4682062	Yes
FAF1	0.209026173	0.4539978	Yes
PPARD	0.196257785	0.47010383	Yes
TAF4B	0.175315574	0.47596845	Yes

d



Supplementary Fig. 1. DNER expression in human lung and murine bone marrow derived dendritic cells. **(a)** Lung *DNER* mRNA levels in males versus females subjects used in Fig. 1a. One-way ANOVA. **(b)** Correlation between age and *DNER* expression in human samples used in Fig. 1a. Spearman test. **(c)** Representative picture of immunofluorescence staining of DNER and Galectin 3 in lung tissue from an additional COPD patient. **(d)** BMDM characterization by FACS analysis with markers for macrophages (F4/80, CD11b), DC (Ly6c, CD11c) and neutrophils (Ly6g). 1 experiment, *n*=1. **(e)** *Dner* and *Ifng* mRNA abundance in 24h LPS (1μg/ml) treated murine bone marrow derived dendritic cells isolated from WT mice. 1 experiment, n=5. Unpaired t-test, *p=0.0213. Data shown mean values ± SD.

Supplementary Fig. 2. Efficiency of *Dner* deletion in C57BL/6 mice and cellular phenotype of Dner-/- BMDM. **(a)** Schematic representation of *Dner* gene deletion strategy in Dner deficent mice. **(b)** Dner mRNA abundance in brain tissue and untreated or M1 (LPS 1μg/ml + IFNγ) BMDM from WT and Dner deficient mice quantified by end point PCR. **(c)** Protein levels of Dner in brain and lung tissue from WT and Dner deficent mice. **(d)** Principal component analysis of Dner-/- vs. WT BMDM microarray data. **(e)** mRNA levels of M1 (*Tnf, Il-12a*) and M2 (*Arg1, Fizz1*) markers in WT and Dner deficient BMDM. Two-way ANOVA, Tukey's multiple comparisons test, **p<0.01, ****p<0.0001. Data shown mean values ± SD. **(f)** List of genes enriched in WT M1 from the IFNγ signaling dataset of the GSEA analysis shown in Fig. 2f.

Supplementary Fig. 3. The pathophysiological and immunophenotypic analysis of Dner deficient mice after CS exposure. **(a)** Schematic representation of experimental design. **(b)** Forced expiratory volume after 100ms of FA and 2 months CS exposed Dner deficient and WT mice. **(c)** Mean chord length measurement of lung tissue sections from same samples as in b. **(d)** Percentages of innate immune cell populations in whole lung from FA, 3 days and 2 month CS-exposed WT and Dner deficient mice analyzed by flow cytometry. **(e)** Cell numbers and MFI values of adaptive immune cell populations in whole lung from samples shown in e. **(f)** mRNA levels of positive markers for *in vitro* differentiated T cell subpopulations: Th1 (*Tbet*), Th2 (*Gata3*), Th17 (*Rorgt*) and Treg (*Foxp3*) (see more details in materials and methods). n=2/3, 1 experiment. **(g)** *Dner* expression in T cell subpopulations from f. Two-way ANOVA, Tukey's multiple comparisons test, *p<0.05, **p<0.01, ***p<0.001, ****P<0.0001. (b-e). One-way ANOVA, Tukey's multiple comparisons test, Th1***p-value=0.0008, Th2 *p-value=0.0231, Th17** p-value=0.0019, Treg** p-value=0.0048 (f-g). Data shown mean values ± SD.

Supplementary Fig. 4. Gene datasets of enriched Notch1 and NFKB signalling in M1 WT BMDM compared to Dner deficient M1 BMDM. **a)** List of enriched genes in WT M1 BMDM from the Notch1 pathway dataset of the GSEA analysis shown in Fig. 2C. **b)** IFNγ cytokine concentration in cell supernatants obtained from WT and Dner deficient BMDM treated with LPS (1ug/ml) for 24h and untreated (2 independent experiments, n=3). Two-way ANOVA, Tukey's multiple comparisons test, *p<0.05. Data shown mean values ± SD. **c)** Enriched genes in WT M1 BMDM from NFKB binding dataset (GO:0051059) from the GSEA analysis of the WT M1 vs Dner deficient M1 microarray data . **d)** Upstream regulator prediction based on 614 significantly (p<0.05) regulated genes between Dner deficient M1 vs WT M1 in our microarray analysis. The plot represents the top 9 inhibited regulators with the lowest activation z-scores.

Supplementary Table 1. Demographics and clinical characteristics of healthy and COPD transplant patients (Mean ± SEM). **FEV1**: Forced expiratory volume in the first second; **FVC**: Forced vital capacity; ICS: inhaled corticosteroids.

Supplementary Table 2. Primer sequences used for RT-PCR.