Supplemental Materials

Supplemental 1

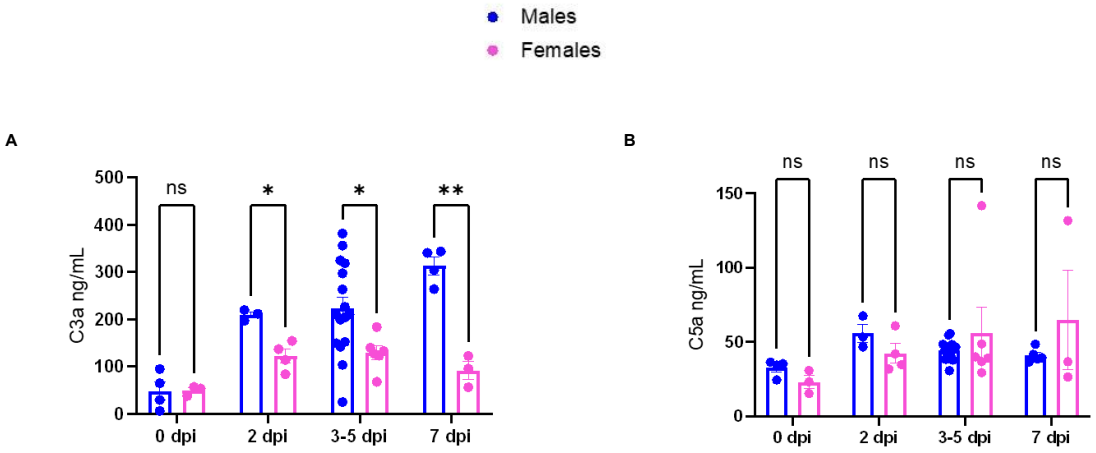

Figure S1: Sex comparison of serum C3a and C5a after MA30 infection (A-B) Sera from male and female mice after infection with sublethal and lethal doses of SARS-CoV-2 MA30. Serum C3a (A) and C5a levels (B) detected by sandwich ELISA. Statistics performed with mixed-effects analysis using Sidak's multiple comparisons, * $p < 0.05$, ** $p < 0.01$.

Supplemental 2

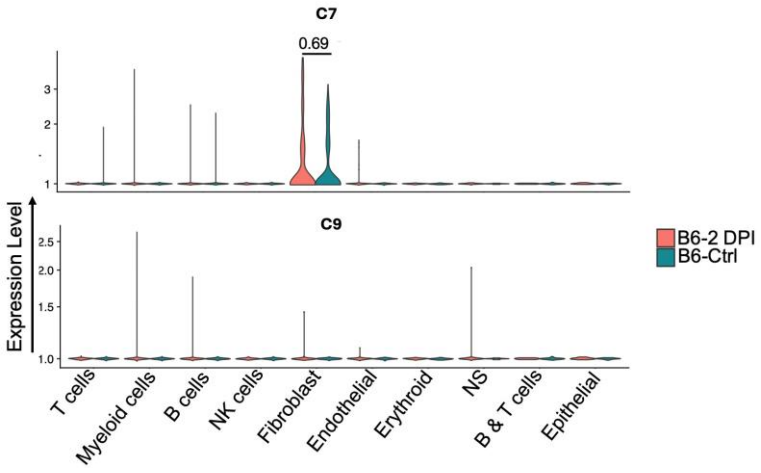

Figure S2: Complement components C7 and C9 in single-cell clusters after MA30 infection. Violin plots of C7 and C9 expression level in multiple cell clusters for MA30 (1×10^4 $TCID_{50}$) infected B6 mice at 2DPI by scRNA-sequencing.

Supplemental 3

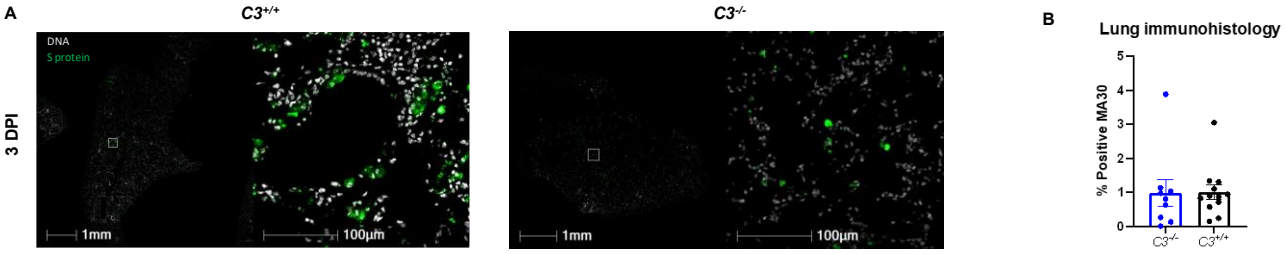

Figure S3: S protein staining in *C3* sufficient and sufficient mice after infection (A) Immunofluorescence staining of viral S protein (green) and DAPI (white) from C3 sufficient and deficient mice after infection with MA30 (1×10^4 $TCID_{50}$) at 3-4 DPI. **(B)** Quantification of the percent viral positive cells showing no significant difference between the two groups using Student *t*-test.

Supplemental 4

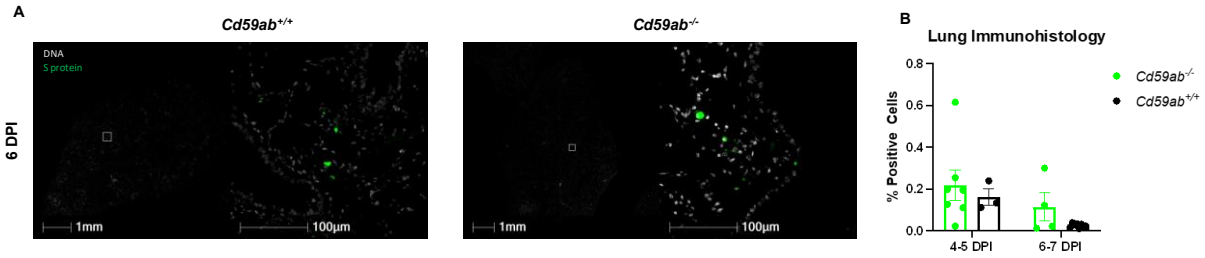

Figure S4: S protein staining in CD59 sufficient and sufficient mice after infection **(A)** Immunofluorescence staining of viral S protein (green) and DAPI (white) in *Cd59ab* sufficient and deficient mice after infection with 1×10^4 $TCID_{50}$ MA30 at 6 DPI. **(B)** Quantification of SARS-CoV-2 S protein positive cells with no significance as assessed by One-way ANOVA on the right at 4-5 and 6-7 DPI.

Supplemental 5

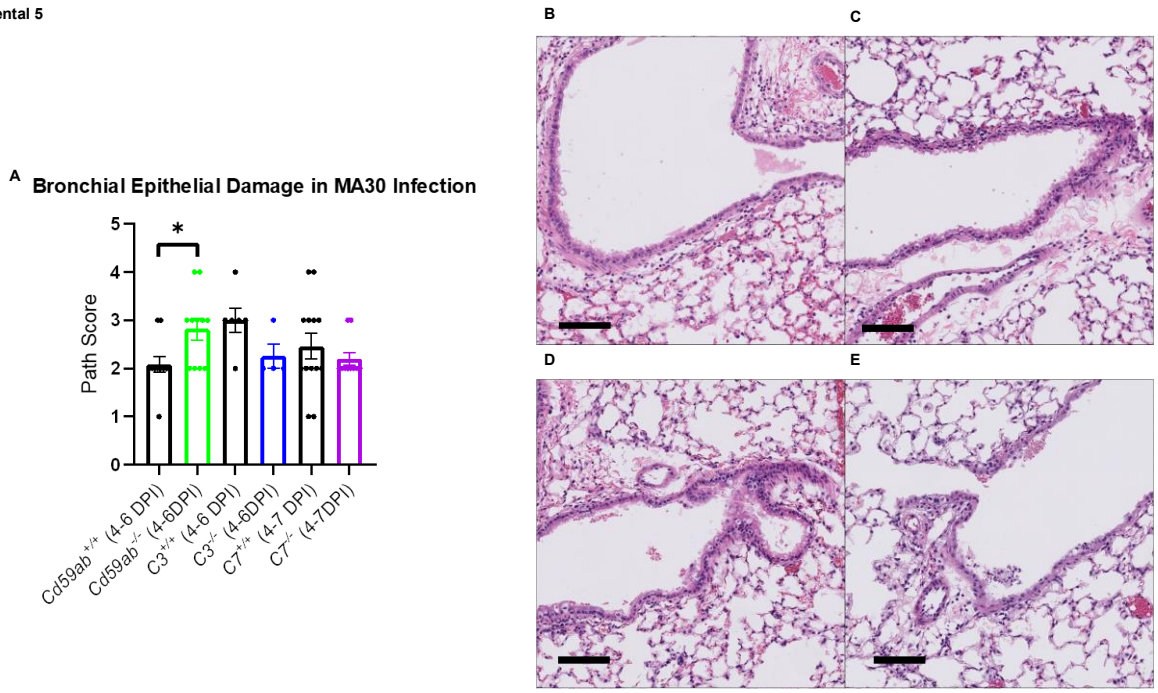

Figure S5. Pathologic quantification of bronchial epithelial damage in MA30 infection. **(A)** Histopathologic scoring of bronchial epithelial damage in B6 (control) mice and mice with deficiencies in complement components. Deficiency of the complement inhibitor (*Cd59ab*$^{-/-}$) resulted in a significant increase in bronchial epithelial damage (p=0.01, unpaired *t*-test); whereas *C3*$^{-/-}$ tended to result in lower levels bronchial damage (p=0.08, unpaired *t*-test) when compared to their *C3*$^{+/+}$ controls. **(B-E)** Mild (2+) epithelial damage in *C3*$^{+/+}$ (B) and *C3*$^{-/-}$ (C) mice characterized by vacuolation and apical blebbing. Representative image of moderate (3+) bronchial epithelial damage in *Cd59ab*$^{+/+}$ control mice (D) and bronchial epithelial damage (4+) in a *Cd59ab*$^{-/-}$ mice (E) characterized by sloughing and loss of the lining epithelial cells. H&E, Bar =100μm.

Supplemental 6

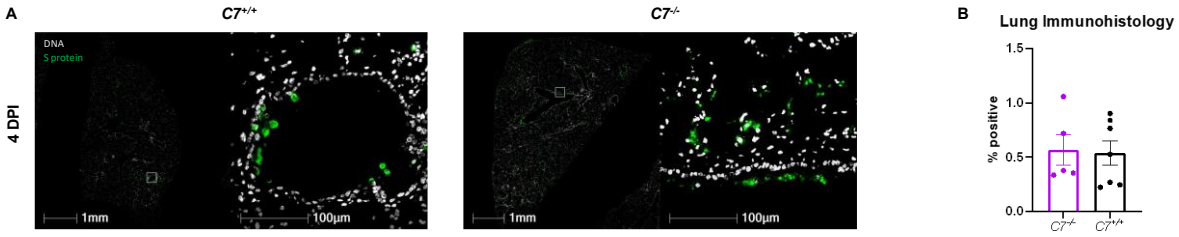

Figure S6: S protein staining in *C7* sufficient and sufficient mice after infection. **(A)** Immunofluorescence staining of viral S protein (green) and DAPI (white) in *C7* sufficient and deficient mice after infection with 2.5×10^4 $TCID_{50}$ at 4DPI. **(B)** Quantification of the percent viral S posivtive cells showing no significant difference between the two groups.

Supplemental 7

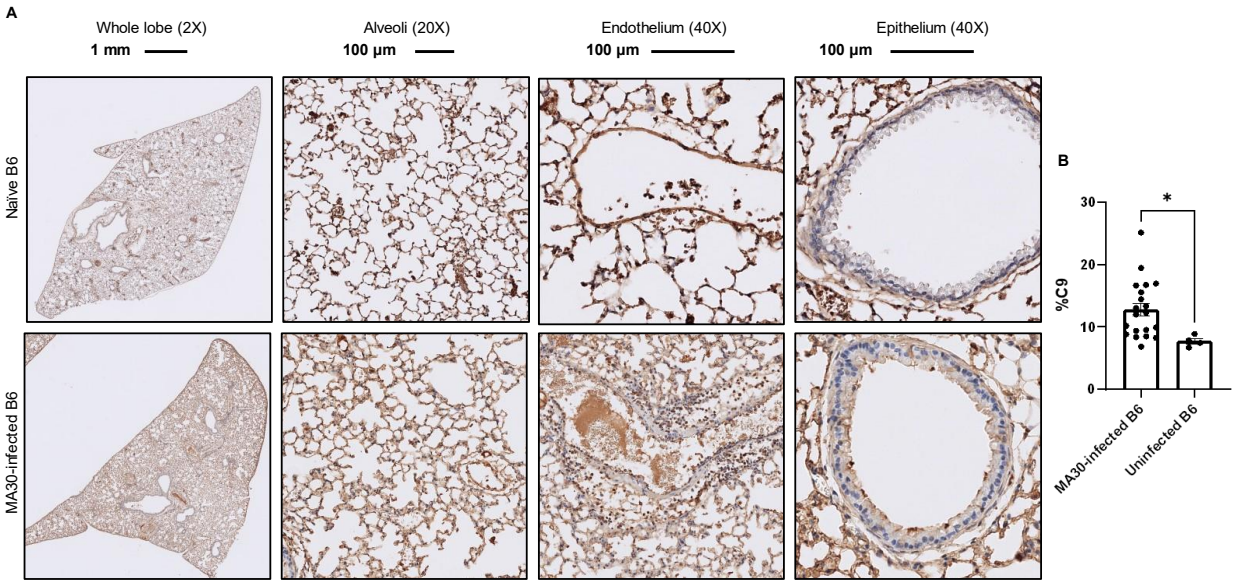

Figure S7: MAC deposition in the lungs of wild-type infected and uninfected mice as assessed by C9 staining. B6 mice were infected with a dose of MA30 (1×10^4 $TCID_{50}$) and stained along with naïve controls with polyclonal rabbit anti-rat C9 (kindly provided by Dr. Paul Morgan) at a 1:400 dilution. **(A-B)** Representative images (A) of the above showing whole lung lobe at magnification 2X, Alveoli at 20X, and epithelium and endothelium at 40X. Quantification (B) of C9 between infected and naïve, *P < 0.05 by two-tailed Student *t*-test.

Supplemental 8

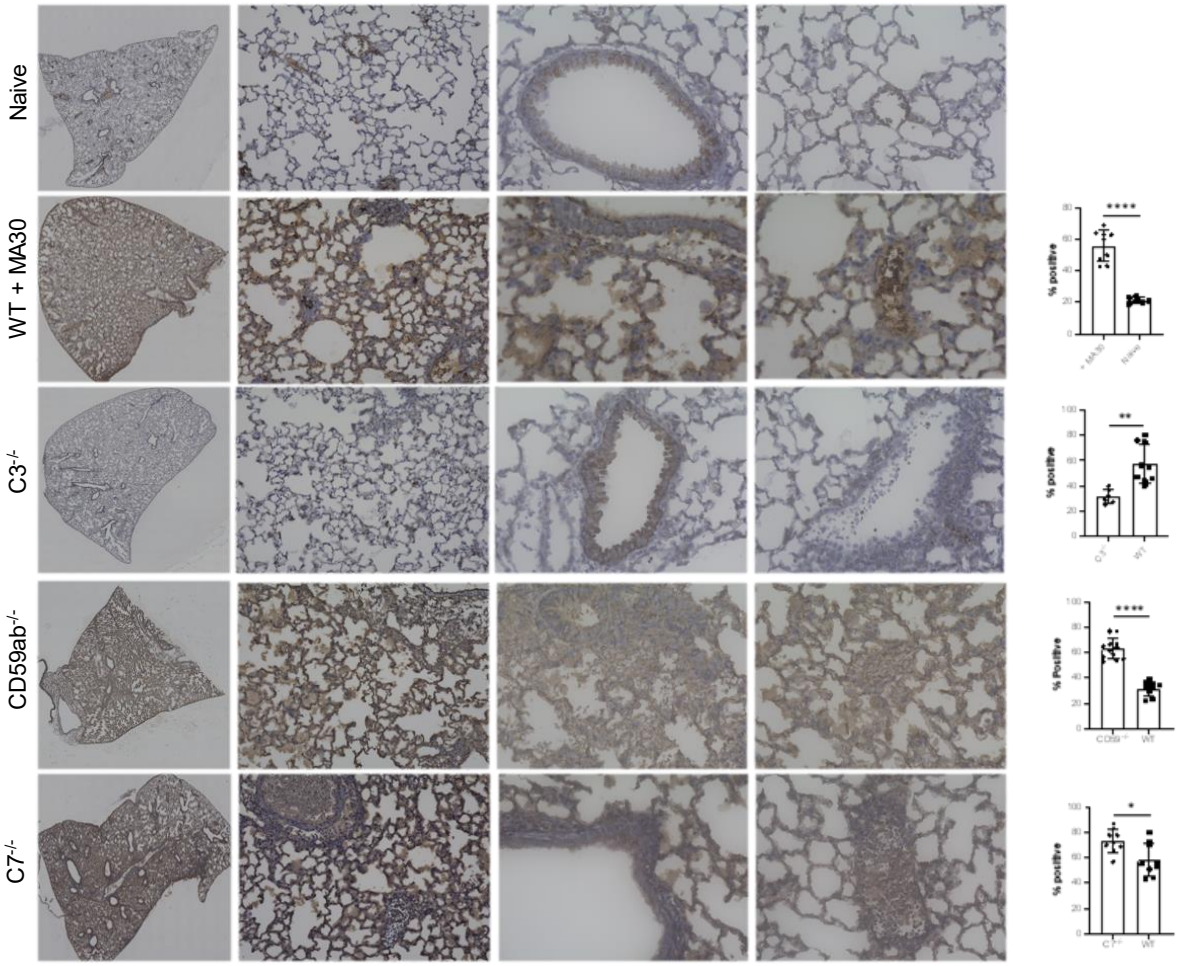

Figure S8: C3b deposition in the lungs as assessed by C3 staining. The following mice groups were infected with respective doses of MA30 SARS-CoV-2: Infected B6 (*n*=3 mice, 9 regions), 5×10^4 ×$TCID_{50}$ vs Naïve (*n*=2 mice, 6 regions). $C3^{-/-}$ (*n*=2 mice, 6 regions) vs $C3^{+/+}$ (*n*=3 mice, 9 regions), 5×10^4 $TCID_{50}$. $C7^{-/-}$(*n*=3 mice, 9 regions) vs $C7^{+/+}$ (*n*=3 mice, 9 regions), 2.5×10^4. $Cd59ab^{-/-}$ (*n*=4 mice, 12 regions) vs $Cd59ab^{+/+}$ (*n*=3 mice, 9 regions), 1×10^4 $TCID_{50}$. Representative images of the above groups showing whole lung lobe at magnification 2X, Alveoli at 20X, and epithelium and endothelium at 40X. Each mouse group was stained and quantified against these corresponding infected age-matched controls for quantification on the right.