**1 The inflammatory microenvironment of the lung at the time of

infection governs innate control of SARS-CoV-2 replication

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25 **ABSTRACT**
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26
27 ABSTRACT
28 SARS-CoV-2 infection leads to vastly divergent cli

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30 27
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32 27 **ABSTRACT**
28 **SARS-CoV-2**
30 infection to fa
31 to affect dise
32 CoV-2 expo:
33 demonstrate - 2901
- 2901
333345 29 SARS-CoV-2 infection leads to vastly divergent clinical outcomes ranging from asymptomatic

20 infection to fatal disease. Co-morbidities, sex, age, host genetics and vaccine status are known

21 to affect disease seve infection to fatal disease. Co-morbidities, sex, age, host genetics and vaccine status are known
31 to affect disease severity. Yet, how the inflammatory milieu of the lung at the time of SARS-CoV-2 exposure impacts the co 131 to affect disease severity. Yet, how the inflammatory milieu of the lung at the time of SARS-CoV-2 exposure impacts the control of viral replication remains poorly understood. We demonstrate here that immune events in CoV-2 exposure impacts the control of viral replication remains poorly understood. We
33 demonstrate here that immune events in the mouse lung closely preceding SARS-CoV-2
34 infection significantly impact viral control an demonstrate here that immune events in the mouse lung closely preceding SARS-CoV-2

infection significantly impact viral control and we identify key innate immune pathways required

to limit viral replication. A diverse se infection significantly impact viral control and we identify key innate immune pathways required
35 to limit viral replication. A diverse set of pulmonary inflammatory stimuli, including resolved
36 antecedent respiratory to limit viral replication. A diverse set of pulmonary inflammatory stimuli, including resolved
36 antecedent respiratory infections with S. aureus or influenza, ongoing pulmonary M.
37 tuberculosis infection, ovalbumin/al antecedent respiratory infections with *S. aureus* or influenza, ongoing pulmonary *M.*
 tuberculosis infection, ovalbumin/alum-induced asthma or airway administration of defined TLR

ligands and recombinant cytokines, *tuberculosis* infection, ovalbumin/alum-induced asthma or airway administration of defined TLR

igands and recombinant cytokines, all establish an antiviral state in the lung that restricts

SARS-CoV-2 replication upon in 38 ligands and recombinant cytokines, all establish an antiviral state in the lung that restricts
39 SARS-CoV-2 replication upon infection. In addition to antiviral type I interferons, the broadly
40 inducible inflammato SARS-CoV-2 replication upon infection. In addition to antiviral type I interferons, the broadly

40 inducible inflammatory cytokines TNFα and IL-1 precondition the lung for enhanced viral control.

41 Collectively, our wo inducible inflammatory cytokines TNFα and IL-1 precondition the lung for enhanced viral control.

41 Collectively, our work shows that SARS-CoV-2 may benefit from an immunologically quiescent

42 lung microenvironment and 41 Collectively, our work shows that SARS-CoV-2 may benefit from an immunologically quiescent
42 lung microenvironment and suggests that heterogeneity in pulmonary inflammation that
43 precedes or accompanies SARS-CoV-2 ex 42 lung microenvironment and suggests that heterogeneity in pulmonary inflammation that
43 precedes or accompanies SARS-CoV-2 exposure may be a significant factor contributing to the
44 population-wide variability in COVID 43 precedes or accompanies SARS-CoV-2 exposure may be a significant factor contributing to the
population-wide variability in COVID-19 disease outcomes.
45 44 population-wide variability in COVID-19 disease outcomes.
45

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46 **INTRODUCTION**
47 By the end of 202
49 CoV-2 (hereafter
50 variability in disea
51 pulmonary sympto 48
49
50
51
52 By the end of 2021, half of the global population had been infected at least once with SARS-
CoV-2 (hereafter SCV2)¹, the causative virus of COVID-19, with striking population-wide
variability in disease outcome. Prognos CoV-2 (hereafter SCV2) 1 CoV-2 (hereafter SCV2)⁻¹, the causative virus of COVID-19, with striking population-wide
50 variability in disease outcome. Prognoses include asymptomatic infection, mild, non-specific
51 pulmonary symptoms with or witho variability in disease outcome. Prognoses include asymptomatic infection, mild, non-specific
51 pulmonary symptoms with or without the development of post-acute sequelae of COVID-19 or
52 severe respiratory distress requir 51 pulmonary symptoms with or without the development of post-acute sequelae of COVID-19 or
52 severe respiratory distress requiring hospitalization and mechanical ventilation, which can lead
53 to death. Better understand severe respiratory distress requiring hospitalization and mechanical ventilation, which can lead
to death. Better understanding of the genetic and immunological determinants of heterogenous
disease outcomes could lead to m

to death. Better understanding of the genetic and immunological determinants of heterogenous
disease outcomes could lead to measures that improve the clinical management of COVID-19.
Contributing factors to the diversity i disease outcomes could lead to measures that improve the clinical management of COVID-19.
Contributing factors to the diversity in clinical outcomes include infectious dose and vira
strain differences, alongside host facto 55 Contributing factors to the diversity in clinical outcomes include infectious dose and viral
56 strain differences, alongside host factors like age, sex, genetics, and vaccination status, as well
57 as defects in innate strain differences, alongside host factors like age, sex, genetics, and vaccination status, as well
as defects in innate antiviral immunity or underlying comorbidities including obesity and diabetes
 $^{2+6}$. Human genetic as defects in innate antiviral immunity or underlying comorbidities including obesity and diabetes

58 ²⁻¹⁶. Human genetic variation associated with disease severity has revealed defective innate

59 immune responses as ²⁻¹⁶. Human genetic variation associated with disease severity has revealed defective innate $^{2-16}$. Human genetic variation associated with disease severity has revealed defective innate

immune responses as another key determinant in COVID-19 disease outcomes. Patients with

inborn errors in components of RNA 59 immune responses as another key determinant in COVID-19 disease outcomes. Patients with
60 inborn errors in components of RNA-sensing and innate signaling pathways, including toll-like
61 receptor 3 (TLR3), TLR7, inter 60 inborn errors in components of RNA-sensing and innate signaling pathways, including toll-like
61 receptor 3 (TLR3), TLR7, interferon-regulatory factor 7 (IRF7), type-I IFN (IFN-I) receptors
62 IFNAR1 and IFNAR2, tyrosi 61 receptor 3 (TLR3), TLR7, interferon-regulatory factor 7 (IRF7), type-I IFN (IFN-I) receptors
62 IFNAR1 and IFNAR2, tyrosine kinase 2 (TYK2) and oligoadenylate synthetase 1 (OAS1) are at
63 high risk of developing criti 62 IFNAR1 and IFNAR2, tyrosine kinase 2 (TYK2) and oligoadenylate synthetase 1 (OAS1) are at
63 high risk of developing critical and severe COVID-19 disease $2-4,15,17-19$ 12,20-22. The crucial
64 importance of innate-der high risk of developing critical and severe COVID-19 disease ^{2-4,15,17-19 12,20-22} high risk of developing critical and severe COVID-19 disease $2-4,15,17-19$ 12,20-22. The crucial
64 importance of innate-derived IFNs is further underscored by the discovery that up to $15 - 20\%$
65 of critically ill pat 64 importance of innate-derived IFNs is further underscored by the discovery that up to $15 - 20\%$ of critically ill patients with COVID-19 had preexisting auto-antibodies to IFN-I, which delayed viral clearance $^{23-26}$ 65 of critically ill patients with COVID-19 had preexisting auto-antibodies to IFN-I, which delayed
66 viral clearance $^{23-26}$. Thus, during the early phase of SCV2 infection, defective innate immune
67 responses due to viral clearance $23-26$. Thus, during the early phase of SCV2 infection, defective innate immune For the contract content of SCV2 infection, defective innate immune

responses due to genetic defects or auto-autoantibodies fundamentally influence disease

outcome 3.27 . Understanding pulmonary innate antiviral respon outcome ^{3,27}

For the sponses due to genetic defects or auto-autoantibodies fundamentally influence disease

68 outcome 3.27 . Understanding pulmonary innate antiviral responsiveness prior to SCV2 exposure

69 may, therefore, shed fur 68 outcome $32'$. Understanding pulmonary innate antiviral responsiveness prior to SCV2 exposure
69 may, therefore, shed further light on the variability in clinical presentations.
70 Patient populations with pre-existing 69 may, therefore, shed further light on the variability in clinical presentations.

70 Patient populations with pre-existing pulmonary diseases, although

71 be more vulnerable to SCV2 infection, have unexpected heteroge Patient populations with pre-existing pulmonary diseases, although initially predicted to

71 be more vulnerable to SCV2 infection, have unexpected heterogeneity in COVID-19 outcomes.

72 While certain chronic lung disease 21 be more vulnerable to SCV2 infection, have unexpected heterogeneity in COVID-19 outcomes.

22 While certain chronic lung diseases, including tuberculosis (TB) 28,29 and chronic obstructive

23 pulmonary disease (CO While certain chronic lung diseases, including tuberculosis (TB) 28,29 and chronic obstructive While certain chronic lung diseases, including tuberculosis (TB) 28,29 and chronic obstructive
pulmonary disease (COPD) $^{30\text{-}33}$ have been associated with increased severity of COVID-19 in
most studies, other chro pulmonary disease (COPD) ³⁰⁻³³ pulmonary disease (COPD) $30-33$ have been associated with increased severity of COVID-19 in

T4 most studies, other chronic pulmonary conditions, such as asthma $32-35$ and cystic fibrosis (CF)
 $36-38$ did not consisten most studies, other chronic pulmonary conditions, such as asthma $32-35$ most studies, other chronic pulmonary conditions, such as asthma $32-35$ and cystic fibrosis (CF)
75 $36-38$ did not consistently correlate with worsened COVID-19 presentation and have even been
876 associated with improv 36-38 ³⁶⁻³⁸ did not consistently correlate with worsened COVID-19 presentation and have even been
associated with improved disease outcomes. The immunological factors in the lung that
determine such variability in early viral 76 associated with improved disease outcomes. The immunological factors in the lung that
77 determine such variability in early viral control, and thus the likelihood of developing severe
18 disease, are incompletely under 77 determine such variability in early viral control, and thus the likelihood of developing severe
78 disease, are incompletely understood, and challenging to examine in clinical settings.
79 disease, are incompletely unde 78 disease, are incompletely understood, and challenging to examine in clinical settings.

There, we demonstrate using experimental mouse models of respiratory SCV2 infection

80 that recent pulmonary bacterial or viral infections or underlying allergic inflammation

81 precondition the lung for enhanced contro that recent pulmonary bacterial or viral infections or underlying allergic inflammation
81 precondition the lung for enhanced control of SCV2 replication. Importantly, administration of
82 individual TLR9 or TLR1/2 ligands precondition the lung for enhanced control of SCV2 replication. Importantly, administration of
82 individual TLR9 or TLR1/2 ligands, recombinant TNFα or recombinant IL-1 to the lung prior to
83 SCV2 infection also resulte individual TLR9 or TLR1/2 ligands, recombinant TNFα or recombinant IL-1 to the lung prior to
82 SCV2 infection also resulted in lower viral titers early after infection. Additionally, we surveyed
84 pulmonary innate infla SCV2 infection also resulted in lower viral titers early after infection. Additionally, we surveyed

84 pulmonary innate inflammatory pathways and identified a range of innate immune signaling

85 components necessary for 94 pulmonary innate inflammatory pathways and identified a range of innate immune signaling
95 components necessary for controlling early SCV2 replication in the lungs of mice. Collectively,
96 our work reveals that the in components necessary for controlling early SCV2 replication in the lungs of mice. Collectively,

86 our work reveals that the inflammatory lung microenvironment during SCV2 exposure may be a

97 previously underappreciated our work reveals that the inflammatory lung microenvironment during SCV2 exposure may be a

87 previously underappreciated, important factor in influencing disease variability and outcome

188 through potent innate restric 87 previously underappreciated, important factor in influencing disease variability and outcome
88 through potent innate restriction of early viral replication.
89 RESULTS
91 Recent infection or underlying inflammation of

88 through potent innate restriction of early viral replication.
89
91 RESULTS
92 Recent infection or underlying inflammation of the lu
93 exposure limits pulmonary viral replication 90
91
92
93
94

90 **RESULTS**
91 **Recent informational State State State**
94 To
95 **impact earl** 92
93
94
95
96 Recent infection or underlying inflammation of the lung at the time of SARS-CoV-2
exposure limits pulmonary viral replication
To explore whether the recent infectious and inflammatory history of the lung
impact early viral exposure limits pulmonary viral replication
94 To explore whether the recent infecti
95 impact early viral replication, we exposed mic
96 inflammatory stimuli prior to SCV2 infection.
97 demonstrated that ongoing 94 To explore whether the recent infectious and inflammatory history of the lung could
95 impact early viral replication, we exposed mice to a variety of respiratory pathogens or sterile
96 inflammatory stimuli prior to SC 95 impact early viral replication, we exposed mice to a variety of respiratory pathogens or sterile
96 inflammatory stimuli prior to SCV2 infection. For example, we and others have previously
97 demonstrated that ongoing 96 inflammatory stimuli prior to SCV2 infection. For example, we and others have previously
97 demonstrated that ongoing presence of mycobacteria in the lungs after infection with chronic
98 mycobacterial pathogens such as 97 demonstrated that ongoing presence of mycobacteria in the lungs after infection with chronic
98 mycobacterial pathogens such as *Mycobacterium tuberculosis* (*Mtb*) or Bacille Calmette-Guérin
99 (BCG) results in lower mycobacterial pathogens such as *Mycobacterium tuberculosis* (*Mtb*) or Bacille Calmette-Guérin (BCG) results in lower viral titers and protection against SCV2³⁹⁻⁴⁴. C57BL/6 wild type (WT) mice were infected with *Mtb* 3 (BCG) results in lower viral titers and protection against SCV2 $39-44$ 99 (BCG) results in lower viral titers and protection against SCV2 $39-44$. C57BL/6 wild type (WT)
100 mice were infected with *Mtb* 3 – 4 months prior to infection with SCV2 variant of concern (VOC)
101 B.1.351 (beta var 100 mice were infected with *Mtb* 3 – 4 months prior to infection with SCV2 variant of concern (VOC)
101 B.1.351 (beta variant) (Fig 1A). Consistent with our previous data, mice with an ongoing *Mtb*
102 infection exhibite 101 B.1.351 (beta variant) (Fig 1A). Consistent with our previous data, mice with an ongoing *Mtb*
102 infection exhibited significantly decreased lung viral titers three days post SCV2 infection
103 compared to mice witho 102 infection exhibited significantly decreased lung viral titers three days post SCV2 infection

103 compared to mice without underlying infection as detected by both TCID₅₀ assay and qPCR for

104 the SCV2 envelope (E 103 compared to mice without underlying infection as detected by both $TCID_{50}$ assay and qPCR for

104 the SCV2 envelope (E) gene in its actively replicating form, (subgenomic, sub-gRNA) (Fig 1A).

105 To investigate whet 104 the SCV2 envelope (E) gene in its actively replicating form, (subgenomic, sub-gRNA) (Fig 1A).

105 To investigate whether suppression of SCV2 replication is specific to mycobacterial

106 coinfections, we next exposed 105 To investigate whether suppression of SCV2 replication is specific to mycobacterial
106 coinfections, we next exposed mice to Methicillin-resistant *Staphylococcus aureus* (*S. aureus*,
107 USA300), a gram-positive bac 106 coinfections, we next exposed mice to Methicillin-resistant *Staphylococcus aureus* (*S. aureus*, 107 USA300), a gram-positive bacterial pathogen that is a major cause of nosocomial infections ⁴⁵.
108 While intratrac USA300), a gram-positive bacterial pathogen that is a major cause of nosocomial infections ⁴⁵ USA300), a gram-positive bacterial pathogen that is a major cause of nosocomial infections ⁴⁵.
108 While intratracheal inoculation of *S. aureus* induces a potent immune infiltrate in the lungs, it is
109 rapidly cleared 108 While intratracheal inoculation of S. aureus induces a potent immune infiltrate in the lungs, it is

109 rapidly cleared within 48 hours in mice ⁴⁶. Taking advantage of the rapid bacterial clearance in

110 this mode rapidly cleared within 48 hours in mice 46 . Taking advantage of the rapid bacterial clearance in 109 rapidly cleared within 48 hours in mice ⁴⁶. Taking advantage of the rapid bacterial clearance in
110 this model, we tested whether recent inflammation elicited in response to extracellular bacteria
111 is equally pro 110 this model, we tested whether recent inflammation elicited in response to extracellular bacteria
111 is equally protective as actively replicating intracellular mycobacteria. Indeed, when we
112 intrapharyngeally (i.ph 111 is equally protective as actively replicating intracellular mycobacteria. Indeed, when we
112 intrapharyngeally (i.ph.) exposed the lungs of WT mice to S. aureus three days prior to SCV2 112 intrapharyngeally (i.ph.) exposed the lungs of WT mice to *S. aureus* three days prior to SCV2 113 B.1.351 infection, mice with recently cleared *S. aureus* infection exhibited significantly lower
114 SCV2 viral titers than mice without prior exposure to *S. aureus* (Fig 1B). Thus, both very recent
115 and chronic p 114 SCV2 viral titers than mice without prior exposure to *S. aureus* (Fig 1B). Thus, both very recent
115 and chronic pulmonary bacterial infections can promote an antiviral state in the mouse lung that
116 lowers SCV2 ti

and chronic pulmonary bacterial infections can promote an antiviral state in the mouse lung that
116 lowers SCV2 titers prior to the onset of adaptive immunity and this protective feature is not
117 unique to mycobacteria. 116 lowers SCV2 titers prior to the onset of adaptive immunity and this protective feature is not
117 unique to mycobacteria.
118 We then asked whether this innate antiviral state is specific to previous bacterial lung
119 117 unique to mycobacteria.

118 We then asked \

119 infections or whether prior

120 viral control in the lungs

121 been shown in both *in*

122 phenomenon known as 118 We then asked whether this innate antiviral state is specific to previous bacterial lung
119 infections or whether prior lower-respiratory viral infections can similarly confer improved innate
120 viral control in the 119 infections or whether prior lower-respiratory viral infections can similarly confer improved innate

120 viral control in the lungs of mice. Simultaneous co-infection with Influenza A Virus (IAV) has

121 been shown in 120 viral control in the lungs of mice. Simultaneous co-infection with Influenza A Virus (IAV) has

121 been shown in both *in vitro* and *in vivo* studies to potently interfere with SCV2 replication, a

122 phenomenon kn 121 been shown in both *in vitro* and *in vivo* studies to potently interfere with SCV2 replication, a
122 phenomenon known as 'viral interference' ⁴⁷⁻⁵¹, but it remains unclear whether a recently
123 resolved and cleare phenomenon known as 'viral interference' ⁴⁷⁻⁵¹ 122 phenomenon known as 'viral interference' $47-51$, but it remains unclear whether a recently
123 resolved and cleared IAV infection could also affect early viral SCV2 replication. Thus, rather
124 than simultaneously c resolved and cleared IAV infection could also affect early viral SCV2 replication. Thus, rather
124 than simultaneously co-infecting mice, we intranasally (i.n.) infected with IAV one month prior to
125 SCV2 infection, a t 124 than simultaneously co-infecting mice, we intranasally (i.n.) infected with IAV one month prior to
125 SCV2 infection, a time frame by which IAV has been cleared for a minimum of two weeks ^{52,53}.
126 Mice that had re SCV2 infection, a time frame by which IAV has been cleared for a minimum of two weeks $52,53$. SCV2 infection, a time frame by which IAV has been cleared for a minimum of two weeks ^{52,53}.
126 Mice that had recently cleared IAV infection displayed a significant reduction in lung SCV2 viral
127 titers compared to mi Mice that had recently cleared IAV infection displayed a significant reduction in lung SCV2 viral
127 titers compared to mice without a recent IAV infection (Fig 1C). These data suggest that the
128 pulmonary anti-SCV2 sta titers compared to mice without a recent IAV infection (Fig 1C). These data suggest that the
128 pulmonary anti-SCV2 state induced by prior pathogen exposure does not require ongoing
129 infection and can persist for at le

pulmonary anti-SCV2 state induced by prior pathogen exposure does not require ongoing
infection and can persist for at least two weeks after prior pathogen clearance.
Finally, to determine whether only prior live pathogens 129 infection and can persist for at least two weeks after prior pathogen clearance.

130 Finally, to determine whether only prior live pathogens and/or type I in

131 are necessary to restrict SCV2 replication in the mous 130 Finally, to determine whether only prior live pathogens and/or type I immune responses
131 are necessary to restrict SCV2 replication in the mouse lung, we induced a sterile type II
132 immune-driven allergic inflammat 131 are necessary to restrict SCV2 replication in the mouse lung, we induced a sterile type II
132 immune-driven allergic inflammatory response using the ovalbumin (OVA)/alum-driven asthma
133 model. Five days after i.n. c 132 immune-driven allergic inflammatory response using the ovalbumin (OVA)/alum-driven asthma
133 model. Five days after i.n. challenge with OVA, mice were infected with SCV2 B.1.351 and we
134 found that mice with underly model. Five days after i.n. challenge with OVA, mice were infected with SCV2 B.1.351 and we
134 found that mice with underlying type II inflammation displayed a significantly reduced lung
135 burden of SCV2 (Fig 1D). These 134 found that mice with underlying type II inflammation displayed a significantly reduced lung

135 burden of SCV2 (Fig 1D). These results establish that both live pathogen and sterile type I - or

136 type II -driven, re 135 burden of SCV2 (Fig 1D). These results establish that both live pathogen and sterile type I - or
136 type II -driven, recent, or ongoing inflammatory responses restrain initial SCV2 replication in the
137 mouse lung an type II -driven, recent, or ongoing inflammatory responses restrain initial SCV2 replication in the

137 mouse lung and suggest that the recent pulmonary exposure history contributes to disease

138 trajectory.

140 **Previ**

mouse lung and suggest that the recent pulmonary exposure history contributes to disease
138 trajectory.
139 **Previous pulmonary TLR stimulation is sufficient to suppress SCV2 replication.**
141 While we showed that recent 138 trajectory.
139
140 **Previous**
141 Wh
142 sterile ast
143 underlying 139
140
141
142
143
144 **Previous pulmonary TLR stimulation is sufficient to suppress SCV2 replication.**

141 While we showed that recent diverse pulmonary exposures, ranging from pat

142 sterile asthmatic inflammation, condition the lung for im 141 While we showed that recent diverse pulmonary exposures, ranging from pathogens to
142 sterile asthmatic inflammation, condition the lung for improved viral SCV2 control, the precise
143 underlying cellular and molecul 142 sterile asthmatic inflammation, condition the lung for improved viral SCV2 control, the precise
143 underlying cellular and molecular mechanisms in each setting are likely very complex.
144 Therefore, we evaluated whet 143 underlying cellular and molecular mechanisms in each setting are likely very complex.

144 Therefore, we evaluated whether a single pulmonary administration of a TLR ligand, one week

145 prior to SCV2 infection would 144 Therefore, we evaluated whether a single pulmonary administration of a TLR ligand, one week
145 prior to SCV2 infection would be sufficient to promote an antiviral state in the lungs of mice,
146 allowing for more amen 145 prior to SCV2 infection would be sufficient to promote an antiviral state in the lungs of mice,
146 allowing for more amenable exploration of potential mechanisms that contribute to viral
146 allowing for more amenable 146 allowing for more amenable exploration of potential mechanisms that contribute to viral

147 restriction. Such an approach would also inform on the effects of TLR agonists used as
148 adjuvants in conjunction with antigens in mucosally delivered vaccines. Importantly, we found
149 that i.ph. administration of 148 adjuvants in conjunction with antigens in mucosally delivered vaccines. Importantly, we found
149 that i.ph. administration of the TLR9 agonist type B CpG (CpG) or the TLR1/TLR2 agonist
150 Pam3CSK4 (Pm3) to WT mice on 149 that i.ph. administration of the TLR9 agonist type B CpG (CpG) or the TLR1/TLR2 agonist
150 Pam3CSK4 (Pm3) to WT mice one week prior to SCV2 B.1.351 infection, resulted in a
151 significant reduction in SCV2 burden com 150 Pam3CSK4 (Pm3) to WT mice one week prior to SCV2 B.1.351 infection, resulted in a
151 significant reduction in SCV2 burden compared to mice that were not pre-treated with TLR
152 ligands (Fig 2A, S1A). To investigate t 151 significant reduction in SCV2 burden compared to mice that were not pre-treated with TLR
152 ligands (Fig 2A, S1A). To investigate the duration of protection afforded by one-time prior TLR
153 activation in the lung fo ligands (Fig 2A, S1A). To investigate the duration of protection afforded by one-time prior TLR
activation in the lung following CpG administration, rather than seven days, we rested mice for
seven weeks before infecting t activation in the lung following CpG administration, rather than seven days, we rested mice for
154 seven weeks before infecting them with SCV2. Remarkably, the protection afforded by prior
155 pulmonary CpG administration seven weeks before infecting them with SCV2. Remarkably, the protection afforded by prior
155 pulmonary CpG administration did not persist, as lung SCV2 titers were unchanged between
156 CpG pre-treated and untreated mice pulmonary CpG administration did not persist, as lung SCV2 titers were unchanged between
156 CpG pre-treated and untreated mice seven weeks after CpG preconditioning (Fig 2B, S1B).
157 Thus, only recent pulmonary exposure

CpG pre-treated and untreated mice seven weeks after CpG preconditioning (Fig 2B, S1B).
157 Thus, only recent pulmonary exposure to the TLR9 agonist CpG provided early viral replication
158 control.
159 To extend our obser Thus, only recent pulmonary exposure to the TLR9 agonist CpG provided early viral replication
158 control.
159 To extend our observations to another mouse model of SCV2 infection and to rule out
160 the possibility that ou 158 control.
159 160 161 162 162 164
162 under th
163 or Pm3 159 To extend our observations to another mouse model of SCV2 infection and to rule out
160 the possibility that our findings may be unique to infections of C57BL/6 mice with the SCV2
161 VOC B.1.351, we similarly pre-expo 160 the possibility that our findings may be unique to infections of C57BL/6 mice with the SCV2
161 VOC B.1.351, we similarly pre-exposed lungs of mice transgenically expressing human ACE2
162 under the control of the epit VOC B.1.351, we similarly pre-exposed lungs of mice transgenically expressing human ACE2
162 under the control of the epithelial K18 promoter (K18-hACE2 Tg) mice to a single dose of CpG
163 or Pm3 one week prior to infecti under the control of the epithelial K18 promoter (K18-hACE2 Tg) mice to a single dose of CpG
or Pm3 one week prior to infection with the ancestral clinical isolate of SCV2 USA-WA1/2020.
Consistent with our results from C57 163 or Pm3 one week prior to infection with the ancestral clinical isolate of SCV2 USA-WA1/2020.
164 Consistent with our results from C57BL/6 mice, only K18-hACE2 Tg mice whose lungs were
165 pre-exposed to TLR ligands dis 164 Consistent with our results from C57BL/6 mice, only K18-hACE2 Tg mice whose lungs were
165 pre-exposed to TLR ligands displayed a significant reduction in lung viral titers when assessed
166 by either TCID₅₀ or qPCR 165 pre-exposed to TLR ligands displayed a significant reduction in lung viral titers when assessed
166 by either TCID₅₀ or qPCR assays three days after infection (Fig 2C). This model is acutely
167 susceptible to SCV2-166 by either TCID₅₀ or qPCR assays three days after infection **(Fig 2C).** This model is acutely
167 susceptible to SCV2-induced disease, and we saw that reduced viral replication was reflected in
168 significantly reduc susceptible to SCV2-induced disease, and we saw that reduced viral replication was reflected in
168 significantly reduced SCV2-induced moribundity with CpG, but not Pm3 pre-treatment (Fig 2D),
169 despite no detectable dif 168 significantly reduced SCV2-induced moribundity with CpG, but not Pm3 pre-treatment **(Fig 2D)**,
169 despite no detectable differences in SCV2-induced lung pathology as determined by histological
170 analysis three days

despite no detectable differences in SCV2-induced lung pathology as determined by histological
170 analysis three days after infection (Fig S1C).
171 We next hypothesized that CpG- and Pm3-triggered protection after SCV2 i analysis three days after infection (Fig S1C).
171 We next hypothesized that CpG- and
172 be associated with transcriptional changes
173 performed bulk RNA sequencing of K18-hAC
174 CpG or Pm3. Gene Ontology (GO) enrichmer 171 We next hypothesized that CpG- and Pm3-triggered protection after SCV2 infection may
172 be associated with transcriptional changes in the lung. Three days after SCV2 infection we
173 performed bulk RNA sequencing of K 172 be associated with transcriptional changes in the lung. Three days after SCV2 infection we
173 performed bulk RNA sequencing of K18-hACE2 Tg lungs that had been previously treated with
174 CpG or Pm3. Gene Ontology (GO 173 performed bulk RNA sequencing of K18-hACE2 Tg lungs that had been previously treated with
174 CpG or Pm3. Gene Ontology (GO) enrichment analysis on differentially expressed genes (DEG)
175 revealed genes involved in "a 174 CpG or Pm3. Gene Ontology (GO) enrichment analysis on differentially expressed genes (DEG)
175 revealed genes involved in "antimicrobial peptide" responses for CpG pre-treated mice, while
176 genes associated with "cel 175 revealed genes involved in "antimicrobial peptide" responses for CpG pre-treated mice, while
176 genes associated with "cellular interactions between lymphoid and non-lymphoid cells" were
177 enriched in Pm3 pre-treate queres associated with "cellular interactions between lymphoid and non-lymphoid cells" were
enriched in Pm3 pre-treated mice compared to SCV2 infected mice without prior TLR ligand
exposure (Fig 2E). The pathways shared by 177 enriched in Pm3 pre-treated mice compared to SCV2 infected mice without prior TLR ligand
178 exposure (Fig 2E). The pathways shared by both CpG and Pm3 pre-treatments were
179 associated with the activation of scavenge 178 exposure (Fig 2E). The pathways shared by both CpG and Pm3 pre-treatments were
179 associated with the activation of scavenger receptors, DAP12 signaling, and omega-3 and
180 omega-6-derived bioactive lipid pathways (F 179 associated with the activation of scavenger receptors, DAP12 signaling, and omega-3 and
180 omega-6-derived bioactive lipid pathways (Fig 2E). Four significantly upregulated (*Fcrls, Ms4a7,* 180 omega-6-derived bioactive lipid pathways **(Fig 2E).** Four significantly upregulated (*Fcrls, Ms4a7,*

181 *Siglece, A930001A20Rik)* and three significantly downregulated (*Alox15, Marco, Mt2*) DEGs
182 were shared between the SCV2 infected mice that were pre-treated with TLR agonists (Fig 2F),
183 which together reflect a were shared between the SCV2 infected mice that were pre-treated with TLR agonists (Fig 2F),

183 which together reflect a transcriptional signature predominantly expressed in macrophages

184 (ImmGen MyGeneSet) (Fig 2G). 183 which together reflect a transcriptional signature predominantly expressed in macrophages

184 (ImmGen MyGeneSet) (Fig 2G). It was notable that $A/\alpha x/5$, which encodes the 12/15-

185 lipoxygenase (12/15-LO) was found 184 (ImmGen MyGeneSet) (Fig 2G). It was notable that *Alox15*, which encodes the 12/15-
185 lipoxygenase (12/15-LO) was found to be a significantly downregulated DEG. Lipoxygenases
186 are key enzymes for the processing of 185 lipoxygenase (12/15-LO) was found to be a significantly downregulated DEG. Lipoxygenases
186 are key enzymes for the processing of omega-3 and omega-6-derived fatty acids into a variety
187 of bioactive lipid mediator 186 are key enzymes for the processing of omega-3 and omega-6-derived fatty acids into a variety
187 of bioactive lipid mediators of inflammation and resolution $54-56$. We hypothesized that TLR-
188 induced downregulatio of bioactive lipid mediators of inflammation and resolution $54-56$ 187 of bioactive lipid mediators of inflammation and resolution $54-56$. We hypothesized that TLR-
188 induced downregulation of 12/15-LO in the lungs at the time of SCV2 exposure could decrease
189 viral titers and, if s 188 induced downregulation of 12/15-LO in the lungs at the time of SCV2 exposure could decrease

189 viral titers and, if so, 12/15-LO-deficient mice would accordingly display lower viral titers.

190 However, when we inf 189 viral titers and, if so, 12/15-LO-deficient mice would accordingly display lower viral titers.

190 However, when we infected $A/\alpha x 15^{-/-}$ mice with SCV2 B.1.351, lung viral titers were instead

191 significantly elev However, when we infected *Alox15-/-* 190 However, when we infected $A/\sqrt{5}$ mice with SCV2 B.1.351, lung viral titers were instead
191 significantly elevated in the knockout animals (Fig 2H), suggesting that 12/15-LO deficiency
192 does not license enhanced 191 significantly elevated in the knockout animals (Fig 2H), suggesting that 12/15-LO deficiency
192 does not license enhanced viral replication and instead is necessary for optimal SCV2 control.
193 Together, these data r does not license enhanced viral replication and instead is necessary for optimal SCV2 control.
193 Together, these data revealed that the lungs of mice previously exposed to TLR-driven
194 inflammation display relatively f 193 Together, these data revealed that the lungs of mice previously exposed to TLR-driven

194 inflammation display relatively few transcriptional changes after SCV2 infection when compared

195 to SCV2-infected lungs of m

inflammation display relatively few transcriptional changes after SCV2 infection when compared
195 to SCV2-infected lungs of mice not pre-treated with TLR agonists.
196 Recent pulmonary TLR stimulation results in sustained

to SCV2-infected lungs of mice not pre-treated with TLR agonists.
196
**Recent pulmonary TLR stimulation results in sustained time activation and inflammatory cytokines levels at the time of SC
199 To understand how the rec** 196
197
198
199
200
201 197 **Recent pulmonary TLR stimulation results in sustained tissue resident macrophage**
198 **activation and inflammatory cytokines levels at the time of SCV2 exposure**
199 To understand how the recent inflammatory history o activation and inflammatory cytokines levels at the time of SCV2 exposure
199 To understand how the recent inflammatory history of the lung may condition
200 microenvironment for improved viral control prior to SCV2 exposu 199 To understand how the recent inflammatory history of the lung may condition the pulmonary

190 microenvironment for improved viral control prior to SCV2 exposure, we analyzed lungs one

191 week after TLR stimulation b 200 microenvironment for improved viral control prior to SCV2 exposure, we analyzed lungs one
201 week after TLR stimulation but before SCV2 infection. We started by asking whether improved
202 viral control following rece week after TLR stimulation but before SCV2 infection. We started by asking whether improved
202 viral control following recent local inflammation may simply be due to CpG or Pm3-mediated
203 downregulation of the SCV2 entr 202 viral control following recent local inflammation may simply be due to CpG or Pm3-mediated

203 downregulation of the SCV2 entry receptor ACE2 prior to infection. We quantified ACE2 protein

204 levels in lung homogen downregulation of the SCV2 entry receptor ACE2 prior to infection. We quantified ACE2 protein

204 levels in lung homogenates of WT or K18-hACE2 Tg mice 7 – 10 days post-i.ph. treatment with

205 TLR ligands and did not ob 204 levels in lung homogenates of WT or K18-hACE2 Tg mice 7 – 10 days post-i.ph. treatment with
205 TLR ligands and did not observe a reduction in the overall expression of either murine or human
206 ACE2 protein (Fig S2A) TLR ligands and did not observe a reduction in the overall expression of either murine or human

206 ACE2 protein (Fig S2A). These data suggest that improved viral control in the lungs was not

207 associated with a global

ACE2 protein (Fig S2A). These data suggest that improved viral control in the lungs was not

207 associated with a global reduction of ACE2 entry receptors at the time of SCV2 infection.

208 To further explore the heighte 207 associated with a global reduction of ACE2 entry receptors at the time of SCV2 infection.

208 To further explore the heightened antiviral state after airway administration of

209 agonists, we performed bulk RNA seque 208 To further explore the heightened antiviral state after airway administration of TLR

209 agonists, we performed bulk RNA sequencing 10 days following TLR activation of K18-hACE2

210 Tg lungs without SCV2 infection. I 209 agonists, we performed bulk RNA sequencing 10 days following TLR activation of K18-hACE2
210 Tg lungs without SCV2 infection. In both CpG and Pm3 pre-treatment conditions, all significant
211 DEGs were upregulated comp 210 Tg lungs without SCV2 infection. In both CpG and Pm3 pre-treatment conditions, all significant
211 DEGs were upregulated compared to RNA from control mice that received PBS (Fig 3A). GO
212 enrichment analysis revealed 211 DEGs were upregulated compared to RNA from control mice that received PBS (Fig 3A). GO
212 enrichment analysis revealed that similar pathways were enriched in CpG and Pm3-exposed
213 lungs (Fig 3B). GO terms that were 212 enrichment analysis revealed that similar pathways were enriched in CpG and Pm3-exposed
213 lungs (Fig 3B). GO terms that were shared between both protective conditions included those
214 related to regulation of the c 213 lungs (Fig 3B). GO terms that were shared between both protective conditions included those
214 related to regulation of the complement cascade, chemokine receptors and chemokine signaling
14 related to regulation of t 214 related to regulation of the complement cascade, chemokine receptors and chemokine signaling

The complement cascade, chemokine receptors and chemokine signaling

The complement cascade, chemokine receptors and chemoki

(Fig 3B). Eleven significant DEGs (2010008C14Rik, Aif1, C1qb, C3ar1, Calhm6, Ccr5, Cxcl9, *Irgb10, Ms4a7, Saa3 and Trem2*) were identified in common between the two TLR-agonist treated groups compared to PBS controls (Fig *Irgb10, Ms4a7, Saa3 and Trem2*) were identified in common between the two TLR-agonist

treated groups compared to PBS controls (Fig 3C). Similar to the shared DEGs identified from

lungs of mice that were TLR stimulated p 217 treated groups compared to PBS controls (Fig 3C). Similar to the shared DEGs identified from
218 lungs of mice that were TLR stimulated prior to SCV2 infection (Fig 2G), shared DEGs after
219 CpG or Pm3 lung administra lungs of mice that were TLR stimulated prior to SCV2 infection **(Fig 2G)**, shared DEGs after CpG or Pm3 lung administration were primarily expressed in macrophage subsets (ImmGen MyGeneSet) **(Fig 3C)**. Based on a chemokine 219 CpG or Pm3 lung administration were primarily expressed in macrophage subsets (ImmGen MyGeneSet) (Fig 3C). Based on a chemokine and macrophage-enriched gene signature, we hypothesized that TLR-induced upregulation of 220 MyGeneSet) (Fig 3C). Based on a chemokine and macrophage-enriched gene signature, we
221 hypothesized that TLR-induced upregulation of CCR5, a chemokine receptor also expressed by
222 macrophages and whose suppression 221 hypothesized that TLR-induced upregulation of CCR5, a chemokine receptor also expressed by

222 macrophages and whose suppression has been identified as a genetic risk factor for COVID-19

223 12,21,57 , could acco 222 macrophages and whose suppression has been identified as a genetic risk factor for COVID-19

223 ^{12,21,57}, could account for the observed heightened antiviral state. When $Ccr5^{\prime}$ mice were

224 infected with SCV2 ^{12,21,57}, could account for the observed heightened antiviral state. When $Ccr5$ mice were

224 infected with SCV2 B.1.35, lung viral titers were significantly elevated in the knockout animals

225 compared to WT control 224 infected with SCV2 B.1.35, lung viral titers were significantly elevated in the knockout animals

225 compared to WT controls (Fig 3D), supporting a critical role for CCR5 expression in SCV2

226 restriction, without compared to WT controls (Fig 3D), supporting a critical role for CCR5 expression in SCV2

226 restriction, without prior TLR activation. However, CCR5 was dispensable for TLR agonist pre-

227 treatment-mediated viral cont 226 restriction, without prior TLR activation. However, CCR5 was dispensable for TLR agonist pre-

227 treatment-mediated viral control, as $Ccr5^{\prime}$ mice still had reduced SCV2 viral loads after prior

228 CpG or Pm3 exp treatment-mediated viral control, as *Ccr5-/* treatment-mediated viral control, as *Ccr5*⁻⁻ mice still had reduced SCV2 viral loads after prior
228 CpG or Pm3 exposure compared to untreated *Ccr5*^{-/-} mice (Fig 3E). Of note, although *Trem2*
229 was a significantly CpG or Pm3 exposure compared to untreated *Ccr5-/-* 228 CpG or Pm3 exposure compared to untreated Ccr5^{-/-} mice (Fig 3E). Of note, although *Trem2* was a significantly upregulated DEG following TLR stimulation, Triggering Receptor Expressed
230 on Myeloid cells 2 (TREM2) d was a significantly upregulated DEG following TLR stimulation, Triggering Receptor Expressed

230 on Myeloid cells 2 (TREM2) deficiency did not reverse the protective effect of CpG pre-

231 treatment prior to SCV2 infecti 230 on Myeloid cells 2 (TREM2) deficiency did not reverse the protective effect of CpG pre-
231 treatment prior to SCV2 infection (Fig S2B) nor did deficiency in CCR2, another chemokine
232 receptor highly expressed on mon treatment prior to SCV2 infection (Fig S2B) nor did deficiency in CCR2, another chemokine

232 receptor highly expressed on monocytes and important for monocyte-derived macrophages (Fig

233 S2C).

234 Based on the transcr

receptor highly expressed on monocytes and important for monocyte-derived macrophages (Fig

233 S2C).

234 Based on the transcriptional changes in innate and macrophage-associated genes, we

235 hypothesized that prior pul 233 **S2C**).
234
235 hypoth
236 throug
237 to pla
238 macro Based on the transcriptional changes in innate and macrophage-associated genes, we

235 hypothesized that prior pulmonary inflammation may remodel the lung microenvironment

236 through the tissue-resident macrophage (TRM) 235 hypothesized that prior pulmonary inflammation may remodel the lung microenvironment
236 through the tissue-resident macrophage (TRM) compartment. In fact, TRMs have been shown
237 to play important roles in SCV2 patho 236 through the tissue-resident macrophage (TRM) compartment. In fact, TRMs have been shown
237 to play important roles in SCV2 pathogenesis ranging from modulating lung-epithelial
238 macrophage crosstalk, interferon resp 237 to play important roles in SCV2 pathogenesis ranging from modulating lung-epithelial

238 macrophage crosstalk, interferon responses, and antiviral T cell responses to contributing to

239 pathology and cytokine storm 238 macrophage crosstalk, interferon responses, and antiviral T cell responses to contributing to

239 pathology and cytokine storm at later disease stages $58-63$. We, therefore, directly examined

240 alveolar macrophag pathology and cytokine storm at later disease stages $58-63$ 239 pathology and cytokine storm at later disease stages $^{56-53}$. We, therefore, directly examined
240 alveolar macrophages (AMs) (Fig S3A) and lung parenchymal residing interstitial macrophages
241 (IMs) (Fig S3B) at t alveolar macrophages (AMs) (Fig S3A) and lung parenchymal residing interstitial macrophages

241 (IMs) (Fig S3B) at the single cell level using multiparameter flow cytometry with intravascular

242 (i.v.) staining to ident 241 (IMs) (Fig S3B) at the single cell level using multiparameter flow cytometry with intravascular (i.v.) staining to identify tissue-resident cells ⁶⁴ one week after pulmonary CpG and Pm3 stimulation. In agreement with (i.v.) staining to identify tissue-resident cells 64 242 (i.v.) staining to identify tissue-resident cells 64 one week after pulmonary CpG and Pm3 stimulation. In agreement with the macrophage-expressed genes identified in our transcriptional analysis we observed both q 243 stimulation. In agreement with the macrophage-expressed genes identified in our transcriptional
244 analysis we observed both quantitative and qualitative differences in AM and IM subsets
245 associated with changes in 244 analysis we observed both quantitative and qualitative differences in AM and IM subsets
245 associated with changes in lipid metabolism and alternative activation. While we saw a small but
246 significant reduction of 245 associated with changes in lipid metabolism and alternative activation. While we saw a small but
246 significant reduction of AMs after CpG, but not Pm3 exposure, the expression of class II major
247 histocompatibility 246 significant reduction of AMs after CpG, but not Pm3 exposure, the expression of class II major
247 histocompatibility complex (MHCII) and CD36, a fatty acid translocase scavenger receptor ⁶⁵,
248 were increased after histocompatibility complex (MHCII) and CD36, a fatty acid translocase scavenger receptor 65 , 247 histocompatibility complex (MHCII) and CD36, a fatty acid translocase scavenger receptor ^{to},
248 were increased after stimulation with both TLR agonists (Fig 3F). In addition, expression of 248 were increased after stimulation with both TLR agonists **(Fig 3F)**. In addition, expression of

TREM2, TLR2, CD38 (ecto-NADase, activation and maturation marker 66,67 , CD13 TREM2, TLR2, CD38 (ecto-NADase, activation and maturation marker ^{66,67}, CD13
250 (aminopeptidase N, lung IM activation marker ⁶⁸, ABCA1 (cholesterol efflux transporter), lectin-
251 type oxidized LDL receptor 1 (LOX-1, (aminopeptidase N, lung IM activation marker 68 250 (aminopeptidase N, lung IM activation marker [®], ABCA1 (cholesterol efflux transporter), lectin-
251 type oxidized LDL receptor 1 (LOX-1, scavenger receptor) and CD11b, all remained increased
252 one week after either 251 type oxidized LDL receptor 1 (LOX-1, scavenger receptor) and CD11b, all remained increased
252 one week after either CpG or Pm3 stimulation in AMs (Fig S3A). One week after treatment with
253 TLR agonists we detected a 252 one week after either CpG or Pm3 stimulation in AMs (Fig S3A). One week after treatment with
253 TLR agonists we detected a significant population of CD88, CD11b+ IMs, characterized by low
254 MHCII expression and high 253 TLR agonists we detected a significant population of CD88, CD11b+ IMs, characterized by low
254 MHCII expression and high CD36 expression in CpG and Pm3-treated lungs that was largely
255 absent in PBS control lungs (254 MHCII expression and high CD36 expression in CpG and Pm3-treated lungs that was largely

255 absent in PBS control lungs (Fig 3G, S3B). In addition to TREM2 and CCR5, this TRM

256 population also expressed high level 255 absent in PBS control lungs **(Fig 3G, S3B)**. In addition to TREM2 and CCR5, this TRM
256 population also expressed high levels of CD206, CD169, CD64, TLR2, CD38, LOX-1, ABCA1,
257 CD14, and CD13 **(Fig S3B)**, indicative 256 population also expressed high levels of CD206, CD169, CD64, TLR2, CD38, LOX-1, ABCA1,

257 CD14, and CD13 (Fig S3B), indicative of increased fatty-acid oxidation and lipid catabolism in

258 mature TRMs associated wit 257 CD14, and CD13 (Fig S3B), indicative of increased fatty-acid oxidation and lipid catabolism in

258 mature TRMs associated with tissue repair and homeostasis functions ^{66,69,70}. In line with their

259 phenotypic and mature TRMs associated with tissue repair and homeostasis functions 66,69,70 258 mature TRMs associated with tissue repair and homeostasis functions $\frac{60,69,70}{10}$. In line with their
259 phenotypic and metabolic changes, both AMs and IMs expressed increased levels of arginase-1
260 (Arg1) that 259 phenotypic and metabolic changes, both AMs and IMs expressed increased levels of arginase-1

260 (Arg1) that persisted 7-10 days after one-time pulmonary TLR9 or TLR2 stimulation (Fig S4A).

261 Arginase and arginine 260 (Arg1) that persisted 7-10 days after one-time pulmonary TLR9 or TLR2 stimulation (Fig S4A).

261 Arginase and arginine metabolism have been implicated in COVID-19 severity, with studies

262 supporting an immunosuppr 261 Arginase and arginine metabolism have been implicated in COVID-19 severity, with studies
262 supporting an immunosuppressive role for arginase-expressing myeloid cells in patients $71-74$.
263 However, arginase inhibi supporting an immunosuppressive role for arginase-expressing myeloid cells in patients $71-74$. 262 supporting an immunosuppressive role for arginase-expressing myeloid cells in patients 11.4 .

263 However, arginase inhibition with N ω -hydroxy-nor-arginine (nor-NOHA) during SCV2 infection

264 did not affect vir 263 However, arginase inhibition with N ω -hydroxy-nor-arginine (nor-NOHA) during SCV2 infection
264 did not affect viral replication, nor did it reverse the protective lung conditioning by recent CpG
265 or Pm3 exposure did not affect viral replication, nor did it reverse the protective lung conditioning by recent CpG
265 or Pm3 exposure before SCV2 infection (Fig S4B). Taken together, our data demonstrated that
266 the pulmonary TRM comp 265 or Pm3 exposure before SCV2 infection (Fig S4B). Taken together, our data demonstrated that
266 the pulmonary TRM compartment shows signs of remodeling and sustained activation alongside
267 metabolic changes that are 266 the pulmonary TRM compartment shows signs of remodeling and sustained activation alongside
267 metabolic changes that are also reflected in total lung transcriptional profiling at the time of
268 SCV2 infection.
269 Ne

metabolic changes that are also reflected in total lung transcriptional profiling at the time of
268 SCV2 infection.
269 Next, we screened lung homogenates from CpG or Pm3-treated mice by bead-based multiplex
270 array for 268 SCV2 infection.
269 Next, we screen
270 array for a varie
271 lungs prior to S
272 pulmonary cytok
273 increases in the 269 Next, we screened lung homogenates from CpG or Pm3-treated mice by bead-based multiplex
270 array for a variety of cytokines to better understand the inflammatory microenvironment of the
271 lungs prior to SCV2 infect 270 array for a variety of cytokines to better understand the inflammatory microenvironment of the
271 lungs prior to SCV2 infection. Importantly, we detected a broad and persistent elevation of
272 pulmonary cytokines ev 271 lungs prior to SCV2 infection. Importantly, we detected a broad and persistent elevation of

272 pulmonary cytokines even at $7 - 10$ days after exposure to a single TLR ligand with marked

273 increases in the interfe 272 pulmonary cytokines even at $7 - 10$ days after exposure to a single TLR ligand with marked

273 increases in the interferons IFN β , IFN γ , IFN λ alongside CXCL10, CCL5, TNF α , IL-6 and IL-

274 12p70, IL-18 an 273 increases in the interferons IFNβ, IFNγ, IFNλ alongside CXCL10, CCL5, TNFα, IL-6 and IL-
274 12p70, IL-18 and IL-1 compared to PBS control mice (Fig 3H). Taken together, these data
275 indicate that recent inflammator 274 12p70, IL-18 and IL-1 compared to PBS control mice (Fig 3H). Taken together, these data

275 indicate that recent inflammatory stimulation causes persistent perturbations in the lung

276 microenvironment prior to SCV2 275 indicate that recent inflammatory stimulation causes persistent perturbations in the lung
276 microenvironment prior to SCV2 exposure that are associated with sustained alterations and
277 activation of the TRM compart microenvironment prior to SCV2 exposure that are associated with sustained alterations and
277 activation of the TRM compartment as well as inflammatory cytokines, including antiviral IFNs.
278 **Pulmonary SCV2 replication**

277 activation of the TRM compartment as well as inflammatory cytokines, including antiviral IFNs.
278 **Pulmonary SCV2 replication is restricted by nucleic acid sensing and signaling by type I
179 Pulmonary SCV2 replicati** 278
279
280
281
282 **Pulmonary SCV2 replication is restricted by nucleic acid sensing and signaling by type I
180 IFN and TNF, but not IL-1**
281 Our transcriptional, cellular and cytokine profiling following recent airway TLR exposure
182 of 280 **IFN and TNF, but not IL-1**
281 Our transcriptional,
282 of mouse lungs highlighted 281 Our transcriptional, cellular and cytokine profiling following recent airway TLR exposure
282 of mouse lungs highlighted an expansive and persistent innate immune signature associated
282 282 of mouse lungs highlighted an expansive and persistent innate immune signature associated

282 of mouse lungs highlighted an expansive and persistent innate immune signature associated

282 of mouse lungs highlighted a with antiviral conditioning of the lung microenvironment at the time of SCV2 infection. To better

284 contextualize which innate immune pathways may be contributing to a heightened antiviral state

285 before SCV2 infecti 284 contextualize which innate immune pathways may be contributing to a heightened antiviral state
285 before SCV2 infection, we next sought to determine the relative importance of various PRRs
286 and key innate inflammat 285 before SCV2 infection, we next sought to determine the relative importance of various PRRs

286 and key innate inflammatory cytokine pathways required for early control of SCV2 replication in

287 the lung. Initial pu 286 and key innate inflammatory cytokine pathways required for early control of SCV2 replication in

287 the lung. Initial publications in mouse models reported conflicting results regarding the role of

288 IFN-I in contr 287 the lung. Initial publications in mouse models reported conflicting results regarding the role of
288 IFN-I in control of SCV2 viral replication ^{3,56,75-82}. Therefore, we revisited IFN-I signaling in
289 C57BL/6 mice 188 IFN-I in control of SCV2 viral replication $3.56,75-82$. Therefore, we revisited IFN-I signaling in C57BL/6 mice infected with SCV2 B.1.351. We found that two different IFNAR1 deficient mouse strains had significantly 289 C57BL/6 mice infected with SCV2 B.1.351. We found that two different IFNAR1 deficient mouse
290 strains had significantly increased viral titers as measured by TCID₅₀ assay three days after
291 exposure (Fig 4A). Con 290 strains had significantly increased viral titers as measured by $TCID_{50}$ assay three days after
291 exposure (Fig 4A). Consistent with this, administering an anti-IFNAR1 neutralizing antibody one
292 day prior to SCV2 291 exposure **(Fig 4A)**. Consistent with this, administering an anti-IFNAR1 neutralizing antibody one
292 day prior to SCV2 infection also limited SCV2 replication **(Fig 4B)**. Measurements of SCV2 E
293 sub-gRNA confirmed 292 day prior to SCV2 infection also limited SCV2 replication (Fig 4B). Measurements of SCV2 E

293 sub-gRNA confirmed increased viral loads in all three IFNAR1-deficient models at this early

294 timepoint after infection

293 sub-gRNA confirmed increased viral loads in all three IFNAR1-deficient models at this early

294 timepoint after infection (Fig S5A-B). Thus, consistent with the clinical evidence, initial SCV2

295 replication in the timepoint after infection **(Fig S5A-B)**. Thus, consistent with the clinical evidence, initial SCV2

replication in the lungs of C57BL/6 mice is controlled via IFN-I-dependent pathways.

Next, we examined the role of specif replication in the lungs of C57BL/6 mice is controlled via IFN-I-dependent pathways.

296 Next, we examined the role of specific pattern recognition receptors (PRR:

297 relative importance in the innate restriction of pul 296 Next, we examined the role of specific pattern recognition receptors (PRRs) and their
297 relative importance in the innate restriction of pulmonary SCV2 replication. Consistent with what
298 has been observed in pati 297 relative importance in the innate restriction of pulmonary SCV2 replication. Consistent with what

298 has been observed in patients with inborn errors of TLR3 or TLR7^{2-4,17} we found that mice

299 deficient in TLR3 has been observed in patients with inborn errors of TLR3 or TLR7 $2-4,17$ we found that mice 298 has been observed in patients with inborn errors of TLR3 or TLR7 $^{2-4,17}$ we found that mice

299 deficient in TLR3 (Fig 4C) or TLR7 (Fig 4D) had significantly elevated lung SCV2 titers by

200 TCID₅₀ assay, as di 299 deficient in TLR3 **(Fig 4C)** or TLR7 **(Fig 4D)** had significantly elevated lung SCV2 titers by

200 TCID₅₀ assay, as did mice deficient in the RNA-sensing cytoplasmic PRR melanoma

201 differentiation-associated pro 300 TCID₅₀ assay, as did mice deficient in the RNA-sensing cytoplasmic PRR melanoma
301 differentiation-associated protein 5 (MDA5, encoded by *Ifih1*) (Fig 4E). We next examined mice
302 deficient in TLR2, a PRR report 301 differentiation-associated protein 5 (MDA5, encoded by *Ifih1*) (Fig 4E). We next examined mice
302 deficient in TLR2, a PRR reported to recognize the E and S protein of SCV2^{83,84}. Lungs of *Tlr2^{-/-}*
303 mice infec deficient in TLR2, a PRR reported to recognize the E and S protein of SCV2 83,84. Lungs of *Tlr2*-/- 302
303
304
305
306
307 303 mice infected with SCV2 B.1.351 had significantly higher viral titers compared to WT mice **(Fig 4F)**, suggesting an important role for TLR2-triggered innate immunity in limiting early viral replication in mice. In cont 304 **4F)**, suggesting an important role for TLR2-triggered innate immunity in limiting early viral
305 replication in mice. In contrast, neither TLR4 (Fig 4G) nor TLR9 (Fig 4H) were required for
306 control of SCV2 replica 305 replication in mice. In contrast, neither TLR4 (Fig 4G) nor TLR9 (Fig 4H) were required for
306 control of SCV2 replication in the lungs of mice three days after infection. Consistent with
307 findings in $cGAS^{\prime}$ mic 306 control of SCV2 replication in the lungs of mice three days after infection. Consistent with
307 findings in $cGAS^{\prime}$ mice 85 , mice deficient in stimulator of IFN genes (STING, encoded by
308 *Tmem173*) showed no findings in *cGAS^{-/-}* mice ⁸⁵ 307 findings in $cGAS^{-}$ mice ⁸⁵, mice deficient in stimulator of IFN genes (STING, encoded by *Tmem173*) showed no difference in lung viral titers compared to WT controls (Fig 4I). Mice lacking Z-DNA binding protein 1 (308 *Tmem173*) showed no difference in lung viral titers compared to WT controls (Fig 4I). Mice
309 lacking Z-DNA binding protein 1 (ZBP1) (Fig S5C,D), a nucleic acid sensor detecting both Z-
310 configured DNA and RNA sho 309 lacking Z-DNA binding protein 1 (ZBP1) (Fig S5C,D), a nucleic acid sensor detecting both Z-
310 configured DNA and RNA shown to play an important role in modulating IFN-I mediated lung
311 inflammation in SCV2 at later 310 configured DNA and RNA shown to play an important role in modulating IFN-I mediated lung
311 inflammation in SCV2 at later stages 86,87 , displayed a small yet significant increase in viral loads
312 three days af inflammation in SCV2 at later stages 86,87 311 inflammation in SCV2 at later stages 86,87 , displayed a small yet significant increase in viral loads
312 three days after infection when E sub-gRNA was measured by qPCR (Fig S5E), but when
313 measured by TCID₅ 312 three days after infection when E sub-gRNA was measured by qPCR **(Fig S5E)**, but when

313 measured by TCID₅₀ assay differences in viral titers did not reach statistical significance **(Fig**

314 **4J)**. Our data sugg 313 measured by TCID₅₀ assay differences in viral titers did not reach statistical significance **(Fig 4J)**. Our data suggest, at best, a small effect of Z-formed nucleic acid sensing on viral replication, consistent with 314 **4J)**. Our data suggest, at best, a small effect of Z-formed nucleic acid sensing on viral
315 replication, consistent with observations previously made in a SCV2 Ad-hACE2 mouse model
316 ^{87,88}. 315 replication, consistent with observations previously made in a SCV2 Ad-hACE2 mouse model
316 87.88 . 87,88 316 $87,88$.

317 Because recent airway administration of TLR agonists resulted in elevated lung levels of
318 IL-1β and IL-18, we next investigated whether inflammasome-related pathways contribute to
319 innate control of viral repli 318 IL-1β and IL-18, we next investigated whether inflammasome-related pathways contribute to
319 innate control of viral replication in SCV2 infection. Indeed, both inflammasome activation and
320 pyroptotic cell death h 319 innate control of viral replication in SCV2 infection. Indeed, both inflammasome activation and
320 pyroptotic cell death have been implicated in SCV2 pathogenesis $^{89-92}$. Similar to observations
321 made in an AAV pyroptotic cell death have been implicated in SCV2 pathogenesis $89-92$ 320 pyroptotic cell death have been implicated in SCV2 pathogenesis $^{83-92}$. Similar to observations
321 made in an AAV-hACE2 mouse model of SCV2 infection 93 , *NIrp3*^{-/} mice infected with SCV2
322 B.1.351 exhibit made in an AAV-hACE2 mouse model of SCV2 infection ⁹³, Nlrp3^{-/-} 321 made in an AAV-hACE2 mouse model of SCV2 infection 93 , *Nlrp3*² mice infected with SCV2

322 B.1.351 exhibited significantly lower viral lung titers (Fig 4K). In addition, WT mice treated with

323 the NLRP3 inh 322 B.1.351 exhibited significantly lower viral lung titers **(Fig 4K).** In addition, WT mice treated with
323 the NLRP3 inhibitor MCC950 also had lower lung SCV2 titers **(Fig 4L)**. Next, we infected
324 Casp1^{+/-} and Cas 323 the NLRP3 inhibitor MCC950 also had lower lung SCV2 titers **(Fig 4L)**. Next, we infected Casp1^{+/-} and Casp1,11^{-/-} mice to ask whether the observed decrease in viral loads in *Nlrp3*^{-/-} mice was due to NLRP3-driv *Casp1-/-* and *Casp1,11-/-* mice to ask whether the observed decrease in viral loads in *Nlrp3-/-* 324
325
326
327
328
329 mice was due to NLRP3-driven caspase-1 or caspase-11 activation. However*,* both *Casp1-/-* 325 mice (Fig 4M), as well as $Casp1.11^{-/-}$ mice (Fig 4N), displayed similar lung SCV2 titers 326 mice (Fig 4M), as well as $Casp1,11^{-/}$ mice (Fig 4N), displayed similar lung SCV2 titers
327 compared to WT mice. These data suggest that the inflammatory caspases -1 and -11 are
328 dispensable for early viral control 327 compared to WT mice. These data suggest that the inflammatory caspases -1 and -11 are
328 dispensable for early viral control in the lungs of mice and unlikely operate downstream of
329 NLRP3 to promote SCV2 replicati 328 dispensable for early viral control in the lungs of mice and unlikely operate downstream of
329 NLRP3 to promote SCV2 replication in the first three days after infection. Interestingly, mice
330 doubly-deficient in ga 329 NLRP3 to promote SCV2 replication in the first three days after infection. Interestingly, mice
330 doubly-deficient in gasdermin-D and gasdermin-E (Gsdmd, Gsdme^{-/-}) exhibited significantly
331 increased lung SCV2 ti doubly-deficient in gasdermin-D and gasdermin-E (*Gsdmd,Gsdme^{-/-}*) exhibited significantly 330 doubly-deficient in gasdermin-D and gasdermin-E (*Gsdmd, Gsdme^{-/-}*) exhibited significantly
331 increased lung SCV2 titers as measured by TCID₅₀ assay (Fig 40), suggesting a key role for
332 these terminal pore-fo 331 increased lung SCV2 titers as measured by TCID₅₀ assay (Fig 4O), suggesting a key role for
332 these terminal pore-forming proteins in the innate restriction of SCV2 viral titers in the mouse
333 lung. As inflammaso 332 these terminal pore-forming proteins in the innate restriction of SCV2 viral titers in the mouse
333 lung. As inflammasome activation and pore-formation are essential to both lytic pyroptotic cell
334 death and the ge 333 lung. As inflammasome activation and pore-formation are essential to both lytic pyroptotic cell
334 death and the generation and secretion of leaderless cytokines like IL-1, we asked whether IL-1
335 signaling is requ death and the generation and secretion of leaderless cytokines like IL-1, we asked whether IL-1

signaling is required to control pulmonary SCV2 replication. Both *II1a,b*² and *II1r1*² mice (Fig

4P) were able to con signaling is required to control pulmonary SCV2 replication. Both *II1a,b^{-/}*, and *II1r1^{-/}* mice (Fig. signaling is required to control pulmonary SCV2 replication. Both $II1a, b^{-1}$ and $II1r1^{-1}$ mice (Fig 4P) were able to control lung viral replication similarly to WT mice, arguing that IL-1R1-driven signals are dispensable **4P)** were able to control lung viral replication similarly to WT mice, arguing that IL-1R1-driven
337 signals are dispensable for initial viral control in mice three days after infection with SCV2
8.1.351. Finally, we in

337 signals are dispensable for initial viral control in mice three days after infection with SCV2

338 B.1.351.

Finally, we investigated whether the pro-inflammatory cytokine TNFa was playing a role

340 in modulating v 338 B.1.351.
339 Fi
340 in modula
341 by divers
342 precondit
343 displayed Finally, we investigated whether the pro-inflammatory cytokine TNFa was playing a role
340 in modulating viral replication in the lungs early after SCV2 infection. TNFa is broadly inducible
341 by diverse inflammatory cue 340 in modulating viral replication in the lungs early after SCV2 infection. TNFa is broadly inducible
341 by diverse inflammatory cues and was also elevated in the lungs one week after TLR
342 preconditioning. Of note, T 341 by diverse inflammatory cues and was also elevated in the lungs one week after TLR
342 preconditioning. Of note, TNFR1 deficient (*Tnfrsf1a^{-/-}*) mice infected with SCV2 B.1.351,
343 displayed defective control of vi preconditioning. Of note, TNFR1 deficient (*Tnfrsf1a^{-/-}*) mice infected with SCV2 B.1.351, 342 preconditioning. Of note, TNFR1 deficient $(Thfrsf1a^{-1})$ mice infected with SCV2 B.1.351,
343 displayed defective control of viral replication as quantified by TCID₅₀ assay (Fig 4Q) or by
344 qPCR for E sub-gRNA (Fig S displayed defective control of viral replication as quantified by TCID₅₀ assay (Fig 4Q) or by
344 qPCR for E sub-gRNA (Fig S5F). TNFa neutralization by monoclonal antibody treatment prior to
345 SCV2 infection likewise r 344 qPCR for E sub-gRNA (Fig S5F). TNFα neutralization by monoclonal antibody treatment prior to
345 SCV2 infection likewise resulted in elevated lung viral burdens compared to lgG1 control-treated
346 mice (Fig 4R). Ther SCV2 infection likewise resulted in elevated lung viral burdens compared to IgG1 control-treated

346 mice (Fig 4R). Therefore, our data demonstrate that TNFR1-mediated pro-inflammatory signals

347 contribute to limiting 346 mice (Fig 4R). Therefore, our data demonstrate that TNFR1-mediated pro-inflammatory signals
347 contribute to limiting early SCV2 replication in the lung. Taken together, our survey of innate
348 inflammatory pathways 347 contribute to limiting early SCV2 replication in the lung. Taken together, our survey of innate
348 inflammatory pathways relevant for initial viral control not only revealed an expected important
349 role for IFN-I bu 348 inflammatory pathways relevant for initial viral control not only revealed an expected important
349 role for IFN-I but also delineated key PRRs and pro-inflammatory pathways important for limiting
349 role for IFN-I b 349 role for IFN-I but also delineated key PRRs and pro-inflammatory pathways important for limiting

role for IFN-I but also delineated key PRRs and pro-inflammatory pathways important for limiting

The Section of the Sec

350 pulmonary viral replication prior to the onset of adaptive SCV2-specific responses that may
351 contribute to the establishment of an antiviral lung microenvironment.
352 **Recent IFN-I-dependent and -independent inflam**

contribute to the establishment of an antiviral lung microenvironment.
352 **Recent IFN-I-dependent and -independent inflammatory conditior
354 Promotes suppression of viral replication.**
355 Because we detected elevated l

352
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357 **Recent IFN-I-dependent and -independent inflammatory conditioning of the lung**
354 **promotes suppression of viral replication.**
355 Because we detected elevated levels of interferons (Fig 3H) after TLF
357 conditioning an **promotes suppression of viral replication.**
355 Because we detected elevated lev
357 conditioning and the transcriptional patl
358 interactions between a Lymphoid and a non-L
359 that the inflammatory changes in the lung 356
357
358
359
360 Because we detected elevated levels of interferons (Fig 3H) after TLR agonist
357 conditioning and the transcriptional pathway analyses highlighted "immunoregulatory
358 interactions between a Lymphoid and a non-Lymphoid c 357 conditioning and the transcriptional pathway analyses highlighted "immunoregulatory
358 interactions between a Lymphoid and a non-Lymphoid cells" (Fig 2E, 3B) we next hypothesized
359 that the inflammatory changes in 358 interactions between a Lymphoid and a non-Lymphoid cells" (Fig 2E, 3B) we next hypothesized
359 that the inflammatory changes in the lung microenvironment prior to SCV2 infection might also
360 extend to changes in lun 359 that the inflammatory changes in the lung microenvironment prior to SCV2 infection might also
360 extend to changes in lung epithelial cells (ECs), the primary target and reservoir of SCV2
361 replication 94.95 . Thu 360 extend to changes in lung epithelial cells (ECs), the primary target and reservoir of SCV2 replication 94.95 . Thus, we next examined mouse pulmonary EC subsets prior to SCV2 infection after conditioning with the dif replication ^{94,95}. Thus, we next examined mouse pulmonary EC subsets prior to SCV2 infection 361 replication 94.95 . Thus, we next examined mouse pulmonary EC subsets prior to SCV2 infection
362 after conditioning with the different protective pulmonary inflammatory stimuli described above,
363 ranging from ster after conditioning with the different protective pulmonary inflammatory stimuli described above,

163 anging from sterile inflammation to bacterial and viral infection. Using flow cytometry we

164 assessed CD45^{neg} CD31 363 ranging from sterile inflammation to bacterial and viral infection. Using flow cytometry we
364 assessed CD45^{neg} CD31^{neg} CD326⁺ pulmonary EC subsets in the mouse lung, including
365 CD24^{neg} Podoplanin (PDPN)^{hi} assessed CD45^{neg} CD31^{neg} CD326⁺ pulmonary EC subsets in the mouse lung, including 364 assessed CD45^{neg} CD31^{neg} CD326⁺ pulmonary EC subsets in the mouse lung, including
365 CD24^{neg} Podoplanin (PDPN)^{hi} MHC-II^{low} type I alveolar epithelial cells (AECIs), CD24^{neg} PDPN^{low}
366 MHC-II^{hi} type CD24^{neg} Podoplanin (PDPN)^{hi} MHC-II^{low} type I alveolar epithelial cells (AECIs), CD24^{neg} PDPN^{low} 365
366
367
368
369
370 MHC-II^{hi} type II alveolar epithelial cells (AECIIs), CD24^{neg} PDPN^{neg} MHC-II^{neg} ECs (Other ECs), 366 MHC-IIⁿ type II alveolar epithelial cells (AECIIs), CD24^{neg} PDPN^{neg} MHC-II^{neg} ECs (Other ECs),
367 CD24⁺ CD49f^{hi} Bronchiolar Epithelial Cells (BECs) and CD24⁺ CD49f^{low} club cells (**Fig S6A)**. We
368 mea CD24⁺ CD49f^{hi} Bronchiolar Epithelial Cells (BECs) and CD24⁺ CD49f^{low} CD24⁺ CD49fⁿ Bronchiolar Epithelial Cells (BECs) and CD24⁺ CD49f^{low} club cells (Fig S6A). We
368 measured the IFN-activation of ECs by quantifying the expression of the IFN-inducible surface
369 markers (ISMs) CD31 measured the IFN-activation of ECs by quantifying the expression of the IFN-inducible surface
369 markers (ISMs) CD317 (BST2, HM1.24, PDCA1, tetherin) and Sca-1(Ly6A/E) by flow cytometry
370^{40,96,97} (Fig 5A, S6B). All in 369 markers (ISMs) CD317 (BST2, HM1.24, PDCA1, tetherin) and Sca-1(Ly6A/E) by flow cytometry
370^{40,96,97} (Fig 5A, S6B). All inflammatory and infectious stimuli induced changes in ISM
371 upregulation across all cell type 40,96,97 ^{40,96,97} (Fig 5A, S6B). All inflammatory and infectious stimuli induced changes in ISM
371 upregulation across all cell types, with Pm3 providing the weakest EC ISM activation and,
372 expectedly, chronic *Mtb* infection 371 upregulation across all cell types, with Pm3 providing the weakest EC ISM activation and,
372 expectedly, chronic *Mtb* infection the strongest (Fig 5A, S6B). One week after pulmonary TLR
373 agonist administration, on stratedly, chronic *Mtb* infection the strongest (Fig 5A, S6B). One week after pulmonary TLR
373 agonist administration, only Sca-1 on BECs was significantly elevated with Pm3, while CpG
374 increased both CD317 and Sca-1 373 agonist administration, only Sca-1 on BECs was significantly elevated with Pm3, while CpG
374 increased both CD317 and Sca-1 across most EC subsets, supporting more potent IFN-induced
375 conditioning of the pulmonary 374 increased both CD317 and Sca-1 across most EC subsets, supporting more potent IFN-induced

375 conditioning of the pulmonary epithelium following activation of TLR9 compared to TLR1/2 (Fig

376 5A, S6B). Additionally, conditioning of the pulmonary epithelium following activation of TLR9 compared to TLR1/2 (Fig 5A, S6B). Additionally, 30 days following IAV infection, we detected increased expression of Sca-1, but not CD317, on all ECs ex **5A, S6B)**. Additionally, 30 days following IAV infection, we detected increased expression of Sca-1, but not CD317, on all ECs except the Other ECs group, which had significantly decreased expression of both ISMs one mont Sca-1, but not CD317, on all ECs except the Other ECs group, which had significantly
378 decreased expression of both ISMs one month after IAV infection (Fig 5A, S6B), agreeing with
379 previously published data showing th decreased expression of both ISMs one month after IAV infection (Fig 5A, S6B), agreeing with
previously published data showing that IAV does not induce CD317 on lung ECs ⁹⁸. Three days
after pulmonary *S. aureus* infecti previously published data showing that IAV does not induce CD317 on lung ECs 98 . Three days previously published data showing that IAV does not induce CD317 on lung ECs ⁹⁸. Three days
380 after pulmonary *S. aureus* infection, both ISMs were upregulated on BEC and club cells with the
381 highest CD317 activatio 380 after pulmonary *S. aureus* infection, both ISMs were upregulated on BEC and club cells with the
381 highest CD317 activation in AECIIs and BECs compared to naïve control animals (Fig 5A,
382 **S6B)**. Notably, five days 381 highest CD317 activation in AECIIs and BECs compared to naïve control animals (Fig 5A,
382 S6B). Notably, five days after pulmonary OVA administration, CD317 was very highly elevated
383 on AECIIs and BECs in the OVA/A 382 **S6B)**. Notably, five days after pulmonary OVA administration, CD317 was very highly elevated
383 on AECIIs and BECs in the OVA/Alum model of allergic asthma **(Fig 5A, S6B)**, suggesting IFN
³⁸³ on AECIIs and BECs in 383 on AECIIs and BECs in the OVA/Alum model of allergic asthma **(Fig 5A, S6B)**, suggesting IFN activation of ECs even in a type-II-response-dominated inflammatory setting. Taken together, all
385 tested inflammatory and infectious settings led to heightened IFN-activation of ECs prior to
386 SCV2 exposure when compa 385 tested inflammatory and infectious settings led to heightened IFN-activation of ECs prior to
386 SCV2 exposure when compared to naïve animals, suggesting the possibility that inflammatory
387 conditioning of the lung m

SCV2 exposure when compared to naïve animals, suggesting the possibility that inflammatory

387 conditioning of the lung microenvironment involves direct sensitization of ECs for enhanced

388 Since IFNs were elevated and conditioning of the lung microenvironment involves direct sensitization of ECs for enhanced
388 control of subsequent SCV2 infection.
389 Since IFNs were elevated and we observed increased expression of IFN-inducible
390 m 388 control of subsequent SCV2 infection.
389 Since IFNs were elevated ar
390 markers on lung ECs one week post
391 whether this elevated baseline IFN-I s
392 the viral control induced by prior CpG
393 **2A, S1A)**, *Ifnar1[*] 389 Since IFNs were elevated and we observed increased expression of IFN-inducible
390 markers on lung ECs one week post pulmonary treatment with TLR-agonists, we next tested
391 whether this elevated baseline IFN-I signa 390 markers on lung ECs one week post pulmonary treatment with TLR-agonists, we next tested
391 whether this elevated baseline IFN-I signaling at the time of SCV2 exposure was sufficient for
392 the viral control induced b 391 whether this elevated baseline IFN-I signaling at the time of SCV2 exposure was sufficient for
392 the viral control induced by prior CpG or Pm3 exposure. Indeed, in contrast to WT animals (Fig
393 2A, S1A), *Ifnar1^{-*} 392 the viral control induced by prior CpG or Pm3 exposure. Indeed, in contrast to WT animals **(Fig 2A, S1A)**, *Ifnar1^{-/-}* animals failed to display significantly reduced SCV2 viral titers after recent pulmonary CpG or P 2A, S1A), Ifnar1^{-/-} animals failed to display significantly reduced SCV2 viral titers after recent **2A, S1A)**, *Ifnar1^{-/-}* animals failed to display significantly reduced SCV2 viral titers after recent

394 pulmonary CpG or Pm3 treatment when measured by TCID₅₀ or qPCR (Fig 5B). These data

395 support the hypothes 394 pulmonary CpG or Pm3 treatment when measured by TCID₅₀ or qPCR (Fig 5B). These data
395 support the hypothesis that recent IFN-I-driven changes in the lung microenvironment may be
396 sufficient to condition the lung support the hypothesis that recent IFN-I-driven changes in the lung microenvironment may be
396 sufficient to condition the lung for enhanced viral restriction when exposed to SCV2.
397 Remarkably, Pm3-mediated protection 396 sufficient to condition the lung for enhanced viral restriction when exposed to SCV2.
397 Remarkably, Pm3-mediated protection was abrogated in the absence of *Ifnar1*, despite being a
398 more potent inducer of NF-kB 397 Remarkably, Pm3-mediated protection was abrogated in the absence of *Ifnar1*, despite being a
398 more potent inducer of NF-kB than CpG and only very weakly sustaining Sca-1 expression in
399 BECs (Fig 5A). Because we 398 more potent inducer of NF- k B than CpG and only very weakly sustaining Sca-1 expression in
399 BECs (Fig 5A). Because we observed increased levels of TNFa in the lungs after CpG or Pm3
400 treatment (Fig 3H) and a re 399 BECs (Fig 5A). Because we observed increased levels of TNFα in the lungs after CpG or Pm3
400 treatment (Fig 3H) and a requirement for TNFR1 in initial viral control after SCV2 infection (Fig
401 4Q, 4R), we next ask 400 treatment (Fig 3H) and a requirement for TNFR1 in initial viral control after SCV2 infection (Fig 40, 4R), we next asked whether the sustained increase in TNFa seen after TLR conditioning was contributing to the heigh 401 **4Q, 4R)**, we next asked whether the sustained increase in TNF α seen after TLR conditioning
402 was contributing to the heightened antiviral state, similar to what we observed with IFN-I.
403 However, when we expos 402 was contributing to the heightened antiviral state, similar to what we observed with IFN-I.
403 However, when we exposed TNFR1 deficient (*Tnfrsf1a^{-/-}*) mice to CpG or Pm3 one week prior to
404 infection with SCV2 B However, when we exposed TNFR1 deficient (*Tnfrsf1a^{-/-}*) mice to CpG or Pm3 one week prior to 403 However, when we exposed TNFR1 deficient (*Tnfrsf1a^{-/-}*) mice to CpG or Pm3 one week prior to
404 infection with SCV2 B.1.351, the ability of CpG or Pm3 to significantly suppress pulmonary
405 SCV2 loads was retain 404 infection with SCV2 B.1.351, the ability of CpG or Pm3 to significantly suppress pulmonary
405 SCV2 loads was retained in *Tnfrsf1a^{-/-}* animals (Fig 5C). Thus, while TNFa appears to be critical
406 for viral control SCV2 loads was retained in *Tnfrsf1a^{-/-}* animals (Fig 5C). Thus, while $TNF\alpha$ appears to be critical 405 SCV2 loads was retained in *Tnfrsf1a^{-/-}* animals (Fig 5C). Thus, while TNFα appears to be critical
406 for viral control after SCV2 infection, it is dispensable for TLR9 or TLR1/2-mediated enhanced
407 antiviral con 406 for viral control after SCV2 infection, it is dispensable for TLR9 or TLR1/2-mediated enhanced
407 antiviral conditioning of the lungs. Importantly, although IL-1R1 was not required for control of
408 SCV2 (Fig 4P), I antiviral conditioning of the lungs. Importantly, although IL-1R1 was not required for control of
408 SCV2 (Fig 4P), IL-1β remained elevated in lung homogenates one week after TLR1/2
409 stimulation (Fig 3H). We, therefor 408 SCV2 (Fig 4P), IL-1β remained elevated in lung homogenates one week after TLR1/2
409 stimulation (Fig 3H). We, therefore, tested the contribution of IL-1 to enhanced viral control
410 following CpG or Pm3 exposure and 409 stimulation (Fig 3H). We, therefore, tested the contribution of IL-1 to enhanced viral control
410 following CpG or Pm3 exposure and found that unlike WT and like *Ifnar1^{-/} mice*, *II1r1^{-/}* mice
411 failed to restr following CpG or Pm3 exposure and found that unlike WT and like *Ifnar1^{-/} mice*, *II1r1^{-/-}* mice 410 following CpG or Pm3 exposure and found that unlike WT and like *Ifnar1^{-/} mice*, $\frac{1}{11}$ ^{-/-} mice
411 failed to restrict SCV2 replication when measured by either TCID₅₀ or qPCR (Fig 5D). These
412 data suggest 411 failed to restrict SCV2 replication when measured by either TCID₅₀ or qPCR **(Fig 5D)**. These
412 data suggest a requirement for effective signaling through either IFNAR1 or IL-1R1, but not
413 TNFR1 to effectively s 412 data suggest a requirement for effective signaling through either IFNAR1 or IL-1R1, but not
413 TNFR1 to effectively suppress SCV2 following TLR9 or TLR1/2 conditioning. Moreover, while
414 without recent exposure to i 413 TNFR1 to effectively suppress SCV2 following TLR9 or TLR1/2 conditioning. Moreover, while
414 without recent exposure to inflammatory stimuli or other pathogens, IL-1R1 was dispensable for
415 viral control after SCV2 414 without recent exposure to inflammatory stimuli or other pathogens, IL-1R1 was dispensable for
415 viral control after SCV2 infection, inflammatory conditioning via TLRs was nonetheless able to
416 co-opt the IL-1 path 415 viral control after SCV2 infection, inflammatory conditioning via TLRs was nonetheless able to
416 co-opt the IL-1 pathway to promote a heightened antiviral state in the lungs of mice.
416 co-opt the IL-1 pathway to pr 416 co-opt the IL-1 pathway to promote a heightened antiviral state in the lungs of mice.

Allowsky to promote a heightened antiviral state in the lungs of mice.

Lastly, to further de-construct how diverse inflammatory stimuli may condition the lung

418 microenvironment to improve early viral control, we asked whether exposure to inflammatory

419 cytokines themselves is sufficien microenvironment to improve early viral control, we asked whether exposure to inflammatory

cytokines themselves is sufficient. Based on the ISM profiling results of lung EC subsets, we

420 hypothesized that IFNs are like 419 cytokines themselves is sufficient. Based on the ISM profiling results of lung EC subsets, we
420 hypothesized that IFNs are likely variably expressed amongst the diverse settings of lung
421 perturbations examined, w 420 hypothesized that IFNs are likely variably expressed amongst the diverse settings of lung
421 perturbations examined, while TNFa is likely more broadly induced across a wide range of
422 inflammatory stimuli. Thus, to 421 perturbations examined, while TNFα is likely more broadly induced across a wide range of
422 inflammatory stimuli. Thus, to determine whether recent activation of IFNAR1 or TNFR1
423 signaling pathways is sufficient 422 inflammatory stimuli. Thus, to determine whether recent activation of IFNAR1 or TNFR1 signaling pathways is sufficient to create a heightened antiviral state and effectively restrict SVC2 replication in the mouse lung 423 signaling pathways is sufficient to create a heightened antiviral state and effectively restrict
424 SVC2 replication in the mouse lung, recombinant IFNβ, or TNFα were given to K18-hACE2 Tg
425 mice by i.ph. seven day 424 SVC2 replication in the mouse lung, recombinant IFNβ, or TNFα were given to K18-hACE2 Tg
425 mice by i.ph. seven days prior to infection with SCV2 USA-WA1/2020. Notably, both IFNβ and
426 TNFα were able to significan 425 mice by i.ph. seven days prior to infection with SCV2 USA-WA1/2020. Notably, both IFNβ and
426 TNFα were able to significantly reduce the SCV2 burden as measured by TCID₅₀ assay at three
427 days post infection by 426 TNFα were able to significantly reduce the SCV2 burden as measured by TCID₅₀ assay at three
427 days post infection by ~1.5 logs (Fig 5E). Moreover, when we profiled ISM expression on ECs
428 in WT mice one week af days post infection by ~1.5 logs (Fig 5E). Moreover, when we profiled ISM expression on ECs
428 in WT mice one week after receiving pulmonary stimulation with recombinant IFNβ, or TNFα,
641 only mice that received IFNβ, b 428 in WT mice one week after receiving pulmonary stimulation with recombinant IFNβ, or TNFα,
429 only mice that received IFNβ, but not TNFα, showed significant upregulation of CD317 (Fig 5F),
430 despite equal suppressio only mice that received IFNβ, but not TNFα, showed significant upregulation of CD317 **(Fig 5F)**,
430 despite equal suppression of viral replication. This finding demonstrates that CD317 ISM
431 upregulation is specific to despite equal suppression of viral replication. This finding demonstrates that CD317 ISM
431 upregulation is specific to IFNs and that TNFa-mediated antiviral protection occurs
432 independently of upregulation of ISM in E 431 upregulation is specific to IFNs and that $TNF\alpha$ -mediated antiviral protection occurs
432 independently of upregulation of ISM in ECs measured here. Thus, in addition to the known
433 antiviral effects of IFN β , our 432 independently of upregulation of ISM in ECs measured here. Thus, in addition to the known
433 antiviral effects of IFN β , our data reveal that increased TNF α driven inflammation at the time of
434 SCV2 exposure i 433 antiviral effects of IFNβ, our data reveal that increased TNFα driven inflammation at the time of
434 SCV2 exposure is potently able to confer a heightened antiviral state in the lung. Finally, we
435 asked whether I 434 SCV2 exposure is potently able to confer a heightened antiviral state in the lung. Finally, we
435 asked whether IL-1 α and IL-1 β are equally able to provide antiviral inflammatory conditioning of
436 the lung. I 435 asked whether IL-1α and IL-1β are equally able to provide antiviral inflammatory conditioning of
436 the lung. Indeed, pulmonary administration of either IL-1α or IL-1β one week prior to SCV2
437 infection of C57BL/6 436 the lung. Indeed, pulmonary administration of either IL-1 α or IL-1 β one week prior to SCV2
437 infection of C57BL/6 mice, was able to significantly enhance early viral control in the lungs of
438 WT but not $l/l\$ 437 infection of C57BL/6 mice, was able to significantly enhance early viral control in the lungs of
438 WT but not $\frac{1}{1111}$ animals as measured by TCID₅₀ (Fig 5G). Similar to TNFa administration, IL-1
439 precondit WT but not $II11^{-/-}$ animals as measured by TCID₅₀ (Fig 5G). Similar to TNFa administration, IL-1 438 WT but not I/111° animals as measured by TCID₅₀ (Fig 5G). Similar to TNF α administration, IL-1 preconditioning of the lung did not result in indirect activation of IFN pathways in the pulmonary epitheliu que 449 preconditioning of the lung did not result in indirect activation of IFN pathways in the pulmonary

440 epithelium, as we failed to detect ISM marker expression on different lung EC subsets prior to

441 infection epithelium, as we failed to detect ISM marker expression on different lung EC subsets prior to
441 infection with SCV2 (Fig 5H). In summary, the above data revealed that both IFN-I-dependent
442 and -independent pro-inflam 441 infection with SCV2 (Fig 5H). In summary, the above data revealed that both IFN-I-dependent
442 and -independent pro-inflammatory pathways can promote an effective, antiviral inflammatory
443 tone in the mouse lung an and -independent pro-inflammatory pathways can promote an effective, antiviral inflammatory

443 tone in the mouse lung and suggest that prior engagement of the IL-1 or TNFa signaling

444 pathways is sufficient to restric tone in the mouse lung and suggest that prior engagement of the IL-1 or TNFα signaling
444 pathways is sufficient to restrict pulmonary SCV2 replication in mice. Taken together our
445 findings provide a molecular framewo 444 pathways is sufficient to restrict pulmonary SCV2 replication in mice. Taken together our
445 findings provide a molecular framework and *in vivo* evidence that immunologically diverse
446 pulmonary exposure histories, 445 findings provide a molecular framework and *in vivo* evidence that immunologically diverse
446 pulmonary exposure histories, including those that only modestly trigger IFN responses, can
447 potently impact initial pul 446 pulmonary exposure histories, including those that only modestly trigger IFN responses, can
447 potently impact initial pulmonary SCV2 replication.
448
DISCUSSION 447 potently impact initial pulmonary SCV2 replication.
448
449 **DISCUSSION**

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- 448
- 450 450 **DISCUSSION**

451 Here, we establish that recent or ongoing pulmonary inflammatory stimuli, such as newly
452 resolved respiratory infections, sterile allergic inflammation, or TLR agonist and cytokine-
453 induced responses, modulate esolved respiratory infections, sterile allergic inflammation, or TLR agonist and cytokine-
453 induced responses, modulate the early antiviral response in the lungs upon SCV2 encounter.
454 We demonstrate that elevated ba induced responses, modulate the early antiviral response in the lungs upon SCV2 encounter.
454 We demonstrate that elevated baseline induction of pro-inflammatory TNFa or IL-1 responses,
455 in addition to IFN-I, impart an 454 We demonstrate that elevated baseline induction of pro-inflammatory TNFα or IL-1 responses,
455 in addition to IFN-I, impart antiviral activities capable of lowering initial viral titers. Moreover, our
456 findings s 455 in addition to IFN-I, impart antiviral activities capable of lowering initial viral titers. Moreover, our
456 findings suggest that prior engagement of the IL-1 or TNF α signaling pathways can restrict
457 SCV2 repl

456 findings suggest that prior engagement of the IL-1 or TNF α signaling pathways can restrict
457 SCV2 replication in the mouse lung.
458 IFNs play critical roles in limiting viral replication early after SCV2 infecti SCV2 replication in the mouse lung.
458 IFNs play critical roles in lim
459 stages of infection and when dysreg
460 is centered around innate factors
461 adaptive immunity. Most of the infl
462 innate control of viral tite IFNs play critical roles in limiting viral replication early after SCV2 infection, yet at later
459 stages of infection and when dysregulated, they also contribute to disease 8,81,85,99-103. Our study
460 is centered aroun stages of infection and when dysregulated, they also contribute to disease $^{8,81,85,99\cdot103}$ stages of infection and when dysregulated, they also contribute to disease 8,81,85,99-103. Our study
460 is centered around innate factors limiting viral replication in the lung prior to the onset of
461 adaptive immunity. 460 is centered around innate factors limiting viral replication in the lung prior to the onset of adaptive immunity. Most of the inflammatory pathways we show here as required for early innate control of viral titers have 461 adaptive immunity. Most of the inflammatory pathways we show here as required for early
462 innate control of viral titers have been implicated in disease progression and mortality at later
463 stages and have, therefo 462 innate control of viral titers have been implicated in disease progression and mortality at later
463 stages and have, therefore, contextual roles depending on disease stage. For example, while
464 the SCV2 spike and 463 stages and have, therefore, contextual roles depending on disease stage. For example, while
464 the SCV2 spike and envelope proteins trigger inflammation through the binding of TLR2 and
465 blockade of TLR2 signaling 464 the SCV2 spike and envelope proteins trigger inflammation through the binding of TLR2 and
465 blockade of TLR2 signaling extended survival in mice $83,84$, we demonstrate that TLR2 is
466 required for optimal control blockade of TLR2 signaling extended survival in mice $83,84$ 465 blockade of TLR2 signaling extended survival in mice 83.84 , we demonstrate that TLR2 is
466 required for optimal control of viral replication in the lungs of mice early after infection. Similarly,
467 TNF α , IL-1 466 required for optimal control of viral replication in the lungs of mice early after infection. Similarly,
467 TNFα, IL-1 and inflammasome pathways have been implicated in the deleterious effects of
468 cytokine storms 467 TNFα, IL-1 and inflammasome pathways have been implicated in the deleterious effects of
468 cytokine storms and cell death later in disease $89,92,104-106$. We found that the pro-inflammatory
469 TNFR1 pathway is cri cytokine storms and cell death later in disease $89,92,104-106$ 468 cytokine storms and cell death later in disease $89,92,104-106$. We found that the pro-inflammatory
469 TNFR1 pathway is critical for early viral control of SCV2 replication in mice and that pulmonary
470 precondition TNFR1 pathway is critical for early viral control of SCV2 replication in mice and that pulmonary

470 preconditioning with recombinant TNF α potently limits SCV2 viral titers in the lung. Of note,

471 patients undergoi 470 preconditioning with recombinant TNF α potently limits SCV2 viral titers in the lung. Of note,
471 patients undergoing TNF α blockade as a long-term treatment for dermatological or rheumatic
472 diseases showed no 471 patients undergoing TNF α blockade as a long-term treatment for dermatological or rheumatic
472 diseases showed no increase in hospitalizations or severe COVID-19 disease ¹⁰⁷⁻¹⁰⁹. However,
473 the impact on early diseases showed no increase in hospitalizations or severe COVID-19 disease $107-109$. However, diseases showed no increase in hospitalizations or severe COVID-19 disease 10^{74} However,
473 the impact on early control of viral replication is difficult to ascertain from such clinical studies. In
474 regard to IL-1 473 the impact on early control of viral replication is difficult to ascertain from such clinical studies. In
474 regard to IL-1 and inflammasomes, our data agree with prior findings of decreased viral titers
475 early af 474 regard to IL-1 and inflammasomes, our data agree with prior findings of decreased viral titers
475 early after infection in *Nlrp3*^{-/-} mice ⁹³, supporting a negative role for NLRP3 activation at both
476 early and early after infection in *Nlrp3*² mice ⁹³ 475 early after infection in *NIrp3^{-/-}* mice ⁹³, supporting a negative role for NLRP3 activation at both
476 early and later stages of SCV2 infection. However, we also provide evidence that uncouples
477 NLRP3 from it 476 early and later stages of SCV2 infection. However, we also provide evidence that uncouples
477 NLRP3 from its known downstream effector proteins as we show here that early viral titers were
478 unchanged in $Casp1^{-/-}$, 477 NLRP3 from its known downstream effector proteins as we show here that early viral titers were
478 unchanged in $Casp1^{-/-}$, $Casp1,11^{-/-}$, $I/I11^{-/-}$ and $I/Ia,b^{-/-}$ animals and were in fact higher in
479 Gsdmd, Gsdme^{-/-} m unchanged in *Casp1-/-*, *Casp1,11*-/-, *Il1r1-/-* and *Il1a,b-/-* 478 unchanged in $Casp1^{77}$, $Casp111^{77}$ and $ll1a,b^{77}$ animals and were in fact higher in Gsdmd, Gsdme^{-/-} mice. Further studies will be required to address the differential roles revealed here for gasdermins and NLRP3 i *Gsdmd, Gsdme^{-/-}* mice. Further studies will be required to address the differential roles revealed 479 Gsdmd, Gsdme^{-/-} mice. Further studies will be required to address the differential roles revealed
480 here for gasdermins and NLRP3 in early innate mucosal immunity to SCV2 compared to later
481 stages of disease. M 480 here for gasdermins and NLRP3 in early innate mucosal immunity to SCV2 compared to later
481 stages of disease. Moreover, although the IL-1R1 signaling pathway was not required to control
482 early viral replication d 481 stages of disease. Moreover, although the IL-1R1 signaling pathway was not required to control
482 early viral replication during SCV2 infection, pulmonary IL-1-driven inflammatory preconditioning
483 prior to SCV2 in 482 early viral replication during SCV2 infection, pulmonary IL-1-driven inflammatory preconditioning
483 prior to SCV2 infection established an antiviral state, like TNFα and IFNβ preconditioning. Thus,
484 TNFα and IL-1 483 prior to SCV2 infection established an antiviral state, like TNFα and IFNβ preconditioning. Thus,
484 TNFα and IL-1, in addition to IFNs, are important for viral control in the lung around the time of
5.
TNFα and IL-1 484 TNF α and IL-1, in addition to IFNs, are important for viral control in the lung around the time of α

SCV2 exposure, while at later stages their release must be controlled to prevent systemic

486 cytokine storm and pathogenic inflammation.

487 While an important conclusion from the present study is that diverse infectiou cytokine storm and pathogenic inflammation.
487 While an important conclusion from
488 sterile inflammatory stimuli can precondition
499 replication, the precise molecular and cellu
490 are most likely as varied as the sti 487 While an important conclusion from the present study is that diverse infectious and
488 sterile inflammatory stimuli can precondition the lung for enhanced early innate control of SCV2
489 replication, the precise mole 488 sterile inflammatory stimuli can precondition the lung for enhanced early innate control of SCV2 replication, the precise molecular and cellular mechanisms underlying enhanced viral control are most likely as varied as replication, the precise molecular and cellular mechanisms underlying enhanced viral control
490 are most likely as varied as the stimuli used. Future studies will be required to carefully
491 delineate cellular and molecu 490 are most likely as varied as the stimuli used. Future studies will be required to carefully
491 delineate cellular and molecular mechanisms *in vivo* for each inflammatory scenario. By
492 narrowing from complex pathog delineate cellular and molecular mechanisms *in vivo* for each inflammatory scenario. By

492 narrowing from complex pathogens to TLR ligands and individual cytokine responses we can,

493 however, speculate on some genera 492 narrowing from complex pathogens to TLR ligands and individual cytokine responses we can,
493 however, speculate on some general features that may be common among those stimuli and
494 induce an innately protective an 493 however, speculate on some general features that may be common among those stimuli and
494 induce an innately protective antiviral state in the lungs of mice. First, it is conceivable that
495 distinct inflammatory ax 494 induce an innately protective antiviral state in the lungs of mice. First, it is conceivable that
495 distinct inflammatory axes converge on the induction of antiviral IFNs and that broad IFN-driven
496 responses are 495 distinct inflammatory axes converge on the induction of antiviral IFNs and that broad IFN-driven
496 responses are sufficient and necessary for enhanced antiviral immunity in the lung. Indeed,
497 pulmonary administra 496 responses are sufficient and necessary for enhanced antiviral immunity in the lung. Indeed,
497 pulmonary administration of IFN-I (IFNa¹⁰² or IFNβ as shown here), IFN-II (IFNγ⁴⁰) or IFN-III
498 (IFNλ^{85,110,111}) pulmonary administration of IFN-I (IFNα 102 or IFNβ as shown here), IFN-II (IFNγ 40 quimonary administration of IFN-I (IFNa¹⁰² or IFNβ as shown here), IFN-II (IFNγ⁴⁰) or IFN-III
498 (IFNλ^{85,110,111}) prior to infection all lowered SCV2 viral titers in the lungs of mice. Pulmonary
499 delivery of the $(IFNA ^{85,110,111})$ prior to infection all lowered SCV2 viral titers in the lungs of mice. Pulmonary 498 (IFNA 85,110,111) prior to infection all lowered SCV2 viral titers in the lungs of mice. Pulmonary
499 delivery of the STING agonist 2'3' cGAMP ¹¹², the TLR3/MDA5 agonist Poly (I:C) ¹¹³ or the RIG-I
500 agonis delivery of the STING agonist 2'3' cGAMP 112 , the TLR3/MDA5 agonist Poly (I:C) 113 or the RIG-I delivery of the STING agonist 2'3' cGAMP 112 , the TLR3/MDA5 agonist Poly (I:C) 113 or the RIG-I
500 agonist SLR14 114 were also shown to effectively reduce lung viral SCV2 burden when given
501 prophylacticall agonist SLR14¹¹⁴ 500 agonist SLR14 ¹¹⁴ were also shown to effectively reduce lung viral SCV2 burden when given
501 prophylactically. In addition, IFN-I and IFN-III dependent control of viral replication in lung ECs
502 has been shown to 501 prophylactically. In addition, IFN-I and IFN-III dependent control of viral replication in lung ECs
502 has been shown to affect disease trajectories prior to the onset of T cell-mediated control
503 8,15,103,115 . 502 has been shown to affect disease trajectories prior to the onset of T cell-mediated control
503 8,15,103,115 . In fact, SCV2 replication levels are associated with the likelihood of viral transmission,
504 and the ^{8,15,103,115}. In fact, SCV2 replication levels are associated with the likelihood of viral transmission,

so4 and the ability of children to mount a more robust protective innate immune response compared

to adults corr 504 and the ability of children to mount a more robust protective innate immune response compared
505 to adults correlates with reduced viral replication in ECs $^{5,6,116-119}$. We provide evidence that the
506 diverse in to adults correlates with reduced viral replication in ECs $5,6,116-119$. We provide evidence that the 505 to adults correlates with reduced viral replication in ECs $5,6,116-119$. We provide evidence that the diverse inflammatory stimuli used in the current study, apart from recombinant TNF α and IL-1 administrations, a 506 diverse inflammatory stimuli used in the current study, apart from recombinant TNF α and IL-1
507 administrations, all promoted IFN-driven activation of lung ECs as we observed increased
508 expression of the ISMs S 507 administrations, all promoted IFN-driven activation of lung ECs as we observed increased
508 expression of the ISMs Sca-1 or CD317 on various ECs in most settings prior to SCV2 infection.
509 The pro-inflammatory cyto 508 expression of the ISMs Sca-1 or CD317 on various ECs in most settings prior to SCV2 infection.
509 The pro-inflammatory cytokines IL-1 and TNFα can stimulate IRF-1 and IRF-3, transcriptional
510 activators of chemoki 509 The pro-inflammatory cytokines IL-1 and TNFα can stimulate IRF-1 and IRF-3, transcriptional
510 activators of chemokines and IFN-Is, thus promoting antiviral responses indirectly via IFN
511 induction ¹²⁰⁻¹²⁴. Neve 510 activators of chemokines and IFN-Is, thus promoting antiviral responses indirectly via IFN
511 induction ¹²⁰⁻¹²⁴. Nevertheless, any potential indirect up-regulation of IFN-I by recombinant TNF α
512 or IL-1 was in induction $120-124$. Nevertheless, any potential indirect up-regulation of IFN-I by recombinant TNF α 511 induction $120-124$. Nevertheless, any potential indirect up-regulation of IFN-I by recombinant TNF α or IL-1 was insufficient to cause lung EC ISM expression when compared to recombinant IFN β administration itse 512 or IL-1 was insufficient to cause lung EC ISM expression when compared to recombinant IFNβ administration itself. While TNFα and IL-1 administration failed to upregulate Sca-1 or CD317 on ECs, it is possible that ISM 513 administration itself. While TNFα and IL-1 administration failed to upregulate Sca-1 or CD317 on
514 ECs, it is possible that ISMs not examined in this study could have been activated indirectly by
515 TNFα or IL-1. ECs, it is possible that ISMs not examined in this study could have been activated indirectly by

TNFα or IL-1. Additionally, the infectious and inflammatory stimuli used in our study are known

to result in changes to t 515 TNFα or IL-1. Additionally, the infectious and inflammatory stimuli used in our study are known
516 to result in changes to the TRM compartment ⁷⁰, and we show here that recent one-time TLR
517 preconditioning pote to result in changes to the TRM compartment 70 516 to result in changes to the TRM compartment ⁷⁰, and we show here that recent one-time TLR
517 preconditioning potently remodeled the TRM compartment towards a metabolically altered
518 tissue repair phenotype with in 517 preconditioning potently remodeled the TRM compartment towards a metabolically altered
518 tissue repair phenotype with increased arginase-1 expression. However, when we functionally
518 tissue repair phenotype with in 518 tissue repair phenotype with increased arginase-1 expression. However, when we functionally

issue repair phenotype with increased arginase-1 expression. However, when we functionally

issue repair phenotype with incre

519 inhibited arginase or tested IM involvement via CCR5, CCR2, or Trem2 deficient mice, TLR
520 agonist-mediated protection was not abrogated, suggesting that arginase or IMs may not be
521 sufficient to create the observ 520 agonist-mediated protection was not abrogated, suggesting that arginase or IMs may not be
521 sufficient to create the observed heightened antiviral state. We have also not ruled out that AMs
522 may produce IFN-I in r sum sufficient to create the observed heightened antiviral state. We have also not ruled out that AMs
522 may produce IFN-I in response to TLR stimulation, as reported during infections with other
523 respiratory RNA virus 522 may produce IFN-I in response to TLR stimulation, as reported during infections with other
523 respiratory RNA viruses 125,126 , or that lung ECs directly respond to CpG or Pm3 to generate
524 IFNs and limit viral respiratory RNA viruses ^{125,126} 523 respiratory RNA viruses 125,126 , or that lung ECs directly respond to CpG or Pm3 to generate
524 IFNs and limit viral replication. Thus, direct or indirect activation of broad IFN responses close to
525 the time o

524 IFNs and limit viral replication. Thus, direct or indirect activation of broad IFN responses close to
525 the time of SCV2 exposure may be sufficient to enhance early innate viral resistance.
526 A second possibility 525 the time of SCV2 exposure may be sufficient to enhance early innate viral resistance.
526 A second possibility is that TNFa and IL-1 exert IFN-independent antivir
527 functions $127-130$. TNFa induces pro-inflammatory 526 A second possibility is that TNFα and IL-1 exert IFN-independent antiviral effector
527 functions ¹²⁷⁻¹³⁰. TNFα induces pro-inflammatory responses through TNFR1 complex I and
528 noncanonical NF-κB activation as we functions $127-130$. TNF α induces pro-inflammatory responses through TNFR1 complex I and 527 functions $^{127 \cdot 130}$. TNFa induces pro-inflammatory responses through TNFR1 complex I and
528 noncanonical NF-kB activation as well as modulating cell death via complex II 131 . Although
529 excessive inflammato noncanonical NF-κB activation as well as modulating cell death via complex II¹³¹ moncanonical NF-kB activation as well as modulating cell death via complex II⁻¹³¹. Although

sz0 excessive inflammatory cell death has been implicated in severe COVID-19 disease ^{132,133},

killing infected cells and mo excessive inflammatory cell death has been implicated in severe COVID-19 disease 132,133 529 excessive inflammatory cell death has been implicated in severe COVID-19 disease 132,133 , killing infected cells and modulating cell death also represents a central antiviral strategy. TNFα can induce both apopto 630 killing infected cells and modulating cell death also represents a central antiviral strategy. TNFα

can induce both apoptosis through caspase-8 and necroptosis, which utilizes the pseudokinase

Mixed Lineage Kinase D 531 can induce both apoptosis through caspase-8 and necroptosis, which utilizes the pseudokinase
532 Mixed Lineage Kinase Domain-Like (MLKL). While we report here increased viral titers in
533 TNFR1 deficient mice, mice l 532 Mixed Lineage Kinase Domain-Like (MLKL). While we report here increased viral titers in
533 TNFR1 deficient mice, mice lacking caspase-8 and/or MLKL had similar SCV2 viral titers when
534 compared to lungs of WT anima 533 TNFR1 deficient mice, mice lacking caspase-8 and/or MLKL had similar SCV2 viral titers when
534 compared to lungs of WT animals 134,135 . Besides modulation of cell death, TNFa drives changes
535 in intracellular m compared to lungs of WT animals 134,135 534 compared to lungs of WT animals 134,135 . Besides modulation of cell death, TNFα drives changes
535 in intracellular metabolism, including glycolysis, shown to be important for its cell-intrinsic
536 antiviral act 535 in intracellular metabolism, including glycolysis, shown to be important for its cell-intrinsic
536 antiviral activities ¹²⁷. Both TNFa and IL-1 are also strong inducers of inflammatory chemokines
537 and early and antiviral activities 127 . Both TNF α and IL-1 are also strong inducers of inflammatory chemokines 536 antiviral activities ¹²⁷. Both TNF α and IL-1 are also strong inducers of inflammatory chemokines
537 and early and effective recruitment of innate immune cells has emerged as an important factor
538 for viral rep 537 and early and effective recruitment of innate immune cells has emerged as an important factor
538 for viral replication in mice 136 , while risk for severe COVID-19 has been linked to genetic
539 regions expressing for viral replication in mice ¹³⁶ 538 for viral replication in mice 136 , while risk for severe COVID-19 has been linked to genetic
539 regions expressing multiple chemokines 12,21,57 . Thus, future studies will need to thoroughly
540 delineate IFNregions expressing multiple chemokines ^{12,21,57} 539 regions expressing multiple chemokines 12,21,57 . Thus, future studies will need to thoroughly delineate IFN-dependent and independent antiviral effects of TNFα and IL-1 during both antiviral preconditioning of th delineate IFN-dependent and independent antiviral effects of TNFα and IL-1 during both
541 antiviral preconditioning of the lung as well as in response to SCV2 infection. These effects may
542 include initial TRM-EC inter 541 antiviral preconditioning of the lung as well as in response to SCV2 infection. These effects may
542 include initial TRM-EC interactions, the contribution of epigenetic modifications in TRMs and
543 ECs, early cell de include initial TRM-EC interactions, the contribution of epigenetic modifications in TRMs and
543 ECs, early cell death events, activation of AMs, induction of chemokines required for IM
544 recruitment, or cell-intrinsic

ECs, early cell death events, activation of AMs, induction of chemokines required for IM

secruitment, or cell-intrinsic effects within lung EC subsets.

Nonhuman primates infected with SCV2, despite being genetically dive recruitment, or cell-intrinsic effects within lung EC subsets.
545 • Nonhuman primates infected with SCV2, despite b
546 similar to the human population, present with only very mi
547 viral replication prior to antigen-spe 545 Nonhuman primates infected with SCV2, despite being genetically diverse and outbred,
546 similar to the human population, present with only very mild disease associated with control of
547 viral replication prior to an similar to the human population, present with only very mild disease associated with control of
547 viral replication prior to antigen-specific T-cell responses ^{137,138}. Importantly, nonhuman primates
548 are typically n viral replication prior to antigen-specific T-cell responses 137,138 viral replication prior to antigen-specific T-cell responses 137,138. Importantly, nonhuman primates
548 are typically not housed under abnormally hygienic specific pathogen-free (SPF) conditions, like
550 most experimenta 548 are typically not housed under abnormally hygienic specific pathogen-free (SPF) conditions, like
549 most experimental mice, and have experienced diverse infectious immunological stimuli. In
550 contrast to SPF mice, f 549 most experimental mice, and have experienced diverse infectious immunological stimuli. In
550 contrast to SPF mice, feral and pet-store mice that have been microbially exposed to naturally
551 occurring infections exhi 550 contrast to SPF mice, feral and pet-store mice that have been microbially exposed to naturally
551 occurring infections exhibit elevated IFN and inflammatory responses and mount more human-
552 like responses, resultin 551 occurring infections exhibit elevated IFN and inflammatory responses and mount more human-
552 like responses, resulting in increased viral control compared to SPF mice ¹³⁹⁻¹⁴¹. Moreover, like responses, resulting in increased viral control compared to SPF mice $139-141$ like responses, resulting in increased viral control compared to SPF mice 139-141. Moreover, sequential infection of SPF mice can recapitulate some aspects of the naturally occurring prior
554 exposure histories in wild mice and similarly promotes more human-like inflammatory immune
555 responses ¹⁴². Our findin s54 exposure histories in wild mice and similarly promotes more human-like inflammatory immune
555 responses ¹⁴². Our findings here are consistent with these prior observations on how
556 immunological exposure history c responses 142 . Our findings here are consistent with these prior observations on how 555 responses 142 . Our findings here are consistent with these prior observations on how
556 immunological exposure history can shape the outcome of subsequent infections and we
557 propose that feral or pet-store mic 556 immunological exposure history can shape the outcome of subsequent infections and we
557 propose that feral or pet-store mice, like the preconditioned mice used here, would display
558 enhanced SCV2 viral control compa propose that feral or pet-store mice, like the preconditioned mice used here, would display
558 enhanced SCV2 viral control compared to SPF mice, as has already been reported for infection
559 with Lymphocytic Choriomening with Lymphocytic Choriomeningitis Virus ¹³⁹.

enhanced SCV2 viral control compared to SPF mice, as has already been reported for infection

with Lymphocytic Choriomeningitis Virus¹³⁹.

Our findings may also help provide an immunological basis for certain clinical

o 559 . 560 Our findings may also help provide an immunological basis for certain clinical
561 observations in specific patient populations. For example, children are among the most widely
562 infection-exposed patient populations 561 observations in specific patient populations. For example, children are among the most widely
562 infection-exposed patient populations, and most children have milder SCV2 infection outcomes
563 compared to adults or t infection-exposed patient populations, and most children have milder SCV2 infection outcomes

compared to adults or the elderly. Besides age itself, one additional factor contributing to milder

solary outcomes may also be compared to adults or the elderly. Besides age itself, one additional factor contributing to milder
564 outcomes may also be recent infectious exposure histories. The concept of 'immune debt' and
565 'immunity gap' ¹⁴³⁻¹⁴ outcomes may also be recent infectious exposure histories. The concept of 'immune debt' and
565 'immunity gap' ¹⁴³⁻¹⁴⁶ suggests that during the pandemic, the unprecedented non-pharmaceutical
566 interventions, including 'immunity gap' ¹⁴³⁻¹⁴⁶ suggests that during the pandemic, the unprecedented non-pharmaceutical 565 \degree 'immunity gap' $^{143 \cdot 146}$ suggests that during the pandemic, the unprecedented non-pharmaceutical
566 interventions, including lock-down and masking, led to a significant decrease in exposure to
567 common res 566 interventions, including lock-down and masking, led to a significant decrease in exposure to
567 common respiratory childhood diseases. After restrictions were lifted, however, a dramatic
568 surge in pediatric respira common respiratory childhood diseases. After restrictions were lifted, however, a dramatic
568 surge in pediatric respiratory disease was observed, arguing that the lack of pulmonary immune
559 stimulation made children mo stimulation made children more vulnerable to community-acquired infections ¹⁴⁶⁻¹⁵⁰. Our study
569 stimulation made children more vulnerable to community-acquired infections ¹⁴⁶⁻¹⁵⁰. Our study
570 provides experimental stimulation made children more vulnerable to community-acquired infections ¹⁴⁶⁻¹⁵⁰ stimulation made children more vulnerable to community-acquired infections ¹⁴⁶⁻¹⁵⁰. Our study
570 provides experimental evidence that diverse recent pulmonary exposures can indeed
571 significantly impact subsequent inna

570 provides experimental evidence that diverse recent pulmonary exposures can indeed
571 significantly impact subsequent innate viral infection control in the lung.
572 Children and adults with asthmatic diseases were ini significantly impact subsequent innate viral infection control in the lung.
572 Children and adults with asthmatic diseases were initially thoug
573 COVID-19 outcomes, given known deficits in antiviral immunity and t
574 v 572 Children and adults with asthmatic diseases were initially thought to have more severe
573 COVID-19 outcomes, given known deficits in antiviral immunity and that common respiratory
574 viruses can exacerbate asthma. Ho 573 COVID-19 outcomes, given known deficits in antiviral immunity and that common respiratory
574 viruses can exacerbate asthma. However, many clinical studies failed to show an expected
575 increase in the prevalence of a 574 viruses can exacerbate asthma. However, many clinical studies failed to show an expected
575 increase in the prevalence of asthmatic patients among COVID-19-infected individuals and
576 instead concluded that the relat increase in the prevalence of asthmatic patients among COVID-19-infected individuals and
576 instead concluded that the relative risk of severe COVID-19 was relatively small $32,34,151-153$. We
577 show here in a murine ex instead concluded that the relative risk of severe COVID-19 was relatively small $32,34,151-153$. We instead concluded that the relative risk of severe COVID-19 was relatively small ^{32,34,151-153}. We

show here in a murine experimental OVA/Alum asthma model that underlying allergic-type II-

driven inflammation at the t 577 show here in a murine experimental OVA/Alum asthma model that underlying allergic-type II-
578 driven inflammation at the time of SCV2 exposure significantly enhances innate viral replication
579 control in the lungs, 578 driven inflammation at the time of SCV2 exposure significantly enhances innate viral replication
579 control in the lungs, arguing that innate aspects of type II immune responses might provide
580 potential antiviral p 579 control in the lungs, arguing that innate aspects of type II immune responses might provide
580 potential antiviral protective rather than detrimental effects early during SCV2 infection.
581 Delineating the precise ro 580 potential antiviral protective rather than detrimental effects early during SCV2 infection.
581 Delineating the precise role type II associated cytokine, chemokines, and cell types promoting
582 innate early control of Delineating the precise role type II associated cytokine, chemokines, and cell types promoting
582 innate early control of SARS-CoV-2 replication will provide important mechanistic insight and
583 context for clinical stud innate early control of SARS-CoV-2 replication will provide important mechanistic insight and
583 context for clinical studies where type-2 associated immune responses were shown to either
584 positively or negatively asso positively or negatively associate with COVID-19 outcomes ^{151,154}.

583 context for clinical studies where type-2 associated immune responses were shown to either
584 positively or negatively associate with COVID-19 outcomes ^{151,154}.
585 There was also increased concern for patients with positively or negatively associate with COVID-19 outcomes ^{151,154}.
585 There was also increased concern for patients with C
586 recessive disorder caused by mutations in the gene encoding the a
586 recessive disorder cau 585 There was also increased concern for patients with CF, an inherited, autosomal
586 recessive disorder caused by mutations in the gene encoding the anion channel Cystic Fibrosis
586 recessive disorder caused by mutation 586 recessive disorder caused by mutations in the gene encoding the anion channel Cystic Fibrosis

The gene encoding the anion channel Cystic Fibrosis

The gene encoding the anion channel Cystic Fibrosis

The gene encoding

Transmembrane Conductance Regulator (CFTR) that can lead to chronic pulmonary infections
588 and respiratory failure. However, COVID-19 incidence estimates in CF were reported to be
589 lower than in the general population 588 and respiratory failure. However, COVID-19 incidence estimates in CF were reported to be
589 lower than in the general population with often less severe outcomes than originally anticipated
590 ^{36,155,156}. In our exp 589 lower than in the general population with often less severe outcomes than originally anticipated
590 ^{36,155,156}. In our experimental mouse model, we demonstrate that recent pulmonary infection with
591 *S. aureus* re 36,155,156 590 ^{36,155}. In our experimental mouse model, we demonstrate that recent pulmonary infection with
591 *S. aureus* resulted in significantly enhanced innate control of SCV2 replication. The most
592 common lung pathogens 591 *S. aureus* resulted in significantly enhanced innate control of SCV2 replication. The most
592 common lung pathogens that colonize CF patient include *Pseudomonas aeruginosa* and *S.*
593 *aureus*, including methicill 592 common lung pathogens that colonize CF patient include *Pseudomonas aeruginosa* and *S.*
593 *aureus*, including methicillin-resistant *S. aureus* (MRSA), and *Aspergillus* ¹⁵⁷. Therefore, it may
594 be worth explori *aureus*, including methicillin-resistant *S. aureus* (MRSA), and *Aspergillus* ¹⁵⁷ spanning methicillin-resistant S. aureus (MRSA), and Aspergillus ¹⁵⁷. Therefore, it may
594 be worth exploring whether bacterial colonization status at the time of SARS-CoV2 exposure is
595 a contributing factor to the c

594 be worth exploring whether bacterial colonization status at the time of SARS-CoV2 exposure is
595 a contributing factor to the clinical outcome of COVID-19 in CF patients.
596 In conclusion, our study provides a founda 595 a contributing factor to the clinical outcome of COVID-19 in CF patients.
596 In conclusion, our study provides a foundational experimental fra
597 *vivo* evidence that immunologically diverse pulmonary exposure histor In conclusion, our study provides a foundational experimental framework together with *in*
597 *vivo* evidence that immunologically diverse pulmonary exposure histories, including those that
598 only modestly trigger IFN r *vivo* evidence that immunologically diverse pulmonary exposure histories, including those that
598 only modestly trigger IFN responses, can potently impact initial pulmonary SCV2 replication.
599 Our findings open up the 598 only modestly trigger IFN responses, can potently impact initial pulmonary SCV2 replication.
599 Our findings open up the intriguing possibility that the recent exposure history and the
600 inflammatory microenvironmen 599 Our findings open up the intriguing possibility that the recent exposure history and the
600 inflammatory microenvironment of the lung proximal to the time of SCV2 exposure may be a
601 significant factor contributing 600 inflammatory microenvironment of the lung proximal to the time of SCV2 exposure may be a
601 significant factor contributing to the diverse clinical outcomes seen in people with COVID-19.
602
604 601 significant factor contributing to the diverse clinical outcomes seen in people with COVID-19.
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621 **MATERIALS & METHODS**
623 **Mice**
624 *TIr4¹* mice (B6(Cg)-
625 #3080) ¹⁵⁸, K18-hACE2 hem
626 ¹⁵⁹, *Tmem173*^{gt} I199N mu 622
623
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625
626
627 623 **Mice**
624 #3080
625 #3080
626 ¹⁵⁹, 7
627 (C57E
628 ¹⁶², 4 *Tlr4¹⁻* mice (B6(Cg)-*Tlr4^{tm1.2Karp}/J; JAX #29015), <i>Tlr7¹⁻* mice (B6.129S1-*Tlr7^{tm1Flv}/J; JAX* $Tlr4$ ["] mice (B6(Cg)- $Tlr4$ ^{m_{1.2Karp}/J; JAX #29015), $Tlr7$ ["] mice (B6.129S1- $Tlr7$ ^{m+ r/v}/J; JAX
625 #3080)¹⁵⁸, K18-hACE2 hemizygous transgenic mice (B6.Cg-Tg(K18-ACE2)2^{Prlmn/J}; JAX #34860)
626 ¹⁵⁹, *Tmem173*^{at}</sup>} $\#3080$)¹⁵⁸, K18-hACE2 hemizygous transgenic mice (B6.Cg-Tg(K18-ACE2)2^{Primn/J}; JAX $\#34860$) 625 #3080) ¹⁵⁸, K18-hACE2 hemizygous transgenic mice (B6.Cg-Tg(K18-ACE2)2^{Primm}³; JAX #34860)
626 ¹⁵⁹, *Tmem173*^{gt} 1199N mutant mice (C57BL/6J-Sting1^{gt}/J; JAX #17537) ¹⁶⁰, *Trem2^{-/-}* mice
627 (C57BL/6J-*Tre* ¹⁵⁹, *Tmem173*^{gt} I199N mutant mice (C57BL/6J-Sting1^{gt}/J; JAX #17537) ¹⁶⁰, *Trem2^{-/-}* mice 626 is Tmem173^{gt} 1199N mutant mice (C57BL/6J-Sting1^{gr}/J; JAX #17537) is Trem2^r mice
627 (C57BL/6J-Trem2^{em2Adiuj}/J; JAX #27197) ¹⁶¹, Casp1^{-/-} mice (B6.Cg-Casp1^{em1Vnce}/J; JAX #32662)
628 ¹⁶², Alox15^{*l*-} mi (C57BL/6J-*Trem2em2Adiuj*/J; JAX #27197) 161, *Casp1*-/- mice (B6.Cg-*Casp1em1Vnce* 627 (C57BL/6J-*Trem2^{em2Adiul}/J*; JAX #27197) ¹⁶¹, Casp1^{-/-} mice (B6.Cg-Casp1^{em1vnce}/J; JAX #32662)
628 ¹⁶², Alox15^{*l*-} mice (B6.129S2-Alox15^{tm1Fun}/J; JAX #2778) ¹⁶³, and *Ifnar1^{-/-}* mice (B6(Cg)-
630 Ifn ¹⁶², *Alox15^{1.}* mice (B6.129S2-*Alox15^{tm1Fun}/J*; JAX #2778) ¹⁶³, and *Ifnar1⁻¹* 628 ¹⁶², *Alox15¹* mice (B6.129S2-*Alox15^{tm1Fun}l*J; JAX #2778) ¹⁶³, and *Ifnar1⁻¹* mice (B6(Cg)-
629 Ifnar1^{tm1.2Ees}/J; JAX stock #28288) ¹⁶⁴, were purchased from Jackson Laboratories (Bar Harbor,
630 ME). *T* Ifnar1^{tm1.2Ees}/J; JAX stock #28288) ¹⁶⁴ 629 Ifnar1^{tm1.2Ees}/J; JAX stock #28288) ¹⁶⁴, were purchased from Jackson Laboratories (Bar Harbor, ME). *Tlr2^{-/-}* mice ¹⁶⁵, *ll1a,b^{-/-}* mice ¹⁶⁶, *Tlr9^{-/-}* mice ¹⁶⁷ were previously described. *Gsdmd, Gsdme* ME). *Tlr2*-/- mice 165, *Il1a,b*-/- mice 166, *Tlr9*-/- mice 167 were previously described. *Gsdmd,Gsdme*-/- 631
632
633
634 mice 168 were kind gifts of Dr. Feng Shao (NIBS, China). C57BL/6 mice (Taconic farms), 631 mice ¹⁶⁸ were kind gifts of Dr. Feng Shao (NIBS, China). C57BL/6 mice (Taconic farms),
632 C57BL/6 mice expressing a *Foxp3*-GFP reporter (C57BL/6-*Foxp3^{tm1Kuch}*) ¹⁶⁹ or the Thy1.1 allele
633 (B6.PL-Thy1^a/CyJ) C57BL/6 mice expressing a *Foxp3*-GFP reporter (C57BL/6-*Foxp3tm1Kuch*) ¹⁶⁹ 632 C57BL/6 mice expressing a *Foxp3*-GFP reporter (C57BL/6-*Foxp3^{m1Kuch}*) ¹⁶⁹ or the Thy1.1 allele
633 (B6.PL-Thy1^a/CyJ) were used as wild type C57BL/6 controls in experiments. *Foxp3*-GFP mice,
634 Thy1.1 mice, *I* (B6.PL-Thy1^a/CyJ) were used as wild type C57BL/6 controls in experiments. Foxp3-GFP mice, 633 (B6.PL-Thy1^a/CyJ) were used as wild type C57BL/6 controls in experiments. *Foxp3*-GFP mice,
634 Thy1.1 mice, *Ifnar1⁻¹⁻* mice (B6.129S2-*Ifnar1^{tm1Agt}* backcrossed to B6 for 12 generations) ¹⁷⁰, *TIr3*
635 ^{*F*} Thy1.1 mice, *Ifnar1^{-/-}* mice (B6.129S2-*Ifnar1^{tm1Agt}* backcrossed to B6 for 12 generations) ¹⁷⁰, *Tlr3* 635
636
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639 /- mice (B6;129S1-*Tlr3tm1Flv*/J backcrossed to B6 for 11 generations) 171, *Ifih1*-/- 635 $^{\prime\prime}$ mice (B6;129S1-*Tlr3^{tm1Flv}l*J backcrossed to B6 for 11 generations) $^{1/1}$, *Ifih1¹* mice (B6.Cg-
636 *Ifih1^{tm1.1Cln}lJ*) ¹⁷², *Ccr2^{-/-}* mice (B6.129S4-*Ccr2^{tm1ffc}lJ*) ¹⁷³, *NIrp3^{<i>i*} mice (B6N *Ifih1tm1.1Cln*/J) 172, *Ccr2*-/- mice (B6.129S4-*Ccr2tm1Ifc*/J) 173, *Nlrp3*-/- mice (B6N.129-*Nlrp3tm2Hhf*/J) ¹⁷⁴ 636 *Ifih1^{tm1.1Cln}*/J)¹⁷², Ccr2⁻⁷ mice (B6.129S4-Ccr2^{tm11c}/J)¹⁷³, Nlrp3⁻⁷ mice (B6N.129-Nlrp3^{tm2Hm}/J)¹⁷⁴,
637 *Tnfrsf1a^{-/-}* mice (C57BL/6-*Tnfrsf1a*^{tm1lmx}/J)¹⁷⁵, Ccr5^{/-} mice (B6.129P2-Ccr5^{tm1Kuz}/ *Tnfrsf1a-/-* mice (C57BL/6-*Tnfrsf1a*tm1Imx/J) 175, *Ccr5*-/- mice (B6.129P2-*Ccr5tm1Kuz*/J) 176, *Casp1,11*- 638
639
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642 /- mice (B6N.129S2-*Casp1tm1Flv*/J) 177, *Il1r1*-/- mice (B6;129S1-*Il1r1tm1Rom* 638 \cdot mice (B6N.129S2-*Casp1^{tm1FN}/J)* ¹⁷⁷, *Il1r1*¹ mice (B6;129S1-*Il1r1^{tm1Fom}I/J* backcrossed to B6 for
639 12 generations) ¹⁷⁸ were all obtained through a supply breeding contract between NIAID and
640 Tac 12 generations)¹⁷⁸ were all obtained through a supply breeding contract between NIAID and 639 12 generations) $^{1/8}$ were all obtained through a supply breeding contract between NIAID and
640 Taconic Farms. $Zbp1^{-/-}$ mice were made in-house by CRISPR/Cas9 genetic targeting as
641 detailed below. Both male and Taconic Farms. *Zbp1^{-/-}* mice were made in-house by CRISPR/Cas9 genetic targeting as Faconic Farms. $Zbp1^{-/-}$ mice were made in-house by CRISPR/Cas9 genetic targeting as
641 detailed below. Both male and female mice, 8-16 weeks old, were used in experiments and all
642 mice within individual experiments we 641 detailed below. Both male and female mice, 8-16 weeks old, were used in experiments and all
642 mice within individual experiments were age and sex matched. Genotyping was performed by
643 Transnetyx using real-time PC 642 mice within individual experiments were age and sex matched. Genotyping was performed by
643 Transnetyx using real-time PCR and genetic background analysis was submitted through
644 Transnetyx and performed by Neogen u 643 Transnetyx using real-time PCR and genetic background analysis was submitted through
644 Transnetyx and performed by Neogen using the MiniMUGA platform to confirm that all mice
645 were on a C57BL/6 background. All ani 644 Transnetyx and performed by Neogen using the MiniMUGA platform to confirm that all mice
645 were on a C57BL/6 background. All animals were bred and maintained in an AAALAC-
646 accredited ABSL2 or ABSL3 facility at th 645 were on a C57BL/6 background. All animals were bred and maintained in an AAALAC-
646 accredited ABSL2 or ABSL3 facility at the NIH and experiments were performed in compliance
647 with an animal study proposal approve 646 accredited ABSL2 or ABSL3 facility at the NIH and experiments were performed in compliance
647 with an animal study proposal approved by the NIAID Animal Care and Use Committee.
648 **Generation of Zbp1^{-/-} mice**
650

Generation of *Zbp1***-/-**

647 with an animal study proposal approved by the NIAID Animal Care and Use Committee.
648 **Generation of Zbp1¹¹ mice**
650 $Zbp1^{1}$ mice were made by the NIAID Mouse Genetics and Gene Modification (
651 Section by mic 648
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651
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653 649 **Generation of Zbp1⁻¹⁻ mice**
650 *Zbp1*⁻¹⁻ mice were ma
651 Section by microinjection
652 GTTTCCGGGATGGTAACA
653 embryos resulting in deletio
654 G0 was crossed to C57Bl/6N *Zbp1*-/- 650 $Zbp1$ ^{-/-} mice were made by the NIAID Mouse Genetics and Gene Modification (MGGM)
651 Section by microinjection of *Cas9* mRNA and the following guides: 5' sgRNA
652 GTTTCCGGGATGGTAACAGC and 3' sgRNA CTGGGACCCACGCGAG 651 Section by microinjection of *Cas9* mRNA and the following guides: 5' sgRNA
652 GTTTCCGGGATGGTAACAGC and 3' sgRNA CTGGGACCCACGCGAGGTGA into mouse
653 embryos resulting in deletion of exon 1 to create null allele *Zbp1* 652 GTTTCCGGGATGGTAACAGC and 3' sgRNA CTGGGACCCACGCGAGGTGA into mouse
653 embryos resulting in deletion of exon 1 to create null allele *Zbp1* c.-119_34+22del (**Fig S1C)**.
654 G0 was crossed to C57Bl/6NTac mice to isolate 653 embryos resulting in deletion of exon 1 to create null allele *Zbp1* c.-119_34+22del (**Fig S1C)**.
654 G0 was crossed to C57Bl/6NTac mice to isolate the null allele in G1, which were intercrossed to
654 G0 was crossed t 654 G0 was crossed to C57Bl/6NTac mice to isolate the null allele in G1, which were intercrossed to 655 homozygosity (screened using genotyping primers fwd: TCAGATAGAGCTCTCCCGGT, rev:
656 TAGACAGGGTATGTAGTCTCAGC). Zbp1 knockout was validated at the protein level by
657 western blotting of lysates from bone marrow-derived 656 TAGACAGGGTATGTAGTCTCAGC). Zbp1 knockout was validated at the protein level by
657 western blotting of lysates from bone marrow-derived macrophages (BMDMs, differentiated for
658 seven days with 50ng/mL M-CSF) and adhe 657 western blotting of lysates from bone marrow-derived macrophages (BMDMs, differentiated for
658 seven days with 50ng/mL M-CSF) and adherent peritoneal exudate cells (PECs) incubated with
659 and without 200ng/mL lipop 658 seven days with 50ng/mL M-CSF) and adherent peritoneal exudate cells (PECs) incubated with
659 and without 200ng/mL lipopolysaccharide (LPS, InvivoGen, #tlrlpb5lps) for 6 hours (Fig S1D).
660 Cells were lysed in RIPA 659 and without 200ng/mL lipopolysaccharide (LPS, InvivoGen, #Irlpb5lps) for 6 hours **(Fig S1D)**.
660 Cells were lysed in RIPA buffer and denatured by boiling in a final concentration of 70 mM SDS.
661 Lysate from 5.6x10 660 Cells were lysed in RIPA buffer and denatured by boiling in a final concentration of 70 mM SDS.
661 Lysate from 5.6x10⁴ cells per lane was separated by SDS-PAGE and transferred to 0.2 µm
1662 nitrocellulose membrane Lysate from $5.6x10^4$ cells per lane was separated by SDS-PAGE and transferred to 0.2 μ m 661 Lysate from 5.6x10⁴ cells per lane was separated by SDS-PAGE and transferred to 0.2 μm
662 nitrocellulose membranes. ZBP1 was detected using mouse-α-ZBP1 (Adipogen, #AG-20B-
663 0010-C100, 1:1000) and donkey-α-mous 662 nitrocellulose membranes. ZBP1 was detected using mouse-α-ZBP1 (Adipogen, #AG-20B-
663 0010-C100, 1:1000) and donkey-α-mouse-HRP (Jackson ImmunoResearch, #715-035-150,
664 1:10000), as a positive control for LPS stim 663 0010-C100, 1:1000) and donkey-α-mouse-HRP (Jackson ImmunoResearch, #715-035-150,
664 1:10000), as a positive control for LPS stimulation, pro-IL-1β was detected using goat-α-IL-1β
665 (R&D, #AB-401-NA, 1:1500) and bo 664 1:10000), as a positive control for LPS stimulation, pro-IL-1β was detected using goat-α-IL-1β
665 (R&D, #AB-401-NA, 1:1500) and bovine-α-goat-HRP (Jackson ImmunoResearch, #805-035-
666 180, 1:10,000) and actin was d 665 (R&D, #AB-401-NA, 1:1500) and bovine-α-goat-HRP (Jackson ImmunoResearch, #805-035-
666 180, 1:10,000) and actin was detected using mouse-α-actin-HRP (Santa Cruz, #sc-47778,
667 1:5000).
SCV2 infections SCV2 hCoV-19 666 180, 1:10,000) and actin was detected using mouse-α-actin-HRP (Santa Cruz, #sc-47778,
667 1:5000).
668 **SCV2 infections** SCV2 hCoV-19/USA-WA1/2020 (Pango lineage A, GISAID reference:
671 EPI_ISL_404895.2) (USA-WA1/20

667 1:5000).
668 **SCV2 int
670 S**
671 EPI_ISL_
672 variant o 668
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671
672
673 669 **SCV2 infections**
670 SCV2 *t*
671 EPI_ISL_404895.
672 variant of concern
673 obtained from BE
674 previously descrit 670 SCV2 hCoV-19/USA-WA1/2020 (Pango lineage A, GISAID reference:
671 EPI_ISL_404895.2) (USA-WA1/2020) and SCV2/human/ZAF/KRISP-K005325/2020 beta
672 variant of concern (Pango lineage B.1.351, GISAID reference: EPI_ISL_67 671 EPI_ISL_404895.2) (USA-WA1/2020) and SCV2/human/ZAF/KRISP-K005325/2020 beta
672 variant of concern (Pango lineage B.1.351, GISAID reference: EPI_ISL_678615) (B.1.351) were
673 obtained from BEI resources (NIAID, NIH). 672 variant of concern (Pango lineage B.1.351, GISAID reference: EPI_ISL_678615) (B.1.351) were
673 obtained from BEI resources (NIAID, NIH). Viral stocks were generated and sequenced as
674 previously described $39,179$. 673 obtained from BEI resources (NIAID, NIH). Viral stocks were generated and sequenced as
674 previously described $39,179$. Mice were anesthetized with isoflurane and infected i.n. with 35µL
675 inoculum containing 1.0x previously described 39,179 674 previously described $39,179$. Mice were anesthetized with isoflurane and infected i.n. with 35µL
675 inoculum containing 1.0x10³ TCID₅₀ USA-WA1/2020 or 3.5x10⁴ TCID₅₀ B.1.351. Inoculum was
676 quantified by T inoculum containing 1.0x10³ TCID₅₀ USA-WA1/2020 or 3.5x10⁴ 675 inoculum containing $1.0x10^3$ TCID₅₀ USA-WA1/2020 or $3.5x10^4$ TCID₅₀ B.1.351. Inoculum was
676 quantified by TCID₅₀ assay in Vero E6 cells (American Type Culture Collection, #CRL-1586).
677 **Mtb infection of**

676 quantified by TCID₅₀ assay in Vero E6 cells (American Type Culture Collection, #CRL-1586).
677 **Mtb infection of mice**
679 Mice were infected with *Mtb* H37Rv-mCherry (50 – 200 CFU) by aerosol using a Gl
680 Col who 678
679
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682 678 **Mtb infection of mice**
679 Mice were infec
680 Col whole-body inhalati
681 SCV2 75 – 100 days po
682 **Staphylococcus aure**r Mice were infected with *Mtb* H37Rv-mCherry (50 – 200 CFU) by aerosol using a Glas-
680 Col whole-body inhalation exposure system as previously described ¹⁸⁰. Mice were infected with
681 SCV2 75 – 100 days post *Mtb* inf Col whole-body inhalation exposure system as previously described ¹⁸⁰. Mice were infected with

680 Col whole-body inhalation exposure system as previously described ¹⁸⁰. Mice were infected with
681 $SCV2 75 - 100$ days post *Mtb* infection.
682 **Staphylococcus aureus infection of mice**
684 Mice were anesthetized wi 681 SCV2 75 – 100 days post *Mtb* infection.
682 **Staphylococcus aureus infection of m**
684 Mice were anesthetized with iso
685 (USA300). Pulmonary delivery doses we
686 agar (BD Biosciences, #241830) and i 683
684
685
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687 **Staphylococcus aureus infection of mice**
684 Mice were anesthetized with isoflura
685 (USA300). Pulmonary delivery doses were of
686 agar (BD Biosciences, #241830) and incut
687 SCV2 three days post S. aureus infection.
6 Mice were anesthetized with isoflurane and infected i.ph. with $5.6x10⁷$ CFU S. aureus Mice were anesthetized with isoflurane and infected i.ph. with 5.6x10['] CFU *S. aureus*
685 (USA300). Pulmonary delivery doses were confirmed by plating inocula on brain-heart infusion
686 agar (BD Biosciences, #241830) a 685 (USA300). Pulmonary delivery doses were confirmed by plating inocula on brain-heart infusion
686 agar (BD Biosciences, #241830) and incubating at 37°C overnight. Mice were infected with
687 SCV2 three days post S. aur 686 agar (BD Biosciences, #241830) and incubating at 37°C overnight. Mice were infected with SCV2 three days post S. aureus infection.
688
688 687 SCV2 three days post *S. aureus* infection.

689 **Influenza A virus H1N1 infections**
690 Mice were anesthetized with
691 virus (IAV; A/Puerto Rico/8/34, H1N
692 post IAV infection.
693 **OVA-Alum lung allergy model** 690 Mice were anesthetized with isoflurane and infected i.n. with 500 TCID₅₀ Influenza A
691 virus (IAV; A/Puerto Rico/8/34, H1N1 [PR8]) ¹⁸¹. Mice were then infected with SCV2 30 days
693 **OVA-Alum lung allergy model** virus (IAV; A/Puerto Rico/8/34, H1N1 [PR8]) ¹⁸¹

ost IAV; A/Puerto Rico/8/34, H1N1 [PR8]) ¹⁸¹. Mice were then infected with SCV2 30 days
692 post IAV infection.
693 **OVA-Alum lung allergy model** Mice were injected intraperitoneally (i.p.) twice, 14 days apart, with 10 692 post IAV infection.
693 **OVA-Alum lung a**
695 Mice were
696 (OVA, Sigma-Ald
697 (ThermoFisher, # 693
694
695
696
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698 **OVA-Alum lung allergy model**
695 Mice were injected intra
696 (OVA, Sigma-Aldrich, #A550;
697 (ThermoFisher, #77161). Ten
698 isoflurane and challenged i.n. w
699 infected with SCV2 5 – 6 days af Mice were injected intraperitoneally (i.p.) twice, 14 days apart, with 100µg Ovalbumin (OVA, Sigma-Aldrich, #A5503) in 200µl containing 12.5% Imject[™] alum adjuvant (ThermoFisher, #77161). Ten days after the last injecti (OVA, Sigma-Aldrich, #A5503) in 200µl containing 12.5% Imject[™] 696 (OVA, Sigma-Aldrich, #A5503) in 200µl containing 12.5% Imject^{1M} alum adjuvant
697 (ThermoFisher, #77161). Ten days after the last injection mice were anaesthetized with
698 isoflurane and challenged i.n. with 30µg O 697 (ThermoFisher, #77161). Ten days after the last injection mice were anaesthetized with
698 isoflurane and challenged i.n. with 30µg OVA in 30µL injection grade sterile saline. Mice were
1699 infected with SCV2 5 – 6 da

698 isoflurane and challenged i.n. with 30µg OVA in 30µL injection grade sterile saline. Mice were
699 infected with SCV2 5 – 6 days after i.n. OVA challenge.
700 Treatment of mice with TLR agonists, recombinant cytokines, 699 infected with SCV2 5 – 6 days after i.n. OVA challenge.

700 **Treatment of mice with TLR agonists, recombinant

702 antibodies**

703 Mice were anesthetized with isoflurane and trea

704 saline containing TLR agonists

700
701
702
703
704
705 Treatment of mice with TLR agonists, recombinant cytokines, inhibitors or neutralizing

102 antibodies

103 Mice were anesthetized with isoflurane and treated i.ph. with 30 – 50µL injection-grade

104 saline containing TLR 702 **antibodies**

703 Mice

704 saline conta

705 Pam3CSK4

706 #315-01A; 2

707 both togeth Mice were anesthetized with isoflurane and treated i.ph. with 30 – 50μL injection-grade

704 saline containing TLR agonists (10μg CpG ODN 2088, CpG type B, Invivogen, #tlrl-1826; 50μg

705 Pam3CSK4 (Pm3), Invivogen, #vac-704 saline containing TLR agonists (10μg CpG ODN 2088, CpG type B, Invivogen, #tlrl-1826; 50μg

705 Pam3CSK4 (Pm3), Invivogen, #vac-pms) or recombinant cytokines (5μg TNFα, PeproTech,

706 #315-01A; 2.0x10⁴U IFNβ, PBL, 705 Pam3CSK4 (Pm3), Invivogen, #vac-pms) or recombinant cytokines (5µg TNFα, PeproTech,

706 #315-01A; 2.0x10⁴U IFNβ, PBL, #12400-1; 200U IL-1α #211-11A, 200U IL-1β #211-11B or

707 both together at 200U total, PeproTec #315-01A; 2.0x10⁴U IFNB, PBL, #12400-1; 200U IL-1a #211-11A, 200U IL-1B #211-11B or 4315-01A; 2.0x10⁴U IFNβ, PBL, #12400-1; 200U IL-1α #211-11A, 200U IL-1β #211-11B or
707 both together at 200U total, PeproTech) to allow for pulmonary delivery one week (unless
708 otherwise stated in the figure legends 707 both together at 200U total, PeproTech) to allow for pulmonary delivery one week (unless

708 otherwise stated in the figure legends) prior to SCV2 infection. For neutralization of cytokine

709 signaling, mice were otherwise stated in the figure legends) prior to SCV2 infection. For neutralization of cytokine

709 signaling, mice were i.p. injected with 500μg anti-TNFα (BioXCell clone XT3.11), 500μg anti-

710 IFNAR1 (BioXCell clone 109 signaling, mice were i.p. injected with 500μg anti-TNFα (BioXCell clone XT3.11), 500μg anti-710 IFNAR1 (BioXCell clone MAR1-5A3) and/or 500μg IgG1 isotype control (BioXCell clone MOPC-
11 21) in injection-grade saline 10 IFNAR1 (BioXCell clone MAR1-5A3) and/or 500μg IgG1 isotype control (BioXCell clone MOPC-

711 21) in injection-grade saline. For inhibition of NIrp3, mice were injected i.p. with 600μg MCC950

712 (SelleckChem #S7809) 711 21) in injection-grade saline. For inhibition of Nlrp3, mice were injected i.p. with 600μg MCC950

712 (SelleckChem #S7809) on the day of SCV2 infection and again two days later. For inhibition of

713 arginase-1, mic 712 (SelleckChem #S7809) on the day of SCV2 infection and again two days later. For inhibition of
713 arginase-1, mice were administered 100µg Nor-NOHA (Cayman Chemical #10006861) i.n. once
714 daily on the day before, the

713 arginase-1, mice were administered 100µg Nor-NOHA (Cayman Chemical #10006861) i.n. once
714 daily on the day before, the day of, and two days following SCV2 infection.
715 **Viral quantification by TCID₅₀ assay or RNA**

daily on the day before, the day of, and two days following SCV2 infection.
715 **Viral quantification by TCID₅₀ assay or RNA extraction and quant genomes** Viral quantitation was performed as previously described ^{39,179} 715
716
717
718
719
720 Viral quantification by TCID₅₀ assay or RNA extraction and quantitative PCR of viral

717 genomes

Viral quantitation was performed as previously described ^{39,179}. Briefly, after harvesting

719 lungs from mice, the in 9917 **genomes**

118 Vira

119 lungs from

120 in PBS for

121 cells (Ame

122 Muench m Viral quantitation was performed as previously described $39,179$. Briefly, after harvesting Viral quantitation was performed as previously described $39,179$. Briefly, after harvesting

719 lungs from mice, the inferior lobe, post-caval lobe and left lung were immediately homogenized

720 in PBS for TCID₅₀ ass 719 lungs from mice, the inferior lobe, post-caval lobe and left lung were immediately homogenized
720 in PBS for TCID₅₀ assays. 10-fold serial dilutions were performed before plating on Vero E6
721 cells (American Type 720 in PBS for TCID₅₀ assays. 10-fold serial dilutions were performed before plating on Vero E6
721 cells (American Type Culture Collection, #CRL-1586). TCID₅₀ was calculated using the Reed–
722 Muench method after 96 721 cells (American Type Culture Collection, #CRL-1586). TCID₅₀ was calculated using the Reed–
722 Muench method after 96 hours of incubation. To measure viral gene copy number, the superior
722 Muench method after 96 h 722 Muench method after 96 hours of incubation. To measure viral gene copy number, the superior

723 lobe was homogenized in RLT Plus buffer (QIAGEN, #1053393) with β-mercaptoethanol

724 following storage at -80°C in RNAlater (ThermoFisher, #AM7021). RNA was extracted from RLT

725 Plus lysates using the RNeasy Plu 724 following storage at -80°C in RNAlater (ThermoFisher, #AM7021). RNA was extracted from RLT
725 Plus lysates using the RNeasy Plus Mini Kit (QIAGEN, #74136), including on-column DNase
726 treatment using the RNase-Free Plus lysates using the RNeasy Plus Mini Kit (QIAGEN, #74136), including on-column DNase

treatment using the RNase-Free DNase set (QIAGEN, #79256). The actively replicating (sub-

genomic, sgRNA) conformation of the SCV2 E The actively replicating (subgreed treatment using the RNase-Free DNase set (QIAGEN, #79256). The actively replicating (subgreed 727 enomic, sgRNA) conformation of the SCV2 E gene ¹⁸² was detected using primers at 500nM
 genomic, sgRNA) conformation of the SCV2 E gene ¹⁸² was detected using primers at 500nM

728 as follows: Forward (5'- CGATCTCTTG TAGATCTGTTCTC-3'), Reverse (5'-

739 ATATTGCAGCAGTACGCACACA -3') and the probe was used at 728 as follows: Forward (5'- CGATCTCTTG TAGATCTGTTCTC-3'), Reverse (5'-
729 ATATTGCAGCAGTACGCACACA -3') and the probe was used at 125nM (5'- (FAM)-
730 ACACTAGCCATCCTTACTGCGCTTCG-(3IABkFQ) -3'). Copy numbers were calculate The probe was used at 125nM (5'- (FAM)-
730 ACACTAGCCATCCTTACTGCGCTTCG-(3IABkFQ) -3'). Copy numbers were calculated using a
731 standard curve from a stock of known concentration ¹³⁷.
732 **RNA sequencing and transcriptio** ACACTAGCCATCCTTACTGCGCTTCG-(3IABkFQ) -3'). Copy numbers were calculated using a
731 standard curve from a stock of known concentration ¹³⁷.
732 **RNA sequencing and transcriptional analysis**
734 RNA was extracted as descr standard curve from a stock of known concentration ¹³⁷.

standard curve from a stock of known concentration 137.

732 **RNA sequencing and transcriptional analysis**

734 **RNA was extracted as described above and Corporation as previously described ¹⁸³. Sequencing us

736 was pe** 735
736
737 RNA sequencing and transcriptional analysis

734 RNA was extracted as described abo

735 Corporation as previously described ¹⁸³. Sequend

736 was performed to generate paired-end 150-bp i

737 transcriptome (GRCm38, mm1 RNA was extracted as described above and sent for sequencing by Novogene

735 Corporation as previously described ¹⁸³. Sequencing using the Illumina NovaSeq 6000 platform

736 was performed to generate paired-end 150-bp Corporation as previously described ¹⁸³ Corporation as previously described 183 . Sequencing using the Illumina NovaSeq 6000 platform

vas performed to generate paired-end 150-bp reads. Sequences were aligned to the mouse

transcriptome (GRCm38, mm10), compr was performed to generate paired-end 150-bp reads. Sequences were aligned to the mouse
transcriptome (GRCm38, mm10), comprising mRNA and ncRNA, using STAR 184 after quality
control. The output from the mapping step wa transcriptome (GRCm38, mm10), comprising mRNA and ncRNA, using STAR 184 control. The output from the mapping step was then converted to count tables using the tximport

739 R package 185 . The read count gene expression matrix was examined using the DESeq2 R

740 package 186 to identif 738 control. The output from the mapping step was then converted to count tables using the tximport

739 R package ¹⁸⁵. The read count gene expression matrix was examined using the DESeq2 R

740 package ¹⁸⁶ to identif R package ¹⁸⁵. The read count gene expression matrix was examined using the DESeg2 R 739 R package ¹⁸⁵. The read count gene expression matrix was examined using the DESeq2 R package ¹⁸⁶ to identify differentially expressed genes (DEG) in experimental groups. Changes in gene expression with a false dis package ¹⁸⁶ to identify differentially expressed genes (DEG) in experimental groups. Changes in 740 package ¹⁸⁶ to identify differentially expressed genes (DEG) in experimental groups. Changes in
741 gene expression with a false discovery rate (FDR)-adjusted of p-value <0.05 and log2fold-
742 change of ±1.3 were c 741 gene expression with a false discovery rate (FDR)-adjusted of p-value <0.05 and log2fold-

742 change of ±1.3 were considered significant. Gene set enrichment analysis was then performed

743 om the DEGs using the clu 742 change of ±1.3 were considered significant. Gene set enrichment analysis was then performed

743 on the DEGs using the clusterProfiler R package ¹⁸⁷ with the REACTOME database ¹⁸⁸. DEGs

744 common to both TLR-liga on the DEGs using the clusterProfiler R package 187 with the REACTOME database 188 on the DEGs using the clusterProfiler R package ¹⁸⁷ with the REACTOME database ¹⁸⁸. DEGs

common to both TLR-ligand pre-treated groups were entered into ImmGen's MyGeneSet

Prowser (http://rstats.immgen.org/MyGeneSet_N 744 common to both TLR-ligand pre-treated groups were entered into ImmGen's MyGeneSet
745 Browser (http://rstats.immgen.org/MyGeneSet_New/index.html) ¹⁸⁹ to identify cell types in which
746 those genes are commonly expre Browser (http://rstats.immgen.org/MyGeneSet_New/index.html) ¹⁸⁹ to identify cell types in which The Browser (http://rstats.immgen.org/MyGeneSet_New/index.html) ¹⁸⁹ to identify cell types in which

746 those genes are commonly expressed based on the existing ImmGen ultra-low-input (ULI) cell-

747 type specific RNA-The those genes are commonly expressed based on the existing ImmGen ultra-low-input (ULI) cell-

747 type specific RNA-Seq datasets. The entire gene expression dataset is available in Gene

748 Expression Omnibus under acc

The specific RNA-Seq datasets. The entire gene expression dataset is available in Gene

748 Expression Omnibus under accession no. GSE254993.

749 **Cell isolation for flow cytometry**

751 Three minutes prior to euthanasia Expression Omnibus under accession no. GSE254993.

749 **Cell isolation for flow cytometry**

751 Three minutes prior to euthanasia, mice were i

752 per mouse of SuperBright 780 or BV711 labeled CD45

753 reported ⁶⁴. Lun 749
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754 **Cell isolation for flow cytometry**

751 Three minutes prior to eut

752 per mouse of SuperBright 780 or E

753 reported ⁶⁴. Lungs from infected

754 dissociator (Miltenyi Biotec) and c

755 The following antibody clones Three minutes prior to euthanasia, mice were intravenously (i.v.) injected with $5 - 6\mu$ g

752 per mouse of SuperBright 780 or BV711 labeled CD45 (30-F11) or CD45.2 (104) as previously

753 reported 64 . Lungs from inf per mouse of SuperBright 780 or BV711 labeled CD45 (30-F11) or CD45.2 (104) as previously

reported ⁶⁴. Lungs from infected mice were dissociated using scissors or a GentleMACS

dissociator (Miltenyi Biotec) and cells we reported 64 . Lungs from infected mice were dissociated using scissors or a GentleMACS reported ⁶⁴. Lungs from infected mice were dissociated using scissors or a GentleMACS
754 dissociator (Miltenyi Biotec) and cells were isolated and analyzed as previously described ¹⁹⁰.
755 The following antibody clone dissociator (Miltenyi Biotec) and cells were isolated and analyzed as previously described ¹⁹⁰ 754 dissociator (Miltenyi Biotec) and cells were isolated and analyzed as previously described ¹⁹⁰.
755 The following antibody clones were purchased from Biolegend, Bio-Rad, R&D Systems, BD or
756 ThermoFisher: anti-CD45 755 The following antibody clones were purchased from Biolegend, Bio-Rad, R&D Systems, BD or
756 ThermoFisher: anti-CD45.2 (clone 104), anti-CD45 (30-F11), anti-CD31 (390), anti-CD326
756 ThermoFisher: anti-CD45.2 (clone 1 756 ThermoFisher: anti-CD45.2 (clone 104), anti-CD45 (30-F11), anti-CD31 (390), anti-CD326

757 (G8.8), anti-CD24 (M1/69), anti-CD49f (GoH3), anti-I-Ab/I-E/MHC-II (M5/114.15.2), anti-
758 podoplanin/PDPN/Gp38 (8.1.1), anti-Sca-1 (D7), anti-CD317/BST2/Tetherin (927), anti-Siglec-F
759 (E50-2440 or 1RNM44N), anti-L 758 podoplanin/PDPN/Gp38 (8.1.1), anti-Sca-1 (D7), anti-CD317/BST2/Tetherin (927), anti-Siglec-F
759 (E50-2440 or 1RNM44N), anti-Ly6G (1A8), anti-CD68 (FA-11), anti-Ly6C (HK1.4), anti-CD11b
760 (M1/70), anti-CD88 (20/70), 759 (E50-2440 or 1RNM44N), anti-Ly6G (1A8), anti-CD68 (FA-11), anti-Ly6C (HK1.4), anti-CD11b
760 (M1/70), anti-CD88 (20/70), anti-CD11c (N418 or HL3), anti-CD169 (SER-4), anti-TREM2
761 (237920), anti-CD64 (X54-5/7.1), ant 760 (M1/70), anti-CD88 (20/70), anti-CD11c (N418 or HL3), anti-CD169 (SER-4), anti-TREM2
761 (237920), anti-CD64 (X54-5/7.1), anti-CD195/CCR5 (HM-CCR5, 7A4), anti-CD192/CCR2
762 (475301), anti-CD36 (HM36 or No. 72-1), ant 761 (237920), anti-CD64 (X54-5/7.1), anti-CD195/CCR5 (HM-CCR5, 7A4), anti-CD192/CCR2
762 (475301), anti-CD36 (HM36 or No. 72-1), anti-CD282/TLR2 (6C2), anti-arginase1/Arg1
763 (A1exF5), anti-Nos2 (CXNFT), anti-CD206 (C068 762 (475301), anti-CD36 (HM36 or No. 72-1), anti-CD282/TLR2 (6C2), anti-arginase1/Arg1
763 (A1exF5), anti-Nos2 (CXNFT), anti-CD206 (C068C2), anti-CD38 (90), anti-Hif1α (241812), anti-
764 LOX-1/OLR1 (214012), anti-ABCA1 (763 (A1exF5), anti-Nos2 (CXNFT), anti-CD206 (C068C2), anti-CD38 (90), anti-Hif1α (241812), anti-
764 LOX-1/OLR1 (214012), anti-ABCA1 (5A1-1422), anti-CD13 (R3-63), anti-CD14 (Sa14-2).
765 **Histopathology**
767 The middle r

264 LOX-1/OLR1 (214012), anti-ABCA1 (5A1-1422), anti-CD13 (R3-63), anti-CD14 (Sa14-2).
765 Histopathology
767 The middle right lung lobe from each mouse was fixed in 4% paraformaldehyde, transferre
268 70% ethanol, and par 765
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768
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770 766 **Histopathology**
767 The middle right
768 70% ethanol, and
769 staining with hem
770 an Aperio Versa i 767 The middle right lung lobe from each mouse was fixed in 4% paraformaldehyde, transferred to
768 70% ethanol, and paraffin-embedded before sectioning and mounting on glass slides for
769 staining with hematoxylin and eo 768 70% ethanol, and paraffin-embedded before sectioning and mounting on glass slides for
769 staining with hematoxylin and eosin (H&E). Stained slides were imaged by light microsco
770 an Aperio Versa 200 (Leica). Images 769 staining with hematoxylin and eosin (H&E). Stained slides were imaged by light microscopy on
770 an Aperio Versa 200 (Leica). Images were processed using QuPath v0.3.2 and ImageJ v1.53t
771 (NIH) as previously describe (NIH) as previously described 39 .

770 an Aperio Versa 200 (Leica). Images were processed using QuPath v0.3.2 and ImageJ v1.53t
771 (NIH) as previously described ³⁹.
772 **Multiplex cytokine array and ELISAs**
774 Lung homogenates were prepared as described 771 (NIH) as previously described ³⁹.
772 **Multiplex cytokine array and E**
774 Lung homogenates were
775 were measured using a Procar
776 Instrument (R&D Systems) acc 772
773
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777 **Multiplex cytokine array and ELISAs**

774 Lung homogenates were prepar

775 were measured using a ProcartaPlex

776 Instrument (R&D Systems) according

777 ACE2 protein levels were quantified

778 #DY3437, #DY933). Lung homogenates were prepared as described above for TCID₅₀ assays and cytokines
775 were measured using a ProcartaPlex Luminex kit (Thermo Fisher Scientific) on a MAGPIX
1776 Instrument (R&D Systems) according to the m 775 were measured using a ProcartaPlex Luminex kit (Thermo Fisher Scientific) on a MAGPIX
776 Instrument (R&D Systems) according to the manufacturer's instructions. Mouse and human
777 ACE2 protein levels were quantified f 776 Instrument (R&D Systems) according to the manufacturer's instructions. Mouse and human
777 ACE2 protein levels were quantified from lung homogenates by ELISA (R&D Systems
78 #DY3437,#DY933).
780 Statistical analyses we 777 ACE2 protein levels were quantified from lung homogenates by ELISA (R&D Systems
778 #DY3437, #DY933).
779 **Statistical analyses**
781 Statistical analyses were performed using Prism software version 9.0 for Mac OS X
782

778 #DY3437, #DY933).
779 **Statistical analyses
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784 780 **Statistical analyses**

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784 using the ROUT met

785 otherwise expressed The Statistical analyses were performed using Prism software version 9.0 for Mac OS X

782 (GraphPad Software). The statistical details of experiments, including the statistical tests used,

783 are listed within each fig 782 (GraphPad Software). The statistical details of experiments, including the statistical tests used,

783 are listed within each figure legend. Outlier data points were identified and removed when $n > 10$

784 using the 783 are listed within each figure legend. Outlier data points were identified and removed when n >10

784 using the ROUT method (Q=1%) in Prism. P values are indicated directly in the figures or are

785 otherwise express 1974 using the ROUT method (Q=1%) in Prism. P values are indicated directly in the figures or are

1978 otherwise expressed as $p < 0.05$ (*), $p < 0.01$ (**), $p < 0.001$ (***) with p values >0.05 considered

1978 otherwise 785 otherwise expressed as p < 0.05 (*), p < 0.01(**), p < 0.001 (***) with p values >0.05 considered
786 not significant (n.s.). Data presented are combined of a minimum of two or more independent
787 experiments unless o 786 not significant (n.s.). Data presented are combined of a minimum of two or more independent

787 experiments unless otherwise stated in the figure legend.

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799 787 experiments unless otherwise stated in the figure legend.
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802 **AUTHOR CONTRIBUTIONS:**
804 Conceptualization: KDMB, PJB
805 Methodology: 801 Scientific and Technological Development (CNPq).
803 **AUTHOR CONTRIBUTIONS:**
804 Conceptualization: KDMB, PJB
805 Methodology: PJB, RFJ, KLH, JSK, KC
806 Investigation: PJB, ACB, EC, EPA, MSS, FTJ, STG

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- 806 Investigation: PJB, ACB, EC, EPA, MSS, FTJ, STG, ATLQ, ERF, CMJ, KLH
807 Data analysis and visualization: KDMB, PJB, EPA, ATLQ, ERF, KLH,
808 Funding acquisition: KDMB, DLB, RFJ, BBA
809 Supervision: KDMB, DLB, RFJ, BB
- **AUTHOR CONTRIBUTIONS:**

804 Conceptualization: KDMB, PJE

805 Methodology: PJB, RFJ, KLH,

806 Investigation: PJB, ACB, EC, E

807 Data analysis and visualizatior

808 Funding acquisition: KDMB, DI 804 Conceptualization: KDMB, PJB
805 Methodology: PJB, RFJ, KLH, J
806 Investigation: PJB, ACB, EC, EF
807 Data analysis and visualization:
808 Funding acquisition: KDMB, DLI
809 Supervision: KDMB, DLB, RFJ, 805 Methodology: PJB, RFJ, KLH, JSK, KC
806 Investigation: PJB, ACB, EC, EPA, MSS
807 Data analysis and visualization: KDMB,
808 Funding acquisition: KDMB, DLB, RFJ, I
809 Supervision: KDMB, DLB, RFJ, BBA
810 Resources: KD 987 Data analysis and visualization: KDMB, PJB, EPA, ATLQ, ERF, KLH,
1908 Funding acquisition: KDMB, DLB, RFJ, BBA
1909 Supervision: KDMB, DLB, RFJ, BBA
1018 Resources: KDMB, DLB, RFJ, BBA
11218 Writing - original draft: K
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- 808 Funding acquisition: KDMB, DLB, RFJ, BBA
809 Supervision: KDMB, DLB, RFJ, BBA
810 Resources: KDMB, DLB, RFJ, BBA
811 Writing original draft: KDMB, PJB
812 Writing review & editing: KDMB, PJB, DLB,
813 809 Supervision: KDMB, DLB, RFJ, BBA
810 Resources: KDMB, DLB, RFJ, BBA
811 Writing - original draft: KDMB, PJB
812 Writing – review & editing: KDMB, PJ
813 810 Resources: KDMB, DLB, RFJ, BBA
811 Writing - original draft: KDMB, PJB
812 Writing – review & editing: KDMB, P
813
814 811 Mriting - original draft: KDMB, PJB
812 Mriting – review & editing: KDMB, F
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815 812 Writing – review & editing: KDMB, PJB, DLB, ACB, EPA, RFJ, BBA, ATLQ, KLH
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825 **FIGURE LEGENDS**

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831 **Figure 1: Recent respiratory infection or underlying pulmonary inflammation at the time

of SCV2 exposure limits early viral replication in the lungs of mice

For SCV2 (SCV2) infections, all mice were infected intranasal of SCV2 exposure limits early viral replication in the lungs of mice**

For SCV2 (SCV2) infections, all mice were infected intranasally (i.n.) wi

(B.1.351) and euthanized three days later (d3). Viral loads were meas

E6 c For SCV2 (SCV2) infections, all mice were infected intranasally (i.n.) with $3.5x10^4$ TCID₅₀ SCV2 (B.1.351) and euthanized three days later (d3). Viral loads were measured by TCID₅₀ on Vero 829 For SCV2 (SCV2) infections, all mice were infected intranasally (i.n.) with $3.5x10^4$ TCID₅₀ SCV2 (B.1.351) and euthanized three days later (d3). Viral loads were measured by TCID₅₀ on Vero E6 cells and by qPCR f 830 (B.1.351) and euthanized three days later (d3). Viral loads were measured by TCID₅₀ on Vero
831 E6 cells and by qPCR for the SCV2 E gene in its sub-genomic form (sub-gRNA) (A) Lung viral
832 loads of WT mice infecte 831 E6 cells and by qPCR for the SCV2 E gene in its sub-genomic form (sub-gRNA) (A) Lung viral
832 loads of WT mice infected with *Mtb* by aerosol exposure $2 - 4$ months before infection with
833 SCV2 **(B)** Lung viral loa 832 loads of WT mice infected with *Mtb* by aerosol exposure $2 - 4$ months before infection with
833 SCV2 (B) Lung viral loads of WT mice infected intraphayngeally (i.ph.) with *S. aureus* USA300
834 three days before SCV 833 SCV2 **(B)** Lung viral loads of WT mice infected intraphayngeally (i.ph.) with *S. aureus* USA300 three days before SCV2 infection **(C)** Lung SCV2 loads of WT mice i.n. infected with Influenza A virus (IAV, PR8) one mon 834 three days before SCV2 infection **(C)** Lung SCV2 loads of WT mice i.n. infected with Influenza A virus (IAV, PR8) one month before SCV2 infection **(D)** Lung viral loads of WT mice intraperitoneally (i.p.) injected twic virus (IAV, PR8) one month before SCV2 infection (D) Lung viral loads of WT mice

836 intraperitoneally (i.p.) injected twice with ovalbumin and aluminum hydroxide (ova-alum) 30 and

837 16 days before SCV2 infection and i 836 intraperitoneally (i.p.) injected twice with ovalbumin and aluminum hydroxide (ova-alum) 30 and
837 16 days before SCV2 infection and i.n. OVAwas given 5 days before SCV2 infection. n= 9 – 18,
838 data combined from 2 837 16 days before SCV2 infection and i.n. OVAwas given 5 days before SCV2 infection. n= $9 - 18$,
838 data combined from $2 - 3$ independent experiments, geometric mean, statistical significance
839 calculated by two-taile

data combined from 2 – 3 independent experiments, geometric mean, statistical significance

839 calculated by two-tailed Mann Whitney test, LD= limit of detection.

840 **Figure 2: Recent one-time pulmonary TLR pre-stimulat**

calculated by two-tailed Mann Whitney test, LD= limit of detection.
840
**Figure 2: Recent one-time pulmonary TLR pre-stimulation is
SCV2 replication in the lung
843 (A) Left: WT mice were administered PBS, 10µg CpG B (ODN1** 840
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847 **Figure 2: Recent one-time pulmonary TLR pre-stimulation is sufficient to suppress early SCV2 replication in the lung**
 842 (A) Left: WT mice were administered PBS, 10μg CpG B (ODN1826, CpG) or 50μg Pam3CSK4 (Pm3) i.p **SCV2 replication in the lung

843 (A)** Left: WT mice were admin

844 (Pm3) i.ph. one week before

845 assessed for lung viral loads the

846 combined from five independe

847 10µg CpG i.ph seven weeks

848 TClD₅₀ lung v **(A)** Left: WT mice were administered PBS, 10μg CpG B (ODN1826, CpG) or 50μg Pam3CSK4 (Pm3) i.ph. one week before i.n. infection with $3.5x10^4$ TClD₅₀ SCV2 (SCV2) (B.1.351) and assessed for lung viral loads three days (Pm3) i.ph. one week before i.n. infection with $3.5x10^4$ TCID₅₀ SCV2 (SCV2) (B.1.351) and 844 (Pm3) i.ph. one week before i.n. infection with $3.5x10^4$ TCID₅₀ SCV2 (SCV2) (B.1.351) and
845 assessed for lung viral loads three days later (3dpi). Right: TCID₅₀ lung viral loads n=20-26, data
846 combined from assessed for lung viral loads three days later (3dpi). Right: $TCID_{50}$ lung viral loads n=20-26, data combined from five independent experiments (B) Left: WT mice were i.ph. administered PBS or 845 assessed for lung viral loads three days later (3dpi). Right: TCID₅₀ lung viral loads n=20-26, data
846 combined from five independent experiments (B) Left: WT mice were i.ph. administered PBS or
847 10µg CpG i.ph s 846 combined from five independent experiments **(B)** Left: WT mice were i.ph. administered PBS or
847 10µg CpG i.ph seven weeks before i.n. infection with $3.5x10^4$ TCID₅₀ SCV2 (B.1.351). Right:
848 TCID₅₀ lung viral 10μg CpG i.ph seven weeks before i.n. infection with $3.5x10^4$ TCID₅₀ SCV2 (B.1.351). Right: 2847 10µg CpG i.ph seven weeks before i.n. infection with $3.5x10^4$ TCID₅₀ SCV2 (B.1.351). Right:

2848 TCID₅₀ lung viral loads at 3dpi, n= 8-9, data combined from two independent experiments. (C)

2849 Left: K18-hAC TCID₅₀ lung viral loads at 3dpi, n= 8-9, data combined from two independent experiments. (C) Left: K18-hACE2 Tg mice were i.ph. administered PBS, 10 μ g CpG or 50 μ g Pm3 one week 848 TCID₅₀ lung viral loads at 3dpi, n= 8-9, data combined from two independent experiments. **(C)**
849 Left: K18-hACE2 Tg mice were i.ph. administered PBS, 10µg CpG or 50µg Pm3 one week
850 before i.n. infection with 1 Left: K18-hACE2 Tg mice were i.ph. administered PBS, 10μg CpG or 50μg Pm3 one week

850 before i.n. infection with $1x10^3$ TCID₅₀ SCV2 (USA-WA1/2020) Right: lung viral loads 3dpi

851 measured by TCID₅₀ or qPCR for s before i.n. infection with 1x10 3 850 before i.n. infection with 1×10^3 TCID₅₀ SCV2 (USA-WA1/2020) Right: lung viral loads 3dpi
851 measured by TCID₅₀ or qPCR for sub-gRNA SCV2 E gene, n= 11-13, data combined from three
852 independent experiments 851 measured by TCID₅₀ or qPCR for sub-gRNA SCV2 E gene, n= 11-13, data combined from three
852 independent experiments. (D) K18-hACE2 Tg mice were treated and infected as described in
853 (C) and monitored for time to imdependent experiments. **(D)** K18-hACE2 Tg mice were treated and infected as described in

853 (C) and monitored for time to clinical endpoint (survival) for 18 days post SCV2 infection. Mouse

854 survival is shown as a 853 (C) and monitored for time to clinical endpoint (survival) for 18 days post SCV2 infection. Mouse
854 survival is shown as a Kaplan-Meier curve with significance determined by Mantel-Cox test, n=
855 24-33, data combi 854 survival is shown as a Kaplan-Meier curve with significance determined by Mantel-Cox test, n=
855 24-33, data combined from six independent experiments $(E - G)$. K18-hACE2 Tg mice i.ph.
856 administered PBS, CpG or Pm3 24-33, data combined from six independent experiments **(E – G)**. K18-hACE2 Tg mice i.ph.

856 administered PBS, CpG or Pm3 and one week later infected i.n. with SCV2 USA-WA1/2020

857 Lung total RNA sequencing was performe 856 administered PBS, CpG or Pm3 and one week later infected i.n. with SCV2 USA-WA1/2020
857 Lung total RNA sequencing was performed at 3dpi (n = 3-4 mice per group in one experiment).
858 **(E)** GO analysis of significant 857 Lung total RNA sequencing was performed at 3dpi (n = 3-4 mice per group in one experiment).
858 **(E)** GO analysis of significant DEGs **(F)** Volcano plots of candidate DEGs comparing SCV2
859 infected mice pre-treated 858 **(E)** GO analysis of significant DEGs **(F)** Volcano plots of candidate DEGs comparing SCV2 infected mice pre-treated with CpG (left panel) or Pm3 (right panel) to SCV2-only infected control animals. DEGs significantly 859 infected mice pre-treated with CpG (left panel) or Pm3 (right panel) to SCV2-only infected
860 control animals. DEGs significantly upregulated in both treatment groups are labeled. (G) DEGs
861 after SCV2 infection in 860 control animals. DEGs significantly upregulated in both treatment groups are labeled. **(G)** DEGs
861 after SCV2 infection in common to both TLR pretreatment groups were entered into ImmGen
862 MyGeneSet. Expression ac 861 after SCV2 infection in common to both TLR pretreatment groups were entered into ImmGen
862 MyGeneSet. Expression across cell types as analyzed by ImmGen are visualized in a heatmap,
863 AU (arbitrary units), navy= lo 862 MyGeneSet. Expression across cell types as analyzed by ImmGen are visualized in a heatmap,
863 AU (arbitrary units), navy= lowest expression, orange= highest expression; ILCs (innate
864 lymphoid cells), DCs (dendriti 863 AU (arbitrary units), navy= lowest expression, orange= highest expression; ILCs (innate lymphoid cells), DCs (dendritic cells), Monos (monocytes), Grans (granulocytes), Mast (mast cells) (H) Viral loads in lungs of WT 864 lymphoid cells), DCs (dendritic cells), Monos (monocytes), Grans (granulocytes), Mast (mast cells) (H) Viral loads in lungs of WT and $A/\alpha x 15^{-/-}$ mice 3 days post-i.n. infection with 3.5x10⁴ TCID₅₀ SCV2 (B.1.351) cells) (H) Viral loads in lungs of WT and *Alox15¹* mice 3 days post-i.n. infection with 3.5x10⁴ 865
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868 866 TCID₅₀ SCV2 (B.1.351) as measured by TCID₅₀ on Vero E6 cells, n= 6-8, data combined from 2
867 independent experiments. (A – C, H) geometric mean, statistical significance determined by
868 two-tailed Mann Whitney 867 independent experiments. $(A - C, H)$ geometric mean, statistical significance determined by
868 two-tailed Mann Whitney test, LD= limit of detection, n.s.= not significant. 868 two-tailed Mann Whitney test, LD= limit of detection, n.s.= not significant.

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Figure 3: Recent pulmonary exposure to TLR agonists results in remodeling of the tissue-resident macrophage compartment and sustained inflammatory cytokine responses prior to SCV2 exposure
873 (A – C) K18-hACE2 Tg mice wer 871 **tissue-resident macrophage compartment and sustained inflammatory cytokine**
872 **(A – C)** K18-hACE2 Tg mice were i.ph. treated with PBS, 10µg CpG or 50µg Pm3. Ten days
874 later, mice were euthanized, RNA was extracte 872 **responses prior to SCV2 exposure**
873 **(A – C)** K18-hACE2 Tg mice were i.
874 later, mice were euthanized, RNA w
875 was performed; data is from 3-4
876 Candidate DEGs visualized by volcar
877 treated mice to the PBS 873 $(A - C)$ K18-hACE2 Tg mice were i.ph. treated with PBS, 10 μ g CpG or 50 μ g Pm3. Ten days
874 later, mice were euthanized, RNA was extracted from lung tissue and total RNA sequencing
875 was performed; data is from 3 874 later, mice were euthanized, RNA was extracted from lung tissue and total RNA sequencing
875 was performed; data is from 3-4 mice per group from one independent experiment (A)
876 Candidate DEGs visualized by volcano p was performed; data is from 3-4 mice per group from one independent experiment **(A)**
876 Candidate DEGs visualized by volcano plots comparing CpG- (left panel) or Pm3- (right panel)
877 treated mice to the PBS control anim 876 Candidate DEGs visualized by volcano plots comparing CpG- (left panel) or Pm3- (right panel)
877 treated mice to the PBS control animals. DEGs upregulated and common to both treatment
878 groups are labeled. (B) GO ana 877 treated mice to the PBS control animals. DEGs upregulated and common to both treatment
878 groups are labeled. (B) GO analysis of identified significant DEGs in the indicated groups
879 compared to the PBS only control 878 groups are labeled. **(B)** GO analysis of identified significant DEGs in the indicated groups
879 compared to the PBS only controls. **(C)** Venn diagram showing the DEGs in common between
880 the CpG- and Pm3-treated gro 879 compared to the PBS only controls. **(C)** Venn diagram showing the DEGs in common between
880 the CpG- and Pm3-treated groups compared to PBS controls. The candidate DEGs were
881 entered into ImmGen's MyGeneset browser 880 the CpG- and Pm3-treated groups compared to PBS controls. The candidate DEGs were
881 entered into ImmGen's MyGeneset browser. Expression across cell types as analyzed by
882 ImmGen are visualized in a heatmap, AU (ar 881 entered into ImmGen's MyGeneset browser. Expression across cell types as analyzed by
882 ImmGen are visualized in a heatmap, AU (arbitrary units), navy= lowest expression, orange=
883 highest expression; ILCs (innate 882 ImmGen are visualized in a heatmap, AU (arbitrary units), navy= lowest expression, orange=
883 highest expression; ILCs (innate lymphoid cells), DCs (dendritic cells), Monos (monocytes),
884 Grans (granulocytes), Mast 883 highest expression; ILCs (innate lymphoid cells), DCs (dendritic cells), Monos (monocytes), 884 Grans (granulocytes), Mast (mast cells) (D & E) For the SCV2 (SCV2) infection, all mice were infected i.n. with SCV2 (B.1 SR4 Grans (granulocytes), Mast (mast cells) **(D & E)** For the SCV2 (SCV2) infection, all mice were infected i.n. with SCV2 (B.1.351) and euthanized three days later as measured by TCID₅₀, geometric mean, LD= limit of de 885 infected i.n. with SCV2 (B.1.351) and euthanized three days later as measured by TCID₅₀, geometric mean, LD= limit of detection. **(D)** TCID₅₀ viral loads in lungs of WT and Ccr5¹ mice, n=19, data combined from f geometric mean, LD= limit of detection. **(D)** TCID₅₀ viral loads in lungs of WT and $Ccr5'$ mice, 886 geometric mean, LD= limit of detection. (D) TClD₅₀ viral loads in lungs of WT and Ccr5⁷ mice,
887 n=19, data combined from five independent experiments. (E) Ccr5⁷ mice were given PBS, 10µg
888 CpG or 50µg Pm3 on n=19, data combined from five independent experiments. **(E)** $Ccr5^{-/-}$ mice were given PBS, 10 μ g n=19, data combined from five independent experiments. (**E**) *Ccr5*^{'-} mice were given PBS, 10μg

888 CpG or 50μg Pm3 one week before SCV2 infection with n=6-8, data combined from 2

889 independent experiments, geometr 888 CpG or 50μg Pm3 one week before SCV2 infection with n=6-8, data combined from 2 independent experiments, geometric mean, LD= limit of detection. (F) Quantification of alveolar macrophages (AM) by flow cytometry as a independent experiments, geometric mean, LD= limit of detection. **(F)** Quantification of alveolar macrophages (AM) by flow cytometry as a percentage of CD45⁺ cells in whole lung from WT mice treated with PBS, 10µg CpG or macrophages (AM) by flow cytometry as a percentage of CD45⁺ 890 macrophages (AM) by flow cytometry as a percentage of CD45⁺ cells in whole lung from WT
891 mice treated with PBS, 10 μ g CpG or 50 μ g Pm3 i.ph. one week prior and histograms depicting
892 relative expression of 891 mice treated with PBS, 10μg CpG or 50μg Pm3 i.ph. one week prior and histograms depicting
892 relative expression of MHC-II and CD36 (G) Quantification of CD11b⁺, CD88⁺ interstitial
893 macrophages (IM) that are r relative expression of MHC-II and CD36 (G) Quantification of CD11b⁺, CD88⁺ 892 relative expression of MHC-II and CD36 (G) Quantification of CD11b⁺, CD88⁺ interstitial
893 macrophages (IM) that are recruited into the lung parenchyma (intravascular CD45 negative
894 (i.v^{neg})) by flow cytomet 893 macrophages (IM) that are recruited into the lung parenchyma (intravascular CD45 negative
894 (i.v^{neg})) by flow cytometry as a percentage of CD45⁺ cells in whole lung from WT mice treated
895 with PBS, CpG or Pm3 $(i.v^{neg})$) by flow cytometry as a percentage of CD45⁺ cells in whole lung from WT mice treated with PBS. CpG or Pm3 i.ph. one week prior and histograms depicting relative expression of 894 (i.v^{neg})) by flow cytometry as a percentage of CD45⁺ cells in whole lung from WT mice treated
895 with PBS, CpG or Pm3 i.ph. one week prior and histograms depicting relative expression of
896 MHC-II and CD36, n= 8 895 with PBS, CpG or Pm3 i.ph. one week prior and histograms depicting relative expression of MHC-II and CD36, n= 8-9, data combined from two representative experiments, geometric mean and standard deviation. (H) Lungs we 896 MHC-II and CD36, n= 8-9, data combined from two representative experiments, geometric mean and standard deviation. (H) Lungs were collected at seven and ten days after PBS, 10µg CpG or 50µg Pm3 i.ph. administration an mean and standard deviation. (H) Lungs were collected at seven and ten days after PBS, 10µg

898 CpG or 50µg Pm3 i.ph. administration and homogenates were assayed for the indicated

899 cytokines by multiplex bead array, n CpG or 50µg Pm3 i.ph. administration and homogenates were assayed for the indicated

899 cytokines by multiplex bead array, n = 6-8, data combined from two experiments, geometric

900 mean. (D – H) Statistical significance 899 cytokines by multiplex bead array, $n = 6-8$, data combined from two experiments, geometric
900 mean. (D – H) Statistical significances compared to PBS pretreated controls were determined
901 by two-tailed Mann Whitney

900 mean. **(D – H)** Statistical significances compared to PBS pretreated controls were determined
901 by two-tailed Mann Whitney test.
902 **Figure 4: Pulmonary SCV2 replication is constrained by nucleic acid sensing, and
9** 901 by two-tailed Mann Whitney test.
902 **Figure 4: Pulmonary SCV2 r
904 signaling by IFNAR1 and TNFF
905 All mice were infected i.n. with 3
906 (d3). Viral loads were measured**

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908 Figure 4: Pulmonary SCV2 replication is constrained by nucleic acid sensing, and

904 signaling by IFNAR1 and TNFR1 but not IL-1R1

905 All mice were infected i.n. with $3.5x10^4$ TCID₅₀ SCV2 (B.1.351) and euthanized th 904 **signaling by IFNAR1 and TNFR1 but not IL-1R1**
905 All mice were infected i.n. with 3.5×10^4 TCID₅₀ SC
906 (d3). Viral loads were measured by TCID₅₀ on Ve
907 lungs of WT and two different strains of *Ifnar1^{-*} All mice were infected i.n. with $3.5x10^4$ TCID₅₀ SCV2 (B.1.351) and euthanized three days later 905 All mice were infected i.n. with $3.5x10^4$ TClD₅₀ SCV2 (B.1.351) and euthanized three days later
906 (d3). Viral loads were measured by TClD₅₀ on Vero E6 cells except in (R). (A) Viral loads in
907 lungs of WT an 906 (d3). Viral loads were measured by TCID₅₀ on Vero E6 cells except in (R). **(A)** Viral loads in
907 lungs of WT and two different strains of *Ifnar1⁻¹* mice. **(B)** Experimental set-up where WT mice
908 were i.p. in lungs of WT and two different strains of *Ifnar1*-/- 907 lungs of WT and two different strains of *lfnar1⁻¹⁻* mice. **(B)** Experimental set-up where WT mice
908 were i.p. injected with a neutralizing anti-IFNAR1 monoclonal antibody one day before SCV2
909 infection and lun 908 were i.p. injected with a neutralizing anti-IFNAR1 monoclonal antibody one day before SCV2
909 infection and lung viral loads (C – K) Viral loads in lungs of WT and various PRR KO mice: (C)
910 *Tlr3¹*; (D) *Tlr7¹* 909 infection and lung viral loads $(C - K)$ Viral loads in lungs of WT and various PRR KO mice: **(C)** $T/r3^{1/2}$, **(D)** $T/r7^{1/2}$, **(E)** MDA5, *Ifih1⁻¹*, **(F)** $T/r2^{1/2}$, **(G)** $T/r4^{1/2}$, **(H)** $T/r9^{1/2}$, **(I)** $Tmem17$ T *Ir3*^{\prime}, **(D)** T *Ir7*^{\prime}, **(E)** MDA5, *Ifih1*^{\prime}, **(F)** T *Ir2*^{\prime}, **(G)** T *Ir4*^{\prime}, **(H)** T *Ir9*^{\prime}, **(I)** T *mem173*^{gt} (expresses an 910 $T/r3^{1/2}$, (D) $T/r7^{1/2}$, (E) MDA5, $Ifin1^{1/2}$, (F) $T/I2^{1/2}$, (G) $TIr4^{1/2}$, (H) $TIr9^{1/2}$, (I) $Tmem173^{01}$ (expresses an inactive variant of STING), (J) $Zbp1^{1/2}$, (K) $Nlrp3^{1/2}$. (L) Viral loads in lungs of inactive variant of STING), **(J)** *Zbp1*-/-, **(K)** *Nlrp3*-/- 911 inactive variant of STING), (J) Zbp1^{-/-}, (K) Nlrp3^{-/}- (L) Viral loads in lungs of WT mice that were
912 i.p. injected with either PBS (-) or the NLRP3 inhibitor MCC950 (+) one day before and one day
913 after SCV2 912 i.p. injected with either PBS (-) or the NLRP3 inhibitor MCC950 (+) one day before and one day
913 after SCV2 infection (M – Q) TCID₅₀ viral loads in lungs of WT mice and mice deficient in
914 inflammatory caspases 913 after SCV2 infection **(M – Q)** TCID₅₀ viral loads in lungs of WT mice and mice deficient in inflammatory caspases or their substrates: **(M)** Casp1,¹¹¹ **(N)** Casp1,11^{¹ **(O)** Gsdmd, Gsdme⁻¹ **(P)** The inflamma} inflammatory caspases or their substrates: **(M)** *Casp1*-/- **(N)** *Casp1,11*-/- **(O)** *Gsdmd,Gsdme*-/ inflammatory caspases or their substrates: **(M)** Casp1^{-/-} **(N)** Casp1,11^{-/-} **(O)** Gsdmd,Gsdme^{-/-} **(P)**
inflammatory caspases or their substrates: **(M)** Casp1^{-/-} **(N)** Casp1,11^{-/-} **(O)** Gsdmd,Gsdme^{-/-} **(P)**

Il1a,b^{-/-} and *II1r1^{-/}*. **(Q)** Viral loads in lungs of WT mice and mice deficient in TNFR1, *Tnfrsf1a^{-/-}* 915
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922 916 **(R)** Schematic of experimental set-up where WT mice were i.p. injected with a neutralizing anti-
917 TNF α monoclonal antibody seven days before SCV2 infection and viral loads in lung as
918 measured by qPCR for th 917 TNFα monoclonal antibody seven days before SCV2 infection and viral loads in lung as
918 measured by qPCR for the SCV2 E gene with and without anti-TNFα treatment. n indicated
919 below each group, data combined from 918 measured by qPCR for the SCV2 E gene with and without anti-TNF α treatment. n indicated
919 below each group, data combined from 2 – 6 independent experiments, geometric mean,
920 statistical significance calculated 919 below each group, data combined from $2 - 6$ independent experiments, geometric mean,
920 statistical significance calculated by Mann Whitney test, LD= limit of detection, n.s.= not
921 significant, $\#$ = indicates res 920 statistical significance calculated by Mann Whitney test, LD= limit of detection, n.s.= not
921 significant, #= indicates result that was not significant by TCID₅₀ but showed a significant
922 difference by qPCR (se

921 significant, #= indicates result that was not significant by $TCID_{50}$ but showed a significant
922 difference by qPCR (see **Fig S5E**).
923 **Figure 5: Recent IFN-I dependent and - independent inflammatory conditioning** 922 difference by qPCR (see **Fig S5E**).
923 **Figure 5: Recent IFN-I dependent
925 Iung promotes SCV2 replication of**
926 **(A)** Heatmap of fold change in the inducible surface marker (ISM) exp

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929 Figure 5: Recent IFN-I dependent and - independent inflammatory conditioning of the
925 **Immer Properties SCV2 replication control at the tissue level**
926 **(A)** Heatmap of fold change in the geometric mean fluorescence in **lung promotes SCV2 replication control at the tissue level**

926 **(A)** Heatmap of fold change in the geometric mean fluore

927 inducible surface marker (ISM) expression of Sca-1 and CD31

928 lung epithelial cell (EC) su 926 **(A)** Heatmap of fold change in the geometric mean fluorescence intensity (gMFI) of IFN-
927 inducible surface marker (ISM) expression of Sca-1 and CD317 measured by flow cytometry on
928 lung epithelial cell (EC) sub 927 inducible surface marker (ISM) expression of Sca-1 and CD317 measured by flow cytometry on
928 lung epithelial cell (EC) subsets from lungs of mice treated with various inflammatory or
929 infectious stimuli compared 928 lung epithelial cell (EC) subsets from lungs of mice treated with various inflammatory or
929 infectious stimuli compared to those from PBS control animals at the indicated time points
930 without SCV2 infection, n=5-929 infectious stimuli compared to those from PBS control animals at the indicated time points
930 without SCV2 infection, n=5-14, data is pooled from 2 – 4 independent experiments, for all
931 conditions except OVA/Alum 930 without SCV2 infection, n=5-14, data is pooled from $2 - 4$ independent experiments, for all
931 conditions except OVA/Alum which was done once. (B) *lfnar1^{-/-}*, (C) *Tnfrsf1a^{-/-}*, or (D) *ll1r1^{-/-}*
932 mice were conditions except OVA/Alum which was done once. **(B)** *Ifnar1*-/-, **(C)** *Tnfrsf1a*-/-, or **(D)** *Il1r1*-/- 931
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939 932 mice were i.ph. treated with PBS, 10µg CpG or 50µg Pm3 one week before SCV2 (B.1.351) infection. Viral loads in lungs were quantified by TCID₅₀ or sub-gRNA SCV2 E qPCR, n=10-26, 934 data are combined from 2 – 3 inde 933 infection. Viral loads in lungs were quantified by TCID₅₀ or sub-gRNA SCV2 E qPCR, n=10-26,
934 data are combined from 2 – 3 independent experiments each (E) Schematic of K18-hACE2 Tg
935 mice administered 5µg recom 934 data are combined from 2 – 3 independent experiments each **(E)** Schematic of K18-hACE2 Tg
935 mice administered 5µg recombinant mouse TNF α (rmTNF α) or 2.0x10⁴U recombinant mouse
936 IFN β (rmIFN β) once, o mice administered 5μg recombinant mouse TNF α (rmTNF α) or 2.0x10⁴U recombinant mouse 935 mice administered 5µg recombinant mouse TNF α (mTNF α) or 2.0x10⁴U recombinant mouse
936 IFN β (mIFN β) once, one week before infection with SCV2 (USA-WA1/2020) and lung viral
937 titers, n=7-10, two indepen 936 IFNβ (rmIFNβ) once, one week before infection with SCV2 (USA-WA1/2020) and lung viral
937 titers, n=7-10, two independent experiments (F) Fold change in gMFI of Sca-1 and CD317
938 measured by flow cytometry on lung titers, n=7-10, two independent experiments **(F)** Fold change in gMFI of Sca-1 and CD317

measured by flow cytometry on lung EC subsets of mice treated one week prior with rmTNF α or

939 milFNβ, data is pooled from th 938 measured by flow cytometry on lung EC subsets of mice treated one week prior with rmTNFα or mlFNβ, data is pooled from three independent experiments, n= 15-22, *= p<0.05, **=p<0.01, ***=p<0.001, if not indicated, dif of millarly, data is pooled from three independent experiments, n= 15-22, *= p<0.05, **=p<0.01,

940 ***=p<0.001, if not indicated, differences were not significant. (G) WT or *II1r1⁻¹* mice given 200U

941 recombinant ***=p<0.001, if not indicated, differences were not significant. **(G)** WT or *II1r1^{-/-}* mice given 200U 940 ***=p<0.001, if not indicated, differences were not significant. (G) WT or *ll1r1*^{-/-} mice given 200U recombinant mouse IL-1α (rmIL-1α) or IL-1β (rmIL-1β) i.ph. one week before SCV2 (B.1.351) infection and ung vira 941 recombinant mouse IL-1α (rmIL-1α) or IL-1β (rmIL-1β) i.ph. one week before SCV2 (B.1.351)
942 infection and ung viral titers, n=8-10, data are combined from two independent experiments. (H)
943 Fold change in gMFI of 942 infection and ung viral titers, n=8-10, data are combined from two independent experiments. **(H)**
943 Fold change in gMFI of Sca-1 and CD317 measured by flow cytometry on EC subsets from
944 lungs of mice treated one 943 Fold change in gMFI of Sca-1 and CD317 measured by flow cytometry on EC subsets from
944 lungs of mice treated one week prior with 200U rmlL-1 α + rmlL-1 β (100U each), n= 9-10, data is
945 pooled from two indepen 944 lungs of mice treated one week prior with 200U rmIL-1 α + rmIL-1 β (100U each), n= 9-10, data is
945 pooled from two independent experiments. Geometric mean, statistical significance determined
946 by two-tailed M 945 pooled from two independent experiments. Geometric mean, statistical significance determined
946 by two-tailed Mann-Whitney test, LD= limit of detection, *= p<0.05, **=p<0.01, ***=p<0.001,
947 n.s.= not significant, if 946 by two-tailed Mann-Whitney test, LD= limit of detection, $*$ = p<0.05, $*$ ^{*}=p<0.01, $*$ ^{**}=p<0.001, n.s.= not significant, if not indicated differences were not significant, white arrows indicate direction of fold c 947 n.s.= not significant, if not indicated differences were not significant, white arrows indicate
948 direction of fold change.
950 **SUPPLEMENTARY FIGURE LEGENDS**
952 **Figure S1: Recent one-time pulmonary TLR conditionin**

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948 direction of fold change.
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951 **SUPPLEMENTARY FIG
952 Figure S1: Recent one**
953 **replication in the lung** 950
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955 **SUPPLEMENTARY FIGURE LEGENDS**
952 **Figure S1: Recent one-time pulmonary**
953 **replication in the lung with no changes**
954 **(A)** Schematic of WT mice given PBS, 1
955 days prior to intranasal (i.n.) infection with
956 in Figure S1: Recent one-time pulmonary TLR conditioning is sufficient to suppress SCV2

replication in the lung with no changes in gross lung pathology

(A) Schematic of WT mice given PBS, 10µg CpG or 50µg Pm3 intrapharyngea replication in the lung with no changes in gross lung pathology
954 (A) Schematic of WT mice given PBS, 10μg CpG or 50μg Pm3 int
955 days prior to intranasal (i.n.) infection with 3.5x10⁴ TClD₅₀ SCV2 (B
956 in lungs a 954 **(A**) Schematic of WT mice given PBS, 10μg CpG or 50μg Pm3 intrapharyngeally (i.ph.) seven days prior to intranasal (i.n.) infection with $3.5x10^4$ TClD₅₀ SCV2 (B.1.351) and SCV2 viral load in lungs as measured by days prior to intranasal (i.n.) infection with $3.5x10^4$ TCID₅₀ SCV2 (B.1.351) and SCV2 viral load 955 days prior to intranasal (i.n.) infection with $3.5x10^4$ TCID₅₀ SCV2 (B.1.351) and SCV2 viral load
956 in lungs as measured by qPCR for the SCV2 E gene in its sub-genomic form (sub-gRNA) at
957 three days post-infe 956 in lungs as measured by qPCR for the SCV2 E gene in its sub-genomic form (sub-gRNA) at three days post-infection (3dpi), n= 19-25, data combined from five independent experiments.
958 **(B)** Schematic of WT mice given 957 three days post-infection (3dpi), n= 19-25, data combined from five independent experiments.
958 **(B)** Schematic of WT mice given either PBS or 10µg CpG i.ph. seven weeks before i.n. infection
the interval of WT mice g **(B)** Schematic of WT mice given either PBS or 10μg CpG i.ph. seven weeks before i.n. infection
 (B) Schematic of WT mice given either PBS or 10μg CpG i.ph. seven weeks before i.n. infection
 (B) Schematic of WT mice

with $3.5x10^4$ TCID₅₀ SCV2 (B.1.351), and SCV2 viral load in lungs as measured by qPCR for 959 with 3.5x10⁴ TCID₅₀ SCV2 (B.1.351), and SCV2 viral load in lungs as measured by qPCR for sub-gRNA SCV2 E gene on 3dpi, n= 9-10, data combined from two independent experiments. (C) Representative H&E staining of lu 960 sub-gRNA SCV2 E gene on 3dpi, n= 9-10, data combined from two independent experiments.

961 (C) Representative H&E staining of lung tissue from K18-hACE2 Tg mice given PBS or 10µg

962 CpG i.ph. one week before infect (C) Representative H&E staining of lung tissue from K18-hACE2 Tg mice given PBS or 10μg
962 CpG i.ph. one week before infection i.n. with 1x10³ TCID₅₀ SCV2 (USA-WA1/2020), mice were
963 euthanized 3dpi (scale bars ind CpG i.ph. one week before infection i.n. with $1x10^3$ TCID₅₀ SCV2 (USA-WA1/2020), mice were Golden intertion i.n. with $1x10^3$ TCID₅₀ SCV2 (USA-WA1/2020), mice were

963 euthanized 3dpi (scale bars indicate magnification) and percentage of parenchymal

964 enlargement was quantified, n= 8, data combined from 963 euthanized 3dpi (scale bars indicate magnification) and percentage of parenchymal
964 enlargement was quantified, n= 8, data combined from two independent experiments.
965 Geometric mean, significance determined by tw 964 enlargement was quantified, n= 8, data combined from two independent experiments.
965 Geometric mean, significance determined by two-tailed Mann-Whitney test, LD= limit of
966 detection, n.s.= not significant.
967 Figu

Geometric mean, significance determined by two-tailed Mann-Whitney test, LD= limit of
966 detection, n.s.= not significant.
967 **Figure S2: TLR-induced SCV2 restriction is not mediated through reduced ACE2 protein**
968 **ex** 966 detection, n.s.= not significant.
967 **Figure S2: TLR-induced SCV**
expression and is not revers
969 **(A)** Left: WT mice were admir
970 collected at seven days post
971 ELISA. Right: K18-hACE2 Tg Figure S2: TLR-induced SCV2 restriction is not mediated through reduced ACE2 protein

968 expression and is not reversed by deleting *Ccr2* or *Trem2*.

970 (A) Left: WT mice were administered PBS, CpG or Pm3 intrapharynge expression and is not reversed by deleting *Ccr2* or *Trem2*.

969 (A) Left: WT mice were administered PBS, CpG or Pm3 intra

970 collected at seven days post treatment and homogenates we

971 ELISA. Right: K18-hACE2 Tg mi 969 **(A)** Left: WT mice were administered PBS, CpG or Pm3 intrapharyngeally (i.ph.). Lungs were collected at seven days post treatment and homogenates were assayed for mouse ACE2 by ELISA. Right: K18-hACE2 Tg mice were ad 970 collected at seven days post treatment and homogenates were assayed for mouse ACE2 by
971 ELISA. Right: K18-hACE2 Tg mice were administered PBS, CpG or Pm3 i.ph., lungs were
972 collected at 10 days post-treatment and 971 ELISA. Right: K18-hACE2 Tg mice were administered PBS, CpG or Pm3 i.ph., lungs were

972 collected at 10 days post-treatment and homogenates were assayed for human ACE2 by

973 ELISA, n= 3 – 8, data combined from 1 – 972 collected at 10 days post-treatment and homogenates were assayed for human ACE2 by
973 ELISA, n= 3 – 8, data combined from 1 – 2 independent experiments. (B) Trem2^{-/-} or (C) Ccr2^{-/-}
974 mice were given either PBS ELISA, n= 3 – 8, data combined from 1 – 2 independent experiments. **(B)** *Trem2⁻¹* or **(C)** *Ccr2⁻¹* 973
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980 974 mice were given either PBS or 10µg CpG i.ph. seven days prior to being i.n. infected with
975 3.5x10⁴ TCID₅₀ SCV2 (B.1.351), mice were euthanized 3 days later. Viral loads in lung are
976 shown as measured by TCID $3.5x10⁴$ TCID₅₀ SCV2 (B.1.351), mice were euthanized 3 days later. Viral loads in lung are 975 3.5x10⁴ TCID₅₀ SCV2 (B.1.351), mice were euthanized 3 days later. Viral loads in lung are
976 shown as measured by TCID₅₀ on Vero E6 cells, n= 3 – 8, data combined from 1 – 2
977 independent experiments. Geometr 976 shown as measured by TCID₅₀ on Vero E6 cells, n= $3 - 8$, data combined from $1 - 2$
977 independent experiments. Geometric mean, significance determined by two-tailed Mann
978 Whitney test, LD= limit of detection, n.

977 independent experiments. Geometric mean, significance determined by two-tailed Mann
978 Whitney test, LD= limit of detection, n.s.= not significant.
980 **Figure S3: Recent pulmonary TLR pre-stimulation results in quant** 978 Whitney test, LD= limit of detection, n.s.= not significant.
979 **Figure S3: Recent pulmonary TLR pre-stimulation res**
**changes to the tissue-resident macrophage comparti
981 (A)** Example flow cytometry plots depictin Figure S3: Recent pulmonary TLR pre-stimulation results in quantitative and qualitative

980 changes to the tissue-resident macrophage compartment

981 (A) Example flow cytometry plots depicting gating strategy for identif changes to the tissue-resident macrophage compartment

981 **(A)** Example flow cytometry plots depicting gating strategy for

982 **Fig 3**, and **Fig S4A** as alveolar macrophages (AM), and lung

983 negative (i.v.^{neg})) CD68 (A) Example flow cytometry plots depicting gating strategy for identification of TRM related to

982 **Fig 3**, and **Fig S4A** as alveolar macrophages (AM), and lung parenchymal (intravascular CD45

983 negative (i.v.^{neg})) **Fig 3**, and **Fig S4A** as alveolar macrophages (AM), and lung parenchymal (intravascular CD45 negative (i.v.^{neg})) CD68⁺ interstitial macrophages (IM) cells from lungs of mice treated with 10µg CpG or 50µg Pm3 intraphar negative (i.v.^{neg})) CD68⁺ interstitial macrophages (IM) cells from lungs of mice treated with 10 μ g 983 negative (i.v.^{neg})) CD68⁺ interstitial macrophages (IM) cells from lungs of mice treated with 10µg CpG or 50µg Pm3 intrapharyngeally (i.ph.) seven days prior. Right: Histograms depicting relative expression of ind 984 CpG or 50µg Pm3 intrapharyngeally (i.ph.) seven days prior. Right: Histograms depicting
985 relative expression of indicated markers on AM. (B) Example flow cytometry plots of CD11b⁺
986 CD88⁺ interstitial macroph relative expression of indicated markers on AM. **(B)** Example flow cytometry plots of CD11b+ 985
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991 CD88⁺ interstitial macrophages (IM) from the lung parenchymal residing CD68⁺ 986 $CD88⁺$ interstitial macrophages (IM) from the lung parenchymal residing CD68⁺ myeloid cell
987 population identified in (A) showing the distribution of TREM2, CCR5, MHC-II, CD11c and Ly6C
988 expressing cells w 987 population identified in (A) showing the distribution of TREM2, CCR5, MHC-II, CD11c and Ly6C expressing cells within the lung parenchymal CD68⁺ myeloid cell population are also depicted.
989 Histograms depicting the expressing cells within the lung parenchymal CD68⁺ myeloid cell population are also depicted. 988 expressing cells within the lung parenchymal $CD68⁺$ myeloid cell population are also depicted.
989 Histograms depicting the relative expression of indicated markers, $n=8-9$, data combined from
990 two independen

Histograms depicting the relative expression of indicated markers, n= 8 – 9, data combined from

two independent experiments.
 991 Figure S4: Arginase expression by TRM is elevated by recent pulmonary TLR stimulation

b 990 two independent experiments.
991 **Figure S4: Arginase express
992 but does not contribute to TL
993 (A) Left: Example flow cytomy
994 alveolar macrophages (AM, top
995 Summary data of Arg1⁺ cells a** Figure S4: Arginase expression by TRM is elevated by recent pulmonary TLR stimulation

but does not contribute to TLR-induced restriction of SCV2 viral replication

(A) Left: Example flow cytomwetry plots showing iNOS and but does not contribute to TLR-induced restriction of SCV2 viral replication
993 (A) Left: Example flow cytomwetry plots showing iNOS and arginase-1 (Arg1) e.
994 alveolar macrophages (AM, top) and CD11b⁺ CD88⁺ interst 993 **(A)** Left: Example flow cytomwetry plots showing iNOS and arginase-1 (Arg1) expression from
994 alveolar macrophages (AM, top) and CD11b⁺ CD88⁺ interstitial macrophages (IM, bottom) Right:
995 Summary data of Arg alveolar macrophages (AM, top) and CD11b⁺ CD88⁺ 994 alveolar macrophages (AM, top) and CD11b⁺ CD88⁺ interstitial macrophages (IM, bottom) Right:
995 Summary data of Arg1⁺ cells as a percentage of AMs (left panel) and IMs (right panel) n= 8 –
996 10, data combined Summary data of Arg1⁺ cells as a percentage of AMs (left panel) and IMs (right panel) $n=8-$ 995 Summary data of Arg1⁺ cells as a percentage of AMs (left panel) and IMs (right panel) n= 8 – 996 10, data combined from two independent experiments (B) Schematic of K18-hACE2 Tg mice given PBS, 10 μ g CpG or 50 μ 996 10, data combined from two independent experiments **(B)** Schematic of K18-hACE2 Tg mice
997 given PBS, 10µg CpG or 50µg Pm3 intrapharyngeally (i.ph) sevemn days before intranasal (i.n.)
998 infection with 1x10³ TClD 997 given PBS, 10μg CpG or 50μg Pm3 intrapharyngeally (i.ph) sevemn days before intranasal (i.n.)
998 infection with 1x10³ TCID₅₀ SCV2 (SCV2, USA-WA1/2020) while given PBS or 100μg of the
999 arginase inhibitor Nor-N infection with $1x10^3$ TCID₅₀ SCV2 (SCV2, USA-WA1/2020) while given PBS or 100µg of the 998 infection with $1x10^3$ TCID₅₀ SCV2 (SCV2, USA-WA1/2020) while given PBS or 100µg of the arginase inhibitor Nor-NOHA i.n. once daily from one day before SCV2 infection until two days after infection. Right: viral lo 999 arginase inhibitor Nor-NOHA i.n. once daily from one day before SCV2 infection until two days
000 after infection. Right: viral loads in the lung of PBS (filled circles) or Nor-NOHA (open circles)
001 treated mice as m 1000 after infection. Right: viral loads in the lung of PBS (filled circles) or Nor-NOHA (open circles)
1001 treated mice as measured by qPCR for the SCV2E gene in its sub-genomic form (sub-gRNA),
 $\frac{1}{2}$
1001 treated mi 1001 treated mice as measured by qPCR for the SCV2E gene in its sub-genomic form (sub-gRNA),

1001 treated mice as measured by qPCR for the SCV2E gene in its sub-genomic form (sub-gRNA),

Figure S5: Description of the generation of *Zbp1-/-*

1002 n= 8 – 10, data combined from two independent experiments. Geometric mean, significance

1003 determined by two tailed Mann Whitney test, LD= limit of detection, n.s.= not significant.

1004 **Figure S5: Description o** 1003 determined by two tailed Mann Whitney test, LD= limit of detection, n.s.= not significant.

1004 Figure S5: Description of the generation of $Zbp1^{-/-}$ mice and increased viral t

1005 *finar1*, $Zbp1$ and $Tnfrsf1a$ Figure S5: Description of the generation of $Zbp1^{-/-}$ mice and increased viral titers in 1005 *ffnar1*, $Zbp1$ and $Tnfrsf1a$ deficient mice measured by qPCR for sub-genomic E gene (A – B) Viral loads as measured by RT-qP 1005 *Ifnar1, Zbp1* **and** *Tnfrsf1a* **deficient mice measured by qPCR for sub-genomic E gene 1006 (A – B) Viral loads as measured by RT-qPCR for the SCV2 E gene in its actively replice 1007 sub-genomic form (sub-gRNA) accor** 1006 **(A – B)** Viral loads as measured by RT-qPCR for the SCV2 E gene in its actively replicating

1007 sub-genomic form (sub-gRNA) according to experimental setups shown in **Figure 4A & Fig 4B**:

1008 **(A)** two different 1007 sub-genomic form (sub-gRNA) according to experimental setups shown in **Figure 4A & Fig 4B**:

1008 **(A)** two different strains of *Ifnar1⁻¹*- mice, **(B)** WT mice injected intraperitoneally with an anti-

1009 IFNAR1 **(A)** two different strains of *Ifnar1*-/- **(A)** two different strains of *lfnar1⁻¹⁻* mice, **(B)** WT mice injected intraperitoneally with an anti-
1009 IFNAR1 monoclonal antibody. **(C)** Schematic showing the *Zbp1* gene (exons shown as white
1010 boxes with corr 1009 IFNAR1 monoclonal antibody. **(C)** Schematic showing the *Zbp1* gene (exons shown as white 1010 boxes with corresponding exon number), the binding sites for CRISPR sub-gRNAs used to 1011 create $Zbp1^{/-}$ mice (red and 1010 boxes with corresponding exon number), the binding sites for CRISPR sub-gRNAs used to 1011 create $Zbp1^{1/-}$ mice (red and blue bars) and the resulting allele from deletion of the $Zbp15' \text{UTR}$ 1012 and exon 1 by this create $Zbp1^{-/-}$ mice (red and blue bars) and the resulting allele from deletion of the $Zbp15' \text{UTR}$ 1011 create $Zbp1^{-/}$ mice (red and blue bars) and the resulting allele from deletion of the $Zbp15'$ UTR
and exon 1 by this strategy as confirmed by Sanger sequencing. (**D**) Western immunoblots of
1013 lysates prepared from bone marrow-derived macrophages (BMDMs) or peritoneal exudate cells
1014 (PECs) from either WT or the $Zbp1^{-/}$ mice. Cells were incubated with or without 200ng/mL LPS
1015 for six hours before collection for immunoblotting. Short and long exposures of Zbp1 are shown
1016 (the correct band for Zbp1 at 44kDa is indicated by the black arrow). Expression of pro-IL1 β is
1017 included1012 and exon 1 by this strategy as confirmed by Sanger sequencing. **(D)** Western immunoblots of lysates prepared from bone marrow-derived macrophages (BMDMs) or peritoneal exudate cells 1014 (PECs) from either WT or the 1013 lysates prepared from bone marrow-derived macrophages (BMDMs) or peritoneal exudate cells

1014 (PECs) from either WT or the Zbp1^{-/-} mice. Cells were incubated with or without 200ng/mL LPS

1015 for six hours befor (PECs) from either WT or the *Zbp1*-/- 1014 (PECs) from either WT or the *Zbp1^{-/-}* mice. Cells were incubated with or without 200ng/mL LPS
1015 for six hours before collection for immunoblotting. Short and long exposures of *Zbp1* are shown
1016 (the correct 1015 for six hours before collection for immunoblotting. Short and long exposures of Zbp1 are shown

1016 (the correct band for Zbp1 at 44kDa is indicated by the black arrow). Expression of pro-IL1β is

1017 included as a 1016 (the correct band for Zbp1 at 44kDa is indicated by the black arrow). Expression of pro-IL1β is

1017 included as a control for LPS stimulation and actin is shown as a loading control. (E − F) Viral

1018 loads as included as a control for LPS stimulation and actin is shown as a loading control. $(E - F)$ Viral
1018 loads as measured by qPCR for the SCV2 E gene in its sub-genomic (sub-gRNA) form in lung
1019 lysates from WT and $(E) Zbp1$ 1018 loads as measured by qPCR for the SCV2 E gene in its sub-genomic (sub-gRNA) form in lung

1019 lysates from WT and (E) Zbp1⁻¹ or (F) Trifrsf1a^{-/-} mice infected with SCV2 as described in Fig

1020 **4A**, n= 9 – 29, lysates from WT and (E) *Zbp1¹* or (F) *Tnfrsf1a^{-/-}* 1019 lysates from WT and (E) $Zbp1^{17}$ or (F) Trifrsf1a^{-/-} mice infected with SCV2 as described in Fig 1020 **4A**, n= 9 – 29, viral titer data combined from 2 – 6 independent experiments, geometric mean, statistical sign

4A, n= 9 – 29, viral titer data combined from 2 – 6 independent experiments, geometric mean,

1021 statistical significance calculated by two-tailed Mann Whitney test.
 1022 Figure S6: Prior pulmonary exposure to vario statistical significance calculated by two-tailed Mann Whitney test.
1022 Figure S6: Prior pulmonary exposure to various inflammate
1023 remodeling of the lung epithelium.
1024 (A) Example flow cytometry plots from naive l Figure S6: Prior pulmonary exposure to various inflammatory stimuli induces diverse
1023 remodeling of the lung epithelium.
1024 (A) Example flow cytometry plots from naive lungs of WT mice depicting the gating strategy fo **remodeling of the lung epithelium.**

1024 **(A)** Example flow cytometry plots from

1025 lung epithelial cell (EC) subsets and

1026 from of mice treated with various infla

1027 control animals at the indicated tim

1028 (A) Example flow cytometry plots from naive lungs of WT mice depicting the gating strategy for

1025 lung epithelial cell (EC) subsets and pie charts depict the proportion of epithelial cell subsets

1026 from of mice trea lung epithelial cell (EC) subsets and pie charts depict the proportion of epithelial cell subsets
1026 from of mice treated with various inflammatory or infectious stimuli compared to those from PBS
1027 control animals at 1026 from of mice treated with various inflammatory or infectious stimuli compared to those from PBS

1027 control animals at the indicated time points without SCV2 (SCV2) infection, AEC (alveolar

1028 epithelial cells), 1027 control animals at the indicated time points without SCV2 (SCV2) infection, AEC (alveolar epithelial cells), BEC (bronchial epithelial cells), n=5-14, data is pooled from $2 - 4$ independent experiments, for all condi 1028 epithelial cells), BEC (bronchial epithelial cells), n=5-14, data is pooled from $2 - 4$ independent

1029 experiments, for all conditions except OVA/Alum, which was done once (B) Fold change

1030 geometric mean fluo 1029 experiments, for all conditions except OVA/Alum, which was done once **(B)** Fold change geometric mean fluorescence intensity (gMFI) of IFN-inducible surface marker (ISM) expression 1031 of Sca-1 and CD317 measured by 1030 geometric mean fluorescence intensity (gMFI) of IFN-inducible surface marker (ISM) expression

1031 of Sca-1 and CD317 measured by flow cytometry on lung epithelial cell (EC) subsets from lungs

1032 of mice treated 1031 of Sca-1 and CD317 measured by flow cytometry on lung epithelial cell (EC) subsets from lungs

1032 of mice treated with various inflammatory or infectious stimuli compared to those from PBS

1033 control animals at 1032 of mice treated with various inflammatory or infectious stimuli compared to those from PBS

1033 control animals at the indicated time points without SCV2 infection, n=5-14, data is pooled from

1034 2 – 4 independen 1033 control animals at the indicated time points without SCV2 infection, n=5-14, data is pooled from

1034 2 – 4 independent experiments, for all conditions except OVA/Alum, which was done once.

1035 Geometric mean, sig 1034 2 – 4 independent experiments, for all conditions except OVA/Alum, which was done once.

1035 Geometric mean, significance calculated by two-tailed Mann Whitney test, $* = p < 0.05$, $** = p < 0.01$, $*** = p < 0.001$, n.s.= not 1035 Geometric mean, significance calculated by two-tailed Mann Whitney test, $* = p < 0.05$, $** = p < 0.01$, $*** = p < 0.001$, n.s.= not significant.
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1038 REFERENCES 1036 p<0.01, *** = p<0.001, n.s.= not significant.
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