Acute respiratory distress syndrome (ARDS), the most severe form of acute lung injury, is a devastating clinical syndrome with a high mortality rate (30–60%) (refs 1–3). Predisposing factors for ARDS are diverse1–3 and include sepsis, aspiration, pneumonias and infections with the severe acute respiratory syndrome (SARS) coronavirus1–3. Although ACE2 is expressed in the lungs9,10. Here we report that ACE2 and the angiotensin II type 2 receptor (AT2) protect mice from severe acute lung injury induced by acid aspiration or sepsis. However, other components of the renin–angiotensin system, including ACE, angiotensin II and the angiotensin II type 1a receptor (AT1a), promote disease pathogenesis, induce lung oedemas and impair lung function. We show that mice deficient for Ace show markedly improved disease, and also that recombinant ACE2 can protect mice from severe acute lung injury. Our data identify a critical function for ACE2 in acute lung injury, pointing to a possible therapy for a syndrome affecting millions of people worldwide every year.

The renin–angiotensin system has an important role in maintaining blood pressure homeostasis, as well as fluid and salt balance6–8. Although ACE2 is expressed in the lungs of humans9 and mice (see Supplementary Fig. 1a, b), nothing is known about its function in the lungs. However, mortality following SARS coronavirus infections approaches almost 10% owing to the development of ARDS14–16. To elucidate the role of ACE2 in acute lung injury, we examined the effect of Ace2 gene deficiency in mouse experimental models that mimic the common lung failure pathology observed in several human diseases, including sepsis, acid aspiration and pneumonias such as SARS and avian influenza A17. 

Acute lung injury in response to acid aspiration results in massive lung oedema (Fig. 1c), increased inflammatory cell infiltration and hyaline membrane formations (Fig. 1d) in response to acid aspiration. It should be noted that ACE2 protein expression is typically downregulated in wild-type mice following acid challenge (Fig. 1e).

Sepsis is the most common cause of acute lung injury/ARDS1–3. We therefore examined the effect of Ace2 gene deficiency on sepsis-induced acute lung injury using caecal ligation and perforation (CLP)18,19. CLP causes lethal peritonitis and sepsis due to a polymicrobial infection that is accompanied by acute lung failure19. Whereas all CLP-treated wild-type mice survived, only two out of ten CLP-treated Ace2 knockout mice survived the 6 h experimental observation period (Fig. 2a). CLP resulted in lung failure defined by increased elastance (Fig. 2a), pulmonary oedema (Fig. 2b) and leukocyte accumulation (Fig. 2c) in wild-type mice. CLP-treated Ace2 knockout mice had a marked worsening of lung functions (Fig. 2a), increased oedema (Fig. 2b) and leukocyte accumulation (Fig. 2c) compared with wild-type mice. In addition, Ace2 knockout mice also developed markedly enhanced acute lung injury after endotoxin challenge18 (see Supplementary Fig. 2a–c). Ace2 maps to the X chromosome, and it should be noted that loss of ACE2 expression resulted in equally severe acute lung injury phenotypes in male (Ace2−/−) and female (Ace2−/−) mice. Our data from three different acute lung injury models show that loss of Ace2 expression precipitates severe acute lung failure.

To test whether loss of ACE2 is essential for disease pathogenesis, we performed a rescue experiment using recombinant human ACE2 protein (rhuACE2) (see Supplementary Fig. 3a, b). Injection of rhuACE2 into acid-treated Ace2 knockout mice decreased the degree of acute lung injury, as assessed by lung elastance (Fig. 2d) and pulmonary oedema formation (Fig. 2e). When we injected rhuACE2 protein into acid-treated wild-type mice, lung function (Fig. 2f) and oedema formation (see Supplementary Fig. 3c) were also rescued. In saline-treated wild-type or Ace2 knockout mice, injections of (Fig. 1b) and the development of pulmonary oedema (Fig. 1c). Acid aspiration resulted in increased alveolar wall thickness, oedema, bleeding, inflammatory cell infiltrates and formation of hyaline membranes (Fig. 1d). Notably, acid-treated Ace2 knockout mice showed significantly greater lung elastance compared with control wild-type mice, but there were no differences in lung elastance between saline-treated Ace2 knockout and wild-type mice (Fig. 1a). Moreover, loss of Ace2 resulted in worsened oxygenation (Fig. 1b), massive lung oedema (Fig. 1c), increased inflammatory cell infiltration and hyaline membrane formations (Fig. 1d) in response to acid aspiration. It should be noted that ACE2 protein expression is typically downregulated in wild-type mice following acid challenge (Fig. 1e).
rhuACE2 did not affect pulmonary functions (Fig. 2d–f). Catalytically inactive ACE2 protein (mut-rhuACE2) (see Supplementary Fig. 3a, b) did not rescue the severe lung phenotype in Ace2 knockout mice (Fig. 2d, e) and had no effect on the severity of acute lung injury in wild-type animals (Fig. 2f and Supplementary Fig. 3c). These results show that the catalytic activity of ACE2 can directly protect lungs from acute lung injury.

ACE2 is a homologue of ACE, both of which are central enzymes in the renin–angiotensin system6–8. ACE cleaves the decapetide angiotensin (AngI) into the octapeptide AngII (refs 11, 12). ACE2 cleaves a single residue from AngI to generate Ang1–9 (refs 6, 7), and a residue from AngII to generate AngI–7 (ref. 6). In this way, ACE2 negatively regulates the renin–angiotensin system by inactivating AngII from AngI to generate Ang1–7 (ref. 6). In this way, ACE2 negatively regulates the renin–angiotensin system by inactivating AngII.

Results show that the catalytic activity of ACE2 can directly protect mice (Fig. 2d, e) and had no effect on the severity of acute lung injury in rhuACE2 did not affect pulmonary functions (Fig. 2d–f). Catalytically inactive ACE2 protein (mut-rhuACE2) (see Supplementary Fig. 3a, b) did not rescue the severe lung phenotype in Ace2 knockout mice (Fig. 2d, e) and had no effect on the severity of acute lung injury in wild-type animals (Fig. 2f and Supplementary Fig. 3c). These results show that the catalytic activity of ACE2 can directly protect lungs from acute lung injury.

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Lung elastance after acute lung injury in WT and Ace2 knockout (KO) mice induced by caecal ligation and perforation (CLP). Eighteen hours after sham or CLP surgery, animals received mechanical ventilation for 6 h (n = 10 in CLP-treated groups, n = 6 in sham-treated groups). As B/10 CLP-treated Ace2 knockout mice died at 4–4.5 h, only data up to 4 h are shown. CLP-treated Ace2 knockout mice had significantly higher elastance than CLP-treated WT mice (P < 0.01). b, c, Wet-to-dry weight ratios of lungs (b) and lung histopathology (c) in sham or CLP-treated WT and Ace2 knockout mice determined after 4 h of ventilation. Asterisk denotes a significant difference (P < 0.05) between CLP-treated WT and Ace2 knockout mice. Note the enhanced lung oedema and inflammatory infiltrates in Ace2 knockout mice (H&E staining, × 200). d, e, Lung elastance (d) and wet-to-dry weight ratios (e) after acid or saline instillation of Ace2 knockout mice injected intraperitoneally with recombinant human ACE2 protein (rhuACE2; 0.1 mg kg\(^{-1}\)), mutant rhuACE2 (mut-rhuACE2; 0.1 mg kg\(^{-1}\)) or vehicle (n = 6 per group). Asterisk denotes a significant difference (P < 0.05) comparing rhuACE2-treated Ace2 knockout mice with mut-rhuACE2-treated and vehicle-treated Ace2 knockout mice at 3 h. f, Lung elastance after acid instillation in WT mice treated with rhuACE2 protein (0.1 mg kg\(^{-1}\), mut-rhuACE2 protein (0.1 mg kg\(^{-1}\)) or vehicle (n = 6–8 per group). Asterisk denotes a significant difference (P < 0.05) between WT mice treated with rhuACE2 and mut-rhuACE2 or with vehicle at 3 h. Errors bars indicate s.e.m.

As enhanced pulmonary vascular permeability is a hallmark of acute lung injury/ARDS in humans, we first tested whether AngII can increase hydrostatic pressure using isolated, perfused murine lungs ex vivo\(^7\). In this system, pulmonary perfusion pressures were comparable between wild-type and Ace2 knockout mice under baseline control conditions (wild-type 3.0 ± 1.9 cm H\(_2\)O, n = 6 versus Ace2 knockout 1.8 ± 1.6 cm H\(_2\)O, n = 9; mean ± s.e.m.), and these values were not changed by either acid-treatment or continuous perfusion of the bacterial endotoxin lipopolysaccharide (LPS). Pulmonary perfusion pressures generated by AngI or AngII injection into lungs of acid-instilled animals or into lungs perfused with LPS were also similar between wild-type and Ace2 knockout mice (see Supplementary Fig. 8a, b). Moreover, fractional shortening using echocardiography (an indicator of left ventricular systolic function) and mean arterial pressures were comparable between Ace2 knockout and wild-type mice during the experimental period (see Supplementary Fig. 9a, b). Thus, the severe lung oedemas in Ace2 knockout mice do not seem to be secondary to systemic haemodynamic alterations.

As enhanced pulmonary vascular permeability is a hallmark of acute lung injury/ARDS in humans\(^2\), we examined whether loss of Ace2 results in increased vascular permeability using Evans Blue dye injections as an in vivo indicator of albumin leakage\(^28\). Acid aspiration increased vascular permeability in wild-type mice. In Ace2 knockout mice, pulmonary Evans Blue accumulation was greatly increased after acid aspiration (Fig. 4c, d). These results were confirmed using fluorescein isothiocyanate (FITC)-conjugated dextran (40 kDa) as another marker to assess vascular leakage of macromolecules (data not shown). Vascular permeability was significantly attenuated in the lungs of Agrp1a\(^{-/-}\) mice (Fig. 4e). We suggest that loss of ACE2 expression in acute lung injury leads to leaky pulmonary blood vessels through AT1a receptor stimulation. However, hydrostatic oedemas cannot be excluded, and the effects of local AngII production on lung blood vessels require further investigation\(^27,29\).

ARDS is the most severe form of a wide spectrum of pathological processes designated as acute lung injury\(^2\). ARDS is characterized by pulmonary oedema due to increased vascular permeability, the accumulation of inflammatory cells and severe hypoxia\(^2\). Predisposing factors for ARDS include sepsis, aspiration and pneumonia (including infections with SARS coronavirus\(^1–5\) or avian and human influenza viruses\(^17\)). Our data show that acute lung injury results in a marked downregulation of ACE2, a key enzyme involved in the regulation of the renin–angiotensin system.

It has been previously shown that an insertion/deletion ACE polymorphism that affects ACE activity is associated with ARDS susceptibility and outcome\(^30\). Our data provide a mechanistic
Figure 3 | ACE deficiency reduces the severity of acute lung injury.

a, Schematic diagram of the renin–angiotensin system. b, Lung levels of AngII in control and acid-treated WT and Ace2 knockout (KO) mice determined at 3 h by enzyme immunoassay (n = 3–5 per group). Asterisk denotes a significant difference (P < 0.05) between acid-treated WT and Ace2 knockout mice. c, Lung elastance after acid instillation in Ace2+/+ (WT), Ace2−/−, and Ace2+/− mice (n = 4–6 mice per group). Asterisk denotes a significant difference (P < 0.05) comparing Ace2−/− with Ace2+/+ and Ace2+/− mice at 3 h. d, Lung elastance (d) and wet-to-dry lung weight ratios (e) in acid- or saline-treated Ace2+/+ Ace2 KO, Ace2−/− Ace2 KO, Ace2−/− Ace2 KO and WT mice (n = 5 per group). Asterisk denotes a significant difference (P < 0.05) comparing Ace2−/− Ace2 KO with WT, Ace2−/− Ace2 KO or Ace2−/− Ace2 KO mice 3 h after acid treatment. f, Lung histopathology. Severe lung interstitial oedema and leukocyte infiltration in Ace2 KO mice are attenuated by homozygous (Ace2−/−) or heterozygous (Ace2+/−) mutations of Ace (H&E staining, × 200). Error bars indicate s.e.m.

**Figure 4** | The AngII receptor AT1a controls acute lung injury severity and pulmonary vascular permeability. a, Lung elastance measurements in Agtr1a−/− mice, Agtr2−/− mice and WT mice after acid aspiration (n = 4–6 per group). All acid-treated Agtr2−/− mice died after 2 h. There is a significant difference (P < 0.01) between acid-treated WT and acid-treated Agtr1a−/− mice over the whole time course. Double asterisk denotes a significant difference (P < 0.01) between WT and Agtr2−/− mice at 2 h. b, Lung elastance measurements in Ace2 knockout mice treated with vehicle or inhibitors to AT1 (Losartan, 15 mg kg−1) or AT2 (PD123319, 15 mg kg−1) after acid or saline instillation (see Methods, n = 4–6 per group). Double asterisk denotes a significant difference (P < 0.01) comparing Ace2 knockout mice treated with AT1 inhibitor with vehicle or AT1 inhibitor treatment at 3 h. c, Pulmonary vascular permeability as determined by intravenous injection of Evans Blue. Extravascular Evans Blue in lungs was measured in WT and Ace2 knockout mice 3 h after acid injury (n = 5 per group). Double asterisk denotes a significant difference (P < 0.01) between acid-treated WT and Ace2 knockout mice. d, Representative images of Evans Blue-injected lungs of WT and Ace2 knockout mice 3 h after acid aspiration. e, Extravascular Evans Blue in lungs of WT and Agtr1a−/− mice 3 h after acid injury (n = 5 per group). Asterisk denotes a significant difference (P < 0.05) between acid-treated WT and Agtr1a−/− mice at 3 h. Error bars indicate s.e.m.

Molecular involvement for the clinical findings and indicate that, in the pathogenesis of acute lung injury, AngII is upregulated by ACE and drives severe lung failure through the AT1a receptor. On the other hand, ACE2 and the AT2 receptor protect against lung injury. Exogenous recombinant human ACE2 attenuates acute lung failure in Ace2 knockout as well as in wild-type mice. This combination of genetic, pharmacological and protein rescue experiments defines a new and critical role for the renin–angiotensin system in the pathogenesis of acute lung injury, and show that ACE2 is a key molecule involved in the development and progression of acute lung failure.

METHODS

For detailed methods please refer to the Supplementary Information.

**Animals.** Ace2, Ace, Agtr1a and Agtr2 mutant mice have previously been described. Sex-, age-, and background-matched mice were used as controls. Basal lung functions and lung structure were comparable among all the mice tested. Mice were handled in accordance with institutional guidelines.

**Experimental murine models of acute lung injury.** For acid aspiration-induced acute lung injury, anaesthetized mice were intratracheally instilled with HCl (pH 1.5: 2 ml kg−1) and ventilated for 3 h (refs 18, 19). To study sepsis-induced acute lung injury, we performed caecal ligation perforation (CLP)20. Sham-operated mice underwent the same procedure without ligation and puncture of the caecum. Eighteen hours after sham/CLP surgery, animals were subjected to mechanical ventilation for up to 6 h. For endotoxin-induced acute lung injury, anaesthetized mice received LPS and zymosan intratracheally immediately after starting mechanical ventilation and 1 h later, respectively21. In all acute lung
injury models, total positive end expiratory pressure (PEEP) and plateau pressure ($P_{plat}$) were measured at the end of inspiratory and expiratory occlusion, respectively. Elastance was calculated as ($P_{plat} - PEEP$) divided by tidal volume ($V_{T}$) every 30 min during the ventilation periods.

**Blood oxygenation, pulmonary oedema, pulmonary vascular permeability and histology.** Blood samples were obtained from the left heart ventricle and partial pressure of oxygen in arterial blood ($P_{O_2}$) was measured. To assess pulmonary oedema, the lung wet-to-dry weight ratios were calculated. Pulmonary vascular permeability was assessed by measuring the pulmonary extravasation of Evans Blue. For histological analysis, 5-μm thick sections were cut and stained with haematoxylin and eosin (H&E).

**Recombinant ACE2 and AT$_1$/AT$_2$, receptor inhibitors.** Thirty minutes before acid instillation, mice received intraperitoneal injections of recombinant human ACE2 (rhuACE2) protein (0.1 μg kg$^{-1}$) (R&D Systems or our own rhuACE2 preparation), catalytically inactive (H374N, H378N)$^	ext{15}$ mutant recombinant human ACE2 (mut-rhuACE2) or vehicle (0.1% BSA/PBS). All animals were then ventilated for 3 h. RhuACE2 protein and mut-rhuACE2 protein were purified from transfected CHO cells by affinity chromatography. The catalytic activities of purified recombinant ACE2 proteins were measured using the fluorogenic peptide Substrate VI (R&D Systems). Mut-rhuACE2-Fc showed >95% loss of catalytic activity (see Supplementary Fig. 3a). For inhibitor studies, mice received intraperitoneal injections of the AT$_1$ inhibitor Losartan (15 mg kg$^{-1}$), the AT$_2$ inhibitor PD123.319 (15 mg kg$^{-1}$) or control vehicle 30 min before surgical procedures.

**Angiotensin II peptide levels and western blotting.** AngII peptide levels were measured as described.$^8$ For western blotting, rabbit polyclonal anti-ACE2 antibody$^8$ and rabbit polyclonal anti-mouse ACE antibody (R&D Systems) were used.

**Statistical analyses.** All data are shown as mean ± s.e.m. Measurements at single time points were analysed by analysis of variance (ANOVA). Time courses were analysed by repeated measurements ANOVA with Bonferroni post-tests.

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**Supplementary Information** is linked to the online version of the paper at www.nature.com/nature.

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