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IL-1R1/MyD88 Signaling Is Critical for Elastase-Induced Lung Inflammation and Emphysema

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Lung emphysema and fibrosis are severe complications of chronic obstructive pulmonary disease, and uncontrolled protease activation may be involved in the pathogenesis. Using experimental elastase-induced acute inflammation, we demonstrate here that inflammation and development of emphysema is IL-1R1 and Toll/IL-1R signal transduction adaptor MyD88 dependent; however, TLR recognition is dispensable in this model. Elastase induces IL-1β, TNF-α, keratinocyte-derived chemokine, and IL-6 secretion and neutrophil recruitment in the lung, which is drastically reduced in the absence of IL-1R1 or MyD88. Further, tissue destruction with emphysema and fibrosis is attenuated in the lungs of IL-1R1- and MyD88-deficient mice. Specific blockade of IL-1 by IL-1R antagonist diminishes acute inflammation and emphysema. Finally, IL-1β production and inflammation are reduced in mice deficient for the NALP3 inflammasome component apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), and we identified uric acid, which is produced upon elastase-induced lung injury, as an activator of the NALP3/ASC inflammasome. In conclusion, elastase-mediated lung pathology depends on inflammasome activation with IL-1β production. IL-1β therefore represents a critical mediator and a possible therapeutic target of lung inflammation leading to emphysema. The Journal of Immunology, 2009, 183: 8195–8202.

Chronic obstructive pulmonary disease (COPD),4 manifested as chronic airflow obstruction, chronic bronchitis, and emphysema, is a major public health problem worldwide (1). Emphysema is characterized by a breakdown in the alveolar lung structure due to destruction of the alveolar wall (2). The destruction of the alveolar wall is due to recurrent and chronic inflammation with cytokine production, protease activation, oxidative stress, and other mechanisms that have synergistic effects resulting in increased alveolar size and fibrosis (2, 3). Cigarette smoke, chronic exposure to environmental chemicals, and pollutants are the main exogenous causes of COPD, and numerous studies dwelled on the molecular pathogenesis of emphysema (4).

To investigate the molecular mechanisms of emphysema, rodent models of elastase-induced emphysema have been established (5). The intratracheal administration of porcine pancreatic elastase (PPE) induces acute inflammation with destruction of the alveolar wall. Elastase causes a rapid degradation of extracellular matrix and tissue cells with the release of a broad variety of breakdown products and inflammatory mediators. Therefore, the elastase/PPE-induced model of emphysema allows deciphering of the role of several critical factors in pathogenesis of emphysema downstream of protease activation such as the role of the oxidative stress (6), cytokines, and chemokines (7). However, whether lung injury leading to so-called endogenous danger signals would activate pattern recognition receptors such as TLRs or NACHT-leucine-rich repeats (NOD-like receptor (NLR); Refs. 8 and 9) has not been investigated.

Here using the elastase induced lung tissue injury model (10), we asked whether TLRs are involved in signaling the inflammatory response. We report that inflammation and alveolar destruction occur in the absence of TLR signaling using gene-deficient mice. However, IL-1β is induced upon elastase administration in the lung, and most importantly IL-1R1- and MyD88-deficient mice have reduced inflammation and emphysema. We then investigated the implication of NLRs and found that uric acid is released upon lung injury activating the apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC)-containing NALP3 inflammasome. Therefore, inflammation and IL-1β production are reduced in the absence ofASC. Finally, neutralization of IL-1 with the IL-1 receptor antagonist (IL-1Ra) or Ab reduces lung inflammation and emphysema.

Materials and Methods

Mice

MyD88−/− (11), IL-1R1−/− (12), TLR2−/− (13) and TLR4−/− obtained by crossing TLR2−/− and TLR4−/− (14), TLR3−/− (15), TLR7−− (16), TLR9−− (17), 3D− mice (18), and ASC−/− (19) mice were used; these were backcrossed at least 10 times on the C57BL/6 genetic background. All mice, including control C57BL/6, were bred in our animal facility at
Bronchoalveolar lavage (BAL)

Mice were analyzed at 24 h and 14 days in deep anesthesia. After incision of the trachea, a plastic cannula was inserted, and airspace washes were washed using 5 ml of PBS solution, heated to 37°C. The rib cage was then gently massaged to enable maximum cell collection. The fluid was collected by careful aspiration. This procedure was performed 10 times, and the recovery of the total lavage exceeded 95%. The samples collected were dispatched in two fractions: the first one (1 ml corresponding to the two first lavages) was used for mediator measurement; and the second one was used for the cell determination (4 ml). The first fraction was centrifuged (600 × g for 10 min), and supernatant was fractionated and kept at −80°C until mediator determination. The cell pellet was then resuspended in 0.4 ml of PBS, pooled with the second fraction, and maintained at 4°C until cell determination.

Cell count and determination

Total cell count was determined in BAL fluid using a particle counter (Z2 Coulter; Beckman Coulter). Differential cell counts were performed on cytospin preparations (Cytospin 3) after staining for 4 min in May-Grünwald stain (MG-IL; Sigma-Aldrich) and 8 min in 95% Giemsia stain (GS-500; Sigma-Aldrich). Differential cell counts were made on 200 cells in duplicate using standard morphological criteria.

Lung function

Lung function was analyzed in unrestrained conscious mice immediately upon a single PPE administration during the first day over 6 h using noninvasive whole-body plethysmography chambers (Buxco Electronic) as described (20, 21). Enhanced respiratory pause (Penh) measurement can be conceptualized as the phase shift of the thoracic flow and the nasal flow curves; increased phase shift correlates with increased respiratory system resistance. Penh is calculated by the formula Penh = (Te/RT − 1) × PEF/PF, where Te is expiratory time, RT is relaxation time, PEF is peak expiratory flow, and PF is peak inspiratory flow. For the graphics, the Penh mean values are given over 6 h. The area under the curve was calculated as the sum of all Penh values minus the average of the baseline values. Increase of PenH values indicates inflammatory changes in the airway.

Lung homogenization

After BAL was performed, the whole lung was removed, placed in a disposable homogenization tube in 1 ml of PBS, homogenized (Dispo- mix, Medicool), and centrifuged, and the supernatant was stored at −80°C before mediator, myeloperoxidase (MPO) activity, or collagen determinations.

MPO in lung

Lung tissue MPO activity was evaluated as described (22). In brief, the right heart ventricle was perfused with saline to flush the vascular content, and lungs were frozen at −20°C until use. Lung was homogenized by Polytron and centrifuged, and the supernatant was discarded. The pellets were resuspended in 1 ml of PBS containing 0.5% hexadecyltrimethylammonium bromide and 5 mM EDTA. After centrifugation, 50 μl of supernatants were placed in test tubes with 200 μl of PBS-hexadecyltrimethylammonium bromide-EDTA, 2 ml of HBSS, 100 μl of 0.1 M diamide dihydrochloride (1.25 mg/ml), and 100 μl of 0.05% H₂O₂. After 15 min of mixture incubation at 37°C in an agitator, the reaction was stopped with 100 μl of 1% NaN₃. The MPO activity was determined as OD₄₆₀ against medium.

Mediator measurement

IL-1β, keratinocyte-derived chemokine (KC), TNF, and IL-6 levels in BAL fluid or lung homogenate were determined using ELISA assay kits except for Figs. 3 and 4 (Mouse DuoSet for IL-1β, KC, and IL-6 was purchased from R&D Systems) according to the manufacturer’s instructions. For Fig. 3, IL-1β, KC, and IL-6 were measured by multiplex ELISA cytokine arrays with a limit detection of 1 pg/ml (Upstate).

Uric acid measurement

Uric acid concentration was determined in lung homogenates using an Amplex Red Uric Acid/Uricase Assay Kit (Molecular Probes) as described before (23). Briefly, uricase catalyzes the conversion of uric acid to allantoin, H₂O₂, and carbon dioxide. In the presence of HRP, H₂O₂ reacts stoichiometrically with Amplex Red reagent to generate the red-fluorescent oxidation product, resorufin, measured spectrophotometrically.

Lung collagen measurement

Aliquots of lung homogenate (50 μl) were then assayed for lung collagen levels and compared with a standard curve prepared from bovine skin using the Sircol collagen dye-binding assay according to the manufacturer’s instructions (Biocolor).

Lung histology and quantification of inflammation and tissue destruction

On day 14 after PPE administration, the mice were anesthetized, the lung was perfused and removed, the trachea was cannulated, and the lung was inflated with 4% buffered formaldehyde at a pressure of 20 cm of H₂O for microscopic analysis. Sections 3 μm thick were stained with H&E, periodic acid-Schiff, or chromotrope aniline blue for collagen fiber staining as described previously (20). The severity of the morphological changes (infiltration by neutrophils and mononuclear cells, destruction and thickening of the alveolar septae, fibrosis and enlargement of alveoli) were assessed semiquantitatively using a score (0–5) by two independent author observers (I.C. and B.R.). The air space enlargement was quantified by the mean linear intercept (Lm) in 20 randomly selected fields of the lung tissue sections as described (24).

Statistical analysis

Statistical evaluation of differences between the experimental groups was determined ANOVA followed by a Bonferroni post test. All tests were performed with Graphpad Prism (GraphPad Software). All data are presented as mean ± SD. Values of p < 0.05 were considered significant.

Results

Inflammation upon elastase lung injury is TLR independent

Acute lung injury induced by endotoxin, cigarette smoke, or bleomycin results in degradation of matrix proteins, oxidative stress, and activation of proteases with degradation products that may cause inflammation through activation of TLR (25, 26). Here, using the elastase model to induce lung pathology downstream of protease activation, we asked whether the TLR-MyD88 pathway is required for inflammation and fibrosis. We first demonstrate that elastase elicits a rapid and dose-dependent respiratory dysfunction as measured by noninvasive plethysmography (Penh), indicating an inflammatory response (Fig. 1A), which is detectable at ≥3 U of PPE. Elastase causes a robust inflammation at 24 h with neutrophil recruitment into the lung as assessed by MPO activity (Fig. 1B) and into the BAL fluid (Fig. 1C), protein leak (Fig. 1D), and production of proinflammatory mediators KC and IL-6 in the BAL fluid (Fig. 1, E and F). Total cell in BAL fluid correlated with neutrophil counts, and there was no difference on macrophage counts among the experimental groups (data not shown). There was a dose-dependent increase of most of the inflammatory parameters which is significant at ≥3 U PPE. Because the highest dose causes a substantial extravasation of RBCs in the bronchoalveolar space, PPE was used at 3 U in the subsequent studies.

In view of the fact that endogenous TLR agonists such as hyaluronic acid, heat shock proteins, nucleic acid, and others are likely released upon elastase-induced lung injury, we asked...
Elastase causes dose-dependent chronic inflammation with mononuclear cell inflammation in the alveolar septae and lungs, which was assessed semiquantitatively and detectable at 1 U of PPE (Fig. 2, B and C). The alveolar destruction/emphysema as assessed by the mean linear intercept analysis (24) was found at ≥3 U of PPE (Fig. 2D). Elastase at 3 U induced a significant increase in collagen deposition in the lung (Fig. 2E). Finally, the role of TLR in emphysema was tested using TLR-deficient mice on tissue sections. Chronic inflammation (data not shown) and destruction septae with increased size of the alveoli as assessed by the linear intercept analysis were not affected in the absence of single- or double-TLR-deficient mice (Fig. 2F).

Therefore, elastase-induced lung injury causes lung inflammation and emphysema, and TLRs appear to not be required for the development of lung pathology.

**Elastase induces IL-1β and inflammation is IL-1R1-MyD88 signaling dependent**

Protease-induced lung injury may activate the inflammasome promoting the processing and secretion of proinflammatory cytokines such as IL-1β (27, 28). Administration of elastase induces IL-1β production in the lung at 24 h (Fig. 3A). Therefore, we hypothesized that IL-1R1-MyD88 signaling may be critical in elastase-induced acute lung injury. In fact, IL-1R1- and MyD88-deficient mice have reduced Penh values (depicted as area under curve), indicating airway dysfunction and inflammation (Fig. 3B). Further, neutrophil recruitment in lung assessed by MPO activity in lung (Fig. 3C) and neutrophil counts in BAL fluid (Fig. 3D) were augmented in C57BL/6 mice, but neither in IL-1R1- nor in MyD88-deficient mice. Total cells in BAL fluid correlated with neutrophil counts, but there was no difference in macrophage counts among the experimental groups (data not shown). No neutrophils were found in either experimental group after saline administration (data not shown). Furthermore, protein in BAL fluid protein was increased indicating endothelial damage (Fig. 3E) and the inflammasome mediators IL-1β, TNF, KC, and IL-6 elevated in lung homogenate of C57BL/6 mice only (Fig. 3, F–I). A reduction of IL-1β levels in IL-1R1- and MyD88-deficient mice was found before in the bleomycin-induced injury model and suggests an autocrine loop of IL-1β production (23).

### Table I. Elastase-induced acute lung inflammation is TLR independent

<table>
<thead>
<tr>
<th>TLR Mutant</th>
<th>Neutrophils in BAL (×104/μl)</th>
<th>MPO Activity (OD450)</th>
<th>Protein in BAL (μg/ml)</th>
<th>IL-1β in Lung Homogenate (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean SD</td>
<td>Mean SD</td>
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</tr>
<tr>
<td>B6</td>
<td>96 19</td>
<td>0.062 0.032</td>
<td>1412 32</td>
<td>234 32</td>
</tr>
<tr>
<td>TLR2−/−</td>
<td>91 23</td>
<td>0.057 0.018</td>
<td>1372 27</td>
<td>226 22</td>
</tr>
<tr>
<td>TLR4−/−</td>
<td>94 28</td>
<td>0.061 0.026</td>
<td>1403 43</td>
<td>198 35</td>
</tr>
<tr>
<td>TLR2−4−/−</td>
<td>86 24</td>
<td>0.068 0.022</td>
<td>1384 36</td>
<td>186 25</td>
</tr>
<tr>
<td>TLR3−/−</td>
<td>94 21</td>
<td>0.072 0.024</td>
<td>1481 24</td>
<td>204 28</td>
</tr>
<tr>
<td>TLR7−/−</td>
<td>97 28</td>
<td>0.058 0.021</td>
<td>1375 29</td>
<td>176 35</td>
</tr>
<tr>
<td>TLR9−/−</td>
<td>87 16</td>
<td>0.071 0.028</td>
<td>1536 41</td>
<td>173 32</td>
</tr>
<tr>
<td>3D−/−</td>
<td>94 22</td>
<td>0.061 0.019</td>
<td>1391 38</td>
<td>212 26</td>
</tr>
</tbody>
</table>

*Elastase/PPE was given at 3 U by intranasal instillation to TLR2−, TLR4−, TLR2−4−, TLR3−, TLR7−, TLR9−, and 3D-deficient mice and compared with C57BL/6 mice. Neutrophil recruitment and total protein in BAL fluid and MPO activity and IL-1β in lung homogenate were determined at 24 h. Results are representative of two independent experiments (n = 6 mice/group).*
IL-1β and TNF share some common proinflammatory properties. Therefore, we asked whether TNF, a cytokine that does not use the MyD88 adaptor protein for signaling, participates in the inflammation. TNF-deficient mice showed a vigorous neutrophil influx in response to elastase with no significant difference in comparison with those of C57BL/6 mice, suggesting that TNF is dispensable for neutrophil recruitment (data not shown), but we have not investigated the effect of TNF on emphysema. A previous report showed that TNF-R1–R2 double-deficient mice develop less elastase-induced emphysema, which may suggest that acute inflammation is not necessarily linked to emphysema development (10).

In conclusion, elastase-induced IL-1β secretion appears to be critical for subsequent inflammation, and IL-1R1-MyD88 signaling is required for acute inflammation with the production of at least IL-1β, TNF, KC/CXCL1, and IL-6 and for neutrophil recruitment into the lung and bronchoalveolar space.

Elastase-induced lung emphysema depends on IL-1R1 and MyD88 signaling

Tissue injury induced by elastase leads to chronic inflammation with the destruction of the alveolar wall with emphysema and fibrosis. Microscopic investigations of the lungs 14 days after elastase-PPE (3 U) reveals inflammatory reactions with destruction of alveolar wall and signs of fibrosis in C57BL/6 mice (Fig. 4A) in comparison with the normal alveolar structure of the saline controls. Cellular infiltrates, alveolar wall destruction, and collagen deposition are attenuated in IL-1R1- and MyD88-deficient mice. The inflammatory alterations as assessed semiquantitatively are significantly reduced in the absence of IL-1R1 and MyD88 (Fig. 4B). Emphysema assessed by destruction of the alveolar wall with increase size of alveoli assessed by linear intercept measurement is significantly reduced in IL-1R1- and MyD88-deficient mice as compared with C57BL/6 mice (Fig. 4C). Moreover, biochemically collagen deposition in lung tissues was augmented in C57BL/6 mice, but not in IL-1R1−/− and MyD88−/− mice (Fig. 4D).

Therefore, IL-1β appears to be critical for the pathogenesis of elastase-induced inflammation and emphysema. Neutralization of IL-1 by IL-1Ra attenuated neutrophil recruitment in lung (MPO) and BAL at 24 h (Fig. 5, A and B), and emphysema as assessed by linear intercept determination (Fig. 5C) and lung collagen deposition (Fig. 5D) at 14 days. Similar results were obtained with neutralizing IL-1β Ab (data not shown).

Inflammation and IL-1β production depends on the ASC-containing inflammasome

The cleavage of pro-IL-1β by caspase results in the production of IL-1β. Recent investigation by several groups provided evidence that activation of the NALP3 inflammasome complex is a crucial step (29). Upon NALP3 activation, the adaptor protein ASC is recruited and activates caspase-1 cleaving pro-IL-1β to mature, secreted IL-1β. Therefore, we asked whether the NALP3 inflammasome is involved in elastase injury and demonstrate here that inflammation is dependent on the ASC adaptor protein (Fig. 6). Mice deficient for ASC have reduced neutrophil recruitment in the BAL fluid and lung (Fig. 6, A and B), and as a consequence of defective inflammasome activation, we find reduced IL-1β production (Fig. 5C) and reduced protein in BAL (Fig. 5D). Therefore, ASC inflammasome activation may account for elastase-induced lung injury and inflammation.

Then, we asked which endogenous danger signal might activate the NALP3/ASC inflammasome. Uric acid crystals are potent activators of the NALP3-ASC inflammasome (27). Following lung injury, increased uric acid is locally produced by dying cells (30, 31) and may precipitate to form crystals that activate the inflammasome. We found increased uric acid in BAL after elastase administration (Fig. 5E), which may suggest a mechanism for
inflammasome activation. To test whether uric acid is involved in inflammation, we asked whether depletion of uric acid reduces inflammation. Recombinant uricase, an enzyme that degrades uric acid in the tissue, reduces neutrophil recruitment in the BAL and lung upon elastase administration (Fig. 5, F and G). These data are consistent with a functional role of uric acid inflammation upon tissue damage as described before for bleomycin-induced lung injury (23).

The data support the hypothesis that upon elastase injury uric acid is released by dying cells and participates in inflammasome activation leading to IL-1β production. Therefore, the present data suggest that uric acid as a new mechanism of elastase induced IL-1β production, and IL-1R1-MyD88 signaling is required for the development of pulmonary inflammation, emphysema in response to elastase.

Discussion

We show here that acute lung injury caused by elastase administration leads to acute lung tissue injury with inflammation, production of IL-1β, emphysema, and fibrosis. Lung inflammation and pathology are significantly reduced in IL-1R1- and MyD88-deficient mice, pointing to an essential role of endogenous IL-1β in pulmonary inflammation and emphysema in response to elastase. In support of these data, IL-1 blockade by Anakinra corresponding to IL-1Ra or IL-1β Ab attenuate the inflammatory lung pathology and emphysema. Finally, elastase-induced injury leads to the local release of uric acid from dying cells, which activates the NALP3-ASC inflammasome and caspase-1 with the cleavage of pro-IL-1β and release of IL-1β.

Therefore, upon elastase injury, IL-1β is produced, which is a critical mediator for several inflammatory pathologies (32, 33). A previous investigation reported that elastase-PPE-induced emphysema development is IL-1R1 independent (10). In this work, reduced inflammation is mentioned, but only a detailed morphological analysis of emphysema is presented. Emphysema was diminished in TNF-R1/R2 double-deficient mice, but not significantly reduced in IL-1R1-deficient mice (10). However, a nonsignificant reduction of emphysema at 21 days is apparent. The discrepancy of those data and our study may be due to technical differences such as dose of elastase, administration by intratracheal instillation, and the fact that IL-1R1-deficient mice were not backcrossed to a C57BL6 background (10). In favor of the hypothesis that IL-1β is critical for emphysema development is the fact that lung-specific expression of IL-1β causes chronic inflammation, tissue degradation, and emphysema (34).

Elastase-induced lung injury may lead to the degradation of the extracellular matrix glycosaminoglycan such as hyaluronan, elastin, collagens, and other matrix components inducing inflammation (35). Hyaluronan produced upon elastase injury might induce inflammation which is perpetuated in the absence of the hyaluronan scavenger receptor CD44, which clears hyaluronan (36). Because
TLR2 and TLR4 are both activated by hyaluronan in vitro (37–41), hyaluronan-dependent TLR activation may play a role in vivo inflammation. We investigated the requirement of individual TLRs for lung inflammation and repair and emphysema upon elastase exposure. Our data using several TLR-deficient mice suggest that TLR signaling is dispensable for elastase-induced lung injury (Table I and Fig. 2F). The inflammatory parameters assessed semiquantitatively (B), the linear intercept as a measure of emphysema (C), and lung collagen deposition (D) are reduced in Myd88- and Il-1r1-deficient mice. Results of a single study representative of three independent experiments are shown (n = 5–7 per group; *p < 0.05).

Proteases may cleave a multitude of peptides including elastin-derived peptides. The latter have chemoattractive activity, and Ab neutralization of elastin fragments prevented inflammation (43). Further, a tripeptide derived from extracellular matrix degradation has been reported to induce CXCR2-dependent lung inflammation (44). In addition, CXCR3 signaling appears to be nonredundant in elastase-induced inflammation and fibrosis (45). We show that elastase induced the CXC chemokine KC, confirming the notion that lung injury releases chemotactic mediators enhancing inflammation.

Protease activation is further required for the processing and secretion of the proinflammatory cytokines IL-1β and IL-1α in response to stress and danger signals (28). A new family of pathogen recognition receptors, the NLRs, may be involved as crucial innate sensors of danger signals and have a complementary role to the TLRs (9, 46). Oligomerization of NALPs activates inflammatory caspases within a complex known as the...
inflammasome leading to the processing and maturation of IL-1β and IL-18 (27–29). Therefore, activation of NALPs is critical to produce mature IL-1β in response to danger signals induced by acute lung injury. While the inflammatory response upon elastase injury appears to be TLR independent and TLR4 signaling may be protective (42), we find increased TNF and inflammatory mediators upon elastase exposure. Recent data suggest that TNF and NFκB activation may activate the NALP3 inflammasome and IL-1β production (47, 48).

Therefore we suggest the hypothesis that lung injury caused by elastase instillation activates the NALP3/ASC inflammasome. This activation requires at least two signals: The first signal may be conveyed by TLR activation or as postulated here by TNF leading to NALP3 expression and pro-IL-1β formation; The second signal is provided by uric acid from dying cells, which in its crystal form activates the NALP3-ASC inflammasome leading to caspase-1 activation and IL-1β release.

However, this interpretation of the data may not exclude alternative mechanisms such as activation by several other danger signals including hyaluronan and other degradation products, including tenasin (49), which may provide the signal 1, or extracellular ATP (50) in addition to uric acid crystals (23) presenting signal 2 with inflammasome activation cleaving pro-IL-1β and producing IL-1β.

Lastly, caspase-1-independent cleavage of pro-IL-1β has been investigated in elastase-induced acute lung injury and inflammation. There are differences in the cleavage sites of caspase-1 and elastase-1, but this does not exclude the possibility that pro-IL-1β could be cleaved. Incubation of cultured macrophages primed with LPS and then exposed to high concentrations of elastase-1-PPE overnight, however, did not induce the production of IL-1β (data not shown). Therefore, direct cleavage of pro-IL-1β by elastase would unlikely explain the production of IL-1β in elastase-induced injury and inflammation.

Finally, IL-1R1 blockade with either IL-1Ra (Anakinra) or neutralizing IL-1β Ab (data not shown) substantially attenuated lung inflammation and lung emphysema induced by elastase. IL-1Ra treatment is efficient in several human IL-1-associated inflammatory diseases (51), suggesting a therapeutic benefit in chronic lung inflammation such as COPD with recurrent elastase-induced tissue destruction.

In conclusion, we propose that elastase injury causing cell death with the local production of uric acid, an established danger signal is produced, activating the ASC inflammasome, activating caspase-1 with IL-1β production. We demonstrate that IL-1β is critical for acute inflammation and emphysema development upon elastase lung injury. Therefore, the present data point to the importance of IL-1β and IL-1R1 signaling as potential therapeutic targets in inflammatory and emphysematous lung disease.

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Disclosures
The authors have no financial conflict of interest.

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