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Full paper

Soluble form of the receptor for advanced glycation end-products attenuates inflammatory pathogenesis in a rat model of lipopolysaccharide-induced lung injury

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A B S T R A C T

Acute respiratory distress syndrome (ARDS) is a severe respiratory failure caused by acute lung inflammation. Recently, the receptor for advanced glycation end-products (RAGE) has attracted attention in the lung inflammatory response. However, the function of soluble form of RAGE (sRAGE), which is composed of an extracellular domain of RAGE, in ARDS remains elusive. Therefore, we investigated the dynamics of pulmonary sRAGE and the effects of exogenous recombinant human sRAGE (rsRAGE) under intratracheal lipopolysaccharide (LPS)-induced lung inflammation. Our result revealed that RAGE was highly expressed on the alveolar type I epithelial cells in the healthy rat lung including sRAGE isoform sized 45 kDa. Under LPS-induced injured lung, the release of sRAGE into the alveolar space was increased, whereas the expression of RAGE was decreased with alveolar disruption. Treatment of the injured lung with rsRAGE significantly suppressed the lung edema, the neutrophils infiltration, the release of high mobility group box-1 (HMGB1), and the expressions of TNF-α, IL-1β and iNOS. These results suggest that the alveolar release of sRAGE may play a protective role against HMGB1 as well as exogenous pathogen-associated molecular patterns. Supplementary therapy with sRAGE may be an effective therapeutic strategy for ARDS.

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1. Introduction

Acute respiratory distress syndrome (ARDS) is characterized by the rapid onset of life-threatening respiratory failure as a consequence of severe acute inflammatory diseases (1). ARDS are induced by a diverse range of risk factors, including direct lung injury (e.g., bacterial or viral pneumonia, lung contusion, or toxic inhalation) and indirect lung injury induced by systemic insults (e.g., sepsis, burn, or pancreatitis) (2). The infiltrated neutrophils and macrophages exacerbate the lung inflammation by releasing pro-inflammatory mediators and reactive oxygen species, activating proteolytic enzymes, and so on (3). The pathophysiology of severe pulmonary inflammation is characterized by diffuse alveolar damage, alveolar capillary leakage, and protein rich pulmonary edema with alveolar epithelial and endothelial injury (3,4). Despite our current knowledge of the pathophysiology of ARDS, as described above, and the various therapeutic strategies that have been examined, there remains no established therapy for clinical use (4).

In 1992, an advanced glycation end-products (AGEs)-binding protein was initially purified and identified from the bovine lung and designated a receptor for AGEs (RAGE) (5). RAGE is a single

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transmembrane receptor that is composed of an extracellular ligand-binding domain, a transmembrane domain, and a short cytoplasmic domain which is essential for signal transduction (6,7). Moreover, RAGE has a soluble form protein (soluble RAGE (sRAGE)) composed of an extracellular ligand-binding domain without the transmembrane and cytoplasmic domains (7).

RAGE can bind to not only AGEs but also endogenous damage-associated molecular patterns (DAMPs) such as high mobility group box-1 (HMGB1), several members of the S100 protein family, amyloid β peptide, β2-integrin and pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharide (LPS) (8,9). In addition, RAGE is considered to be a typical pattern-recognition receptors (PRRs), with potential similarity to members of the toll-like receptors (TLRs) family in the innate immune system as a first line of host defense (10,11).

It is particularly worth noting that RAGE is constitutively and predominantly expressed in the lung at high levels, whereas it is expressed at low levels in almost all cells under normal conditions (12). Therefore, it is considered that RAGE may have an important function in lung homeostasis (13).

Recently, it has been reported that sRAGE levels are increased in the plasma and bronchoalveolar lavage fluid (BALF) of rodent models and human patients with ARDS (14). In particular, sRAGE release into BALF may be a good biomarker to estimate the severity of lung injury (15). However, the physiological function of sRAGE remains elusive. *In vivo* experiments using a lung injury model have been inconsistent and controversial in terms of the protective effects of sRAGE (16,17).

In the present study, we investigated the *in vivo* effects of purified recombinant human sRAGE (rsRAGE) administered intratracheally to a rat model of LPS-induced lung injury, and the underlying mechanism of its anti-inflammatory actions in the environment of the injured lung.

2. Material and methods

2.1. Animals and LPS-induced lung injury model

All animal protocols were approved and conducted according to the recommendations of the Okayama University Animal Care and Use Committee. Male Wistar rats at 8–11 weeks old and weighing 300 ± 50 g were purchased from Japan SLC (Shizuoka, Japan) or Japan Charles River (Yokohama, Japan). The LPS-induced lung injury model was established according to the method described previously (14). Under anesthesia, LPS (*Escherichia coli* O111:B4) (Sigma–Aldrich, St. Louis, MO, USA) at 5 mg/kg as a solution of 5 mg/mL or an equivalent volume of saline as a vehicle control was administered intratracheally through a catheter. Rats were sacrificed to obtain tissue samples at 0.5, 6, 24, and 48 h after LPS-induced lung injury. To evaluate the *in vivo* effects of rsRAGE for LPS-induced lung injury, rats were also intratracheally treated with rsRAGE at 1 mg/kg as a solution of 1 mg/mL or an equivalent dose of human serum albumin (HSA) (Sigma–Aldrich) as a protein control after 1 h of LPS-induced lung injury.

2.2. Purification of recombinant human soluble RAGE

rsRAGE was produced by the method as previously described (18).

2.3. BALF analysis

Twenty-four hours after LPS administration, BALF was collected by irrigating the lung 3 times with 5 mL of cold saline for analysis.

2.4. Immunoblot analysis

Immunoblot analysis was performed to detect the RAGE by using the antibody against rsRAGE, which was house-made and raised in a rabbit, and detected both the soluble isoform and transmembrane isoform.

2.5. Immunohistochemistry

Immunohistochemical staining was performed as previously described (19) using antibody against rsRAGE, Podoplanin (Acris, San Diego, CA, USA), P180 LBP (Abcam, Cambridge, UK), CD68 (Abcam), Myeloperoxidase (MPO) (Abcam) and HMGB1 (Abcam and R&D, Minneapolis, MN, USA).

2.6. Measurement of HMGB1 by ELISA

A sensitive and specific anti-HMGB1 monoclonal antibody-based sandwich enzyme-linked immunosorbent assay (ELISA) was established. The capture and detection antibodies were produced by our group as described previously (19).

2.7. Naphthol AS-D chloroacetate esterase stain

Naphthol AS-D chloroacetate esterase stain was performed to count the infiltrating active neutrophils as previously described (20).

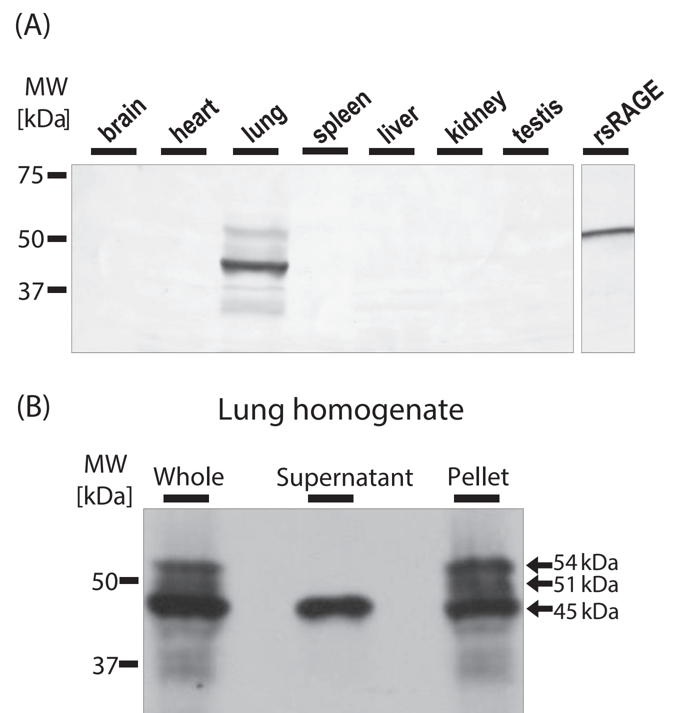

Fig. 1. Tissue distribution of RAGE isoforms in normal rat tissues. (A) Tissue homogenates were prepared from normal rat organs including lung tissue and subjected to immunoblot analysis with anti-rsRAGE antibody. RAGE isoforms in the indicated organs were detected by using a DAB reaction (A) or ECL system (B). Purified rsRAGE with 6 tandem histidine-tags was used as a positive control in (A). The left lane in (B) shows the result when loading a whole fraction of the lung homogenate, including the insoluble components of the plasma membrane, and the middle lane the result for a supernatant fraction including only soluble components. The right lane in (B) shows the result when loading a pellet fraction including the insoluble fraction.

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