News Release

Title

C-type lectin Mincle mediates cell death–triggered inflammation in acute kidney injury

Key Points

- **Mincle deficiency protected against tubular cell death and subsequent renal atrophy in a mouse model of acute kidney injury**
- **We identified β-glucosylceramide as an endogenous Mincle ligand in the injured kidney, which showed synergistic effects on Mincle in combination with free cholesterol**
- **Mincle suppressed clearance of dead cells as well as increased proinflammatory cytokine expression in macrophages**

Summary

Accumulating evidence indicates that cell death triggers sterile inflammation and impaired clearance of dead cells causes non-resolving inflammation, however the underlying mechanisms are still unclear. Here we show that Mincle senses renal tubular cell death to induce sustained inflammation after acute kidney injury in mice. Mincle-deficient mice were protected against tissue damage and subsequent atrophy of the kidney after ischemia–reperfusion injury. Using lipophilic extract from the injured kidney, we identified β-glucosylceramide as an endogenous Mincle ligand. Notably, free cholesterol markedly enhanced the agonistic effect of β-glucosylceramide on Mincle. Moreover, β-glucosylceramide and free cholesterol accumulated in dead renal tubules in proximity to Mincle-expressing macrophages, where Mincle was supposed to inhibit clearance of dead cells and increase proinflammatory cytokine production. This study demonstrates that β-glucosylceramide, in combination with free cholesterol, acts on Mincle as an endogenous ligand to induce cell death–triggered sustained inflammation after acute kidney injury.

Research Background

Macrophage-inducible C-type lectin (Mincle) is a pattern recognition receptor expressed in innate immune cells such as macrophages. Recent studies revealed the role of Mincle in infectious diseases; it recognizes trehalose-6, 6'-dimycolate (TDM), a mycobacterial cell wall glycolipid, to induce production of proinflammatory cytokines and chemokines, and thus protects against Mycobacterium tuberculosis infection. Mincle also senses cell death, suggesting a role in sterile inflammation. In this regard, we previously reported that Mincle expression is localized to macrophages surrounding dead or dying adipocytes during the development of obesity, where Mincle accelerates adipocyte death–triggered chronic inflammation in visceral adipose tissue to induce systemic insulin resistance. However, little is known about how Mincle recognizes dead cells under pathological conditions *in vivo* and how Mincle regulates necroinflammation.

Research Results

In this study, we showed that Mincle deficiency protected against tissue damage and subsequent atrophy of the kidney after ischemia–reperfusion injury, an experimental model of ischemic acute kidney injury. Non-target lipidomics analysis using lipophilic extract from the injured kidney revealed that β-glucosylceramide is an endogenous Mincle ligand in the acute kidney injury model. Interestingly, free cholesterol markedly enhanced β-glucosylceramide-induced Mincle activation, although free cholesterol *per se* did not directly act on murine Mincle. Moreover, Mincle expression was localized to macrophages in proximity to dead renal tubules, where β-glucosylceramide and free cholesterol accumulated. As a molecular mechanism, Mincle induced proinflammatory cytokine production and inhibited dead cell clearance in macrophages, which would contribute to sustained inflammation and renal atrophy.

Research Summary and Future Perspective

In this study, we demonstrated that Mincle induces proinflammatory cytokine production and inhibits dead cell clearance, which forms a vicious cycle between dead tubular cells and macrophages, thereby aggravating inflammation in acute kidney injury. Although acute kidney injury results from various etiologies, including ischemic and toxic insults, the close interaction between severely damaged or dead tubules and immune cells is a common pathogenesis in the reparative phase after an acute destructive event. Because it is clinically difficult to intervene in the acute phase of acute kidney injury (or initial tubular damage), Mincle would be a rational therapeutic target for ameliorating the subsequent progression from acute kidney injury to chronic kidney disease.

Publication

Authors:
Miyako Tanaka[1,2], Marie Saka-Tanaka[1,3], Kozue Ochi[1,2], Kumiko Fujieda[1,2], Yuki Sugiura[4], Tomofumi Miyamoto[5], Hiro Kohda[1,2], Ayaka Ito[1,2], Taiki Miyazawa[6], Akira Matsumoto[6], Seiichiro Aoe[7], Yoshihiro Miyamoto[8], Naotake Tsuboi[3,9], Shoichi Maruyama[3], Makoto Suematsu[4], Sho

Yamasaki[10], Yoshihiro Ogawa[1,11-13], Takayoshi Suganami[1,2]

Institutional Affiliations:

1 Department of Molecular Medicine and Metabolism, Research Institute of Environmental Medicine, Nagoya University, Nagoya, Japan.

2 Department of Immunometabolism, Nagoya University Graduate School of Medicine, Nagoya, Japan.

3 Department of Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Japan.

4 Department of Biochemistry, Keio University School of Medicine, Tokyo, Japan.

5 Department of Natural Products Chemistry, Graduate School of Pharmaceutical Sciences, Kyushu University, Fukuoka, Japan.

6 Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University, Tokyo, Japan.

7 Department of Home Economics, Otsuma Women's University, Tokyo, Japan.

8 Division of Genomic Diagnosis and Healthcare, National Cerebral and Cardiovascular Center, Suita, Japan.

9 Department of Nephrology, Fujita Health University School of Medicine, Toyoake, Japan.

10 Department of Molecular Immunology, Research Institute for Microbial Diseases, Osaka University, Osaka, Japan.

11 Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

12 Department of Molecular and Cellular Metabolism, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan.

13 Japan Agency for Medical Research and Development, CREST, Tokyo, Japan.

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