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Brief Communication

Caspse-11-GSDMD pathway is required for serum ferritin secretion in sepsis

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ABSTRACT

Ferritin is the major iron storage molecule of vertebrates, which can be detected in serum under numerous conditions, including inflammatory, neurodegenerative, and malignant diseases. Given this character, serum ferritin is frequently used as a biomarker in clinical settings. How the ferritin secreted to the serum has attracted much attention. Although some studies have found ferritin was mediated via the endoplasmic reticulum (ER)-Golgi secretion pathway or secretory lysosomes trafficking pathway under normal conditions, the secretion pathway of ferritin under pathological conditions, especially in sepsis is not very clear. In this report, we adopt a murine sepsis model to study the secretion pathway of ferritin in sepsis. We demonstrated caspase-11-GSDMD pathway and associated pyroptosis are required for secretion of ferritin in vitro and in vivo in sepsis. Moreover, our work connects pyroptosis to serum ferritin secretion and suggests a passive release process of ferritin, enhancing our understanding of the mechanism of ferritin secretion.

1. Introduction

Ferritin in mammals is a cytosolic iron-storage and detoxification protein that stores iron atoms in a soluble but bioavailable form[1–3]. It consists of H-and L-subunits that assemble into a 24-subunit multimer in which iron is sequestered[4]. Ferritin plays a pivotal role to keep tissue iron homeostasis, which is crucial to oxygen transport, energy production, and erythropoiesis[5,6]. Ferritin can be also found extracellularly in blood and other body fluids, termed serum ferritin[7–9]. In serum, ferritin serves in the differential diagnosis of anemia and as an indicator for numerous conditions, including inflammatory, neurodegenerative, and malignant diseases[10]. However, little is known about the mechanisms underlying ferritin intracellular trafficking and secretion. Although previous work suggested ferritin is secreted through the ER-Golgi route[11,12], recently, Truman-Rosentsvit M et al. [7,13] demonstrated ferritin can also be secreted via secretory lysosomes or endolysosomal trafficking. These studies all trace the ferritin secretion under the normal or physiological condition, while no study observe the ferritin secretion under the pathological conditions, especially in inflammation.

Sepsis is defined as a life-threatening organ dysfunction caused by a host's dysregulation of infection[14,15]. Numerous studies showed that serum ferritin was significantly associated with unfavorable outcomes in septic patients and regarded as an early marker of severity in pediatric sepsis[16,17], providing a strong link between sepsis and serum ferritin. How serum ferritin secreted in sepsis is quite fascinating to explore. Nowadays, caspase-11-gasdermin D (GSDMD) mediated pyroptosis is considered to play a major role in sepsis[18–20]. Whether this pathway contribute to the secretion of serum ferritin in sepsis attracts our interests.

In this study, we adopt a murine sepsis model to study the secretion pathway of ferritin in sepsis. We demonstrated caspase-11-GSDMD pathway and associated pyroptosis are required for secretion of ferritin in vitro and in vivo in sepsis. Thus, our results connect pyroptosis to

Abbreviations: ATP, adenosine triphosphate; CTB, cholera toxin B; DAMP, damage-associated molecule pattern molecule; ER, endoplasmic reticulum; GSDMD, gasdermin D; LDH, lactate dehydrogenase; IL-1β, interleukin-1β; MSU, monosodium urate monohydrate; NLRP3, NLR family pyrin domain-containing 3; TLR 4, toll-like receptor 4; TNF-α, tumor necrosis factor-α; WT, wild-type

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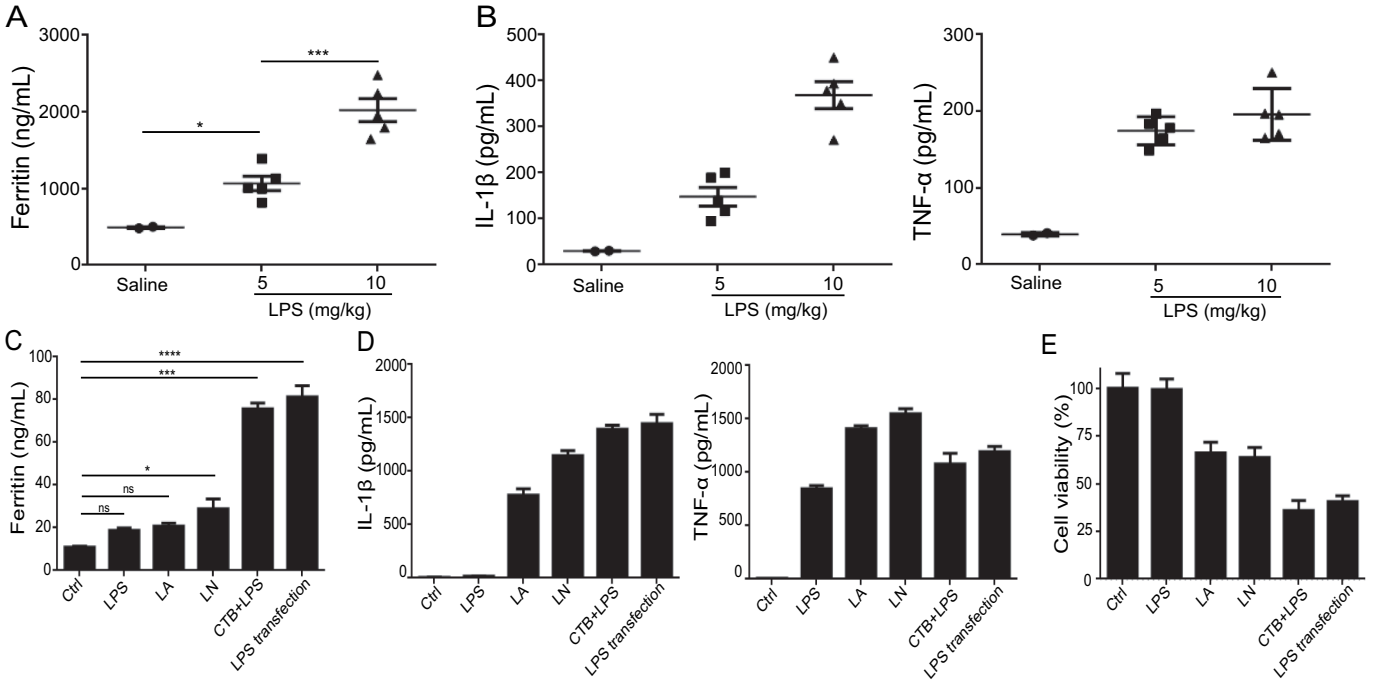

Fig. 1. The secretion of ferritin is detected in murine sepsis model.
LPS 5 mg/kg or 10 mg/kg were injected intraperitoneally to induce endotoxemia model, and serum were collected 12 h later. Serum ferritin level (A), serum IL-1β and TNF-α level (B) were detected by ELISA. Macrophages from WT mice were stimulated by ATP (5 mM, 1 h) or Nigericin (10 μM, 1 h) after LPS (100 ng/mL, 3 h) priming to activate canonical NLRP3 inflammasome. LPS (100 ng/mL) treated 4 h to activate TLR4. LPS (2 μg/mL) combined with CTB (5 μg/mL), and LPS (2 μg/mL) transfected with FuGENE HD (0.25% v/v) for 16 h to activate non-canonical pathway. The ferritin (C), IL-1β, TNF-α (D) in supernatant of culture were measured by ELISA, cell viability (E) was determined by CellTiterGlo Luminescent Cell Viability Assay. Data are representative of three independent experiments with n = 5 (A-B) or 3 (C-E) technical replicates (shown as mean and s.e.m. in A-E). $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

serum ferritin secretion and suggest a passively release process of ferritin, enhancing our understanding of the mechanism of ferritin secretion.

2. Material and methods

2.1. Mice and reagents

The NLRP3−/− and ASC−/−mice were generous gifts from Dr. Rongbin Zhou. GSDMD−/−mice were generous gifts from Dr. Jiahuai Han. Caspase-11−/− mice on a C57BL/6 background were generous gifts from Dr. Timothy R. Billiar. Wild-type (WT) C57BL/6 mice were purchased from Hunan SJA Laboratory Animal Co.Ltd. (Changsha, China). All mice used in our experiments were 8-week-old male mice. All animal experiments were undertaken in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals with the approval of the Institutional Animal Care and Use Committees of the Central South University. Ultra-pure lipopolysaccharide (LPS) for treating cells, adenosine triphosphate (ATP) and Nigericin were obtained from Invivogen. LPS 0111: B4 for animal studies was from Sigma. FuGENE HD transfection reagent was from PROMEGA. Cholera toxin B (CTB) was purchased from Sigma. Ferritin Mouse ELISA Kit (ab157712) was purchased from abcam. Mouse interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) ELISA kit were purchased from eBioscience. CytoTox 96 Non-Radioactive Cytotoxicity Assay kit and CellTiterGlo Luminescent Cell Viability Assay were purchased from Promega.

2.2. Macrophages preparation and stimulation

Mouse peritoneal macrophages were isolated in 10% sucrose following injection of 3 mL 3% thioglycolate intraperitoneally 72 h later. Cells were cultured in RPMI 1640 medium with 10% FBS, 1% penicillin-streptomycin. 5 × 10^5 peritoneal macrophages, plated in 24-well plates, were treated with LPS (2 μg/mL) combined with CTB (5 μg/mL), or LPS (2 μg/mL) transfected with FuGENE HD (0.25% *v*/v) for 16 h to activate caspase-11. To stimulate NLR family pyrin domain-containing 3 (NLRP3) inflammasome, macrophages were stimulated with ATP (5 mM, 1 h), Nigericin (10 μM, 1 h) after priming with LPS (100 ng/mL) for 3 h. To prevent pyroptosis-associated membrane rupture, 5 mM glycine (Sigma-Aldrich) was added to cells at the time of stimulations.

2.3. Cytotoxicity assay and ELISA

Relevant cells were treated as indicated. Cell death was measured by CytoTox 96 Non-Radioactive Cytotoxicity Assay kit. Cell viability was determined by CellTiterGlo Luminescent Cell Viability Assay. Levels of IL-1β, TNF-α and ferritin in the culture medium or mice serum were measured using quantitative ELISA kits according to the manufacture's instructions.

2.4. Statistical analysis

Significance of difference between groups was determined by two-tailed Students *t*-test. A *p*-value < .05 was considered statistically significant for all experiments. All values are presented as the mean ± SEM of at least three independent experiments.

3. Results

3.1. Serum ferritin is induced in murine sepsis model

To explore the secretion pathway of serum ferritin in sepsis, we

firstly adopted LPS-induced endotoxemia model of mice to monitor the variation of serum ferritin in vivo. We used two different doses of LPS, 5 mg/kg or 10 mg/kg, to intraperitoneally inject mice and collected the serum 12 h later. As the results showed, the serum ferritin level increased following LPS increasing (Fig. 1A), complementary to the study in human, where the serum ferritin level is correlated to the severity of sepsis[16,17]. TNF-α and IL-1β were the inflammatory indicators (Fig. 1B). These results suggest serum ferritin can be induced in mice sepsis model, which is very suitable for further exploring the secretion pathway of serum ferritin in sepsis.

3.2. Non-canonical inflammasome agonists promote the secretion of ferritin in macrophages

Previous studies proved macrophages were the major cellular source of serum ferritin [7], accordingly, we chose macrophages to further explore the secretion pathway of serum ferritin in sepsis in vitro. Except for LPS/toll-like receptor 4 (TLR4) signaling which has been revealed in sepsis for about 20 years[21], recently, NLRP3 inflammasome and caspase-11 induced non- canonical inflammasome are recognized to contribute to the pathologic process of sepsis[22,23], so three kinds of agonists: TLR4 agonists (LPS); NLRP3 agonists (LPS + ATP; LPS + Nigericin) and non-canonical inflammasome agonists (LPS + CTB; LPS transfection) were used to stimulate macrophages and the ferritin level in supernatant were detected. We found only non-canonical inflammasome agonists could induce the significant increase of ferritin level, while the other two has little promotion effect (Fig. 1C). IL-1β and TNF-α expression were also detected (Fig. 1D). Cell viability was assessed by the CellTiterGlo Luminescent assay (Fig. 1E). Thus, our data suggests that non-canonical inflammasome activation majorly contributes to the secretion of ferritin in macrophages.

3.3. Caspase-11 is required for ferritin secretion in sepsis in vitro and in vivo

To further investigate the role of non-canonical inflammasome in ferritin secretion in macrophages upon sepsis, the caspase-11 knockout mice were applied to sepsis model in vitro and in vivo. We challenged primary macrophages with three kinds of agonists, which were mentioned in Fig. 1C. We found that the non-canonical inflammasome agonists had no promoting effect on ferritin secretion while induced less cell death in macrophages from caspase-11 knockout mice compared to WT mice (Fig. 2A/B), implying that ferritin secretion is correlated with pyroptosis. Moreover, when we adopt the sepsis model in vivo, we also hardly detected the serum ferritin from caspase-11 knockout mice compared to WT mice (Fig. 2D). IL-1β and TNF-α expression were detected to judge whether the inflammatory responses (Fig. 2C) or sepsis model (Fig. 2E) was successful. Taken together, these results demonstrate that caspase-11 induced non-canonical inflammasome is required for the serum ferritin secretion in sepsis in vitro and in vivo.

3.4. Caspase-11-GSDMD pathway and associated pyroptosis contribute to the serum ferritin secretion in sepsis

Caspase-11 was reported to cleave GSDMD to trigger pyroptosis or NLRP3-dependent caspase-1 activation [18–20]. To explore which pathway plays the key role in serum ferritin production after caspase-11 activation, caspase-11, GSDMD, NLRP3, and ASC deficient mice were applied to sepsis model to detect serum ferritin level. As the results showed, the serum ferritin level declined significantly in GSDMD and caspase11 deficient mice compared with WT mice, while the serum ferritin in NLRP3 and ASC deficient mice had no significant difference from WT mice (Fig. 2F). The IL-1β and TNF-α expression were also

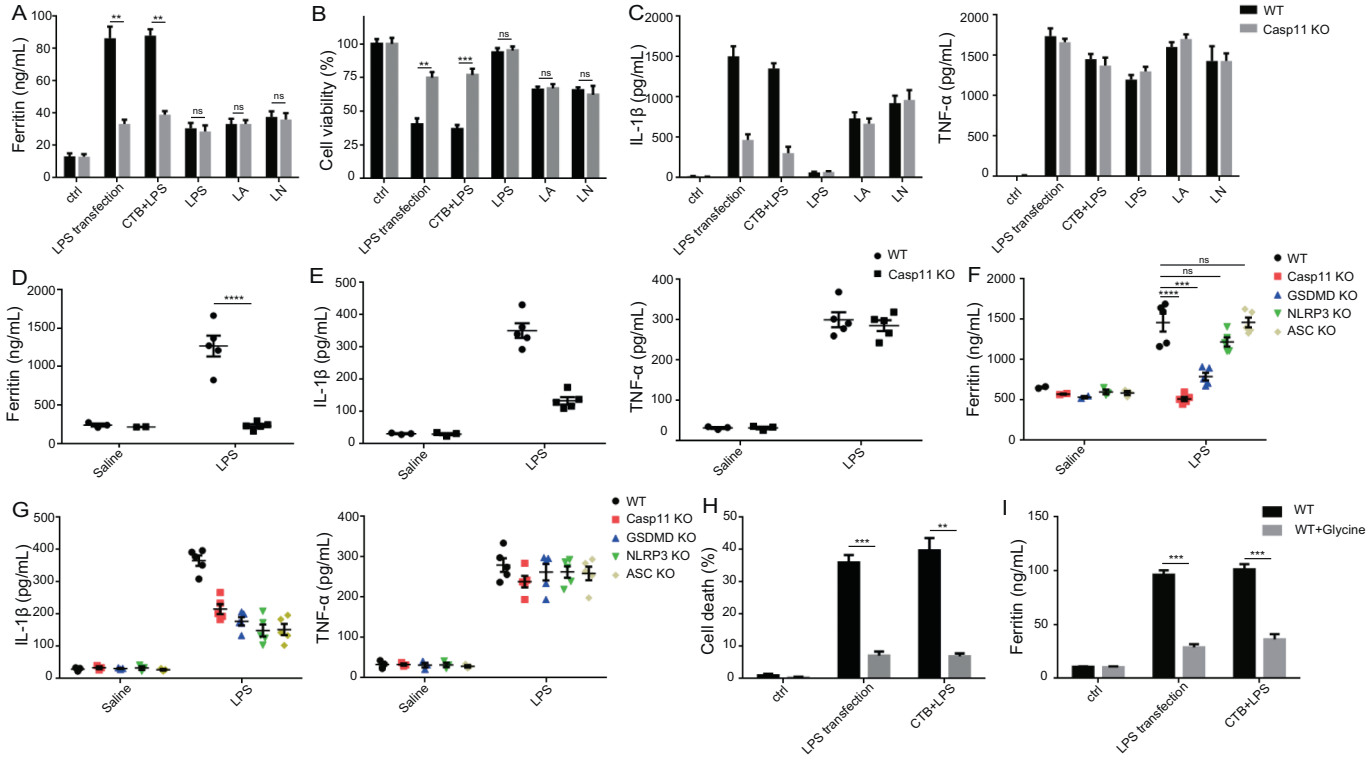

Fig. 2. Caspase-11-GSDMD pathway contributes to the secretion of ferritin in sepsis Macrophages from WT or caspase-11 knockout mice were stimulated by the indicated agonists as used in Fig. 1. The ferritin (A), cell viability (B), IL-1β and TNF-α (C) were measured. Serum samples were collected 12 h after intraperitoneal injection of 10 mg/kg LPS into mice as indicated, serum ferritin level (D, F), serum IL-1β and TNF-α level (E, G) were detected by ELISA. Macrophages were treated with non-canonical pathway agonists and added 0 mM Glycine or 5 mM Glycine simultaneously, LDH (H) and ferritin (I) present in the extracellular media were then quantified. Data are representative of three independent experiments with $n = 3$ (A, C, H, I), $n = 4$ (B) or 5 (D-G) technical replicates (shown as mean and s.e.m. in A-I). $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

detected (Fig. 2G). In addition, we utilized glycine, which was reported to prevent pyroptosis-associated membrane rupture [24,25] to further study the relationship between ferritin secretion and pyroptosis. As the results showed that glycine reduced the LDH release (Fig. 2H) and ferritin level (Fig. 2I) in supernatant of macrophages upon non-canonical inflammasome agonists stimulation, suggesting pyroptosis cause the ferritin secretion under sepsis. Taken together, our data further suggest that caspase-11-GSDMD pathway and associated pyroptosis contribute to serum ferritin secretion.

4. Discussion

Accumulated clinical data have indicated that serum ferritin is closely correlated to the severity of sepsis, although from 20 years ago, researchers have given more attention to the cellular source of ferritin and its secretion pathway [7,11–13], no one has revealed the secretion pathway of serum ferritin in sepsis. In our study, we adopt a murine sepsis model by injecting LPS intraperitoneally to the mouse to track the serum ferritin. Our results showed that serum ferritin level elevated following LPS increasing in vivo. In addition, macrophages, which are the main source of ferritin, when stimulated with non-canonical inflammasome agonists produced the most amount of ferritin, while stimulated with TLR4 or NLRP3 inflammasome agonists, produced little. Furthermore, we demonstrated that the capase-11-GSDMD pathway and associated pyroptosis (an inflammatory form of death) are required for the secretion of serum ferritin in sepsis in vitro and in vivo. Therefore, our findings firstly uncover a novel mechanism of serum ferritin secretion in sepsis.

Ferritin is known as the most important intracellular iron-storage protein in mammalian organisms [1–3]. Increased ferritin could prevent host against infection via depriving bacterial growth of iron and protecting immune cell function [26,27]. Previous studies showed serum ferritin level increased dramatically during sepsis, and it was related to unfavorable outcome of sepsis [16,17]. In our work, the serum ferritin level ascended significantly in a dose dependent manner during LPS-induced sepsis model, supporting the clinical research and indicated serum ferritin may be a good marker to reflect the severity of sepsis.

Although hepatocytes and macrophages have been suggested as cellular sources of ferritin, macrophages are the main cellular source of serum ferritins in mice [7,28]. So in our work, we only chose macrophages to study in vitro, but we could not exclude the role of hepatocytes in secretion of serum ferritin in vivo. Our recent work suggests while in sepsis, hepatocytes produce large amounts of HMGB1, the latter facilitate the uptake of LPS into lysosomes of myeloid cells, then contribute to the activation of caspase-11 [29]. Accordingly, we speculate that both kinds of cells have contribution to the serum ferritin secretion in sepsis, as hepatocytes promote the caspase-11 activation in macrophages. The crosstalk between the two cells in serum ferritin secretion in sepsis remains further investigation.

Numerous studies have focused on the secretion pathway of serum ferritin, while some implies the classical ER-Golgi secretion are the main pathway of ferritin secretion[11,12], the others indicates ferritin secreted via secretory lysosomes or endolysosomal trafficking, suggesting multiple exporting routes[7,13]. Although the work gives some details of serum ferritin secretion, they were all carried on under normal conditions, the pathway of ferritin secretion in pathological conditions such as in sepsis, is not very clear. Based on this, our work demonstrated caspase-11-GSDMD signaling is required for the serum ferritin secretion. Caspase-11-GSDMD signaling is newly discovered for its great role in sepsis, caspase-11 could be activated by cytoplasmic LPS directly and then maturate GSDMD or NLRP3-dependent caspase-1 activation to induce pore formation on plasma membrane or promote IL-1β production [18–20, 30-32]. In our study, we demonstrated caspase-11-GSDMD, other than caspase-11-NLRP3, is more required for ferritin secretion, and when using glycine to prevent pyroptosis-associated membrane rupture, the ferritin level is decreased, suggesting caspase-11-GSDMD mediated pyroptosis is the main pathway. Pyrotosis is considered to be an inflammasome-dependent cell death, and mainly documented to occur in professional phagocytes of the myeloid lineage, such as macrophages [23]. While cells underwent pyroptosis, the danger-associated molecular patterns (DAMPs) could be released, such as IL-1α, HMGB1 [23]. In our findings, serum ferritin secretion in sepsis is dependent on pyroptosis, suggesting ferritin secretion is a passive release process in sepsis, rather than active release. It is different from secretion under normal conditions, giving a new sight for serum ferritin secretion. But for the secretion form of ferritin in sepsis, our study did not give more details, previous work suggests ferritin is in the vesicular compartments of the cell [13], then we wonder whether ferritin secretion in sepsis is in the form of a vesicle, then passive released to the serum. This suppose needs future study.

5. Conclusions

In conclusion, our study demonstrates that caspase-11-GSDMD pathway and associated pyroptosis are required for the ferritin secreting to serum in sepsis, which is the first time to reveal the ferritin secretion under pathological conditions. Our work also connects pyroptosis to serum ferritin secretion and suggests a passive release process of ferritin, enhancing our understanding of the mechanism of ferritin secretion.

LPS 5 mg/kg or 10 mg/kg were injected intraperitoneally to induce endotoxemia model, and serum were collected 12 h later. Serum ferritin level (A), serum IL-1β and TNF-α level (B) were detected by ELISA. Macrophages from WT mice were stimulated by ATP (5 mM, 1 h) or Nigericin (10 μM, 1 h) after LPS (100 ng/mL, 3 h) priming to activate canonical NLRP3 inflammasome. LPS (100 ng/mL) treated 4 h to activate TLR4. LPS (2 μg/mL) combined with CTB (5 μg/mL), and LPS (2 μg/mL) transfected with FuGENE HD (0.25% *v*/v) for 16 h to activate non-canonical pathway. The ferritin (C), IL-1β, TNF-α (D) in supernatant of culture were measured by ELISA, cell viability (E) was determined by CellTiterGlo Luminescent Cell Viability Assay. Data are representative of three independent experiments with $n = 5$ (A-B) or 3 (C-E) technical replicates (shown as mean and s.e.m. in A-E). $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

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Conflict of interest statement

None of the authors has any potential financial conflict of interest related to this manuscript.

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