Salmonella-Infected Aortic Aneurysm: Investigating Pathogenesis Using Salmonella Serotypes

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Abstract

Salmonella infection is most common in patients with infected aortic aneurysm, especially in Asia. When the aortic wall is heavily atherosclerotic, the intima is vulnerable to invasion by Salmonella, leading to the development of infected aortic aneurysm. By using THP-1 macrophage-derived foam cells to mimic atherosclerosis, we investigated the role of three Salmonella enterica serotypes – Typhimurium, Enteritidis, and Choleraesuis – in foam cell autophagy and inflammasome formation. Herein, we provide possible pathogenesis of Salmonella-associated infected aortic aneurysms. Three S. enterica serotypes with or without virulence plasmid were studied. Through Western blotting, we investigated cell autophagy induction and inflammasome formation in Salmonella-infected THP-1 macrophage-derived foam cells, detected CD36 expression after Salmonella infection through flow cytometry, and measured interleukin (IL)-1β, IL-12, and interferon (IFN)-α levels through enzyme-linked immunosorbent assay. At 0.5 h after infection, plasmid-bearing S. Enteritidis OU7130 induced the highest foam cell autophagy – significantly higher than that induced by plasmid-less OU7067. However, plasmid-bearing S. Choleraesuis induced less foam cell autophagy than did its plasmid-less strain. In foam cells, plasmid-less Salmonella infection (particularly S. Choleraesuis OU7266 infection) led to higher CD36 expression than did plasmid-bearing strains infection. OU7130 and OU7266 infection induced the highest IL-1β secretion. OU7067-infected foam cells secreted the highest IL-12p35 level. Plasmid-bearing S. Typhimurium OU5045 induced a higher IFN-α level than did other Salmonella serotypes. Salmonella serotypes are correlated with foam cell autophagy and IL-1β secretion. Salmonella may affect the course of foam cells formation, or even aortic aneurysm, through autophagy.

Key words: Salmonella serotype, virulence plasmid, foam cell, autophagy, inflammasome

Introduction

A healthy aortic wall is highly resistant to infection. However, when its intima is diseased, such as in patients with atherosclerosis, the wall becomes susceptible to infection. Salmonella, the most common genus of the pathogen associated with infected aortic aneurysms, often infects preexisting atherosclerotic aortic aneurysms. Atherosclerosis is a chronic inflammatory, lipid-driven disease. The formation of macrophage foam cells in the arterial intima is a known hallmark of early-stage atherosclerosis lesions (Yu et al. 2013). Within the intimal layer, monocyte-derived macrophage subsequently takes up oxidized low-density lipoprotein (oxLDL) via type B scavenger receptors CD36 and scavenger receptor-A (SR-A), leading to cholesterol-laden foam cell formation (Bekkering et al. 2014).

Autophagy is an evolutionarily conserved process involved in bulk degradation of long-lived proteins and organelles through which these cytoplasmic components are sequestered within double-membrane vesicles, namely autophagosome followed by lysosomal degradation (Nishida et al. 2008; Martinet and De Meyer 2009). In general, this catabolic process is mediated by numerous autophagy and autophagy-related proteins. Two conjugation systems, Atg12-conjugation, and LC3

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(microtubule-associated protein light chain 3)-lipidation are essential for the dynamic process of autophagosome formation (Vural and Kehrl 2014). The conjugate of a phosphatidylethanolamine group to the carboxyl terminus of LC3-I to generate LC3-II, localized to outer and inner autophagosomal membranes, is useful as an autophagosomal marker.

Inflammasomes are important intracellular multiprotein complexes consisting of a cytosolic sensor belonging to the AIM2 (absent in melanoma 2), or NLR (NOD-like receptors), an adaptor protein ASC (an apoptosis-associated speck-like protein containing a CARD), and an effector caspase, primarily caspase-1. Inflammasomes which regulate the processing and releasing of mature pro-inflammatory cytokines interleukin-1β (IL-1β) and IL-18, are activated by a variety of PAMPs and DAMPs (Martinon et al. 2002). Caspase-1, caspase-4, and caspase-5 in humans are the inflammatory caspases that are activated through the stimulation of either the NLRC4 or NLRP3 inflammasome (Martinon and Tschopp 2007). In response to bacterial infection, NLRP3 and NLRC4 inflammasomes can lead to autolysosomal cleavage of caspase-1, followed by secretion of IL-1β and IL-18 resulting in pyroptosis (Bergsbaken et al. 2009). Autophagy and inflammasome are functionally interconnected; they both control cell homeostatic processes such as critically control inflammation and the clearance of pathogens (Seveau et al. 2015). Autophagy can directly regulate IL-1β activation, release, and signaling that are activated by inflamma-some (Sun et al. 2017; Wang et al. 2018).

Salmonella species are the most common pathogens of infected aortic aneurysm in Asia. Salmonella-associated infected aortic aneurysms have a more favorable therapeutic response to endovascular repair compared with those associated with other organisms (e.g., Staphylococcus, Streptococcus, and Enterococcus). We previously demonstrated that different serotypes of Salmonella may affect clinical outcomes (Huang et al. 2014a). In this study, we investigate the role of different serotypes of Salmonella enterica, including Typhimurium, Enteritidis, and Choleraesuis in foam cells autophagy and inflammasome during infection, and we provide possible pathogenesis of Salmonella-associated infected aortic aneurysms.

**Materials and Methods**

**Bacterial strains and growth conditions.** The bacterial strains used in this study are listed in Table I. The wild type strains of *S. enterica* serovar Typhimurium OU5045, *S. enterica* serovar Enteritidis OU7130, and *S. enterica* serovar Choleraesuis OU7085 carried 90-, 60-, and 50-kb virulence plasmids, respectively. We also used strains without a virulence plasmid: *S. Typhimurium* OU5046, *S. Enteritidis* OU7067, and *S. Chole-raesuis* OU7266. All bacterial strains used in this study were routinely grown on xylose lysine deoxycholate agar plate, and every single black colony was later grown in Luria-Bertani (LB) broth at 37°C overnight.

**Cell culture and differentiation.** The monocyte-like THP-1 cell line that derived from the peripheral blood of a childhood case of acute monocytic leukemia was obtained from the Bioresource Collection and Research Center, Taiwan. The cells were grown in RPMI 1640 (Sigma Aldrich, St. Louis, MO, R6504) supplemented with 10% preheated fetal bovine serum (FBS; Sigma Aldrich, St. Louis, MO), 2 mM L-glutamine (Sigma Aldrich, St. Louis, MO, G7513), 1% penicillin-streptomycin (Sigma Aldrich, St. Louis, MO, P0781). The cells were cultured at 37°C in 5% CO₂ and 70% humid-ity. The culture medium was changed every 3–4 days. The cell density was maintained between 2 × 10⁵ and 1 × 10⁶ cells/ml. Furthermore, 5 × 10⁹ THP-1 cells/10 ml were seeded in a 10-cm dish and differentiated using 10⁻³ M phorbol myristate acetate (PMA; Sigma Aldrich, St. Louis, MO, P8139) for 48 h at 37°C in 5% CO₂. For foam cell preparation, the differentiated THP-1 cells were treated with 50 μg/ml oxLDL (Biomedical Techno-

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**Table I**

| Serovars           | Strains          | Characteristics of virulence plasmid                    |
|--------------------|------------------|--------------------------------------------------------|
| S. Typhimurium     | OU5045           | With a 90-kb pSTV as a wild type                        |
|                    | OU5046           | Without pSTV from wild type                            |
| S. Enteritidis     | OU7130           | With a 60-kb pSEV as a wild type                        |
|                    | OU7067           | Without pSEV from wild type                            |
| S. Choleraesuis    | OU7085           | With a 50-kb pSCV as a wild type                        |
|                    | OU7266           | Without pSCV from wild type                            |
of 5 min each, the blots were incubated in commer-
cial ECL reagents (GE Healthcare Life Sciences) and
exposed to photographic film.

**Statistical analysis.** Statistical analyses were per-
formed using SPSS (version 18.0). To compare the dif-
terences between means (two samples), Student’s t-test
was used. Differences among multiple means were
assessed through two-factor analysis of variance, as
indicated by Tukey’s honestly significant difference test.

**Results**

**Plasmid-bearing S. Enteritidis induces more
macrophage autophagy.** To investigate macrophage
autophagy and inflammasome induction during the
infection of different serotypes of *Salmonella*, we
detected LC3 and apoptosis-associated speck-like
protein containing C-terminal caspase recruitment
domain (CARD) (ASC) expression of THP-1-derived
macrophages. Plasmid-bearing S. Enteritidis OU7130
induced significantly more macrophage autophagy
than did the plasmid-less strain OU7067 (Fig. 1A and
1B). Furthermore, plasmid-bearing S. Typhimurium
OU5045 showed a slightly higher ratio of macrophage
autophagy than did plasmid-less OU5046. However,
the trend of macrophage autophagy induced by plas-
id-bearing S. Choleraesuis OU7085 and plasmid-
less OU7266 contradicted that of the S. Typhimurium
strains. ASC protein induction did not significantly
differ among *Salmonella* serotypes. However, infec-
tion by all *Salmonella* serotypes, particularly plasmid-
bearing S. Typhimurium OU5045 and S. Enteritidis
OU7130, induced more of macrophage autophagy than
of inflammasome. The virulence plasmids of *Salmo-
rella* OU7130 are therefore likely involved in the induc-
tion of macrophage autophagy. *Salmonella*-induced macro-
phage autophagy may reduce inflammasome activity.

**Formation of macrophage foam cells, promoted by
oxLDL in the arterial intima, is a hallmark of athero-
sclerosis development (Bobryshev 2006; Yu et al. 2013).
To further investigate the induction of autophagy and
inflammasome in foam cells during infection with dif-
ferent serotypes of *Salmonella*, THP-1 macrophages
were transformed into foam cells through oxLDL
uptake. Among different *Salmonella* serotypes, plas-
id-bearing S. Enteritidis OU7130 showed most foam
cell autophagy, at a level significantly higher than that
demonstrated by plasmid-less strain OU7067 at 0.5 h
after infection (Fig. 1C and 1D). However, a contrary
trend, in which virulence plasmid-bearing strains
induced less foam cell autophagy than did plasmid-
less strains was observed for S. Choleraesuis infection.
ASC protein induction by different serotypes of *Salmo-
rella* demonstrated no significant difference. Consist-
ent with the high ratio of macrophage autophagy, the
virulence plasmid of S. Enteritidis OU7130 played a role in inducing both macrophage and foam cell autophagy. To assess the effect of *Salmonella* infection in foam cell autophagy and inflammasome at different infection stages, we detected LC3 and ASC expression at 0.5 and 2 h after infection. The ratio of foam cell autophagy significantly decreased from 0.5 to 2 h after infection, but the ratio of ASC expression did not change with infection time. Notably, the ratio of foam cell autophagy after plasmid-bearing *S. Choleraesuis* OU7085 infection increased from 0.5 to 2 h after infection, and ASC induction was higher than autophagy induction was at 0.5 h after infection. The mechanism used by plasmid-bearing *S. Choleraesuis* to induce autophagy is potentially different from that used by the other two *Salmonella* serotypes, *S. Enteritidis* and *S. Typhimurium*.

**Plasmid-less *Salmonella* strains enhance foam cell surface CD36 expression.** To understand infection by different serotypes *Salmonella* on foam cells within a preexisting atherosclerotic aortic aneurysm, we performed flow cytometric analysis and investigated CD36 expression in foam cells after *Salmonella* infection. CD36 functions as a high-affinity receptor responsible for oxLDL uptake by macrophages. The recognition and internalization of oxLDL particles by CD36, a specific macrophage scavenger receptor, is a critical step in foam cell formation (Rahaman et al. 2006). CD36 expression on foam cells infected by plasmid-less strains, particularly OU7266, was higher than that on those infected by plasmid-bearing strains (Table II and Fig. 2). The infection by plasmid-less *S. Choleraesuis* OU7266 induced foam cells to
express higher surface CD36 than did that by plasmid-bearing OU7085 to regulate foam cell autophagy. Notably, although plasmid-bearing *S*. Enteritidis OU7130 exhibited the lowest CD36 expression, even lower than that in the uninfected cells.

Plasmid-bearing *S*. Enteritidis and plasmid-less *S*. Cholerae suis enhance IL-1β secretion. Activation of the inflammasomes results in the processing and subsequent secretion of the pro-inflammatory cytokines IL-1β and IL-18. To determine IL-1β production after different serotypes of *Salmonella* infection, we performed ELISA to evaluate the IL-1β secretion of infected THP-1 foam cells. Plasmid-bearing *S*. Enteritidis OU7130 and plasmid-less *S*. Cholerae suis OU7266 induced significantly higher IL-1β secretion in foam cells than did plasmid-less *S*. Enteritidis OU7067 and plasmid-bearing *S*. Cholerae suis OU7085, respectively, at 0.5 and 2 hpi (Fig. 3). These results indicated that the virulence plasmid of *S*. Enteritidis is possibly demonstrated the most foam cell autophagy, it exhibited the lowest CD36 expression, even lower than that in the uninfected cells.

### Table II

| Sample          | %Parent | Mean  |
|----------------|---------|-------|
| Foam NC         | 4.5     | 2 594 |
| Foam NC-CD36 FITC | 5.4     | 8 796 |
| Foam 5045-CD36 FITC | 5.2     | 7 204 |
| Foam 5046-CD36 FITC | 7.7     | 11 194 |
| Foam 7130-CD36 FITC | 1.8     | 4 807 |
| Foam 7067-CD36 FITC | 6.3     | 3 204 |
| Foam 7085-CD36 FITC | 7.2     | 5 341 |
| Foam 7266-CD36 FITC | 9.6     | 11 067 |

Fig. 2. CD36 expression in THP-1 macrophage-derived foam cells after different serotypes *Salmonella* infection. After treated with ox-LDL, THP-1 macrophage-derived foam cells were infected with plasmid-bearing and -less *S*. Typhimurium, Enteritidis, and Cholerae suis, respectively. CD36 expression was analyzed through flow cytometry.
involved in IL-1β maturation during infection, whereas the virulence plasmid of S. Choleraesuis may play an opposite role.

**Salmonella**-infected foam cells secreted high IFN-α levels. The cytokine IL-12 is a potent inducer of T helper 1 (Th1) cell differentiation and is required for resistance against bacterial infections. It is mostly produced by activated hematopoietic phagocytic cells (e.g., monocytes, macrophages, and neutrophils) and is composed of two chains, p40 and p35 (Trinchieri et al. 2003). To detect IL-12 secretion by foam cells after *Salmonella* infection, we performed ELISA. IL-12p40 secretion levels did not differ among different *Salmonella* serotypes (Fig. 4A). Nevertheless, the plasmid-less *S. Enteritidis* OU7067-infected foam cells secreted the highest IL-12p35 level among other infected cells and uninfected cells (Fig. 4B). *S. Enteritidis* infection may play a role in Th1-mediated immune response by increasing IL-12p35 secretion. In addition to IL-12, type I IFNs, considered primary cytokines produced directly in response to microbial products, are key regulators of both innate and adaptive immune responses. Stimulation with gram-negative bacteria, including *S. Typhimurium*, induces type I IFN production (Mancuso et al. 2007). The IFN-α level was significantly higher in *Salmonella*-infected foam cells than it was in uninfected foam cells (Fig. 4C). In foam cells, IFN-α was strongly expressed 0.5 h after infection; however, the IFN-α level decreased 2 h after infection. Plasmid-bearing *S. Typhimurium* OU5045-infected foam cells exhibited the highest IFN-α level 2 h after infection, suggesting that plasmid-bearing *S. Typhimurium* induces a higher level of immune response than other *Salmonella* serotypes do.

**Discussion**

Unlike other pathogens that cause infected aortic aneurysms (e.g., *Staphylococcus* and *Pseudomonas*), *Salmonella* resides in the phagosomes of the host macrophages and other antigen-presenting cells. Notably, compared with the endovascular repair of aortic aneurysms infected by other pathogens, the endovascular repair of *Salmonella*-infected aortic aneurysms by using graft-stents leads to fewer recurrent prosthetic infections (Huang et al. 2014b). *Salmonella* species may propagate by decreasing the innate immunity of the host and induce a systemic inflammatory response, possibly leading to degenerative aortic aneurysms. Foam cell formation from stimulated macrophages is a characteristic of atherosclerotic vascular degeneration. In this study, we investigated autophagy and inflammasome induction in foam cells after infection with different *Salmonella* serotypes to mimic the clinical scenario of *Salmonella*-associated infected aortic aneurysms.

Macrophage autophagy plays a protective role in atherosclerosis (Liao et al. 2012). Autophagy prevents macrophage apoptosis and defective efferocytosis, both of which promote plaque necrosis in advanced atherosclerosis. In this study, virulence plasmid-bearing *S. Enteritidis* OU7130 induced the most foam cell autophagy, whereas plasmid-bearing *S. Cholerae suis* OU7085 induced the least foam cell autophagy. Infection by plasmid-bearing *S. Cholerae suis* OU7085 induced less autophagy than did its plasmid-less strain, potentially promoting atherosclerosis formation. By contrast, infection by plasmid-bearing *S. Enteritidis* OU7130 induced more autophagy than did its plas-
mid-less strain, likely providing negligible promotion of atherosclerosis formation. Sower and Whelan (1962) demonstrated that Salmonella was a common cause of infected aneurysms in patients with preexisting atherosclerosis. Wang et al. (1996) and Chan et al. (1995) have reported that the majority of infected aneurysms in Taiwan are caused by S. Choleraesuis. S. Choleraesuis may seed in atheroma and subsequently induce mycotic aortic aneurysm formation (Chiu et al. 2004). In addition, the virulence plasmid of S. Choleraesuis is possibly involved in inhibiting cell autophagy, causing the formation of atherosclerosis and infected aneurysm. A study also reported that most clinical isolates of S. Choleraesuis carry the virulence plasmid pSCV (Chu et al. 2001). Moreover, our clinical data from a previous study demonstrated that S. Choleraesuis affected surgical death and aneurysm-related death in a patient with infected aortic aneurysm (Huang et al. 2014a).

A crucial part of the innate immune response is the assembly of the inflammasome. Formation of the inflammasome in host cells in response to the detection of PAMPs facilitates the production of the proinflammatory cytokines IL-1β and IL-18 (Man et al. 2014). ASC is a signal adaptor protein that is recruited to canonical inflammasomes, whereupon ASC polymerizes into a large, "speck"-like complex (Bierschenk et al. 2019). ASC specks are also formed during noncanonical inflammasome signaling. In this study, we investigated the induction of inflammasome by detecting ASC expression and IL-1β secretion after Salmonella infection. We found that the ASC expression among different Salmonella serotypes infection was similar. Nevertheless, the secretion of IL-1β was highly induced after plasmid-bearing S. Enteritidis OU7130 and plasmid-less S. Choleraesuis OU7266 infection, suggesting that the activation of inflammasome was induced by different Salmonella serotypes with or without virulence plasmid. The similar ASC expression after different Salmonella serotypes infection indicates that the role of ASC may be dispensable for different Salmonella serotypes with or without virulence plasmid infection. In all, the data indicate that the virulence plasmid of S. Enteritidis OU7130 plays a role in stimulating inflammasome formation while virulence plasmid of S. Choleraesuis OU7266 plays a suppression role.

The proinflammatory cytokine IL-12, produced by macrophages in response to microbial pathogens, comprises an α-chain p35 and β-chain p40. In the activated IL-12-producing antigen-presenting cells, p35 chain production is generally lower than p40 chain production, making p35 molecule formation a rate-limiting step in the bioactive IL-12 formation process (Snijders et al. 1996). The level of bioactive IL-12 production in monocytes in response to lipopolysaccharide and cytokines is determined by the level of p35 expression. In this study, we investigated IL-12 expression after infection by different Salmonella serotypes, and we found that infection by plasmid-less S. Typhimurium

![Fig. 4. Cytokines expression in response to Salmonella infection. ELISA for (A) interleukin (IL)-12p40, (B) IL-12p35, and (C) IFN-α produced after infection by different Salmonella serotypes. THP-1 macrophage-derived foam cells were infected by Salmonella with or without virulence plasmids for 0.5 and 2 h, and the supernatants were harvested and used for experiments. All values are presented as means ± standard error (n = 3). * indicate significant differences between strains 0.5 h after infection (p < 0.05); ** indicate significant differences between strains 2 h after infection (p < 0.05). nc: uninfected cells.](image-url)
and S. Enteritidis induced higher expression of IL-12p35 than did their plasmid-bearing strains. Even after 2 h of infection, plasmid-bearing S. Enteritidis induced lower IL-12p35 expression than did its plasmid-less strain. However, the expression of IL-12p35 after S. Choleraesuis infection demonstrated the opposite trend. These findings imply that S. Typhimurium and S. Enteritidis may induce higher inflammatory response after contact with foam cell or immune cells. By contrast, S. Choleraesuis suppresses inflammatory response and hides in foam cells; this makes eradication of atheromatous plaque difficult. After activation during atherosclerosis, macrophages produce IL-12, which drives inflammation and exacerbates atherosclerosis (Kleemann et al. 2008; Mairui et al. 2013). Plasmid-bearing S. Enteritidis induces more cell autophagy as well as lower IL-12p35 expression than does the plasmid-less strain, suggesting that the virulence plasmid is involved in the induction of cell autophagy and reduction of inflammation to atherosclerosis development.

In conclusion, the virulence plasmid of Salmonella caused different effects after infection; plasmid-bearing S. Enteritidis induced more foam cell autophagy and IL-1β secretion than did its plasmid-less strain, whereas plasmid-bearing S. Choleraesuis induced less foam cell autophagy and IL-1β secretion than did its plasmid-less strain. Salmonella may affect the course of foam cells formation or even aortic aneurysm through autophagy.

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**Conflict of interest**

The authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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