INLB PROTEIN SECRETED BY *LISTERIA MONOCYTOGENES* CONTROLS THE PATHOGEN INTERACTION WITH MACROPHAGES

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The virulence of gram-positive bacterium *Listeria monocytogenes* depends on its capacity to infect non-professional phagocytes and proliferate inside them. *Listerias monocytogenes* captured by mononuclear phagocytic cells during the infectious process are resistant to lysosomal digestion and can proliferate inside macrophages. Internalin B (InlB), one of the key pathogenicity factors of *L. monocytogenes*, interacts with mammalian receptors c-Met and gC1q-R. For epithelial cells, such interactions with surface receptors promote activation of these receptors and cytoskeletal remodeling, which leads to massive bacterial invasion into non-professional phagocytes. For macrophages, by contrast, nothing is known about the role of InlB in their interactions with *L. monocytogenes* apart from the fact that both receptors are abundantly expressed by macrophages and participate in the development of immune reactions. This study aimed at determination of the potential role of InlB in the interactions between *L. monocytogenes* and macrophages. We found that 1) InlB expression promoted a significant 3.5-fold increase in the rates of *L. monocytogenes* capture by macrophages; 2) the 24 h fold increase in bacterial number inside macrophages constituted 182.5 ± 16.7, 96 ± 12 and 13.3 ± 3 for EGDeΔinlB, EGDe and EGDeΔinlB::pInlB strains, respectively; 3) the EGDeΔinlB::pInlB strain, complemented with a plasmid copy of *inlB*, produced InlB at 3.3-fold higher rates than the type strain EGDe. We conclude that InlB negatively affects the survival of listeria inside macrophages. The results enable advanced understanding of the host-pathogen interactions for *L. monocytogenes*.

Keywords: listeriosis, *Listeria monocytogenes*, internalin B, innate immunity, human macrophages

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БЕЛОК INLB, СЕКРЕТИРУЕМЫЙ *LISTERIA MONOCYTOGENES*, КОНТРОЛИРУЕТ ВЗАИМОДЕЙСТВИЕ ВОЗБУДИТЕЛЯ С МАКРОФАГАМИ

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Способность инфицировать и размножаться в непрофессиональных фагоцитах лежит в основе вирулентности грамположительной бактерии *Listeria monocytogenes*. В процессе протекания инфекции захваченные клетками системы мононуклеарных фагоцитов листерии устойчивы к перевариванию и могут размножаться внутри макрофагов. Один из ключевых факторов патогенности *L. monocytogenes* белок интерналин B (InlB) взаимодействует с рецепторами клеток млекопитающих c-Met и gC1qR. При его взаимодействии с рецепторами, находящимися на поверхности эпителиальных клеток, происходит активация рецепторов, перестройки цитоскелета и, как результат, активная инвазия бактерий внутрь непрофессиональных фагоцитов. На сегодняшний день ничего неизвестно о влиянии InlB на взаимодействие *L. monocytogenes* с макрофагами, в то время как оба таргетных рецептора экспрессируются на поверхности макрофагов и вовлечены в развитие иммунных реакций. Целью работы было определить потенциальное влияние InlB на взаимодействие *L. monocytogenes* с макрофагами. Установлено, что 1) наличие InlB в 3,5 раза достоверно улучшает поглощение *L. monocytogenes* макрофагами; 2) через 24 ч штаммы EGDeΔinlB, EGDe и EGDeΔinlB::pInlB увеличили свою численность внутри макрофагов в 182,5 ± 16,7, 96 ± 12 и 13,3 ± 3 раз соответственно; 3) Штамм EGDeΔinlB::pInlB, комплементированный плазмидной копией гена *inlB,* продуцировал InlB в 3,3 раза лучше, чем штамм EGDe. Таким образом мы предполагаем, что InlB влияет на выживаемость листерий внутри макрофагов. Полученные результаты углубляют понимание процессов взаимодействия возбудителя с макрофагами.

Ключевые слова: листериоз, *Listeria monocytogenes*, интерналин B, врожденный иммунитет, макрофаги человека

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The earliest evidence on the existence of Listeria monocytogenes is dated back to 1926 and describes a lethal infection in rabbits accompanied by pronounced monocytosis [1]. The gram-positive bacterium *L. monocytogenes* causes listeriosis — a severe systemic disorder in animals and humans [2]. The main clinical symptoms of listeriosis in humans are sepsis, meningitis and meningoencephalitis [3]. Immune defense against *L. monocytogenes* is mainly ensured by innate and cellular adaptive immunity. The first-line effector cells are macrophages. Since *L. monocytogenes* is a facultative intracellular bacterium, it can survive the phagocytosis by mononuclear phagocytes and proliferate inside them.

The critical step in the infectious process is the invasion of *L. monocytogenes* into non professional phagocytes. This step is mediated by two cell surface proteins of *L. monocytogenes* — internalin A (InlA) and internalin B (InlB). The InlA protein is covalently bound to the bacterial surface, while its interaction with the host target protein E-cadherin mediates cytoskeletal remodeling and bacterial internalization [4]. The InlB protein exists in two forms: one of them is bacterial surface-bound and promotes active invasion of the bacteria into non-professional phagocytic cells; the second form (soluble) is thought to induce the non-specific activation of signaling pathways upon binding the target receptors. The functional role of soluble InlB is still uncertain. Eukaryotic proteins c-Met and gC1q-R have been identified as target receptors for InlB [5, 6]. c-Met is the high-affinity receptor for hepatocyte growth factor (HGF). c-Met activation triggers signaling pathways of cell proliferation and migration, as well as the control of immunity reactions in certain cell types [7]. c-Met is expressed by various epithelial cells and several immune cell lineages: macrophages, monocytes, dendritic cells and T cells [8]. c-Met has been also implicated in shifting macrophage polarization from M1 towards M2-like phenotypes [9].

The second target receptor of InlB is gC1q-R, a ubiquitously expressed protein initially identified as receptor for the globular heads of C1q [10] and subsequently characterized as a multifunctional protein interacting with a wide scope of ligands of endogenous and exogenous origin [11]. The InlB/gC1q-R binding facilitates the invasion of listeria into mammalian cells. Recent studies provide structural and functional details of InlB interactions with its receptors c-Met and gC1q-R and demonstrate the influence of these interactions on the phosphorylation dynamics of PI3K and MAPK signaling cascades in human epithelial cells [12–14]. Similarly with c-Met, gC1q-R is abundantly expressed on the surface of B lymphocytes and macrophages [15].

Thus, both mammalian receptors for InlB participate in multiple signaling pathways that mediate immune responses, which suggests a contribution of InlB to innate immunity through NF-κB activation and PI3K signaling in macrophages [16]. Indeed, the c-Met/InlB interaction enhanced the migratory capacity of certain immune cell lineages and positively regulated the production of pro-inflammatory cytokine IL6 by peritoneal dendritic cells [17]. However, no experimental evidence on the role of InlB in the interactions between *L. monocytogenes* and macrophages was published so far.

This study aimed to specify the functional role of InlB in the interactions of listeria with human macrophages.

METHODS

Isolation of human macrophages from peripheral blood samples

Human macrophages were differentiated from monocytes isolated from the mononuclear fraction of peripheral blood obtained from healthy donors. The isolation involved density gradient centrifugation with Ficoll-Paque Premium (HyClone; USA) followed by adhesion [18]. The monocytes were cultured at 37 °C and 5% CO_2 for 6 days in RPMI-1640 medium containing 2% inactivated human serum, 2 mM L-glutamine, 10 mM HEPES, 50 μM β- mercaptoethanol, 2 mM sodium piruvate and 2× MEM vitamin solution (HyClone; USA). On day 1, the medium was supplemented with GM-CSF to 50 ng/mL (SCI-Store; Russia). On day 4, the medium was replaced with a fresh portion and GM-CSF was added to 50 ng/mL. The cells were stained with fluorophore-conjugated primary antibodies to CD11b (APC-Cy7), CD80 (PE-Cy5), CD86 (BV421) and HLA-DR (PE-Cy7) and analyzed by flow cytometry (Beckman Coulter; USA).

Bacterial strains and culture conditions

The study used the following strains of *L. monocytogenes*: EGDe (type strain), EGDeΔinlB with chromosomal deletion of *inlB* and EGDeΔinlB::pInlB containing a plasmid copy of *inlB* complementing this deletion. The EGDeΔinlB strain was courtesy of Prof. J. Vazquez-Boland of the University of Edinburgh, UK. The InlB-encoding plasmid and the EGDeΔinlB::pInlB strain were described previously [14]. All strains of *L. monocytogenes* were grown in BHI broth (Becton, Dickinson and Company; USA) at 37 °C and 200 rpm continuous shaking. The strains transformed with InlB expression constructs (complemented) were grown with 10 μg/mL erythromycin in order to maintain the plasmid. To obtain infectious cultures, the bacteria were grown to the mid-logarithmic phase, ware washed three times with phosphate-buffered saline (PBS, Amresco; USA) and frozen in 100 μL aliquots in the presence of 10% glycerin (Sigma-Aldrich; USA).

Assay of *L. monocytogenes* capture by macrophages

The macrophages were grown in 24-well plates. The concentrations of bacterial cells in frozen cultures were determined by serial dilution method. The bacteria were added to the macrophages in growth medium at a MOI (multiplicity of infection) ratio of 1 : 100. After 1 h incubation at 37 °C and 5% CO_2 the cells were washed thrice with PBS and placed in DMEM (PanEco; Russia) containing 100 μg/mL gentamycin (Sigma-Aldrich; USA) to eliminate the extracellular bacteria. After 1 h incubation the cells were washed thoroughly with PBS to remove gentamycin and lysed with 1% Triton X-100 (Sigma-Aldrich; USA). The lysates were plated on BHI agar in serial dilutions. For the complemented strain, the solid medium was supplemented with 10 μg/mL erythromycin. The capture efficiency was evaluated by the ratio of the number of captured bacteria to the number of added bacteria.

Assay of *L. monocytogenes* intracellular survival in macrophages

After 1 h incubation at 37 °C and 5% CO_2 the cells were washed thrice with PBS and placed in DMEM (PanEco; Russia) containing 100 μg/mL gentamycin (Sigma-Aldrich; USA) to eliminate the extracellular bacteria. After 1 h incubation at the high gentamycin concentration the cells were washed and placed in fresh DMEM (PanEco; Russia) containing 20 μg/mL gentamycin (Sigma-Aldrich; USA) to prevent the survival of listerias outside macrophages. The plates were incubated for 24 h (since the start of infection) at 37 °C and 5% CO_2. The cells were then washed thrice with PBS) to remove gentamycin and

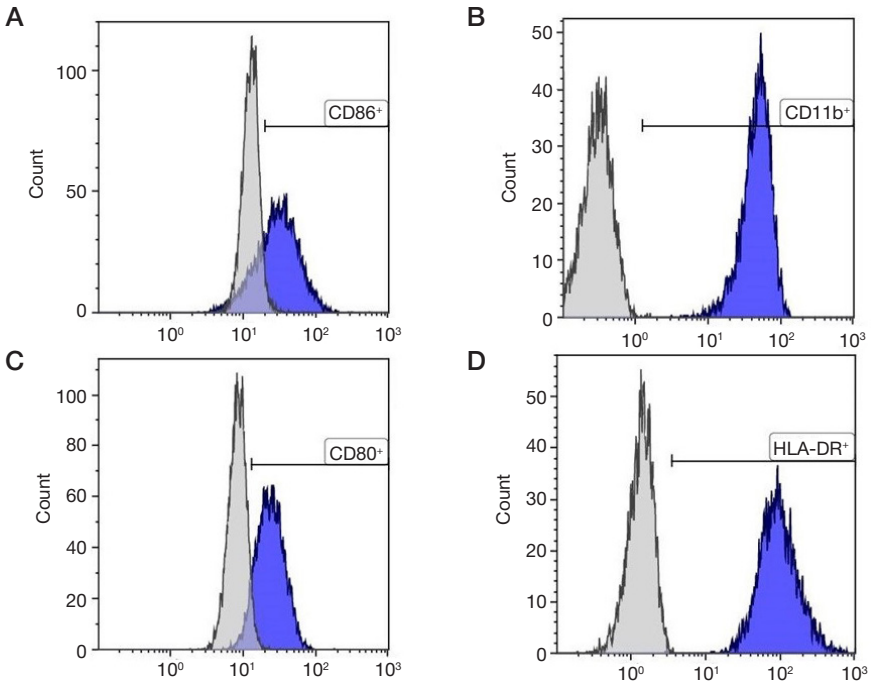

Fig. 1. Flow cytometry analysis of the macrophages obtained from peripheral blood monocytes of healthy donors. The macrophages were differentiated towards M1 phenotype; the plots show positivity for CD86 (**A**), CD11b (**B**), CD80 (**C**) and HLA-DR (**D**) markers

lysed by adding 100 µL of 1% Triton X-100. The lysates were subsequently diluted to 1 mL by adding 900 µL of PBS and plated on BHI agar in serial dilutions. For the complemented strain, the solid medium was supplemented with 10 µg/mL erythromycin. The survival efficiency was assessed by the ratio of the number of surviving bacteria to the number of introduced ELISA bacteria.

Enzyme-linked immunosorbent assay (ELISA) test systems for InlB expression

The *L. monocytogenes* strains were grown in BHI for 18 h. The cells were separated from supernatant by centrifugation (4200 rpm, 15 min), washed thrice in PBS and resuspended in 500 µL of carbonate-bicarbonate buffer (pH 9.6). Cell surface expression levels for InlB were measured by direct ELISA. Briefly, a 96-well plate was loaded with sample aliquots, 100 µL per well, incubated overnight at +4 °C, washed with TTBS, three washes 250 µL each, filled with 200 µL of blocking buffer per well and incubated for 1 h at room temperature. The HRP-conjugated InlB-specific antibodies were used in 1 : 4000 dilution, 100 µL per well. After 1 h incubation at room temperature the wells were washed with TTBS, six washes 250 µL each, and the signal was developed with 100 µL of TMB (Thermo Fisher Scientific; USA) per well. The reactions were stopped by adding 100 µL of 2M H_2SO_4. The optical densities were measured at a wavelength of 450 nm on an iMark microplate absorbance reader (Bio-Rad; USA).

The levels of secreted InlB were measured by sandwich ELISA. Briefly, InlB-specific antibodies (4 µg/mL, diluted in carbonate-bicarbonate buffer pH 9.6) were added to fresh 96-well plate, 100 µL per well, and the plate was incubated overnight at +4 °C. The wells were washed with TTBS, three washes 250 µL each, filled with blocking buffer (2% BSA, 200 µL per well) and incubated for 1 h at room temperature. The blocking buffer was subsequently replaced with the sample and the plate was incubated for 1 h at room temperature. The wells were subsequently washed with TTBS, three washes 250 µL each, and the HRP-conjugated InlB-specific antibodies were added (1 : 4000, 100 µL per well). After 1 h incubation at room temperature the wells were washed with TTBS, six washes 250 µL each. The signal was developed with TMB (Thermo Fisher Scientific; USA), 100 µL per well; the reactions were stopped by adding 100 µL of 2M H_2SO_4. The optical densities were measured at 450 nm in iMark microplate absorbance reader (Bio-Rad; USA). The InlB concentration was determined with the use of calibration curve and recalculated for cell number in a sample.

Statistical analysis

All experiments were carried out in three replicates and at least four repeats. The statistical analysis involved one-way ANOVA with post-hoc Tukey test (https://www.socscistatistics.com/tests/anova/default2.aspx). The differences were considered significant at $p < 0.05$ (see Supplementary 1 and 2).

RESULTS

Characterization of differentiated macrophages

Macrophages play an important role in the innate immune responses and participate in stimulation of the immune effector cells differentiation. Macrophages are among the first cells to be infected and largely define the deployment of innate and adaptive immune reactions to *L. monocytogenes*. The macrophages differentiated from peripheral blood monocytes were analyzed by flow cytometry. The analysis revealed surface expression of CD11b, CD80, CD86 and HLA-DR markers characteristic of the pro-inflammatory M1 macrophage phenotypes [19] (Fig. 1). The cells contained large rounded nuclei with heterochromatin located beneath the nuclear membrane, formed numerous surface processes and were firmly adherent to the plastic (Fig. 2).

Phagocytosis of *L. monocytogenes* by macrophages is InlB-dependent

The interaction of bacterial surface-bound InlB with c-Met expressed at the surface of non-professional phagocytes

mediates cytoskeletal remodeling within the target eukaryotic cells, leading to formation of phagocytic cup and subsequent internalization of the bacteria. At the same time, the contribution of InlB to *L. monocytogenes* interactions with professional phagocytes remains unknown. In the first experiment, we analyzed whether the presence of InlB affects the efficiency of *L. monocytogenes* capture by macrophages. The M1 macrophages were co-incubated with three different strains of *L. monocytogenes*: the wild-type EGDe, the EGDeΔinlB strain, derived from EGDe by inlB deletion (ΔInlB), and EGDeΔinlB::pInlB (ΔInlB complemented with inlB-containing plasmid). The data indicate that the presence of InlB improves the efficiency of *L. monocytogenes* capture by macrophages 3.5-fold (Fig. 3). No significant differences between the type strain EGDe and the complemented EGDeΔinlB::pInlB strains were observed in the experiments (Supplementary 1).

Survival of *L. monocytogenes* inside macrophages is InlB-dependent

The effects of InlB on survival of the captured bacteria inside human macrophages were assessed after 24 h incubation, during which the EGDeΔinlB strain underwent 182.5 ± 16.7 fold increase in bacterial number, whereas for the type strain EGDe strain the rates were significantly lower (96 ± 12 fold increase in bacterial number). Remarkably, the EGDeΔinlB::pInlB strain complemented with a plasmid copy of inlB showed the lowest intracellular proliferation rates with a fold increase of 13.3 ± 3 only (Fig. 4; Supplementary 2). This effect possibly reflected complementation of the strain on the basis of a plasmid that consumed additional cell resources. The assumption was tested by infecting HEp-2 cells with EGDe and EGDeΔinlB::pInlB strains (similarly with the macrophage capture assay). Over 24 h, the numbers of EGDe and EGDeΔinlB::pInlB increased 515.8-fold and 508.9-fold respectively (n = 3), indicating similar intracellular proliferation rates for the type and plasmid-complemented strains of *L. monocytogenes* in HEp-2 cells.

In order to explain the differential survival of the type strain EGDe, its inlB-depleted derivative and plasmid-complemented strains in macrophages, we further hypothesized that the dramatically reduced survival of the complemented strain can be associated with the levels of InlB production. The analysis involved ELISA test systems capable of distinguishing between InlB exposed on the bacterial surface and InlB secreted to the culture medium. We found that EGDe and EGDeΔinlB::pInlB expressed similar levels of InlB associated with the cell surface. However, the levels of secreted InlB measured in supernatant for EGDeΔinlB::pInlB were 3.3-fold higher than for the type strain EGDe (Fig. 5). These results support our assumption that *L. monocytogenes* survival and/or proliferation in human macrophages are affected by InlB in a quantitative manner.

DISCUSSION

In this study we show that interactions between *L. monocytogenes* and human macrophages are InlB-dependent: the presence of the pathogenicity factor InlB at the bacterial surface accelerates the capture of listerias by macrophages and interferes with their survival inside macrophages. Moreover, the InlB production levels negatively correlate with *L. monocytogenes* survival inside macrophages.

This finding is consistent with a recent study comparing inlB expression between non-clinical and clinical isolates and demonstrating significantly lower InlB production levels in the latter [20]. In addition, decreased production levels of InlB

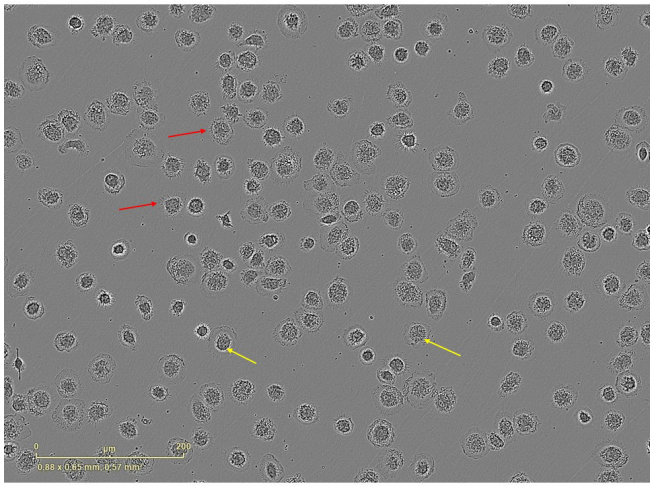

Fig. 2. Cell morphology of the M1 macrophages differentiated from peripheral blood monocytes of healthy donors. Red arrows indicate cell surface protrusions. Yellow arrows indicate large rounded nuclei. The images were acquired in an IncuCyte® S3 Live-Cell Imaging System (Sartorius; Göttingen, Germany)

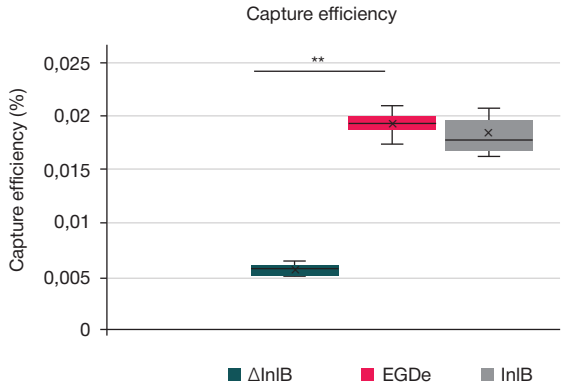

Fig. 3. Capture efficiency of *L. monocytogenes* ΔInlB strain, type strain EGDe and plasmid-complemented ΔInlB (InlB) strain by M1-like phenotype macrophages, $^{**}p < 0.01$ (n = 4).

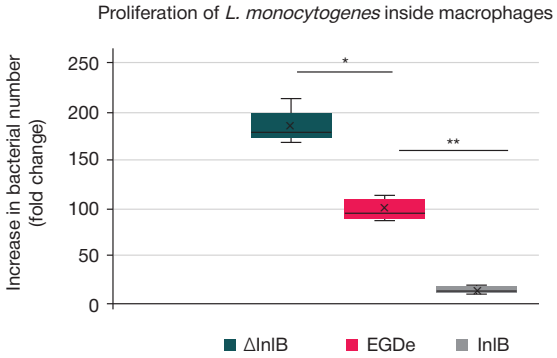

Fig. 4. Proliferation of *L. monocytogenes* ΔInlB strain, type strain EGDe and plasmid-complemented ΔInlB (InlB) strain inside M1-like phenotype macrophages over 24 h infection, * — $p < 0.05$, ** — $p < 0.01$ (n = 4).

were associated with decreased production of IL8 by non-professional phagocytes [20]. The authors suggest that the reduced IL8-inducing capacity of clinical strains may represent an immunity evasion mechanism that comes at a price of reduced efficiency of bacterial invasion into non-professional phagocytes [20]. This view is supported by our finding that higher levels of InlB production negatively affect the survival of listeria inside human macrophages.

Which of the two target receptors of InlB is responsible for this effect is still elusive. The activation of c-Met by its physiological ligand, HGF, promotes an M1-to-M2 shift in macrophage phenotypes [9]. The InlB/c-Met interaction

imitates the activity of HGF, leading to NF-κB activation and triggering of PI3K and MAPK pathways in various cell types including macrophages [14, 16]. The interaction of c-Met with InlB can enhance the motility of certain immune cell types. According to recent studies, this interaction facilitates secretion of the pro-inflammatory cytokine IL6 by peritoneal dendritic cells [16]. The dose-dependent effect of InlB on bacterial survival observed by us in the macrophage capture assay may indicate a contribution of intracellular receptors. A candidate intracellular receptor for InlB is gC1q-R, which has been attributed with both extra- and intracellular localization. The existence of other, as yet undescribed intracellular receptors for InlB cannot be excluded as well.

Overall, our results demonstrate a negative role of InlB in the innate immunity evasion by listerias. At the same time, InlB is required for the full-scale invasion of listerias into non-professional phagocytic cells. The balance of bacterial–host interactions between immune cells and principal target cells of the pathogen may define the degree of virulence for different strains of *L. monocytogenes*.

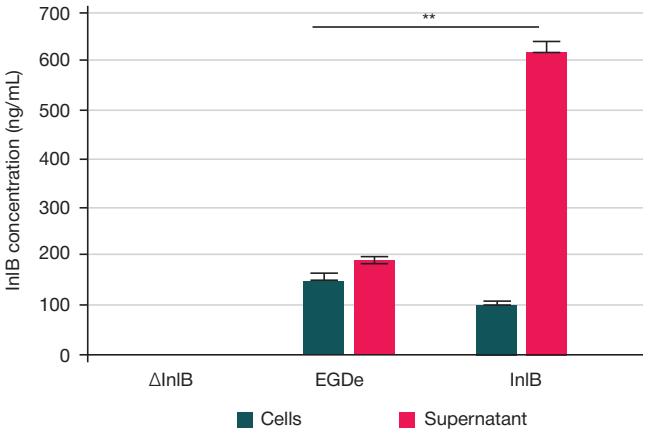

Fig. 5. Production levels of InlB protein in 18 h cultures of *L. monocytogenes*. The ΔInlB cultures contain no InlB protein; the type strain EGDe cultures contain 149.2 ± 13.3 ng/mL of InlB bound to the bacterial surface and 187.3 ± 9.8 ng/mL of InlB in the supernatant; the plasmid-complemented ΔInlB (InlB) cultures contain 100.7 ± 4.2 ng/mL of InlB bound to the bacterial surface and 614.6 ± 23 ng/mL of InlB in the supernatant, ** — $p < 0.01$ ($n = 3$)

CONCLUSIONS

This study focused on the effects of InlB, the pathogenicity factor of *L. monocytogenes*, on the interactions of listerias with human macrophages. In our experiments, InlB significantly enhanced the capture of listerias by macrophages while inhibiting the survival/proliferation of listerias inside macrophages. Thus, we for the first time demonstrate a negative impact of InlB on the innate immunity evasion by listerias. The balance between this newly observed effect of InlB and its decisive positive role in the infectivity of *L. monocytogenes* towards non-professional phagocytes, along with the mechanisms that evolved to maintain this balance, should be considered in detail in order to advance the understanding of pathogen-host interactions for different cell types of the body.

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