Mast cell degranulation impairs pneumococcus clearance in mice via IL-6 dependent and TNF-α independent mechanisms

Jing Yanga,1, Jichao Wangb,1, Xuemei Zhanga, Yulan Qiua, Jurong Yan a, Si Sun a, Yujuan He a, Yibing Yin a, Wenchun Xu a*

a Key Laboratory of Laboratory Medical Diagnostics Designated by the Ministry of Education, School of Laboratory Medicine, Chongqing Medical University, Chongqing, China
b Department of Clinical Laboratory, Chongqing Hospital for Women and Children, Chongqing, China

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ABSTRACT

Background: Mast cells participate in immune responses by releasing potent immune system modifiers via degranulation. Due to currently reported controversial roles of mast cells in Streptococcus pneumoniae infections, this study aimed to determine the role and mechanism of mast cells in clearing S. pneumoniae in mice.

Methods: In vivo mouse model of mast cell degranulation established by administration of C48/80 was evaluated for the influences of mast cell degranulation on bacterial colonization and inflammation. In vitro model was established to observe the influences of mast cell degranulation on phagocytic and bactericidal functions of neutrophils and macrophages. IL-6 null and TNF-α null mice on the C57BL/6 background were used to investigate the effects of inflammatory factors released by mast cell degranulation on bacterial clearance.

Results: Mast cell degranulation increased IL-6 and TNF-α levels and immune cell numbers in nasal lavage fluid, and inhibited the bactericidal function of macrophages and neutrophils in vitro. It decreased the number of neutrophils and macrophages recruited to respiratory tract after S. pneumoniae challenge and inhibited the clearance of S. pneumoniae in mice. After pretreatment with C48/80, S. pneumoniae loads were significantly lower in IL-6 null mice than in wild type mice, while no differences were observed between TNF-α null and wild type mice.

Conclusions: Mast cell degranulation can cause inflammation and impair immune cell recruitment to respiratory tract after S. pneumoniae challenge. Products of mast cell degranulation including IL-6 decreased the bactericidal function of neutrophils and macrophages. Through these mechanisms, mast cell degranulation inhibited clearance of S. pneumoniae in mice.

Introduction

Mast cells are derived from myeloid multipotent hematopoietic progenitors that migrate through blood to peripheral tissues for maturation. These cells are distributed at external environmental interfaces, including the skin and the respiratory and gastrointestinal tracts. These cells are poised to respond to invasive pathogenic microbes when appropriate.1,2

The mast cell cytoplasm contains large amounts of bioactive molecules that include the preformed mediators histamine, proteoglycans, cytokines and neutral proteases, and de novo formed mediators lipid mediators, angiogenic factors, cytokines and chemokines.3 Once activated, mast cells liberate their contents extracellularly primarily through degranulation. This causes increased levels of cytokines and chemokines, immune cell recruitment and increases in vascular permeability due to released factors. These cells thereby regulate both innate and acquired immune responses.1,2

However, mast cells are double-edged swords. On the one hand, they play important roles in physiology such as wound healing, angiogenesis and pathogen defense.5 On the other hand, mast cells promote inflammatory responses that if triggered inappropriately, can result in pathology such as allergic responses.6

* Corresponding author.
E-mail addresses: orangemeyj@163.com (J. Yang), wang77jichao@163.com (J. Wang), apoe@163.com (X. Zhang), 18375874633@163.com (Y. Qiu), 15178844937@163.com (J. Yan), 15086738701@163.com (S. Sun), yjhemail@126.com (Y. He), yibingyin56@126.com (Y. Yin), 100977@cqmu.edu.cn (W. Xu).
1 These authors contributed equally to this work.

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The role of mast cells in pathogen defense is dependent upon the particular pathogen. For instance, mast cells during *Plasmodium* infections accelerate pathogen clearance by secreting TNF-α. *Francisella* reproduction in macrophages is inhibited via mast cell secretion of IL-4 and these cells can directly kill Group A *Streptococcus* by secreting cathelicidin, which limits cutaneous injury. Mast cells also recruit neutrophils by secreting IL-6 and thereby accelerate *Klebsiella pneumoniae* clearance.

In all these examples, mast cells promote bacterial clearance and are beneficial. However, IL-4 secreted by mast cells during sepsis caused by peritonitis can result in an inhibition of macrophage function and an exacerbation of sepsis. During *Chlamydia pneumoniae* infections, mast cell chymase secretion increases vascular permeability and immune cell recruitment. Because *C. pneumoniae* are intracellular bacteria, this increased recruitment assists in dissemination and reproduction of the pathogen. These studies illustrate that mast cell functions are dependent upon pathogen type and that even the same cytokine can have opposite effects with different pathogens.

*Streptococcus pneumoniae* is a leading cause of community-acquired respiratory tract infections that can result in pneumonia, meningitis, otitis media and sepsis. Currently, views on the roles of mast cells in *S. pneumoniae* infections are diverse. For instance, human pulmonary mast cells have direct antibacterial abilities against *S. pneumoniae*, which is dependent on pneumolysin. In the early stages of *S. pneumoniae* infections (3–6 h), mast cells have antibacterial activity but during late stages (>6 h post-infection) the cells adversely affect infection outcomes although the specific mechanisms are obscure.

We used Compound 48/80 (C48/80), mast cell activator, to establish an *in vivo* model of mast cell degranulation. Mice were nasally challenged with *S. pneumoniae* and we studied the effects that mast cell degranulation has on disease development. We found that degranulation inhibited *S. pneumoniae* clearance in mice. Inflammatory factors and chemokines in nasal lavage fluid were increased as was immune cell recruitment in airways. The result was the sloughing of ciliated epithelium cells, erythrocyte overflow and other inflammatory manifestations. The bactericidal functions of macrophages and neutrophils were inhibited. All of these were related to IL-6 secretion.

**Methods**

**Materials, bacterial strains and mice**

C48/80 and sodium cromoglycate were purchased from Sigma-Aldrich (St. Louis, MO, USA). *S. pneumoniae* strain serotype 19F (CMCC 31693) from the National Center for Medical Culture Collections (Beijing, China). C57BL/6 female mice aged 6–8 weeks from Chongqing...

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**Fig. 1.** Mast cell degranulation *in vivo* and *in vitro*. Mast cells derived from C57BL/6 peritoneal cavities were assayed for release of (A) IL-6 and (B) TNF-α in tissue culture supernatants after addition of C48/80 to peritoneal mast cells. Cultures were sampled at 5, 10 and 15 min after C48/80 treatment. (C) β-hexosaminidase levels after 60 min treatment. (D) Toluidine blue staining of tissue culture cells to observe mast cell degranulation (E) Toluidine blue staining of lung tissues from mice after nasal administration of C48/80 in the presence and absence of sodium cromoglycate. The study was repeated for 3 times. **P < 0.01; ***P < 0.001; ns, not significant.
Medical University. IL-6, and TNF-α null mice in the C57BL/6 background from the Jackson Laboratory (Wenzhou, China).

Culture peritoneal macrophages and neutrophils from mice in vitro

To obtain peritoneal macrophages and neutrophils, mice were respectively injected with liquid paraffin (1 mL) and 9% casein (1 mL) into their peritoneal cavities. Peritoneal cells were incubated at a density of $1 \times 10^6$ cells per well, respectively with DMEM containing 10% heat-inactivated FBS (fetal bovine serum) for macrophages, and RPMI1640 containing 10% heat-inactivated FBS and 1% penicillin and streptomycin for neutrophils.

In vitro model of mast cell degranulation

Peritoneal mast cells were cultured according to a previously published method with minor modifications. Cultured mast cells were treated with C48/80 at 4 μg/mL or the same volume of phosphate buffered saline (PBS, control) and incubated for 60 min for experiments outlined below.

In vivo model of mast cell degranulation

Mice were nasally administered for 3 consecutive days. The mice were divided into three groups. The mast cell degranulation group was given C48/80 at 40 μg/day. The second group was given 40 μg of C48/80 at the start of experiment and then sodium cromoglycate at 500 μg/day. The third (control) group was given PBS/day.

Bacterial challenge and cytokine measurements

Mice were challenged intranasally with *S. pneumoniae* at $1 \times 10^8$ CFU per mouse in a total volume of 20 μl the next day after C48/80 or PBS treatment for 3 consecutive days. At 24, 48 and 72 h after infection, nasal lavage fluid and lung homogenates of mice were collected and plated for determination of the numbers of colony-forming units (CFU).

IL-6, TNF-α, IFN-γ and IL-1β levels were determined by commercial ELISA kits (Biolegend, San Diego, CA, USA). CXCL1 and CXCL10 by ELISA kits (Lianke Biotech, Hangzhou, China). β-hexosaminidase levels by a commercial kit (Shanghai Runyu, Shanghai, China).

Histopathological analysis of lung

Paraffin-embedded lung tissue sections (5-μm) were stained with hematoxylin and eosin for light microscopy, analyzed for inflammation and tissue damage, and semiquantitatively scored by a pathologist as described previously. Mast cells were stained with toluidine blue and degranulation was observed by light microscopy.

Flow cytometry

Prior to analytical flow cytometry analysis, cells were incubated for 20 min at 4 °C with anti-FcγRIII/II (Ly-17) by commercial anti-mouse CD16/32 antibodies. Mast cell surface markers were then detected by flow cytometry by phycoerythrin labeled (PE) anti-CD117 (BD Phar-mingen, San Jose, CA, USA) and FITC labeled anti-FcγRIIa after incubation for 1 h at 4 °C I. Macrophage surface markers by APC-anti-CD11b and PE-anti-cy5-F4/80 (eBioscience, San Diego, CA, USA).

Fig. 2. Mast cell degranulation prevented clearance of *S. pneumoniae* in mice. The in vivo model of mast cell degranulation and *S.pn* challenge (A). C57BL/6 mice were nasally challenged with *S. pneumoniae* serotype 19F after administration of (B and C) PBS or C48/80 and PBS or C48/80 with cromoglycate (D) for 3 consecutive days. Bacterial CFU in nasal lavage fluid (B and D) and lung homogenates (C) after a nasal challenge with *S. pneumoniae*. The in vivo study was repeated for more than 3 times. *P < 0.05; **P < 0.01; ns, not significant.
Neutrophil surface markers by APC-anti-CD11b and FITC-Ly6G (BD Pharmingen).

Phagocytosis and killing assays

Mast cells cultured in vitro were treated with C48/80 or PBS and tissue culture supernatants were collected and added to cultured macrophages and neutrophils. *S. pneumoniae* serotype 19F at 1 × 10⁸ CFU were added to the cells in each well followed by a 30-min incubation at 37 °C. The supernatant was abandoned, adherent cells were lysed and plated for determination of CFU to evaluate phagocytic function.

The procedure for the bacterial killing assay was similar as above but the bacteria and cells were incubated together for 2 h at 37 °C before plating.

Statistical analysis

All data were analyzed by GraphPad Prism 5 software (GraphPad Software, La Jolla, CA, USA). Cytokine, chemokine and bacterial loads were compared using the Mann-Whitney U test. A P value < 0.05 was considered statistically significant. The data are presented as mean ± standard error (SE).

Results

**C48/80 promotes mast cell degranulation in vivo and vitro**

To study the influence of mast cell degranulation on clearance of *S. pneumoniae*, we first established in vivo and in vitro models of mast cell degranulation. Previous studies have indicated that peritoneal mast cells are more mature than those from bone marrow with more active substances in their cytoplasm. Therefore, we used peritoneal mast cell cultures and exposed them to compound C48/80, an agonist of mast cell degranulation.

IL-6 and TNF-α released from mast cell degranulation were the highest with 4 μg/mL of C48/80 using a 60 min exposure (Fig. 1A and B). The levels of β-hexosaminidase, a marker for mast cell degranulation, were significantly higher than control by using these optimal conditions.
treatment conditions (Fig. 1C). Toluidine blue staining of C48/80 treated cells revealed irregular cell membranes surrounded by blue-violet particles, an indicator of mast cell degranulation. This was not observed in the PBS control cells (Fig. 1D). These results indicated that the C48/80 dosage we used in vitro was sufficient to stimulate mast cell degranulation.

Our murine model of mast cell degranulation was established by using nasal administration of C48/80 based on a previous study. After administration of C48/80 for 3 consecutive days, lung tissues showed mast cell degranulation in the C48/80 group but not in the PBS controls.

Mast cell degranulation inhibits clearance of S. pneumoniae in mice

The effects of mast cell degranulation on clearance of S. pneumoniae in mice are not clearly defined. We therefore used an in vivo model (Fig. 2A) to determine whether degranulation promotes or inhibits bacterial colonization. At all time points, the bacterial loads in nasal lavage fluid were...
significantly higher in the C48/80 group than in the PBS controls (Fig. 2B). At 24 and 48 h post infection, the CFU in lung homogenates was also significantly higher in the C48/80 group than in the controls (Fig. 2C). Interestingly, at 72 h post infection, the bacterial loads in nasal lavage fluid were lower in the cromoglycate group than in C48/80 group, even lower than in the PBS controls. (Fig. 2D). These results suggested that mast cell degranulation inhibited clearance of *S. pneumoniae* in mice.

**Mast cell degranulation causes local inflammation in mice**

Mast cell degranulation releases a large amount of inflammatory mediators. An inhibition of *S. pneumoniae* clearance could be the result of inflammation induced during this process. To determine if this was the case we measured the amounts of IL-6 and TNF-α in nasal lavage fluid after C48/80 treatment. Treatment with C48/80 resulted in higher levels of both IL-6 and TNF-α whether before *S. pneumoniae* infection or at 24 and 48 h after *S. pneumoniae* challenge (Fig. 3A and B). After *S. pneumoniae* infection, IL-6, TNF-α, IFN-γ and IL-1β in lung homogenates were also significantly higher in the C48/80 group than in controls (Fig. 3C–F). In addition, we found changes of histopathology including pulmonary erythrocyte over-flow, inflammatory cell infiltration and atrophy and sloughing of ciliated columnar epithelial cells of the respiratory tract in the C48/80 group before infection, while tissue morphology was normal in the PBS treatment group (Fig. 3G). These results demonstrated that mast cell degranulation causes inflammatory responses and pathological injuries in mice.

**Mast cell degranulation decreases the number of neutrophils and macrophages recruited to the mouse respiratory tract after an *S. pneumoniae* challenge**

After bacterial infection, neutrophils and macrophages are major contributors to pathogen clearance. We therefore measured the number of immune cells recruited to the respiratory tract after C48/80 treatment, before and after an *S. pneumoniae* challenge. Before the bacterial challenge, neutrophil chemotactic factors CXCL1, CXCL10 and macrophage chemotactic factor CCL2 in nasal lavage fluid were significantly elevated in the C48/80 group over PBS controls (Fig. 4A). Correspondingly, the number of nucleated cells in bronchoalveolar lavage fluid was also higher in C48/80 group (Fig. 4B) as were the number of neutrophils and macrophages (Fig. 4C–E).

After the bacterial challenge, these chemokines were still elevated as were the numbers of nucleated cells and neutrophils (Fig. 4A–D). However, both these cell types were at lower levels in the C48/80 group than the PBS controls. In the case of macrophages, their numbers were greater in the C48/80 group compared with controls before infection, and their numbers decreased after infection (Fig. 4E). These results indicated that mast cell degranulation reduced the number of neutrophils and macrophages recruited to the mouse respiratory tract after an *S. pneumoniae* challenge.

**Mast cell degranulation decreases the bactericidal function of neutrophils and macrophages**

Tissue culture supernatants from mast cells treated with C48/80 enhanced the phagocytic function of macrophages (Fig. 5A), but decreased their bactericidal function (Fig. 5B). These supernatants had no effect on the phagocytic function of neutrophils (Fig. 5C). However, their bactericidal functions decreased (Fig. 5D). These results indicated that mast cell degranulation decreases the bactericidal functions of neutrophils and macrophages.

**Impaired *S. pneumoniae* clearance by mast cell degranulation is associated with IL-6**

Mast cell degranulation releases both IL-6 and TNF-α. To determine if these cytokines affect bacterial clearance, we treated IL-6 null and TNF-α null mice with C48/80 or PBS and then challenged them with *S. pneumoniae*. At 48 h post infection, bacterial loads in nasal lavage...
Fig. 6. Impaired *S. pneumoniae* clearance by mast cell degranulation is associated with IL-6, and mast cell degranulation increases IL-17A and inflammatory cell recruitment in respiratory tract after *S. pneumoniae* challenge in IL-6 null mice. Wild type, IL-6 null and TNF-α null deficient mice were nasally treated with either PBS or C48/80 for 3 consecutive days. The mice were then challenged with *S. pneumoniae* 19F and bacterial loads were measured 48 h post-infection. (A and B) Bacterial loads in nasal lavage fluid and lung homogenates of IL-6 null and wild type mice, respectively. (C and D) Bacterial loads in nasal lavage fluid and lung homogenates of TNF-α null and wild type mice, respectively. (E) Inflammatory mediators assayed from lung homogenates; (F) Nucleated cells from lung lavage fluid; (G) Flow cytometry analysis of neutrophil and macrophage markers from lung lavage cells; and (H) Graphical representation of data from G. The study was repeated for 3 times. *P < 0.05; **P < 0.01; ***P < 0.001; ns, not significant.
fluid and lung homogenates were significantly lower in IL-6 null mice than in wild type mice (Fig. 6A and B). However, this was not observed in TNF-α null mice, and colonization levels were equal to controls (Fig. 6C and D). These results indicated that impaired bacterial clearance by mast cell degranulation in mice is IL-6 dependent but TNF-α independent.

After *S. pneumoniae* infection of wild type and IL-6 null mice treated with C48/80, IL-17A in lung homogenates was much higher in the IL-6 null mice (Fig. 6E). In addition, the number of nucleated cells recruited to the lung was higher in IL-6 null mice than in wild type mice, as were the number of neutrophils and macrophages (Fig. 6F-H). Gating strategy for identification of neutrophils and macrophages was depicted in Additional file 1.

**Discussion**

Controversial roles about mast cells in *S. pneumoniae* infection have been reported. Our results indicated that after mast cell degranulation, *S. pneumoniae* clearance decreased at 24, 48 and 72 h post infection and are consistent with a previous study. Even though the study had determined that this effect was degranulation independent, our study confirmed that decreased *S. pneumoniae* clearance in mice was related to mast cell degranulation...

To study the role of mast cells in *Spn*. clearance, mast cell-knock out (MC KO) mice were possible choices for our study, but they were not used. The main reasons are explained as follows. First of all, manifestations of anaphylactic diseases were mainly caused by mediators released from mast cell degranulation, not due to the presence of mast cells themselves. Therefore, it is the action, degranulation, that we focused on in our study. In view of this, MC KO mice were not suitable for our research purpose. Secondly, it has been reported that the actions of mast cells are important when they are not degranulating. Mast cells release preformed mediators and inflammatory cytokines after degranulation and even without degranulating at all. If mast cells were completely depleted in mice, which means no presence of mast cells at all, the other functions may be affected. As such, MC KO mice were not under consideration in our study, and we used cromoglycate, an inhibitor of mast cell degranulation, to study the role of mast cell degranulation in *Spn*. clearance.

After C48/80 treatment, we administered cromoglycate. The ability to clear *S. pneumoniae* was then restored to these mice and the effect was even larger than the PBS control group. This was most likely related to the small fraction of mast cells that were activated in PBS controls. The result confirmed that clearance of *S. pneumoniae* in mice was related to mast cell degranulation. Furthermore, we determined the mechanism for this process.

Appropriate inflammatory responses are beneficial to the body while hyperstimulation can result in pathological damage. Our results revealed that the murine respiratory tract in the PBS control group was intact, with no sloughing and damage of ciliated columnar epithelium, no inflammatory cell infiltration and a low level of cytokines. This is considered the normal physiology. The number of neutrophils and macrophages in lung tissues of mice in PBS controls were higher after *S. pneumoniae* challenge than before. This is a normal host defense and inflammation to clear the infection.

Macrophages in the lung tissues are the first line of defense against bacterial infections and IL-4 secreted by mast cells can decrease their bactericidal functions during sepsis. Our study suggested that the phagocytic capacity of macrophages increased after mast cell degranulation, whereas their bactericidal function decreased. Neutrophils recruited to lung tissues are also extremely important for timely bacterial clearance. However, our results revealed that mast cell degranulation also impaired bactericidal function of neutrophils. These results indicated that mast cell degranulation decreases the bactericidal function of innate immune cells and thus inhibited the timely clearance of *S. pneumoniae*.

The mechanisms of decreased bactericidal capacity of macrophages and neutrophils by the supernatants of mast cells are still unclear and deserves our further study. IL-4 was reported to impair bactericidal function of macrophages. IL-6 was able to enhance the polarization of AAMs (alternatively activated macrophages). Moreover, AAMs can decrease host protection by suppressing macrophage killing activity.

To determine whether these severe inflammatory responses and impaired anti-bacterial ability induced by mast cell degranulation are due to IL-6, we challenged mice after C48/80 treatment, and found that bacterial loads in the nasopharynx and lungs were lower in IL-6 deficient than in wild type mice. The control treatments with PBS in the two groups resulted in no differences in bacterial loads after bacterial challenge. This suggested that the mast cell degranulation impairing bacterial clearance was associated with IL-6.

Additionally, IL-17A levels in lungs were higher in IL-6 null mice than in wild type mice after C48/80 treatment and then bacterial challenge. Macrophages are the major secretors of IL-17A in the lung of asthmatic patients. We found greater numbers of lung macrophages in IL-6 null mice. This is consistent with higher IL-17A levels in lung tissue homogenates in these same mice. IL-17A plays critical roles in neutrophil recruitment and mucosal immunity. Consequently, increased IL-17A levels in IL-6 null mice favored neutrophil recruitment and accelerated bacterial clearance.

TNF-α is a critical factor in inflammatory responses and increased in rheumatoid arthritis, atherosclerosis, sepsis, etc. TNF-α play favorable or detrimental roles in numerous diseases. TNF-α is also an abundant protein in the cytoplasm of mast cells and is released after degranulation. We found that TNF-α levels were higher in the C48/80 group than the PBS controls. However, bacterial loads in the nasopharynx and lung were not different between TNF-α null mice and wild type mice after C48/80 treatment and then bacterial challenge. These results demonstrated that TNF-α was not involved in the decreased bacterial clearance seen after mast cell degranulation.
Conclusion

In this study, we treated mice nasally with C48/80 to induce mast cell degranulation in respiratory tract. This resulted in increased expression of multiple inflammatory factors, impaired the defensive barrier in the respiratory tract and immune cell recruitment. The products of mast cell degranulation decreased the bactericidal function of neutrophils and macrophages. As such, mast cell degranulation ultimately inhibited clearance of S. pneumoniae through the mechanism above, and this process is IL-6 dependent and TNF-$\alpha$ independent. Moreover, IL-17A levels increased after IL-6 ablation, thus demonstrating that there might be other mediators released during mast cell degranulation that are involved. This research provides a basis for the study of infection avoidance for patients with pathologic mast cell degranulation such as asthma, mastocytosis and allergic dermatitis.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Declarations

Ethics approval and consent to participate

The Institutional Animal Care and Use Committee of Chongqing Medical University approved all animal experiments. Experiments were performed in accordance with Guidelines for Laboratory Animal Care and Use and the National Animal Protection Laws and Applicable Guidelines.

Consent for publication

Not applicable.

Availability of data and materials

Data sharing not applicable to this article as no data-sets were generated or analyzed during the current study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2019.100028.

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