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Following Mycobacterium TB Infection, Eosinophils Are Rapidly Recruited to The Lung through the GPR183 Receptor

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Abstract

Eosinophil infiltration into the lungs is frequently related to type II reactions during allergic reactions and fungal and parasite diseases. However, in humans, macaques, and mice, type I inflammatory responses to Mycobacterium tuberculosis (Mtb) result in eosinophil accumulation in lung lesions, which supports host resistance. Here, we demonstrate that eosinophils enter the lungs of mice and macaques as soon as one week following Mtb exposure [1]. In mice, this influx is not dependent on CCR3, but rather needs the highly expressed oxysterol receptor GPR183 to be expressed intracellularly expressed on eosinophils from humans and macaques. Eosinophil recruitment is compromised in mice lacking the oxysterol-synthesizing enzyme Ch25h because of the direct interaction between murine eosinophils and bacilli-filled alveolar macrophages, which upregulate Ch25h [2]. Our research demonstrates that eosinophils are among the first circulation-derived cells to detect and react to Mtb infection of alveolar macrophages, and it implicates GPR183 in eosinophil migration into lung tissue.

As eosinophil migration into the lung parenchyma peaked around d14, we proposed that recruited eosinophils may be able to detect Mtb or tissue-dwelling Mtb-infected cells or perhaps interact with them. We observed dynamic interactions between eosinophils and Mtb-containing cells using live imaging of ex vivo lung explants from eosinophil EPX-reporter mice that were Mtb-cyan fluorescent protein (CFP)-infected. In the alveoli, we saw eosinophils directly engaging with Mtb or Mtb-infected cells by approaching, sluggishly approaching, and extending pseudopods toward bacilli .The frequency of Mtb-positive eosinophils was subsequently evaluated by single-cell analysis of fluorescent Mtb-mCherry and found to be significantly higher than background in a non-phagocytic SSClow, MHCIIneg, CD68neg, CD11bneg, Ly6Gneg control population (average 0.15%).

Introduction

Here, we demonstrate how exposure to Mtb causes eosinophils to be quickly drawn from the circulation into the lungs of both mice and rhesus macaques, and how these eosinophils can be shown interacting with Mtb-infected cells in mice [3-8]. The classical chemokine receptor CCR3, which controls eosinophil migration during type II inflammation, is not necessary for the recruitment of pulmonary eosinophils in mice. Instead, we demonstrate that GPR183-mediated cell-intrinsic oxysterol sensing is necessary for the best recruitment of circulating eosinophils to Mtb-infected lungs in mice [9]. Additionally, pulmonary recruitment of eosinophils is selectively upregulated in infected mouse alveolar macrophages by the oxysterol-producing enzyme Ch25h. diminished when Ch25h is absent. Therefore, our results show that GPR183-dependent oxysterol sensing is a modulator of eosinophil recruitment to the lungs and functions as an early warning system to cells in circulation signalling the presence of Mtb infection in the airways.

The intracellular bacterial pathogen that causes tuberculosis (TB), a major global cause of mortality, is Mycobacterium tuberculosis (Mtb). Host resistance to Mtb infection depends on T helper type I responses linked to the IFN- and IL-12 pathways, canonical type I immunity's defining characteristics [10-15]. Once lung airway resident alveolar macrophages (AMs) are infected by inhaled bacteria, Mtb infection has been established It is unclear in vivo what happens during the first innate cellular response after Mtb infection of AMs and before T helper cell engagement are now doing an active investigation. Early host responses in the lungs can alter cell recruitment, adaptive immunity, granuloma formation, bacterial dispersion, illness tolerance, and disease progression over the long term. The specific innate immune cell types that respond to or interact with infected AMs in the first two weeks following infection, however, are mostly unknown.

Subjective Heading

Our prior research confirmed the existence of eosinophils in nonhuman primates' (NHPs') developed TB granulomas two to three months after Mtb infection and the significance of eosinophils for host resistance in mice. However, it is unknown when granulocytes initially respond to Mtb infection of alveolar macrophages with lung invasion. Using previously published eosinophil-specific intracellular flow cytometric labelling of the granule protein eosinophil peroxidase (EPX), we measured the eosinophil response to Mtb infection in the airways of rhesus macaques throughout time . We quantified eosinophils in bronchoalveolar lavage (BAL) fluid using this method before and after bronchoscopic Eosinophils were found to be noticeably increased before Mtb instillation. Significantly increased starting from 1% to 15% of all CD45-positive immune cells recovered as early as 7–14 days post–infection (p.i). (Figure 1A). We developed an NHP granulocyte staining method based on the differential expression of

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EPX by eosinophils and myeloperoxidase (MPO) by neutrophils within an NHP granulocyte gate to investigate the kinetics of granulocyte recruitment after Mtb infection and to directly compare eosinophils to neutrophils in the same samples. The NHP granulocyte gate was based on the exclusion of CD68-expressing monocytes and macrophages and the positive expression of CD11b and CD66abce on granulocytes .Whole blood (WB) eosinophils, with an eosinophil to neutrophil ratio (E/N) of 0.1, made up roughly 10% of all CD11b+CD66abce+ granulocytes in uninfected rhesus macaques. Eosinophils, in contrast, were substantially more abundant in uninfected BAL, where they made up between 40% and 50% of the granulocyte gate and showed a significantly higher E/N ratio of 1 compared to blood.To deal with the likelihood that eosinophils were drawn in unintentionally in reaction to microtissue injury after bronchoscopy rather than in response to Mtb We conducted follow-up bronchoscopies at days 14 and 7 and observed the flow of granulocytes into the airways before infection. We discovered that the E/N ratios in the BAL obtained during these first bronchoscopies were generally steady, indicating that bronchoscopy alone was insufficient to cause fast changes in the granulocyte composition of the airways.

Discussion

Next, we tested whether eosinophils in C57BL6 mice respond quickly to low-dose aerosol Mtb infection as a model for examining the underlying processes of eosinophil recruitment. Using intravenous (i.v.) labelling to distinguish between cells in the lung vascular capillary bed and cells that trans-migrated into the lung parenchymal tissue or airways, we measured granulocyte lung migration by multi-parameter flow cytometry .A fluorescently tagged CD45 antibody was administered before to euthanasia to mark circulating (i.v.pos) cells. whereas groups of lung parenchymal cells were unharmed (i.v.neg). As early as day 4 (d4) following Mtb infection, when Mtb is virtually exclusively found in AMs eosinophils began to rapidly concentrate in the lung and were enriched primarily in the pulmonary vasculature. Contrarily, the frequency or number of neutrophils did not change until two weeks following infection (Figure 2A).

As a result, observable changes in lung neutrophil numbers and frequencies occurred more than a week before eosinophil numbers and frequencies did. Additionally, eosinophil infiltration into the lung parenchyma started on day 9 following infection, reaching its peak on day 14.Parenchymal neutrophil migration and numbers began to rapidly increase at this d14 time point, peaking at d21, coincident with a decrease in eosinophil frequencies and numbers .In contrast to ratios found in human lung tissue NHP TB granulomas or NHP BAL reported here, the overall pulmonary E/N ratio in mice was orders of magnitude lower.

The oxysterols hydroxylated at positions 7, 25, and 27 are known to permissively bind to GPR183, with 7,25-dihydroxycholesterol (7,25-di-OHC) being the preferred oxysterol .We used liquid chromatography-tandem mass spectrometry (LC-MS/MS) to directly detect oxysterols in the BAL of rhesus macaques before and after Mtb infection in order to determine whether Mtb infection caused alterations in oxysterol metabolism .Analysis was performed on signals of unesterified oxysterol that were found in more than 50% of the samples. According to the high picomolar range stated dissociation constant and allowing for BAL associated dilution of the alveolar fluid, 7α,25-di-OHC measurements were below our ∼5 nM limit of detection. Similarly, 25-hydroxycholesterol (25-HC) was below the limit of detection.

The hydroxycholesterol levels in two of the three animals under investigation showed time-dependent dynamics after infection, with changes in some classes being apparent as early as seven days after infection (Figure 5A). Out of all the detectable oxysterols, only two oxysterols significantly correlated with the E/N ratio in Mtb-infected NHP BAL, and we did not find any association between eotaxins and E/N ratios across all time points. 7,27-di-OHC, a GPR183 ligand with a mid-nanomolar dissociation constant, correlated with the E/N ratio. E/N ratios and an oxidised derivative of 7-OHC linked negatively, but 3-oxo-7-hydroxycholesterol correlated positively.To completely understand GPR183 signalling architecture at the ligand level in vivo, optimization of oxysterol airway sampling and detection is required. The biological activities of the different oxysterol metabolites in vivo are not well characterised.

Conclusion

Whole blood was used for flow cytometry, and rhesus macaque and human peripheral blood samples were both collected in EDTA tubes. Briefly, 200 mL of whole blood were added directly to antibody cocktails, which were then stained at 37 °C for 20 min. Samples, were then washed twice in 4 mL of 1% FCS/PBS. Following the manufacturer's instructions, fixable live/dead cell stain (Molecular Probes-Invitrogen) was applied. The eBioscience Transcription Factor Staining Buffer Kit (Life Technologies/eBioscience) was used to lyse red blood cells after fixing and permeabilizing the pellets. Intracellular antigen staining was then performed for 30 minutes at 4°C. For murine whole blood, 50 mL of blood samples (retro-orbital bleed) were drawn into EDTA tubes.

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Conflict of Interest

The authors declare that there are no conflict of interest.

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