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Resident Alveolar Macrophages Suppress, whereas Recruited Monocytes Promote, Allergic Lung Inflammation in Murine Models of Asthma

Zbigniew Zaslona,* Sally Przybranowski,* Carol Wilke,* Nico van Rooijen,† Seagal Teitz-Tennenbaum,*‡ John J. Osterholzer,*‡ John E. Wilkinson,*‡ Bethany B. Moore,* and Marc Peters-Golden*

The role and origin of alveolar macrophages (AMs) in asthma are incompletely defined. We sought to clarify these issues in the context of acute allergic lung inflammation using house dust mite and OVA murine models. Use of liposomal clodronate to deplete resident AMs (rAMs) resulted in increased levels of inflammatory cytokines and eosinophil numbers in lavage fluid and augmented the histopathologic evidence of lung inflammation, suggesting a suppressive role for rAMs. Lung digests of asthmatic mice revealed an increased percentage of Ly6C^hi/CD11b^pos inflammatory monocytes. Clodronate depletion of circulating monocytes, by contrast, resulted in an attenuation of allergic inflammation. A CD45.1/CD45.2 chimera model demonstrated that recruitment at least partially contributes to the AM pool in irradiated nonasthmatic mice, but its contribution was no greater in asthma. Ki-67 staining of AMs supported a role for local proliferation, which was increased in asthma. Our data demonstrate that rAMs dampen, whereas circulating monocytes promote, early events in allergic lung inflammation. Moreover, maintenance of the AM pool in the early stages of asthmatic inflammation depends on local proliferation, but not recruitment. The Journal of Immunology, 2014, 193: 4245–4253.

Asthma is a major global health problem affecting both children and adults (1). Alveolar macrophages (AMs) are key orchestrators of pulmonary immune responses (2), and under steady-state conditions they account for 95% of the leukocytes in the lower respiratory tract (3). Nevertheless, compared with studies on dendritic cells, T cells, eosinophils, and mast cells, there are very few studies examining the role of AMs in this condition, and they have been appropriately termed “the forgotten cell in asthma” (4). Resident AMs (rAMs) can actively suppress T cell proliferation induced by Ag (5) and downregulate the Ag presentation capacity of pulmonary dendritic cells (6). By virtue of these various immune-inhibitory functions, together with their ability to protect against airway hyperresponsiveness (7), rAMs might be expected to dampen immune responses and help to preserve physiologic functions of the lung. Indeed, depletion of rAMs by intrapulmonary administration of liposomal clodronate under steady-state conditions was found to increase the subsequent immune response to an intrapulmonary Ag (8).

AM depletion by this method has, however, yielded conflicting results in murine models of allergic asthma, with studies suggesting both pathogenic (9, 10) and suppressive (11, 12) roles for these cells. Inflammatory responses in the lung can lead to recruitment of monocytes with a proinflammatory phenotype (13), but the possibility that recruited AMs contribute to allergic lung inflammation in these models was not considered. Because intratracheal (i.t.) clodronate fails to discriminate between resident and recruited AMs and between differentially polarized subsets of AMs, it therefore has the potential to deplete potentially suppressive as well as pathogenic populations.

In this study, we used both i.t. and i.v. liposomal clodronate to selectively deplete rAM and circulating monocyte populations, respectively. We demonstrate that rAMs are protective in asthma, whereas recruited inflammatory monocytes—putative precursors of AMs—are pathogenic. We also show that during the early stages of allergic inflammation, maintenance of the AM pool depends on local proliferation rather than on recruitment of circulating precursor cells.

Materials and Methods

Animals

Wild-type C57BL/6 (Ly5.1; CD45.2) mice were obtained from The Jackson Laboratory (Bar Harbor, ME). B6Ly5.2 (CD45.1) mice were purchased from the National Cancer Institute Frederick Cancer Research Facility (Frederick, MD). The University of Michigan Committee on Use and Care of Animals approved these experiments.

Asthma protocols

OVA-induced acute allergic inflammation was elicited as previously described by i.p. sensitization with 20 μg OVA (Sigma-Aldrich, St. Louis, MO) mixed with 2 mg alum (Thermo Fisher Scientific, Waltham, MA) (14) on day 0, followed by two nebulizer-delivered airway challenges with 1% OVA on...
decreased by 80% (Fig. 2A). This finding could be compared with 7.6.4 FlowJo software (TreeStar, Ashland, OR).

**Results**

rAMs dampen allergic lung inflammation

To investigate the role of rAMs in allergic lung inflammation, we used a well-characterized depletion model (11). The i.t. administration of liposomal clodronate to naive mice resulted in ~80% depletion of rAMs that was evident on day 2 and that lasted through day 4 post administration (Supplemental Fig. 1A). Such treatment in naive mice resulted in minimal accumulation in BALF of leukocytes other than AMs, as determined by cytospin differential counts (data not shown); neutrophils, eosinophils, and lymphocytes were highest on day 1 post liposomal clodronate and together accounted for 6% of total BALF cells (data not shown). BALF levels of Th2 cytokines (IL-4, IL-5, IL-10, IL-13, IL-17), TGF-β, and IFN-γ protein from BALF were determined by ELISA kits following the instructions of the manufacturer (R&D Systems, Minneapolis, MN).

**Statistical analysis**

Data are presented as mean ± SEM. Statistical significance was analyzed using the GraphPad Prism 5.0 statistical program (GraphPad Software, La Jolla, CA). Comparisons between two experimental groups were performed using the Student t test. A p value < 0.05 was considered statistically significant.
large airways and characterized by infiltration of predominantly mononuclear cells and eosinophils (Fig. 1I–J). PAS staining revealed no significant increase in PAS-positive cells in mice subjected to rAM depletion (data not shown). Increased lung inflammation following rAM depletion, as indicated by BALF cytokine levels and cell counts, was confirmed in the OVA model of allergic airway inflammation (Supplemental Fig. 1B–F). Together, data from both of these models support the conclusion that rAMs constrain allergic airway inflammation.

Depletion of rAMs increases recruitment of Ly6Cpos monocytes in allergic lung inflammation

An increase in total BALF AM numbers in association with the potentiation of allergic inflammation following i.t. clodronate in allergen-challenged mice (Fig. 1B) is consistent with our previous finding of AM accumulation in allergic asthma (14). Expansion of the AM pool could occur by increased recruitment of circulating monocytes and/or increased local proliferation. We addressed the first possibility by measuring Ly6C high CD11bpos monocytes—putative precursors of AMs during inflammatory responses (22)—in lung tissue digests of mice with HDM-induced asthma. Depletion of rAMs by i.t. liposomal clodronate resulted in a significantly higher percentage of Ly6ChighCD11bpos cells in lung tissue (Fig. 3A, 3B), suggesting a contribution of circulating Ly6C high monocytes to increased lung inflammation.

Clodronate administered i.v. has been shown to deplete circulating monocytes within 4 h (18) and for a duration of ≤24 h (17, 18). Upon i.v. clodronate administration, no leukocytes other than AMs were detected in BALF of Ag-unchallenged...
mice, as determined by cytoospin differential counts (data not shown). BALF levels of Th2 cytokines, as well as IFN-γ and IL-17, were undetectable in these animals (data not shown). The i.v. administration of liposomal clodronate 8 h prior to airway challenge with HDM resulted in almost complete elimination of Ly6C\textsuperscript{high} monocytes from the lung tissue digests (Fig. 3C, 3D), establishing the importance of recruitment of Ly6C\textsuperscript{high} monocytes in allergic asthma.

Circulating precursor cells do not contribute to the AM pool in early events in asthma

Having documented above the monocyte recruitment to the lungs using i.v. clodronate, we sought to assess the contribution of the circulating progenitor cells to the AM pool by using CD45.1 (donor)–CD45.2 (recipient) chimeras. Chimeric CD45.2 mice were challenged with HDM, and the percentages of donor (CD45.1) versus recipient (CD45.2) AMs in BALF, identified as

FIGURE 2. Depletion of rAMs reduces TGF-β levels but does not affect Treg percentage in the lungs. (A) TGF-β levels were measured in BALF by ELISA in asthmatic mice subjected to depletion of rAMs. Data are expressed as the mean ± SEM from four experiments with two to three mice per group. *p < 0.05. (B) Lungs from asthmatic mice treated with i.t. liposomal clodronate (CL) or empty liposomes (control) were lavaged, perfused, and processed to obtain single-cell suspensions, as described in Materials and Methods. Gates were set to remove debris, then set on low side scatter, and Fixable Viability Dye eFluor 450 staining was used to eliminate dead cell contamination. Representative dot-plot shows CD4 and Foxp3 staining, with statistical analysis of CD4\textsuperscript{pos}Foxp3\textsuperscript{pos} cell population. (C) Mice were treated as described in (B), and data are expressed as the mean ± SEM from three experiments, each using three mice.

FIGURE 3. Recruitment of Ly6C\textsuperscript{high} monocytes in asthma. (A) Lungs from asthmatic mice treated with i.t. liposomal clodronate (CL) or empty liposomes (control) were lavaged, perfused, and processed to obtain single-cell suspensions, as described in Materials and Methods. Gates were set to remove debris, then set on low side scatter, and Fixable Viability Dye eFluor 450 staining (viability dye) was used to eliminate dead cell contamination. Representative dot-plots show the Ly6C\textsuperscript{high}CD11b\textsuperscript{pos} population denoted within the gates. (B) Statistical analysis of Ly6C\textsuperscript{high}CD11b\textsuperscript{pos} cell populations in lung digests following i.t. administration of liposomal clodronate versus control liposomes. Data presented as the mean ± SEM from four experiments, each using two to three mice per group. ***p < 0.001. (C) Lung digests from mice treated with i.v. clodronate or control liposomes were processed for staining and gated as described above. Representative dot-plots show the Ly6C\textsuperscript{high}CD11b\textsuperscript{pos} population denoted within the gates. (D) Statistical analysis of Ly6C\textsuperscript{high}CD11b\textsuperscript{pos} cell populations in lung digests following i.v. administration of liposomal clodronate versus control liposomes. Data presented as the mean ± SEM from three experiments, each using two to three mice per group. ***p < 0.001.
CD11c<sup>pos</sup> and autofluorescence (AF)<sup>high</sup>, were determined at day 9. BALF at day 9 of our protocol contained two main leukocyte populations—namely, eosinophils and AMs—as evidenced by Wright–Giemsa staining of BALF cytospins. AMs were gated based on forward scatter and side scatter to remove cell debris, negative staining for cell viability dye, and positivity for CD11c and AF<sup>high</sup> (Fig. 4A), and analyzed for their expression of CD45.1 and CD45.2 markers (Fig. 4B). The percentage of AMs in BALF of donor origin (CD45.1<sup>pos</sup>) was similar between asthmatic mice and irradiated nonasthmatic controls (Fig. 4C). This finding suggests that although recruitment of Ly6C<sup>pos</sup> cells to the lung occurs, it does not contribute to accumulation of cells identified as AMs during the early events of asthma, as also demonstrated previously for AMs under steady-state conditions (23).

**Depletion of circulating monocytes attenuates allergic lung inflammation**

Having established that recruitment of circulating monocytes may not contribute to the accumulation of AMs in asthma, we next sought to interrogate their biologic role in allergic inflammation using i.v. clodronate depletion before each airway challenge with HDM (Fig. 5A). This procedure resulted in attenuated parameters of allergic asthmatic inflammation, including decreased cytokine levels, such as those of TGF-β (Fig. 5C–I), decreased eosinophil numbers (Fig. 5B), and decreased histologic evidence of inflammatory cell infiltration (Fig. 5J–K). Although levels of IL-13 and IFN-γ were higher in Fig. 5 than in Fig. 1, these data derived from different experiments; when compared directly within the same experiment, administration of control liposomes i.v. versus i.t. resulted in cytokine levels that were similar and comparable to those in Fig. 1 (data not shown).

Blood monocyte depletion did not affect numbers of total cells, neutrophils, or AMs (Fig. 5B) in BALF, verifying the observations from chimeric mice that recruited monocytes did not contribute to the maintenance of the AM pool. In the OVA model (Supplemental Fig. 2A), depletion of circulating monocytes caused a significant decrease in BALF eosinophil numbers and total leukocytes (Supplemental Fig. 2B) and caused a nonsignificant reduction in cytokines (Supplemental Fig. 2C–E). H&E staining revealed visible and significant attenuation of inflammatory cell infiltration in mice receiving i.v. liposomal clodronate (Supplemental Fig. 2F, 2G). Taken together, these findings demonstrate the proinflammatory and pathogenic role of circulating monocytes, in opposition to the inhibitory role of rAMs, in allergic lung inflammation.

**Proliferation of AMs in allergic asthma**

Although tissue macrophages, including AMs, have long been thought to derive predominantly from precursor blood monocytes (24, 25), recent studies have challenged this paradigm by identifying a crucial role for local proliferation in the maintenance of tissue macrophage numbers during both steady-state (26–28) and Th2 inflammatory (29) conditions. In fact, in a helminth infection model of Th2 inflammation, macrophage accumulation in the peritoneum was exclusively attributable to local proliferation (29). Although AM proliferation has been demonstrated in response to environmental toxins (30, 31) and cytokines (32–34) and in the context of pulmonary sarcoidosis (35), it has never been reported in experimental models of allergic asthma. We used staining of the proliferation-associated nuclear protein Ki-67 to assess proliferation of AMs, defined as CD11c<sup>pos</sup> SiglecF<sup>pos</sup> cells (23), from PBS-or HDM-challenged mice (Fig. 6A). The utility of this index of proliferation was verified by experiments demonstrating >95% Ki-67 positivity during log-phase growth of monocytic leukemia U937 cells (data not shown). The proportion of proliferating AMs in BALF from control mice was ∼10% (Fig. 6B), consistent with a contribution of local proliferation to the pool of rAMs during steady-state conditions. The proportion of proliferating AMs in BALF from asthmatic mice was not significantly different from that from control mice (Fig. 6D). However, when we analyzed...
AMs from lung digests (Fig. 6C) we did observe a significant increase in the proportion of proliferating cells in asthmatic compared with control mice (Fig. 6E). This difference from AMs recovered in BALF might reflect the fact that lung digests contained mostly nonlavageable AMs, because most lavageable cells would have been removed by repeated lavage performed prior to digestion. Nonlavageable AMs are presumed to be strongly adherent to epithelial cells and perhaps more activated (36). A higher percentage of Ki-67 positivity was also noted in nonlavageable (Fig. 6C) than in lavageable (Fig. 6B) AMs from control mice, which supports the likelihood of intrinsic differences between these two subpopulations. These results suggest a contribution of local proliferation to maintenance of the AM pool during the early inflammatory events in allergic asthma.

**FIGURE 5.** Depletion of circulating monocytes attenuates allergic lung inflammation. (A) Schematic representation of the protocol for i.v. administration of liposomal clodronate (CL) relative to HDM challenge. Asthmatic mice treated with i.v. clodronate or empty liposomes (control) were sacrificed at day 9 of the protocol. (B) Total BALF cells, eosinophils, macrophages, and neutrophils were determined by counting under light microscopy; differential cell count after Wright–Giemsa staining was performed on 300 cells. (C–I) Cytokines in BALF of asthmatic mice were assessed by ELISA following depletion of circulating monocytes. Data presented in all panels are expressed as the mean ± SEM from four experiments, each using two to three mice per group. *p < 0.05, **p < 0.01. (J) Representative lung sections stained with H&E (original magnification ×10) to visualize peribronchial leukocyte infiltration and thickened smooth muscle tissue (arrow). (K) Quantitation of inflammation area (square micron per micron of basement membrane) in H&E-stained lung of asthmatic mice treated with i.v. liposomal clodronate or empty liposomes (control). Data presented in (J) are expressed as the mean ± SEM from 10 bronchi from each of three experiments with two mice per group.*p < 0.05.
Discussion

In this study, we have used both HDM and OVA mouse models to interrogate the roles of macrophages in allergic inflammation in the lung. We have shown that depletion of rAMs increased allergic lung inflammation, verifying the protective role of rAMs in models of allergic asthma. In distinct contrast, we have demonstrated the pathogenic role of circulating monocytes in early allergic inflammation. Finally, we have delineated the contributions of recruitment and local proliferation to maintenance of the AM pool in allergic asthma.

In considering the potential mechanisms by which rAMs mediate protection against allergic inflammation, we profiled BALF levels of potentially anti-inflammatory cytokines. Although levels of one such inhibitory cytokine, IL-10, were increased following rAM depletion, levels of another, TGF-β, were decreased. Activated AMs secrete TGF-β (37), and a recent study suggested that lung tissue macrophages promote airway tolerance by elaborating TGF-β, which in turn induces Tregs (21). We quantified the frequency of Tregs in the lungs of allergen-challenged mice but observed no reduction following rAM depletion. These data suggest that rAMs suppress allergic inflammation by a mechanism independent of Treg generation. Although TGF-β can inhibit both Th1 and Th2 immune responses independent of Treg induction (38, 39), the fact that TGF-β levels in BALF were reduced following elimination of circulating monocytes—an intervention that led to attenuation of asthma—argues for a mechanism not involving TGF-β. A number of years ago, elimination of rAMs was found to upregulate the capacity of lung DCs to present Ag to T cells (6), and suppressive effects of rAMs on DC-mediated allergic inflammation were recently described in a rat model (40). The mechanisms underlying rAM-mediated inhibition of DC functions remain to be determined, but this phenomenon may represent an important means of immune control in the lung in a broad variety of circumstances also beyond asthma.

Although our findings are consistent with a body of literature demonstrating that depletion of rAMs prior to lung challenge increases pulmonary immune responses (8, 11, 12, 41), contrary results have been reported in studies in which depletion was performed on AMs previously polarized toward an M2 phenotype (10) or during allergic inflammation (9). These observations suggest that allergic inflammation results in an alteration of AM phenotype characterized by a loss of inhibitory function. The fact that the development of allergic asthma was favored when rAMs were depleted from rats that were allergy resistant, but not from those that were allergy susceptible (7), emphasizes the important braking function of AMs on pulmonary immune responses. Of interest, Ag sensitization per se was sufficient to abrogate this braking function of AM (42), further demonstrating the exquisite plasticity of these cells.

In the current study, we also sought to understand how maintenance of the AM pool is controlled in asthma. Although AMs have been demonstrated to proliferate in response to environmental factors (30) or endogenous molecules (32, 33), recent studies have focused...
on macrophage proliferation in the context of Th2 disease (29). To
devote the importance of recruitment in maintenance of the AM
pool, we used a chimera model, because differentiation of recruited
and resident macrophages based on markers can be challenging to
interpret. These experiments showed that irradiated and subse-
quently Ag-exposed mice had no greater proportion of circulating
precursor cells within their AM pool than did irradiated controls.
However, Ki-67 staining demonstrated a role for local proliferation
in maintenance of the AM pool. Of interest, this increase in pro-
iferation of AMs was demonstrable only in cells obtained from
lung digests that are enriched in nonlavageable AMs, and not in
lavaged AMs. The resistance to recovery of nonlavageable AMs
may reflect a greater degree of adherence, owing to either a greater
degree of activation and/or preferential localization in inflamed
areas of lung. Possible phenotypic differences between lavageable
and nonlavageable subpopulations of AMs will require further in-
vestigation in future studies. The factor(s) responsible for driving
AM proliferation in this context remain to be determined, but
candidates might include M-CSF, GM-CSF, and IL-3 (32, 33, 43).

In contrast to rAMs, depletion of circulating monocytes revealed
their pathogenic role in allergic inflammation, mainly by affecting
lung eosinophilia and cytokine levels. Candidate molecules re-
ponsible for recruiting monocytes may include chemokines such as
CCL2 or CCL5 (44), or the cytokine IL-17, which has previ-
ously been implicated in AM accumulation (45). As noted previ-
ously, the fact that BALF TGF-β levels decreased upon monocyte
depletion in parallel with those of all other measured cytokines
argues against the importance of TGF-β as an inhibitory factor
in our asthma model. A pathogenic role for monocytes might be
explained by previous observations identifying circulating
monocytes from asthmatic persons as a source of IL-5 (46–48),
which is an eosinophil chemotactrant. Finally although our data
fail to support that circulating monocytes serve as precursors for
AMs, previous studies have shown that blood monocytes can be
precursors for lung dendritic cells both in steady-state conditions
(49) and in models of allergic asthma (50) and infectious lung
disease (51, 52). Indeed, the importance of monocytes as pre-
cursors of CD11b<sup>high</sup> dendritic cells in initiating (by Ag presen-
tation) and maintaining (by chemokine generation) HDM-induced
allergic inflammation was recently demonstrated (53). Therefore,
in our study we cannot exclude the possibility that increased
Ly6C<sup>high</sup> monocytes present in the lung upon rAM depletion
could cause augmented allergic responses by their potential to
differentiate into lung dendritic cells.

Although both asthma models deployed in our study yielded very
similar results when rAMs were eliminated, some differences did
arise upon monocyte depletion. In the HDM model the decrease in
lung cytokine levels in mice treated with clodronate i.v. was very
substantial, whereas in the OVA model there was merely a trend
forward their diminution. Apart from the obvious difference in the
allergen itself, this finding could reflect a difference in the route of
allergen sensitization. We speculate that Ag sensitization in the
lung may be associated with a more pronounced role for monocyte
recruitment. Whether blockade of AM proliferation would yield
results similar to those of inhibition of recruitment remains an
intriguing question. It is alternatively possible that AM proliferation
and monocyte recruitment promote different aspects of asthmatic
lung inflammation.

Another important issue arising from our findings is how pro-
liferation and possibly recruitment affect AM polarization. In
a skin allergy model, Ly6C<sup>high</sup> inflammatory monocytes recruited to
a Th2 tissue environment acquired an M2 phenotype and exerted
anti-inflammatory functions (54), whereas CCR2-deficient mice
that exhibit impaired recruitment of monocytes had exacerbated
inflammation (54). Of note, CCR2-deficient mice exhibited en-
hanced allergic airway responses in two different murine models
(55, 56). Monocytes recruited to the lung have been demon-
strated to lose their proinflammatory properties with time (57).
In this article, we have looked exclusively at early inflammatory
responses, and we cannot exclude the possibility that depletion
of monocytes at later stages of allergic inflammation could yield
different results. Alternatively, CCL2—CCR2 signaling may in-
fluence other relevant phenomena besides merely recruitment.

Defining the relative contributions of monocyte recruitment and
AM proliferation in chronic asthma models, as well as investi-
gating the polarization status of recruited versus locally prolif-
erating macrophages, will shed additional light on the roles of
AMs not only in asthma but also in other forms of allergic lung
inflammation.

Disclosures
The authors have no financial conflicts of interest.

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