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INSIGHTS

Eosinophils can more than kill

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In this issue of *JEM*, Arnold et al. (https://doi.org/10.1084/jem.20172049) demonstrate that eosinophils suppress mucosal inflammation by directly interacting with pro-inflammatory Th1 cells. This emphasizes the dual role of eosinophils, which can act both as effector cells that control an infection and as immunomodulatory cells that promote immune homeostasis.

It will come as a great surprise to most immunologists to learn from the paper of Arnold et al. that eosinophils are not just dangerous effector cells, which release tissue-damaging mediators that promote allergic disorders and are responsible for the exacerbation of allergen-induced asthma, but that they also do good. Under normal conditions and also during infection with *Helicobacter pylori*, eosinophils exert immune regulatory functions in that they suppress Th1 immune responses and promote immune homeostasis in the gastro intestinal (GI) tract.

Recent publications have already suggested that eosinophils contribute to immune homeostasis. Thus, in the lung a population of resident eosinophils suppresses maturation of antigen-loaded dendritic cells, and hence sensitization to allergens. In the absence of these "homeostatic" eosinophils, there is a massive increase in Th2 responses in the lung tissues (Mesnil et al., 2016). Furthermore, in mice infected with the parasitic nematode *Heligmosomoides polygyrus*, which infects the GI tract, the absence of eosinophils caused an enhanced Th2-type response in the Peyer's patches (PPs), and class switching to IgA was impaired (Strandmark et al., 2017). In this case, eosinophils are required to control exaggerated Th2-type responses in the follicular structures of PPs. Now, Arnold et al. (2018) demonstrate that eosinophils are required to dampen Th1 responses in the gastric tissues.

The chemokine eotaxin attracts eosinophils to the GI tissues during fetal life (Rothenberg et al., 2001). This homing of eosinophils is thus independent of the microflora, which populate the gut lumen only after birth. Little is known about the function of these eosinophils, although they constitute a major cell population in the lamina propria (LP). In the absence of eosinophils, PP development is affected and an unbalanced microbiota develops, which may contribute to reduced local TGFβ levels and a consequent reduction in switching to IgA (Chu et al., 2014; Jung et al., 2015). These observations suggest that eosinophils contribute to gut immune homeostasis, an interpretation that is strengthened and extended by the results of Arnold et al. (2018) showing that eosinophils are required to restrict bacteria-induced intestinal inflammation by interacting with pro-inflammatory Th1 T cells.

This scenario was dissected using two infection models, the first of which involves *H. pylori*. This bacterium has coevolved with humanity and now lives in the stomachs of roughly half of the human population. Host and bacterium live in a state of armed neutrality—the bacterium generally behaves itself, and the host, for its part, generally leaves the bacterium in peace. How is the host's peaceful coexistence with *H. pylori* enforced? It now turns out that this is achieved by the action of eosinophils that suppress mucosal Th1 immune responses to *H. pylori*. Infection of mice with *H. pylori* alarms the immune system, and in eosinophil-deficient mice (PHIL mice, in which eosinophil development is prevented by expression of diphtheria toxin under the control of an eosinophil-specific peroxidase or C57Bl/6J mice treated with anti–IL-5 antibodies), this infection induces a strong Th1 and to some extent a Th17 response. The frequency and the absolute number of IFN-γ$^+$ Th1 T cells increases in the LP of the gastric

Insight from Claudia Berek.

tissue, and these T cells up-regulate expression of pro-inflammatory mediators such as TNFα and IL-1β, as well as of the anti-microbial enzyme Nos2. As a consequence, *H. pylori* colonization of the stomach is controlled. Surprisingly, things are quite different when wild-type animals are infected. In these mice, eosinophils are present, and yet the inflammatory response is much less apparent. Indeed, 12 wk after infection, ~10 times as many *H. pylori* are found in the stomach of wild-type mice than in eosinophil-deficient PHIL mice. This reduction in colonization may be due, at least in part, to the impaired mucus formation that is seen in eosinophil-deficient mice and may hinder normal homing of *H. pylori* to the stomach (Chu et al., 2014; Jung et al., 2015).

Eosinophils respond vigorously to the infection with *H. pylori*, which induces a strong influx of these cells from the bone marrow, augmenting the number of eosinophils both in the gastric LP and in mesenteric lymph nodes. In addition, eosinophils are indeed activated by the presence of *H. pylori*, for in infected animals these cells show enhanced expression of the activation markers SiglecF and CD11b, and their gran-

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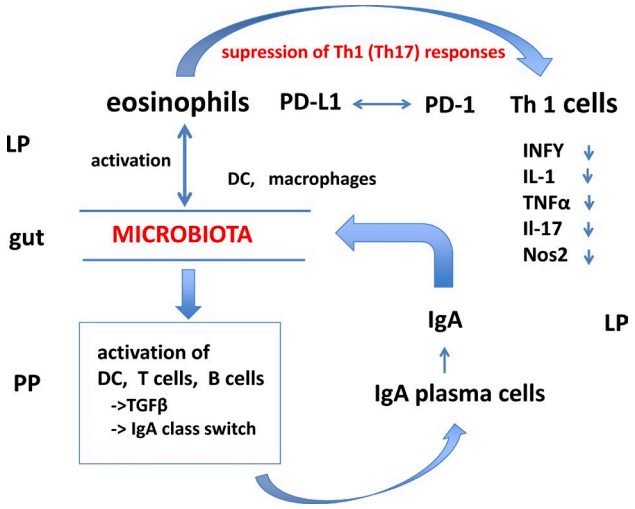


The role of mucosal eosinophils. In the presence of activated eosinophils, Th1 cells down-regulate (↓) cytokine expression. Peyer's patches (PP) and lamina propria (LP) are indicated.

ularity is higher than that of eosinophils in uninfected controls. Furthermore, gene expression profiling showed up-regulation of numerous genes, in particular, interferon response genes. However, expression of CD63, a marker for degranulation, is not enhanced in eosinophils in wild-type mice infected with *H. pylori*, and the frequency of Annexin V$^+$ eosinophils is decreased, suggesting that their viability is sustained.

The second infection model used involved *Citrobacter rodentium*, a mouse pathogen, which serves as a model of enteropathogenic *Escherichia coli* in humans. The response of eosinophils to infection with *C. rodentium* is surprisingly different from their response to *H. pylori*. Eosinophils do to *C. rodentium* what one might expect from them: they degranulate and release cytotoxic substances such as major basic protein, eosinophil peroxidases, and bactericidal metabolites. In addition, eosinophils throw out mitochondrial DNA as extracellular DNA traps, in which the *C. rodentium* is entangled and killed. As a result, in animals with functional eosinophils, the number of colony-forming units in the colonic tissues is much reduced.

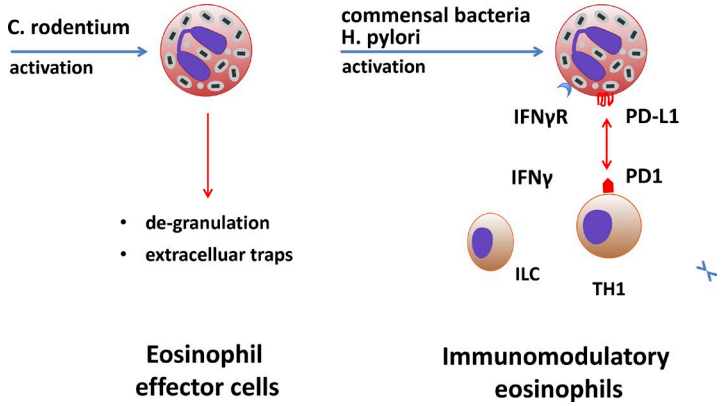
It seems that in the long period of coevolution of *H. pylori* and humans, eosinophils have acquired immunomodulatory functions that prevent gastric immunopathology and enable *H. pylori* to survive for decades in the stomach without inducing a detrimental inflammatory reaction. In vitro coculturing of eosinophils and T cells showed that *H. pylori*–educated eosinophils up-regulate PD-L1, and only those PD-L1–expressing eosinophils have the ability to suppress T cell proliferation. Direct contact between T cells and eosinophils is required to induce their immunoregulatory function. However, blocking the PD-1/PD-L1 interaction only partly inhibits the immunomodulation, suggesting that there are additional signals required to drive suppression of mucosal Th1 immune responses induced by bacterial antigens.

The finding that the level of the Th2 cytokine IL-4 is comparable in wild-type and eosinophil-deficient mice supports the notion that the observed effects are not simply the result of a preferential Th2 conditioning of wild-type Th cells. Instead, to exert their suppressive function, eosinophils require the Th1 cytokine IFN-γ. Animals with an eosinophil-specific deficiency in IFN-γR expression demonstrate the dependence on cell-autonomous IFN-γ signaling for PD-L1 up-regulation and the subsequent development of immunomodulatory capability. Indeed, animals with eosinophil-specific deficiency of the IFN-γR resemble the phenotype of eosinophil-deficient PHIL mice.

The response to *H. pylori* is comparable to the normal situation when eosinophils come in contact with commensal bacteria or their products. Again, eosinophils showed elevated granularity, and enhanced expression of SiglecF and CD11b as compared with eosinophils isolated from the LP of animals treated with antibiotics. Nevertheless, here the interaction with bacterial antigens does not induce an inflammatory response. This raises the question as to what *H. pylori* has in common with commensal bacteria, or, put another way, what distinguishes *H. pylori* from a pathogenic bacterium. One would have expected that direct contact of eosinophils with live bacteria would induce activation and degranulation or extracellular trap formation. However, this is not what is seen when eosinophils are cultured with *H. pylori*, indicating that there are still large gaps in our understanding of the mechanisms of eosinophil activation and differentiation.

In numerous publications, a population of GR1^{lo}, F480$^+$, and CD11b$^+$ myeloid-derived suppressor cells (MDSCs) is described that accumulate in practically all cancer patients (Ostrand-Rosenberg and Fenselau, 2018). As MDSCs inhibit T cell–mediated anti-tumor immunity, this has opened the way to new cancer therapies. In light of the results described by Arnold et al. (2018), it may be worthwhile to reexamine whether, in addition to macrophages and neutrophils, eosinophils also contribute to the heterogeneous population of MDSCs.

It has taken more than 100 years for our understanding of eosinophil biology to mature from the view that these cells



Pathways of eosinophil activation and differentiation.

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are aggressive hooligans to the emerging consensus that they are educated team players, having essential roles in immune responses and in tissue repair and remodeling (Lee et al., 2010). The fascinating results of Arnold et al. (2018) are a milestone in this way. Despite our ignorance of eosinophil function, increasing numbers of patients, mainly those with frequent asthmatic exacerbations, are treated with eosinophil-depleting therapies (Gleich et al., 2013). The finding that eosinophils have a critical role in mucosal immune homeostasis suggests that these patients should be carefully monitored to ensure that they do not become predisposed to inflammatory conditions.

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