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Regulation of neutrophils in type 2 immune responses

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Type 2 immune responses contribute to the resistance to helminths and toxins as well as several physiological processes. Although they usually do not participate in type 2 immune responses, neutrophils have been shown in mice to enhance the anti-helminth response, but they also contribute to increased target tissue damage. Increased pathology and morbidity is also observed in type 2 immune-mediated disorders, such as allergic asthma, when neutrophils become a predominant subset of the infiltrate. How neutrophil recruitment is regulated during type 2 immune responses is now starting to become clear, with recent data showing that signaling via the prototypic type 2 cytokine interleukin-4 receptor mediates direct and indirect inhibitory actions on neutrophils in mice and humans.

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Introduction

The distinction into different types of immune responses, such as type 1, type 2 and type 3 immunity, is perhaps best illustrated in $CD4^+$ T cells, although other adaptive and innate immune cells also follow these patterns [1,2]. Thus, upon first exposure to their cognate antigen, naïve $CD4^+$ T cells are able to differentiate into different subgroups depending on the stimuli they receive. These subgroups include type 1T helper (T_H1), T_H2, and T_H17 cells, as well as regulatory T cells [3]. T_H2 cells alongside type 2 innate lymphoid cells, basophils, eosinophils, and mast cells are the characteristic immune cells found in type 2-mediated immunity. Together with epithelial cells, these leukocytes secrete the type 2 cytokines interleukin (IL)-4, IL-5, IL-9, IL-13, IL-25, IL-33, and thymic stromal lymphopoietin (Figure 1).

Type 2 cytokines promote the differentiation of naïve T cells to T_H2 cells, B cell antibody production and isotype switching to IgE, expansion of eosinophil and basophil granulocytes (eosinophils and basophils, respectively), mast cell stimulation, development of alternatively-activated macrophages (also named type 2 macrophages), and goblet cell hyperplasia [4]. Although neutrophil granulocytes (neutrophils) are typically associated with type 1 and type 3 immunity, their role in type 2 immunity is less clear. Evidence from mouse models demonstrated that IL-17 and neutrophils help the early response against helminth infection, which however also results in increased tissue damage [5–7,8••,9]. Moreover, the presence of neutrophils in type 2 inflammatory disorders has been associated with unfavorable disease course [10–13]. In mouse models, neutrophils have been shown to contribute to allergic contact hypersensitivity [14,15] and anaphylaxis [16]. However, neutrophils can also be conspicuously absent in situations of type 2 inflammation and infection that they usually control [17–19], and recent data show an inhibitory role of type 2 cytokines for neutrophils [20••].

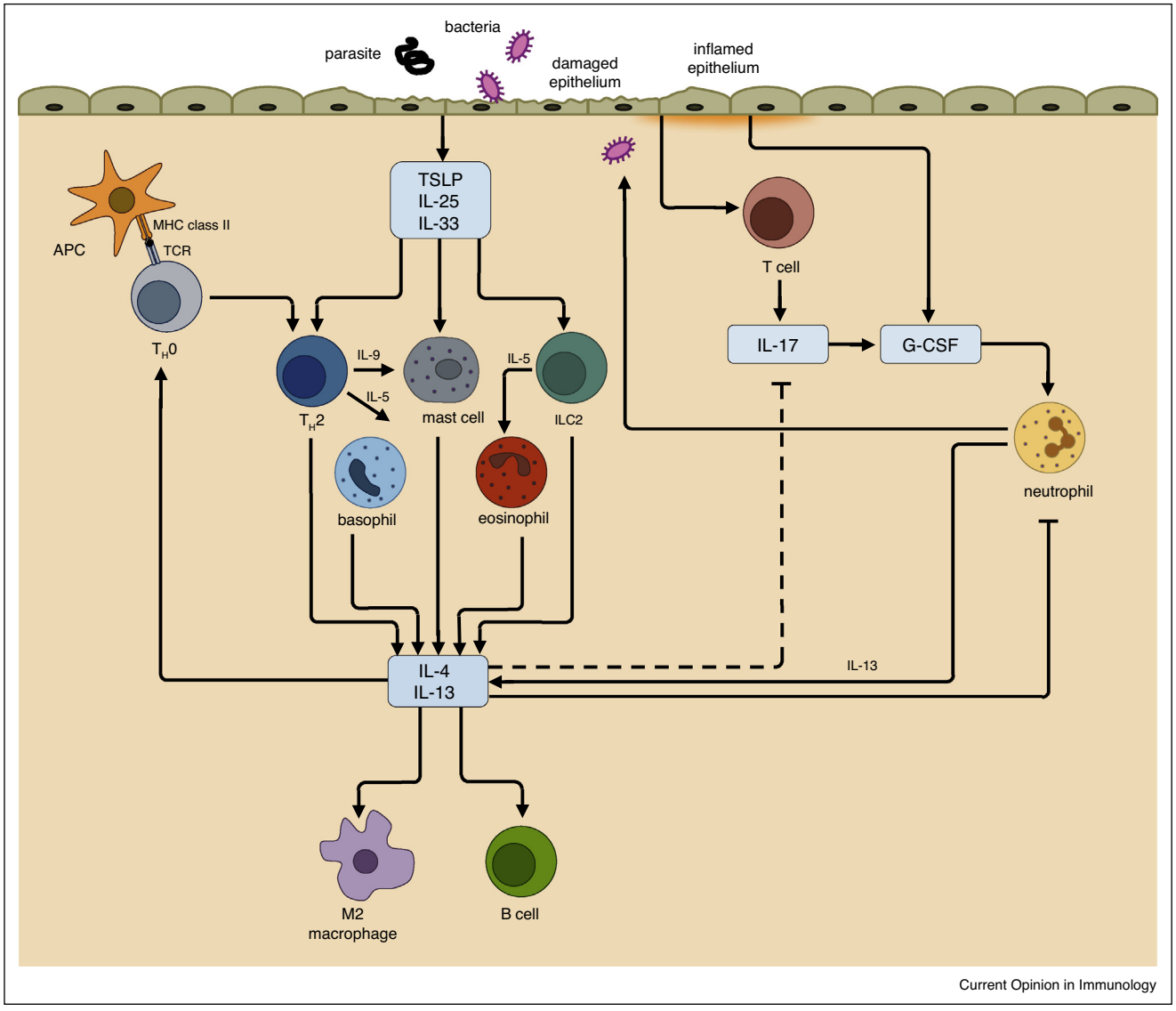
These findings leave a somewhat confusing picture of the contribution of neutrophils to type 2 immune responses and, *vice versa*, their regulation by type 2 mediators. In this review article, we briefly recapitulate the functions of type 2 immunity as well as of neutrophils, before discussing the relationship of these seemingly different actors.

Beneficial and harmful roles of type 2 immunity

Signaling through the IL-4 receptor (IL-4R) α plays an important role in the establishment and maintenance of type 2 immune responses [21]. IL-4Rα constitutes a receptor subunit for both IL-4 and IL-13 signaling. The type 1 IL-4R is composed of IL-4Rα and common gamma chain and the type 2 IL-4R consists of IL-4Rα and IL-13Rα1. IL-4 can bind to and signal via both IL-4R types. Unlike IL-4, IL-13 can only signal via the type 2 IL-4R. Moreover, association of IL-13 with IL-13Rα2, a decoy receptor, does not induce signaling (Figure 2) [22].

The main roles of type 2 immunity are inactivation of toxins as well as induction of resistance and tolerance to helminth

Figure 1



Proposed interactions between type 2 immune mediators and neutrophils. Epithelial damage results in the release of interleukin-25 (IL-25), IL-33 and thymic stromal lymphopoietin (TSLP). This in turn leads to stimulation of immune cells that produce type 2 cytokines. Besides type 2 helper T (T_H2) cells that produce IL-4, IL-5 IL-9 and IL-13, type 2 innate lymphoid cells (ILC2) are also known to produce IL-4, IL-5 and IL-13 [70]. Furthermore, IL-4 can be produced by basophils (*in vivo* evidence) [71], mast cells (*in vivo*) [72] and eosinophils (*in vivo*) [73], and IL-13 by basophils (*in vitro*) [74], mast cells (*in vitro*) [75,76] and eosinophils (*in vitro*) [77]. These cytokines in combination with activated antigen-presenting cells (APC) are able to cause naïve $CD4^+$ T cells (i.e. unskewed T_H0 cells) to differentiate into T_H2 cells and further contribute to the production of type 2 cytokines. These type 2 cytokines also stimulate isotype switching of B cells and production of IgE, activation of eosinophils, and stimulation of alternatively-activated macrophages (also named type 2 (M2) macrophages). Moreover, injury of epithelial cells can lead to IL-17 production by T_H17 and γδ T cells. IL-17 in turn activates neutrophils via granulocyte colony-stimulating factor (G-CSF), stimulates endothelial cells to secrete neutrophil attractant chemokines, and has been proposed to stimulate T_H2 cells, ILC2, and neutrophils to produce IL-13 (at least on RNA level) [6]. Additionally, G-CSF is also released by epithelial cells upon inflammation. Providing a negative feedback loop, type 2 cytokines are able to curb down neutrophils, either via direct inhibition of migration and function or indirectly via interfering with IL-17 production.

infections [23,24]. Type 2 immunity is also well known for its role favoring tissue repair [25] and it contributes to metabolism, thermogenesis and weight regulation [26–30]. Furthermore, IL-4 and IL-13 have been shown to play an important role in cognitive memory and learning via their stimulatory effect on astrocytes [31,32].

Another important aspect of type 2 immunity is its counteracting effects on type 1 immune responses,