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IL-17 and neutrophils: unexpected players in the type 2 immune response

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The study of immunity to helminth infection has been central to understanding the function of type 2 cytokines and their targets. Although type 2 cytokines are considered anti-inflammatory and promote tissue repair, they also contribute to allergy and fibrosis. Here, we utilise data from helminth infection models, to illustrate that IL-17 and neutrophils, typically associated with pro-inflammatory responses, are intimately linked with type 2 immunity. Neutrophils work with IL-4R α -activated macrophages to control incoming larvae but this comes at a cost of enhanced tissue damage. Chitinase like proteins (CLPs) bridge these diverse outcomes, inducing both protective IL-17 and reparative Th2 responses. Dysregulation of CLPs, IL-17 and neutrophils likely contribute to disease severity and pathology associated with type 2 immunity.

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Introduction

It has long been appreciated that type 2 immunity is critical for the control of helminth infections, while also contributing to allergic pathology [1]. More recently, type 2 cytokines have been shown to be unexpected but important players in healthy host metabolism, wound repair and even regulation of body temperature [2]. Indeed, the evolutionary association of type 2 immunity with helminth infection may in part be related to the damage these parasites cause [3] as well as the nutritional demands they place on the host [4]. Adaptive Th2 responses thus likely evolved not only to reduce parasite burden, but foster repair and maintain physiological balance. Moreover, the need to rapidly return the host to

homeostasis [3,5] would apply not only to helminth infection but physical insults in general [6,7].

Understanding how type 2 cytokines regulate such diverse processes as helminth killing, tissue repair, host energy balance and thermoregulation is a serious challenge. However, studying helminth infections will be a major route to enlightenment. From plants to fish, and from domesticated mammals to wild mammal populations, helminth burden is directly and negatively correlated with host fitness [8–11]. Metazoan parasites are therefore likely to have been a central evolutionary force in the shaping of type 2 immune pathways. In a telling example from the unmanaged population of Soay sheep on St Kilda, parasitic nematodes especially in combination with malnutrition and severe weather, are the major determinants of failure to survive [8,12,13,14]. Thus, regulating energy metabolism and body temperature may be crucial to reproductive success in the face of helminth infection, providing a possible explanation for the association of type 2 immunity with these seemingly unrelated processes.

The well-documented downregulation of type 1 immunity by type 2 cytokines can also be understood in the context of adaptation to helminth infection. Faced with large tissue migrating parasites, suppression of a pro-inflammatory type 1 response, would prevent collateral damage to the host as well as facilitate wound healing [3]. More unexpectedly, there is emerging evidence of a positive link between type 2 immunity and IL-17, that may explain some of the more severe pathological consequences of type 2 immunity such as fibrosis and asthma [15]. In this review, we will discuss what has been learned from helminth infection models about the central role of macrophages in type 2 immunity and what we are now learning about their critical interactions with neutrophils and IL-17.

Macrophages – a paradigm for type 2 immunity

Type 2 immunity is a highly complex multi-cellular, multi-factorial system characterized by the cytokines IL-4, 5, 9, 10 and 13 [1]. The IL-4R α chain, a component of both the IL-4 and IL-13 receptor, is fundamental to type 2 immune function [1]. Expression and engagement of IL-4R α on immune effector cells (e.g. macrophages, B cells) and tissue cells (e.g. smooth muscle, epithelial cells) dictates the outcome of a type 2 immune response. Loss of the IL-4R α will render experimental animals more susceptible to infection with nematodes highlighting the importance of type

2 immunity for resistance to helminth infection [16–18]. The impact of type 2 cytokines is not limited to any particular cell, tissue or body system but a central player is the macrophage, present in virtually all tissues of the body and strongly responsive to IL-4 and IL-13. IL-4R α activated macrophages (M ϕ (IL-4)) have a highly distinctive expression profile *in vivo*, characterized in mice by the production of the chitinase-like protein Ym1, RELM α and arginase among others [17,19]. Unravelling macrophage function in response to IL-4R α signalling has opened doors to the enormous spectrum of type 2 immune effector functions [17].

Although the evidence was slow to emerge, M ϕ (IL-4) have a central role in host resistance to nematode infection. A seminal study by Anthony *et al.* demonstrated that clodronate-mediated monocyte depletion prevents worm expulsion from the intestine during secondary infection with the gastrointestinal nematode, *Heligmosomoides polygyrus* [20]. More recently Fc receptor engagement has been shown to play an essential role in activating macrophages to immobilise migrating *H. polygyrus* larvae [21]. Larval trapping *in vitro* did not require the IL-4R α , but it may be required *in vivo* to generate sufficient macrophage numbers [21,22]. Critically, the effects of macrophages on helminth control are not always direct. For example, macrophage depletion alters intestinal smooth muscle function that is needed to expel the hookworm-related nematode, *Nippostrongylus brasiliensis*, from the small intestine [23]. All three of these studies implicated arginase as an important anti-parasite mediator although the IL-4R α was not always required for its expression [21].

Beyond their roles in host resistance, it is evident that macrophages, like type 2 immunity itself, are needed for host tolerance to the damaging effects of infection. For example, many of the type 2 immune pathways involved in host resistance, such as arginine metabolism, are also directly involved in tissue repair [reviewed in [24]]. Indeed, the key markers of M ϕ (IL-4) *in vivo*, Ym1, RELM α and arginase are all associated with injury independently of exposure to helminth infection [25]. The best evidence that macrophages contribute to repair comes from a study in which M ϕ (IL-4) are needed to limit excessive damage caused by migration of *N. brasiliensis* larvae through the lung en route to the intestine [26**]. The well-documented anti-inflammatory properties of M ϕ (IL-4) [24] are key to their wound repair functions, as suppression of classical inflammation is needed for repair to progress [27].

Finally, one of the most exciting areas in type 2 immunity research is energy metabolism. Pro-inflammatory macrophages utilise aerobic glycolysis for energy, while the stat-6 dependent transcription programme of M ϕ (IL-4) relies on fatty acid oxidation [28]. The divergence in metabolic programme is not only evident within macrophages, but

type 2 cytokines can alter the whole body metabolism with major implications for conditions such as obesity and diabetes prevalent in western, helminth-free societies [29]. In the context of resistance to helminth infection, fatty acid oxidation has been shown to be important for IL-4 mediated protection against *H. polygyrus* [30]. However, the consequences of a type 2 mediated metabolic shift for helminth infection remains to be explored more broadly and may relate to the ability of the host to cope with infection when nutritionally compromised.

Neutrophils and type 2 cytokines

As knowledge of macrophage activation by type 2 cytokines grows, there is increasing evidence that these cells rarely act alone to mediate their effector functions. Not surprisingly, eosinophils are essential partners in the performance of type 2 functions [31–33]. More unexpectedly, a number of studies have revealed that macrophages can also act in partnership with neutrophils, to contain or kill nematode parasites. Neutrophils have been described in the macrophage-rich nodules that form around the adult filarial nematode *Litomosoides sigmodontis* in the pleural cavity [34] and the cysts containing *H. polygyrus* larvae in the intestine [20,35]. In *L. sigmodontis* infection, blockade of the type 2 cytokine IL-5 prevented neutrophil accumulation, nodule formation and led to parasite survival [34]. More recently, neutrophils and macrophages have been shown to collaborate in the immobilization and killing of larval stages of the parasitic nematode *Strongyloides stercoralis* [36*]. This joint venture between neutrophils and macrophages is complement dependent [36*] and can also involve neutrophil extracellular traps (NETs) [37]. The requirement for complement is interesting in light of evidence that M ϕ (IL-4) at that site of nematode infection make abundant C3 [38].

Considering the strong link between neutrophils and type 1 pro-inflammatory processes that are typically suppressed by IL-4 [39,40], the association of neutrophils with type 2 immunity has been somewhat surprising. This likely reveals our ignorance of the full capacity of neutrophil function beyond their well-known roles in inflammatory tissue damage and protection against bacterial infection [41]. The idea that neutrophils have distinct subsets, akin to macrophage activation pathways, was presented by Tsuda *et al.* in 2004 [42] and has been discussed in the context of tumor-associated neutrophils [43]. These observations took a major step forward with the recent finding that neutrophils adopt an ‘N2’ phenotype during *N. brasiliensis* infection in the lung, demonstrated by the upregulation of IL-13, IL-33, Igf1, *Retnla* (RELM α) and *Chi3l3* (Ym1) [44]. The N2 neutrophils were induced during primary *N. brasiliensis* infection and then ‘instructed’ macrophages during secondary infection to mediate parasite damage and clearance. This cooperation is dependent on IL-4R α expression by the macrophage [44]. Whether IL-4R α expression on neutrophils is

required was not addressed but inflammatory signals such as TLR ligands can upregulate IL-4R α on neutrophils [45] and these signals may combine to generate the N2 phenotype described by Chen *et al.* [44]. The discovery of N2 neutrophils during helminth infection is likely the tip of the iceberg for the function of neutrophils in type 2 immunity.

We recently showed that neutrophils form organized swarms around larvae in the early stages of *N. brasiliensis* infection in the lung and in the absence of neutrophils more parasites survived to enter the intestine [46**]. However, the neutrophilia associated with migrating larvae comes at a cost. Chen *et al.* elegantly demonstrated that neutrophils are responsible for enhanced lung damage caused by larval migration [26**], which we subsequently confirmed [46**]. Therefore, although neutrophils act in concert with macrophages to contain nematode infection, neutrophils can also enhance the more severe consequences of type 2-mediated pathology as discussed below in relationship to IL-17.

IL-17 and type 2 cytokines

IL-17, through the induction of cytokines and chemokines, is a major driving force for the recruitment and activation of neutrophils [47]. Therefore, the contribution of neutrophils to nematode killing and enhanced lung damage during larval migration pointed towards the involvement of IL-17, and indeed this appears to be the case. Chen *et al.* demonstrated that neutrophil recruitment and the consequent enhanced lung damage was reduced in IL-17ra deficient mice infected with *N. brasiliensis* [26**]. We subsequently showed in the same lung migration model that IL-17A deficient animals were protected from the peak of tissue damage [46**]. In addition, IL-17 is associated with more severe pathology in both murine and human schistosomiasis [48,49] and human onchocerciasis [50]. These data are consistent with the proposal that IL-17 pushes the type 2 response into a more pathological state [51]. The ability of IL-17 to exacerbate type 2 pathology has recently become a central focus of asthma research [reviewed in [15]].

The relationship between IL-17 and type 2 immunity is highly complex (Figure 1). Mice deficient in IL-17A fail to induce IL-13 when infected with *N. brasiliensis* [46**]. This is consistent with previous reports in allergy models in which type 2 cytokines are reduced in IL-17 deficient mice relative to wildtype animals [52,53]. This suggests paradoxically that IL-17 promotes type 2 responses, supported by reports in which neutrophils contribute to the subsequent type 2 response during *N. brasiliensis* infection [44,54]. However, as discussed below, in this same nematode model Th2 cytokines suppress IL-17A in the lung [26**], as also reported by others [55*,56]. Thus, it appears that larval entry into the lung promotes an early IL-17/neutrophil response that is needed to generate the subsequent type 2 response. The type 2 response will mediate

repair of neutrophil induced damage, while shutting down the initial IL-17 response.

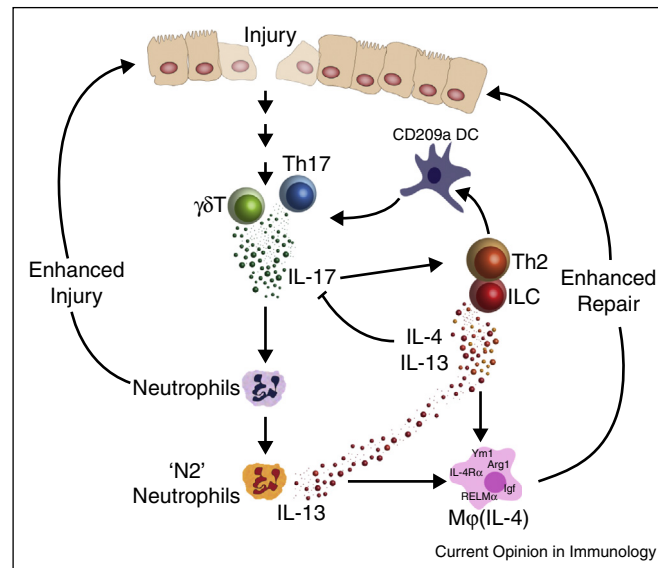
The evidence that IL-17 promotes type 2 responses is strong, but the reverse may also be true. The eggs deposited by schistosome parasites are potent inducers of type 2 cytokines [57] but severe hepatic granulomatous pathology in response to the eggs is due to a pathogenic Th17 response, which is largely dependent on the expression of CD209a by dendritic cells [58]. The expression of CD209a is highly upregulated in response to IL-4 or IL-13 [38,59,60], suggesting the potential for an amplification of IL-17 responses by type 2 cytokines. This is consistent with data in which instillation of IL-13 induces IL-17 producing CD4+ and $\gamma\delta$ T cells [61*]. These observations that type 2 cytokines promote IL-17 production contrasts sharply with the previously described ability of type 2 cytokines to negatively regulate the IL-17 response [26**,55*,56] but this may reflect an important negative feedback loop.

The intricate interplay between IL-17/neutrophils and the type 2 response will play out differently depending on dose, timing and the specific cell types involved (e.g. innate lymphoid cells including $\gamma\delta$ cells vs adaptive Th17/Th2) [61*]. Nonetheless, a general story in which early neutrophil-IL-17 activation initiates events that promote a subsequent type 2 response, which in turn suppresses excessive neutrophilia is likely to be common. When the type 2 response fails to fully suppress the IL-17 response, or indeed further promotes it, excessive type 2 pathology may be the result. Understanding what regulates these IL-17 — IL-4/13 feedback loops will provide invaluable insight into situations in which IL-17 exacerbates type 2 pathology.

Chitinase-like proteins — a bridge between IL-17 and type 2 responses

An important link between type 2 immunity and IL-17 may lie with the glycoside hydrolase family 18 that include chitinases and chitinase-like proteins (CLPs). This protein family is essentially ubiquitous in type 2-dominated pathophysiological conditions with evidence for roles in helminth infection [62,63], allergy [64,65], cancer, and wound healing [25,66]. Chitinases degrade chitin, a sugar polymer found abundantly in nature but not in mammals. However, gene duplication events and loss-of-function mutations have resulted in the CLPs, which cannot degrade chitin. These proteins appear to be undergoing very rapid evolution [67] and thus no two mammalian species express the same set of these proteins. Mice have three CLPs (Ym1, Ym2 and BRP-39), while humans have two (YKL-39 and YKL-40). Ym1 is the most abundant M ϕ (IL-4) protein in many helminth infection models [68], and all the murine CLPs and YKL-40 are induced via IL-4R α signalling [69].

Figure 1



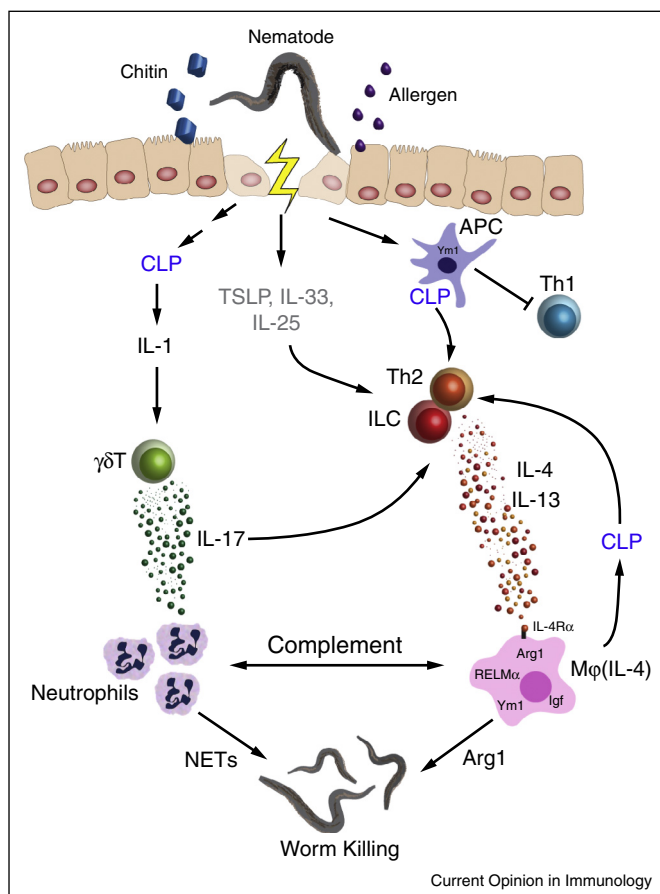
A model for IL-17 interactions with type 2 cytokines. In response to injured epithelium IL-17 is produced by $\gamma\delta$ T cells and by Th17 cells, leading to the accumulation of neutrophils which promote lung injury. IL-17 also enhances the production of IL-4 and IL-13 from innate lymphoid cells and Th2 cells, which can act in a negative feedback loop shutting down further IL-17 production and neutrophilia. Conversely, type 2 cytokines may amplify Th17 responses in a manner dependent on CD209a expression on DCs, thus exacerbating pathology. In some circumstances neutrophils can switch to an N2 phenotype, contributing to the pool of IL-13, which in addition to IL-4, promotes activation of macrophages limiting further injury and promoting repair.

Despite the strong association with type 2 immunity, we recently made the unexpected discovery that the murine CLPs induce IL-1 leading to the expansion of IL-17 producing $\gamma\delta$ T cells [46^{**}]. In the context of *N. brasiliensis* larval migration, Ym1 induced IL-17, which was responsible for increased recruitment of neutrophils to the lung [46^{**}]. These data strongly suggest, but have not yet proven, that CLPs activate the inflammasome and potentially act to alert the host to danger [70]. The abundance of secreted CLPs in both the tissue and serum, does not lend itself to the idea that CLPs have a highly specific receptor. Indeed, yeast two hybrid screening and binding assays have revealed multiple targets of CLPs, although specific binding partners, 12/15 lipoxygenase and IL-13R α 2, were the focus of these manuscripts [71,72]. CLPs bind extracellular matrix components (ECM) and cell-surface glycosaminoglycans [73], which themselves interact with many immune mediators. The impact of CLPs may thus be indirect via interaction or competition for ligands with their carbohydrate partners. In this regard, CLPs may be like other nonstructural proteins expressed in the ECM, such as Osteopontins and various galectins, which are upregulated upon injury and have been described as danger signals [74]. In addition, the propensity of Ym1 to form crystals [75] may be particularly relevant, as crystals are known inflammasome activators [76].

CLPs may prove to be an important bridge between the type 2 immune and IL-17/neutrophil pathways. In this scenario, innate sources of CLPs, perhaps acting as

danger-associated molecular patterns, activate IL-1 release leading to IL-17 production by innate $\gamma\delta$ T cells, which in turn drives a type 2 response needed for repair. Subsequently type 2 cytokines induce even more CLP expression, which likely further contribute to repair (Figure 2). Additionally, Ym1 can promote Th2 differentiation [77] as well as suppress IFN γ [46^{**},78] further promoting type 2 immunity. An ability of CLPs to activate the inflammasome might relate to earlier studies implicating low level triggering of the inflammasome with priming of the Th2 response [79]. The *N. brasiliensis* model suggests that once the full adaptive Th2 response is enabled it effectively suppresses the IL-17 response [26^{**}]. Of note, van Dyken *et al.* recently demonstrated that chitin induces both IL-13-producing ILCs and IL-17-producing $\gamma\delta$ T cells, with the ILCs responsible for suppression of the IL-17 response [55^{*}]. The relationship of CLPs to these effects of chitin exposure has not been explored. A key question that remains is whether CLPs can still promote IL-17 and neutrophils in the context of a memory Th2 response. This seems likely, as mice sensitized to allergen and then treated with anti-Ym1 at the time of challenge have suppressed lung neutrophilia [46^{**}] suggesting that the pro IL-17 functions of CLPs may be relevant beyond their roles in the first few hours and days. Further, it would suggest that CLPs are key players in the IL-17 enhancement of type 2 pathology, consistent with YKL-40, one of the two human CLPs, as a marker of disease severity in a range of conditions [80–83].

Figure 2



A model for CLP regulation of type 2 cytokines and IL-17. Injury or insult to the epithelium, whether by a multicellular parasite, chitin containing pathogen, or allergens, elicits danger signals resulting in the production of chitinase-like proteins (CLPs). CLPs induce IL-1 release leading to increased secretion of IL-17 and downstream neutrophil recruitment. Along with type 2 promoting cytokine such as TSLP, IL-33, and IL-25 [55*], CLPs also promote type 2 immunity via DCs and suppression of IFN- γ . IL-17 and type 2 cytokines can regulate one another as illustrated in Figure 1. The ensuing type 2 response activates the IL-4R α on macrophages which in turn produce further CLPs (i.e. Ym-1). M ϕ (IL-4) act in concert with neutrophils to kill invading worms in a complement, Arg-1 and NET dependent manner, while also repairing the injury caused by the parasite or the increased neutrophilia

Concluding remarks

Studies of the host response to helminth infection have started to elucidate the contribution of neutrophils and IL-17 to type 2 regulated processes. Beyond their role in helminth killing and wound repair, it will be imperative to ask whether neutrophils and IL-17 also contribute to other type 2 cytokine regulated mechanisms (e.g. host metabolism). The relationship of type 2 cytokines to the IL-17 response also suggests fascinating evolutionary commonalities between the immune response to metazoan parasites and to other chitin containing pathogens such as fungi that are highly dependent on IL-17 for control. As with *N. brasiliensis* infection, neutrophils and macrophages act together to limit fungal growth and early IL-1 receptor signalling is central to this process [84]. Because CLPs are upregulated in the context of both helminth and fungal infection [85,86], their study may provide answers to the causes of many pathologies involving

dysregulated type 2 immunity as well as provide opportunities for intervention in severe type 2 pathology.

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