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Human innate lymphoid cells (ILCs) in filarial infections

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Summary

Filarial infections are characteristically chronic and can cause debilitating diseases governed by parasite-induced innate and adaptive immune responses. Filarial parasites traverse or establish niches in the skin (migrating infective larvae), in non-mucosal tissues (adult parasite niche) and in the blood or skin (circulating microfilariae) where they intersect with the host immune response. While several studies have demonstrated that filarial parasites and their antigens can modulate myeloid cells (monocyte, macrophage, and dendritic cell subsets), T- and B-lymphocytes and skin resident cell populations the role of innate lymphoid cells during filarial infections has only recently emerged. Despite the identification and characterization of innate lymphoid cells (ILCs) in murine helminth infections little is actually known about the role of human ILCs during parasitic infections. The focus of this review will be to highlight the composition of ILCs in the skin, lymphatics and blood; where the host-parasite interaction is well-defined and to examine the role of ILCs during filarial infections.

Keywords

Innate Lymphoid cells; Filarial parasites; Monocytes; Dendritic cells; Langerhans cells; Helminth

Introduction – Filarial Parasites

Eight filarial species infect humans; of these, four—*Wuchereria bancrofti*, *Brugia malayi*, *Onchocerca volvulus*, and *Loa loa*—are responsible for most of the filarial-associated disease. In general, each of the parasites is transmitted by biting arthropods. Each goes through a complex life cycle that includes an infective larval stage (L3) carried by the insects and an adult worm stage that resides in humans, either in the lymph nodes, adjacent lymphatics, or in the subcutaneous tissue. The offspring of the adults, the microfilariae (mf), either circulate in the blood or migrate through the skin. The mf then can be ingested by the appropriate biting arthropod and develop over 1–2 weeks into infective larvae, which are capable of initiating the life cycle over again. Adult worms are quite long-lived, whereas mf survive for 3–36 months depending on the species. The bacterial endosymbiont *Wolbachia* has been found intracellularly in all stages of *Brugia*¹, *Wuchereria*¹, *Mansonella*², and *Onchocerca* species^{3, 4}, but not in *Loa loa*^{5, 6}.

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The host immune response to filarial parasites in both mice and humans is considered to be largely a modified Type-2 (or Th2) response, despite an inflammatory response to the infective stage larvae of the filarial parasites (and/or their *Wolbachia* endosymbiont) and a Type-1 (or Th1)⁷ and Type-17 (or Th17)⁸ response prior to microfilarial productions. These responses involve: 1) the production of the cytokines IL-4, IL-5, IL-9, IL-10 and IL-13; 2) the production of the antibody isotypes – IgG1, IgG4 and IgE (in humans) and IgG1 and IgE (in mice), and expanded populations of eosinophils and alternatively activated macrophages⁹ as well as innate lymphoid cells (ILCs)¹⁰. The initiation of this response in mice requires interaction with many different cell types, most notably: 1) dermal cells; 2) epithelial cells 3) stromal cells; 4) dendritic cell and macrophage populations; 5) eosinophils; 6) mast cells and basophils and 7) ILCs. The innate responses that promote Type-2 responses early in infection are often modulated over time by both adaptive and natural regulatory T cells, regulatory monocytes/macrophages (Mregs) and B cells (Breg), eosinophils and other cell populations that have been postulated to reflect an IL-10 dominated milieu¹¹.

Humans are the definitive host for each of the filarial parasites. Several non-human primate species (e.g. chimpanzees and mangabey monkeys for *O. volvulus*, the silver leaf monkey for *W. bancrofti*, rhesus monkeys and baboons for *Loa loa*) have been shown to be fully permissive to these infections¹², but none of the 8 species that infect humans is fully permissive in immunocompetent mice. Therefore, animal models of filarial infections are limited to infection models with *Brugia* and the rodent filarial parasite *Litomosoides sigmodontis*¹³.

Although the small animal models of filariasis do not fully recapitulate disease or the natural life cycle of filarial infections in humans, these models have been integral in the examination of both innate and adaptive immune responses to filarial parasites^{14–16}. Infection with *L. sigmodontis* begins with injection of the L3 stage parasite, which migrates through the thoracic cavity and develops into adult parasites that take residence in the pleural cavity. Infected mice are able to achieve patency, releasing mf into the blood. The life cycle of both human and murine filarial parasites share many similar anatomical locations in which different parasite stages intersect with the host immune response (Table 1). These immunological intersection points can vary in duration from several days, as L3 transit through the skin, to months to years, as mf are released and circulate in the blood or skin. Furthermore, the longevity of adult parasites can persist in the lymphatics or skin nodules for several years. The presence of parasites and circulating parasite antigens results in significant systemic immune alterations.

Filarial parasites exert profound regulatory effects on the host with both parasite antigen-specific and more generalized levels of immune modulation. It has been shown that patients with patent filarial infection have markedly diminished responses to parasite antigens^{11, 17}; in addition, these parasites also can induce attenuated responses to non-helminth antigens^{18–21} including those that are delivered as approved vaccines^{22–26}. The chronicity of many of these filarial parasites is presumed to reflect successful immune evasion strategies that allow these parasites to avoid elimination²⁷; this immune evasion is often dependent on the modulation of the parasite-specific host inflammatory responses.

In the process of establishing a patent infection, the infectious stages must traverse a set of barriers the cells of which form an innate interface that can serve to modulate/induce certain immune or inflammatory functions. This review centers primarily on the interaction between the parasite stages (at their various anatomic niches) and the ILCs that are found at these sites. For the most part, the focus will be on human ILCs given that most of the filarial parasites have humans as their only definitive host.

As is already well-known, ILCs are potent cytokine producers that respond to alarmins and stress indicating molecules released by barrier cells. Although human ILCs have been implicated as being associated with a number of inflammatory diseases^{28–30}, autoimmunity^{31, 32}, HIV³³ and cancer^{34, 35}, the direct or indirect impact of filarial parasites on ILCs in the circulation, the skin or in lymphatic/lymph node tissue remains to be fully explored.

Innate Lymphoid Cells

The identification of ILCs³⁶ as an important innate cell population has expanded our understanding of the role played by lymphocytes in the innate immune response. Unlike T- and B- cells, ILCs lack cell surface-associated antigen receptors (i.e. TCRs and BCRs) and respond rapidly to cytokine signals³⁷. ILCs have been categorized into 3 distinct groups that are strikingly similar to T-helper cells (Th) in both their transcriptional regulation and effector cytokine profile. Mouse ILCs are commonly characterized by their expression of CD127 (IL-7R- α) and the surface markers IL-12R for Group 1 ILCs (ILC1s), CD25, SCA1, ST2, and CD117 for Group 2 ILCs (ILC2s) and NKp46, IL-1R or IL-23R for Group 3 ILCs (ILC3s)³⁶. Human ILCs are also defined as CD127+ lymphocytes that are devoid of common lineage markers and, by some reports, also express CD161³⁸. ILC1s express the surface marker IL-12RB1³⁹ (in the absence of CRTH2 and cKit expression) and when stimulated by IL-12, IL-12/IL-15, or IL-18 these cells produce IFN- γ ⁴⁰. The ILC1 subset also encompasses cytotoxic cells such as conventional natural killer cells (NK cells)⁴⁰ and intraepithelial type 1 ILCs (ieILCs)⁴¹ that are capable of producing IFN- γ as well as cytotoxic granules such as perforin and Granzyme A and B^{40, 41}. ILC2s are defined by their surface expression of CRTH2 and IL-17RB³⁹ and when stimulated by IL-25, IL-33^{38, 39}, TSLP, TL1A⁴² or PGD2⁴³ are capable of producing IL-4, IL-5, IL-9 and IL-13. Lastly, ILC3s are divided into two subpopulations: cKit+ NKp44- cells (ILC3a) and cKit+NKp44+ cells (ILC3b) that, when stimulated by IL-1 β /IL-23, produce IL-17 and IL-22, respectively³⁹.

ILCs are dependent on several transcription factors for both development and maturation. Murine ILC development is highly dependent on transcription factors *Id2*^{44–46}, *Tox*⁴⁷, *Nfil3*^{48, 49} and *RORgamma t (RORgt)*^{50, 51} and the transcription factor GATA3^{52, 53}. Interestingly, the transcriptional profile of both human and murine ILC subsets mirrors that of helper T cell subsets; where ILC1s are associated with Tbet, ILC2s with GATA-3 and ILC3s with *RORgamma t (RORgt)* expression. Recent findings have demonstrated that the expression of transcription factors by ILC subsets may be more dynamic than previously thought⁵⁴, as all three ILC subsets are capable of being generated from *RORgt*+ progenitor cells found in secondary lymphoid tissues⁵⁵ or from CD117+ ILC precursors found in

peripheral blood⁵⁶. A transcriptional analysis of human cKit⁺ ILCs demonstrated that these cells express transcripts for ILC2s and ILC3s as well as transcripts for cytokines, chemokines, chemokine receptors and TLRs¹⁰. These cKit⁺ ILCs were capable of responding to stimulation with a TLR6 ligand by producing copious amounts of GM-CSF, demonstrating the capacity of human ILCs to recognize and respond to pathogen associated molecular patterns (PAMPs). Moreover, ILCs represent a diverse and heterogeneous population of lymphocytes that exist outside of the adaptive immune response.

HUMAN ILCs IN TISSUE AND IN THE PERIPHERAL BLOOD

ILCs in Cutaneous Tissue

The skin is a critical barrier between microbes and the host, and ILCs are among many immune cells that reside in the skin^{57, 58}. The cutaneous ILC composition in healthy adults consist of NK cells, helper ILC1s, ILC2s as well as NKp44⁻ and NKp44⁺ ILC3s^{58, 59} (Table 2). Evidence of conversion of cutaneous NKp44⁻ ILC3s into NKp44⁺ ILC3s has been demonstrated through *ex vivo* cultures in the presence of IL-2, IL-23, and IL-1 β ⁵⁹. *In situ* analysis of the anatomical localization of ILC subsets in the skin and has revealed the absence of ILCs in the epidermis and the hypodermal layers⁶⁰. The majority of cutaneous ILCs were located in the upper dermal layer of the skin, although healthy skin contained very few human ILCs. The ILCs found in the upper dermal layer were composed of ~50% Tbet⁺ ILC1s, a heterogeneous population of ILC3s (expressing either the aryl hydrocarbon receptor [AHR] or RORC) and a sparse number of GATA-3⁺ ILC2s in the skin of healthy individuals. This study diverges from previous examinations of cutaneous ILC subsets using flow cytometry, which identified the presence of all helper ILC populations (including NKp44⁻ and NKp44⁺ ILC3 populations) and a higher frequency of NKp44⁻ ILC3s in normal human skin^{58, 59}. Based on multiple reports ILCs are present in cutaneous tissue where they may encounter antigen and migrating filarial parasites (see below).

Several studies have provided a thorough examination of the changes in frequency and composition of cutaneous ILC populations under inflammatory conditions^{57, 61} such as atopic dermatitis and psoriasis^{58, 59}. These inflammatory conditions consistently resulted in an increase in the frequency of cutaneous ILCs in the skin as well as a predominance of NKp44⁺ ILC3s in psoriatic lesions and ILC2s and AHR+ILC3 in atopic dermatitis lesional skin.

For cutaneous ILC2s it appears that they are regulated by E-cadherin expression⁵⁷ and potentially by basophils⁶¹. Much like in humans, murine basophils and ILC2s are found in clusters, with basophil derived IL-4 aiding in the ILC2 accumulation and proliferation in mice. Human ILC2 have also been shown to be recruited into the cutaneous tissue following intraepidermal injection of house dust mite (HDM) in HDM-allergic individuals⁵⁷. These findings demonstrate that ILC2s in cutaneous tissue support a Th2 microenvironment that, in the context of skin exposed filarial parasites might help to promote a parasite-specific Type 2 response.

ILCs in Lymphatic Tissue

At homeostasis, ILCs also reside in the secondary lymphoid tissues (reviewed in reference⁶²) such as the spleen⁶³, lymph nodes⁶⁴ and tonsils^{40, 54, 65}, the most abundant of which are NK cells⁶⁶. Secondary lymphoid tissues also represent the site of NK cell differentiation⁶⁷. Unlike ILCs in the skin and in the circulation, the distribution of helper ILC subsets in the lymphoid tissues is skewed towards ILC3s. Interestingly, single-cell RNA sequencing of human ILCs sorted from tonsil tissue identified 3 subpopulations of ILC3s: 1) a naïve population that are CD62L+ ILC3s, 2) an activated population of NKp44+ ILC3s and 3) a population of HLA-DR+ ILC3s⁵⁴. A subset of murine^{68, 69} and human⁷⁰ ILC3s in lymphoid tissue can be characterized as lymphoid tissue inducer (LTi) cells. LTi cells play a role in lymphoid organ development and present in early fetal development and in adult lymphoid tissue. Human LTi cells have the capacity to produce IL-17A during fetal development and later switch to predominately IL-22 producing cells postnatally⁷⁰.

ILCs in Peripheral Blood

Human ILCs can be found in both mucosal and non-mucosal tissues⁷¹ although the frequency and heterogeneity of ILC subsets differ between mucosal and non-mucosal tissues⁶⁰. Multiple studies evaluating ILC subsets in the peripheral blood of humans have identified the presence of ILC1s, ILC2s and NKp44- ILC3s in circulation^{59, 72}. NKp44+ ILC3s, in contrast have not been found in the peripheral blood of healthy human donors^{59, 60, 72}. We have also independently verified that NKp44- cells are absent from the circulation under homeostatic conditions; in a North American cohort analyzed by flow cytometry for all helper ILC subsets in whole blood (unpublished observation).

Interestingly, following hematopoietic stem cell transplantation (HSCT), circulating NKp44+ ILC3s could be detected and their presence was also shown to negatively correlate with the incidence of graft-versus host disease (GVHD)⁷². Patients with active psoriasis lesions also demonstrate significantly higher frequencies of CD161+ ILC1s and NKp44+ ILC3s in the peripheral blood. These findings indicate that the presence of NKp44+ ILC3s in the peripheral blood maybe indicative of inflammation given their absence in healthy controls.

All helper ILC subsets found in the periphery have also been shown to express the skin homing marker cutaneous lymphocyte antigen (CLA)^{58, 59} and, to a lesser extent, the skin homing chemokine CCR10⁵⁹. The expression of skin homing markers under homeostatic conditions suggest that ILCs found in circulation can migrate to skin or other tissues and their presence in the peripheral blood may be short-lived.

INNATE IMMUNE RESPONSE DURING FILARIAL INFECTIONS

Cutaneous Innate Cells during Filarial Parasites

The response of skin resident cells such as Langerhans cells (LC), keratinocytes and dendritic cells (DC) to the invading L3 stage of *B. malayi* can be best described as quiescent^{73–75} demonstrating that filarial parasites can evade the immune response in the cutaneous tissue. Whether L3 have a similar effect on skin resident ILC subsets remains

unclear. However, these previous studies do demonstrate that L3 fail to induce ILC stimulating cytokines such as IL-1 β , IL-18⁷³, IL-12p40 or TSLP⁷⁴, alarmins IL-25 and IL-33 were not evaluated. The activation of cutaneous ILCs by LC is further hampered by the spatial disparity between ILCs (found predominately in the upper dermal layer)⁶⁰ and LC (in the epidermal layer) in normal skin. Therefore, LC exposure to transiting L3 may not result in a tissue microenvironment that supports ILC activation.

Lymphatic Endothelial Cells during Filarial Infections

The lymphatics represents the anatomical niche for the adult parasites for 3 of the 8 filarial species, yet the area surrounding the parasites are often devoid of inflammatory cells⁷⁶. Despite, the abundance of NK cells in secondary lymphoid organs (such as the tonsil, spleen and lymph nodes)^{60, 67} the nature of the interaction between NK cells and adult parasites remains unknown. Unlike other innate immune cell populations, NK cells are activated in response to filarial parasites (L3 and mf stages) *in vitro*, resulting in their production of IFN- γ and TNF- α ⁷⁷. Lymphatic endothelial cells (LEC) have proven to be a useful *in vitro* tool for determining the mechanisms surrounding lymphatic damage and the development of lymphedema. Concomitantly, these studies have also revealed the direct and indirect effects of adult filarial parasites and filarial antigens on cells in the lymphatic tissue. Adult parasites and mf induced LEC proliferation and lymphangiogenesis⁷⁸. Filarial excretory secretory products have also been shown to stimulate peripheral blood mononuclear cells (PBMC) to produce the lymphangiogenic molecules IL-6, IL-8 and VEGF-A, which trigger tubule formation in LEC⁷⁹. A *post hoc* examination of filarial-exposed LEC microarray data⁷⁸ for cytokines known to activate ILCs revealed no significant increases in gene expression for the cytokines IL-12p70, IL-33, IL-15, IL-18 and IL-23. It is important to note that other known ILC activating cytokines such as IL-25, TSLP or IL-1 β were not on the microarray used for these analyses. Therefore, activation of ILC2s or ILC3s by LEC derived IL-25, TSLP or IL-1 β , respectively, following filarial parasite exposure cannot be excluded. However, the overall absence in ILC activating cytokine production by LEC suggests that filarial parasites can induce significant structural changes in the lymphatic tissue but not ILC activation (especially ILC1s). Furthermore, the role of LT α cells during filarial infections, given their proximity to adult parasites in lymphoid tissue, remains to be determined.

ILCS DURING FILARIAL INFECTIONS

Murine Filarial Infections

Murine models of helminth infections played a central role in the identification of ILCs and defining the role of ILC2 subsets in the initiation and development of the Th2 response as well as the expulsion and clearance of parasites during *Heligmosomoides polygyrus*⁸⁰ and *Nippostrongylus brasiliensis*^{81, 82} infections. In addition to the protective role of murine ILC2s during helminth infections ILC2s can also have a deleterious effect on pulmonary fibrosis, as demonstrated using the *Schistosoma mansoni* egg-induced pulmonary granuloma model⁸³. The well-described murine model of *L. sigmodontis* has highlighted similarities between the human and mouse immune response to filarial parasites including the progressive loss in Th2 cytokines by CD4⁺ T cells¹⁵, an elevation in IL-10¹⁶ and the induction of T regulatory cells¹⁴ that maintain a T cell hyporesponsive state¹⁵. ILC2

populations were shown to be expanded during the Th2-dominated *L. sigmodontis* infection⁸⁴. The expansion of these cells occurred just prior to patency and was localized to the pleural cavity the future niche of adult parasites. Expansion of ILC2s also coincided with the initiation of the Th2 response in infected mice. Intriguingly, the efficient clearance of mf was dependent in part on the IL-33 receptor ST2⁸⁵, a defining marker of murine ILC2s and a critical component of ILC2 activation that may indicate a role for ILC2s in controlling *L. sigmodontis* mf. A recent study examining antibody production by B cells residing in fat-associated lymphoid clusters (FALC) determined that production of parasite-specific IgM was dependent on B cell activation by ILC2-derived IL-5. Parasite-specific IgM has previously been shown to be important for parasite elimination in a *Brugia* mouse model⁸⁶ and in humans polyreactive IgM antibodies and B-1 cells were positively correlated in patients with Bancroftian filariasis⁸⁷. The activation of FALC ILC2s⁸⁸ was directly linked to the parasite induced production of IL-33 by FALC stromal cells⁸⁹. Collectively, the *L. sigmodontis* infection model illustrates the multifaceted role of ILC2s during filarial infection beginning with the initiation of a Th2 response, direct and indirect association with adult and mf parasite stages and modulation of the parasite-specific humoral response.

Human Filarial Infections

In contrast, to the murine helminth models of infection that were used to first identify and define the role of helper ILC2s^{81, 88, 90} very little is known about phenotype and functionality of ILCs in the context of human parasitic infections. The frequency of cKit+ and cKit+IL-13+ILCs were expanded in filarial-infected individuals¹⁰ (Figure 1). Additional analysis of these cKit+ ILCs by RNASeq revealed expression of ILC2- and ILC3-associated transcripts. In healthy controls the equivalent cKit+ILC population when stimulated *ex vivo* with IL-2, IL-7, IL-25 and IL-33 released predominately ILC2 cytokines IL-4, IL-5, and IL-13. These enriched cKit+ILCs were also associated with IL-17 producing cells that are also expanded during filarial infections⁹¹. Interestingly, these cKit+ILCs produced primarily GM-CSF (and not the prototypical cytokines IL-5, IL-17A and IFN- γ) following TLR agonist-induced stimulation¹⁰. Therefore, cytokine production and TLR signaling represent two pathways by which mf may attenuate ILC function; similar to the modulatory properties demonstrated for mf on monocytes^{92–97} and DC^{98–101}.

Non-filarial helminth infection and ILCs

As many of the helminth infections occur in children, understanding the role of the ILCs in children remains a relatively unexplored area of interest. An analysis of ILCs in human cord blood and adult peripheral blood did reveal that the frequency of ILC2s and NKp44-ILC3s were higher in cord blood than in the adult peripheral blood. The distribution of cytotoxic and helper ILC1s was unquantifiable in this study, as they were undistinguishable from NK and other cell populations⁶⁰. Examination of circulating ILC2s in a study population of Zimbabwe children (ages 6–18 years) with *Schistosoma haematobium* infection¹⁰² demonstrated a decreased proportion of ILC2s that reversed following anthelmintic treatment. The increase in ILC2s post-treatment was associated with an increase in plasma levels of TSLP but not IL-33. Taken together these findings indicate that ILC2s are also susceptible to the post-treatment reversal of the IL-10 mediated immunosuppression, previously described for both filariasis¹⁰³ and schistosomiasis¹⁰⁴.

Conclusions

Modulation of both the innate and adaptive arms of the immune response is vital to the survival of helminth parasites. It is evident that filarial parasites not only modulate multiple cell types at various anatomical locations as the parasite migrates and establishes patency. The significant upregulation of cKit+ILCs from patients with relatively acute filarial infections and the corresponding changes in the transcriptional profile of these cells demonstrates that ILC populations are also susceptible to the effects of filarial parasites and antigens. The presence of all human ILC subsets in the skin, peripheral blood and lymphatic tissues, make filarial infections a unique disease model by which the role of ILCs may be investigated. The scarcity of studies evaluating human ILC populations in filarial or other parasitic infections allow questions about ILCs in acute and chronic infections or the contribution of ILCs on disease pathology to go unanswered.

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ABBREVIATIONS

ILC	Innate lymphoid cells
ILC1	Group 1 innate lymphoid cells
ILC2	Group 2 innate lymphoid cells
ILC3	Group 3 innate lymphoid cells
DC	Dendritic cell
NK	Natural killer cell
LEC	Lymphatic endothelial cells
TSLP	Thymic stromal lymphopoietin
LC	Langerhans cell
PBMC	Peripheral blood mononuclear cell
FALC	Fat-associated lymphoid clusters
TLR	Toll-like receptor
L3	Infective third-stage larvae
CLA	cutaneous lymphocyte antigen
GM-CSF	Granulocyte-macrophage colony-stimulating factor
Mf	Microfilariae

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Figure 1. Interaction of human ILCs and filarial parasites

Skin. The transmission of infective L3 from biting arthropods is the initiating step in filarial infections. As the L3 migrate through the skin they encounter a number of skin resident cells including ILCs. The quiescent response in the skin to L3, is defined by a reduction in cellular activation, production of proinflammatory cytokines and inhibition of key alarmins (IL-1 β , IL-18, IL-12p40 and TSLP) that activate ILCs. Migrating L3 successfully evade the immune response in the skin and develop into adult parasites that reside in the lymphatic tissue, specifically for the 3 species that cause lymphatic filariasis. The life cycle of other filarial parasites diverge shortly after L3 leave the skin resulting in parasite development in diverse anatomical niches, such as the skin for *Onchocerca volvulus* adults and microfilariae (mf). **Lymphatics.** Adult parasites elicit very little inflammation in the lymphatics a finding which is supported by *in vitro* results that demonstrate adult parasites suppress lymphatic endothelial cell (LEC) production of proinflammatory cytokines and cytokines (IL-12p70, IL-33, IL-15, IL-18 and IL-23) vital to ILC activation. However, differentiation and proliferation of lymphatic cells occurs through 1) direct exposure to mf or circulating parasite antigens or 2) production of lymphangiogenic molecules (IL-6, IL-8 and VEGFs) produced by adjacent peripheral blood mononuclear cells (PBMCs), exposed to mf or filarial antigen. **Blood.** Adult parasites release their progeny mf into the circulation where they modulate the functionality of monocytes and dendritic cells (DC) and promote the expansion of cKit+ILCs (ILC2s and ILC3s) and ILC production of IL-13.

Table 1

Localization of filarial parasite stages in human and murine host

	Parasite	Infective L3 larvae	Adults	Microfilaria
Human	<i>Brugia malayi</i>	skin	lymphatics	blood
	<i>Brugia timori</i>	skin	lymphatics	blood
	<i>Wuchereria bancrofti</i>	skin	lymphatics	blood
	<i>Mansonella perstans</i>	skin	peritoneal cavity, pleural cavity or pericardium	blood
	<i>Mansonella ozzardi</i>	skin	subcutaneous tissue	blood
	<i>Mansonella streptocerca</i>	skin	subcutaneous tissue	skin
	<i>Onchocerca volvulus</i>	skin	subcutaneous nodules (surrounded by lymphatic-like endothelial cells)	skin, eye
	<i>Loa loa</i>	skin	subcutaneous tissue	blood
Murine	<i>Litomosoides sigmodontis</i>	skin	pleural cavity	blood

Table 2

Composition of ILC subsets in human skin, blood and secondary lymphoid tissue

Anatomical Location	Average Frequency of ILC subsets % (Range)				References
	ILC1	ILC2	NKp44-ILC3	NKp44+ ILC3	
Skin	28 (1–47)	24 (11–40)	31 (18–44)	8 (1–26)	585910560
Blood	22 (17–27)	47 (41–53)	31 (29–32)	0	5972
Secondary lymphoid tissue	13 (0–23)	9 (1–18)	43 (3–80)	21 (0–30)	645440, 60

Secondary lymphoid tissue includes the following: tonsil, lymph node and spleen %;

Average percent of ILC subsets from total ILCs