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The Importance of Group 2 Innate Lymphoid Cells to Improve the Protective Immunity in Parasitic Helminth Infections

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A B S T R A C T

Helminthiasis is a neglected public health challenge worldwide. The relevance of the important role of group 2 innate lymphoid cells (ILC2s) in the protection induced by type 2 immune responses against helminth infections has recently regained attention. The parasitic helminth infections remain as a major public health concern worldwide, particularly in tropical countries in several areas of Africa, Asia, and South America. It has been demonstrated in the experimental mouse models that ILC2s induce significant secretion of type 2 cytokines and develop protective immunity against parasitic helminths infections. However, the effects of helminth-induced immunity mediated by ILC2s have not yet been clearly defined. This review discusses the current status of the researches related to the evidence of ILC2s to improve the protective immunity in parasitic helminth infections and how these cells promote parasitic helminth expulsion.

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INTRODUCTION

Parasitic helminths cause chronic infections that are a global public health problem with the outcome of important economic consequences [1, 2]. Numerous chronic parasitic infections are associated with the direct tissue damage [3, 4]. The helminths typically induce a type 2 immune response which is potentially protective [5-7]. During this immune response, stimulated epithelial cells exposed to the helminth antigens induce secretion of alarmins and cytokines including interleukins (IL)-25, IL-33, and thymic stromal lymphopoietin (TSLP). In the experimental mouse models, these molecules promote innate immune cell activation and induce the polarization of type 2 T helper (TH2) cells [8]. The immunity against chronic helminth infection produces a wide range of immune responses mainly characterized by the production of a type-2 immune response that involves the induction of TH2 cells [9-11]. This TH2 immunity has evolved as a major protective immune mechanism in parasitic helminth infection [12]. Interestingly, a potential communication between group 2 innate lymphoid cells (ILC2s) and different subsets of TH cells has been demonstrated to change towards a significant TH2 activation. The ILC2s are a family of innate effector cells including NK cells, and lymphoid tissue inducer cells, that secrete several cytokines such as IFN-gamma, IL-5/IL-13, and IL-17/IL-22 which might promote the first-line defense against helminth infection [13]. In 2010, the ILC2s were discovered through experimental mouse models in different helminthic infections [14, 15], while human ILC2s were initially described in 2011 [16]. These ILC2s induce classical TH2 cytokines in response to IL-25 and IL-33. A recent report showed that ILC2s induce a significant immunity against parasitic helminth infection [17]. It showed that ILC2s secrete IL-4, IL-5, IL-9, IL-10, and IL-13 cytokines during parasitic helminth infections. A more recent report demonstrated that ILC2s are involved in parasite expulsion in different helminthic infections as an important immunomodulatory pathway against several helminthic infections [18]. Currently, several studies have demonstrated the importance of ILC2s in promoting helminth-induced TH2 immune responses via release of the cytokines [19-22]. Alternatively, different subsets of TH2-associated dendritic cells are stimulated by the significant immunomodulatory pathways from ILC2s. It is important to consider that Tuft cells, ILC2s and epithelial progenitors induce a significant response circuit that mediates the epithelial remodelling associated with type 2 immunity. In this regard, after human helminth infection, tuft-cell-derived IL-25 further activates the ILC2s to secrete IL-13, which acts on epithelial cells to promote differentiation of the tuft cells. This immune response circuit is responsible for the initiation of the type 2

responses to helminths [23]. To date, the main regulatory mechanisms that mediate TH2 immunity against parasitic helminth infection are constantly enriched with new immunoregulatory molecules. This review will highlight emerging evidence indicating the current knowledge of the function and regulation of ILC2s to parasitic helminths and discuss how ILC2s enhance the control of innate and adaptive immune responses during TH2 immunity against helminths.

The Role of ILC2s in Enhancing Immunity Against Parasitic Helminth Infections

Group 2 innate lymphoid cells (ILC2s) are innate immune cells of the lymphoid lineage that are important mediators of type 2 inflammation during helminth infection. At present, innate lymphoid cells (ILCs) have been recognized as important mediators of the innate immunity to parasitic infections [19]. These cells are classified into ILC1s, ILC2s, and ILC3s according to their expression of transcription factors and cytokine production. To date, ILC2 progenitors have been recognized in different tissue samples such as the fetal liver [19]. The activation and proliferation of ILC2s after helminthic infections are controlled by several cytokines such as IL-25, IL-33, and TSLP, type 2 cytokines such as IL-4 and IL-9, or by inflammatory lipid mediators such as prostaglandin D2 [24-27]. In consequence, the activated ILC2s produce different cytokine molecules (IL-5, IL-9, and IL-13) which induce significant anti-helminthic immune responses. In this regard, the main molecular mechanisms that enable ILC2s to induce efficient triggering TH2 immune responses against helminths include the production of type 2 cytokine molecules. The IL-5-producing ILC2s induce eosinophilia [28-30]. In addition, IL-4 triggers B cells inducing isotype switching to IgE. Furthermore, IL-4 and IL-13 can also induce significant activation of macrophages [31]. Tissue repair is a subset of a broad repertoire of IL-4- and IL-13-dependent host immune responses during human helminth infection. The helminths induce a significant Th2 immune response, resulting in fibrosis and granulomas containing lymphocytes, and macrophages. During the late phase of helminth infection, the macrophages play an important role to counteract the inflammation caused by the Th1/Th17 immune responses [32]. Further, IL-13 in conjunction with IL-9 can activate mucus secretion [33] and regulate dendritic cells migration [34]. Interestingly, IL-9 can also act in an autocrine manner to activate ILC2s [35]. Further, ILC2-derived IL-9 has been shown to increase the immune cytokine production and significant activation of ILC2s following N. brasiliensis infection to produce an efficient worm expulsion [36]. In addition to their innate immunoregulatory effector pathways, the ILC2s lead to the creation of a significant adaptive immunity to induce an efficient parasitic helminth expulsion. In this regard, it has been shown that ILC2s interact with TH2 cells, which induce TH2 immune response and the IL-2 secreted by T cells might further improve the ILC2 responses against parasitic helminths. In particular, ILC2s express co-stimulatory molecules to activate T lymphocytes [37-40]. In this regard, the expression of the co-stimulatory molecule OX40L on ILC2s could induce tissue-restricted T cell co-stimulation that is important for Th2 and regulatory T immune responses against human helminth infections [41]. In addition, ILC2s increase type 2 immune responses and contribute to the parasitic helminth expulsion in an MHC-II-dependent pathway when transferred into IL-13-deficient mice [17]. In support of this, it has been demonstrated that ILC2s manipulate different TH2 immune responses in helminth infections [42]. Finally, the ILC2-derived IL-13 has been reported to increase memory TH2 cellular immune response [43]. The crucial significance of the ILC2s linking the innate and adaptive immune response has important contribution to some aspects of the anti-helminthic immunity. Altogether, these immune mechanisms appear to act independently and/or concurrently to promote TH2 polarization against helminth parasites.

Some of the cellular and molecular mechanisms discussed here indicate the current knowledge of researches related to the important role of the ILC2s in enhancing immunity following N. brasiliensis infection and how these cells promote worm expulsion. Similarly, other studies have highlighted the critical role that ILC2s play in regulating immunity against other helminth infections. Specifically, recent studies demonstrated that ILC2 populations contribute to some mechanisms of the anti-helminthic immune responses against infection with T. spiralis, H. polygyrus, Schistosoma species, and S. venezuelensis [44-47]. In addition, increased ILC2s level in the patients infected with filarial worms has been reported. Interestingly, it has been proved in an experimental mouse model that excretory-secretory antigens of H. polygyrus diminished the production of TH2 cytokines by ILC2s. More recently, in the studies of ILC2s in the natural human helminth infection, it has been demonstrated that ILC2 proportions reduced during Schistosome infection [48], indirectly indicating that the ILC2 proportions have a powerful impact on immune responses for the parasite survival. It is important to note that the current research efforts in immune-enhancing approaches to improve vaccination efficacy, might have significant impact on the human helminth infections. Better delineation of TH2 immune responses against parasitic helminths and understanding the induction and maintenance of the ILC2s as an important source of TH2 immunity to enhance protective immune responses will result in new approaches to control helminth infections.

CONCLUSION

The ILC2s are innate immune cells that accumulate in the tissues during helminth infection. The exciting ongoing research contributes to reveal the new aspects of ILC2s functions during helminth-induced TH2 immune responses. However, much more work needs to be done on this topic. In this context, there are some gaps in our understanding of how ILC2s intersect with the other host and pathogen-derived molecules to control various parasitic helminth infections. In addition, some of the studies discussed here have been conducted in the experimental mouse models of helminth infections, and these findings need more focus to see how ILC2s responses are controlled in helminth infection in humans. Lastly, more studies are needed to dissect how ILC2s responses could improve TH2 immune responses and contribute to the protective immunity against helminth infections. The critical new strategies to treat or prevent the parasitic helminth infections in humans will be addressed in the future studies.

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CONFLICT OF INTEREST

The author declares that she has no conflict of interest.

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