Immunological Responses of Trichuris sp.

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Trichuris sp. infection has appeared as a pathological burden in the population, but the immunomodulation features could result in an opportunity to discover novel treatments for diseases with prominent inflammatory responses. Regarding the immunological aspects, the innate immune responses against Trichuris sp. are also responsible for determining subsequent immune responses, including the activation of innate lymphoid cell type 2 (ILC2s), and encouraging the immune cell polarization of the resistant host phenotype. Nevertheless, this parasite can establish a supportive niche for worm survival and finally avoid host immune interference. Trichuris sp. could skew antigen recognition and immune cell activation and proliferation through the generation of specific substances, called excretory/secretory (ESPs) and soluble products (SPs), which mainly mediate its immunomodulation properties.

antigen   innate lymphoid cells 2 (ILC2s)   Th1   Th2   interleukin-13   interleukin-10

1. Basic Immunology Concept against *Trichuris trichiura*

Trichuris sp. induces a cascade of immunological responses characterized by hyper-IgE and eosinophil or humoral-mediated responses in the human large intestine [1][2][3]. However, several incomplete pictures relating to the immune response against whipworm and other helminth infections have been presented. Besides, the host–parasite interaction could be confounded by several factors that contribute to the complex immunity process against the parasite, including the presence of additional parasite non-self-antigens, ESPs and SPs, infection burden, T helper polarization, antibody responses, host microbiota changes, and bacterial translocation [4][3][5][6][7][8].

Several factors affecting the immune response are also orchestrated locally and systematically during infection, which were represented through a study using peripheral blood lymphocytes (PBL). PBL played a role as a marker for the immunologic response in mesenteric lymph nodes against *T. trichiura*, and ultimately secreted higher levels of type 2 cytokines, including interleukin (IL-4), IL-5, IL-9, and low levels of interferon gamma (IFNϒ) secretion obtained via peripheral blood samples [9]. In another study, trickle infection appeared as a transforming factor of immunological direction. This mode of infection also modulated the immune response during the experimental study more predominantly with Th1-type cytokine. In contrast, a high burden of infection at a single time prevents a large degree of Th1-type cytokine expression, and it is concurrent with a significant change in the resistant phenotype [10][11][12].

In the subsection below, the basic concept of the immunological response against *Trichuris* is discussed regarding the fate of worm expulsion with a potent Th2 response versus chronic infection dominated by Th1-type cytokine

expression.

1.1. Innate Immune System Also Determines the Fate of Infection

A recent review explored the substantial role of the GI epithelium as the first structural barrier against pathogens, as it maintains the homeostasis with the work of mucus, intestinal microbiomes, and functional innate immune cell content [13]. Besides this, the gut microbiome, symptomatic diarrhea, and pathogen recognition receptors (PRRs), such as Toll-like receptors, nucleotide-binding domain (NOD)-like receptors (NLRs), or C-type lectin receptors (CLRs), contribute to the immune response to *Trichuris* infection [14]. As a result, this generates a hostile environment for *Trichuris* development and proliferation if effective anti-helminthic immunity is formulated.

Intestinal epithelial cells have been notably enrolled in the immune response against intestinal bacterial and parasitic infection by inundating the gut environment with Th2-type cytokine during the initial phase of infection [15][13][16]. Previous studies have shown that colonic epithelial cells and mesenteric lymph node cells (MLNCs) secrete high levels of interferon (IFN) ϒ with a low expression of Th2 cytokines produced both in resistant and susceptible laboratory-infected mice, suggesting a multistage process for immune activation [17][18].

The involvement of GI tissue in secreting cytokines against parasitic invasion was also evident in another study provoking IL1, IL6, IFNϒ, and TNFα mRNA expression [19]. Consequently, Th1 cytokine expression then upregulates and shifts to Th2-type cytokine for the resistant state of infection. However, immunity timelines against *Trichuris* have not been entirely delineated, since strong Th2 immune responses alone could trigger worm expulsion without B cell involvement [20]. Still, a mixed response (Th1/Th2) requires B cells to effectively expedite expulsion in an IFNϒ-rich environment, denoting the involvement of B cells in amplifying Th2 polarization [6][21]. Moreover, local intestinal antigen-presenting cells (APCs) could produce retinoic acid for IL10 production and TGFβ —a cytokine hallmark for priming Th2-type phenotypic responses [22].

Classical findings associated with immune activation in *Trichuris* sp. infection have delineated innate and adaptive immune systems as different processes, but recent studies have shown otherwise. The interaction between the two parts of the immune response is responsible for the successful fate of parasite eradication, as it is shown in Figure 1. IL4, IL5, and IL-13 authenticate the activation of Th2 immune response, and these proinflammatory cytokines surge prior to Th2 activation. Intestinal epithelial cells and innate immune cells can upregulate Th2 cytokines via thymic stromal lymphopoietin (TSLP), IL-25, and IL-33 secretion, which are potent inducers for Th2 cytokine expression [23][24][25][26]. Therefore, the innate cellular component could also determine the reactivity and the quality of adaptive immune responses, which could result in a failure during antigenic recognition or cellular induction that consequently reverberates to the priming and proliferation of the adaptive immune system.
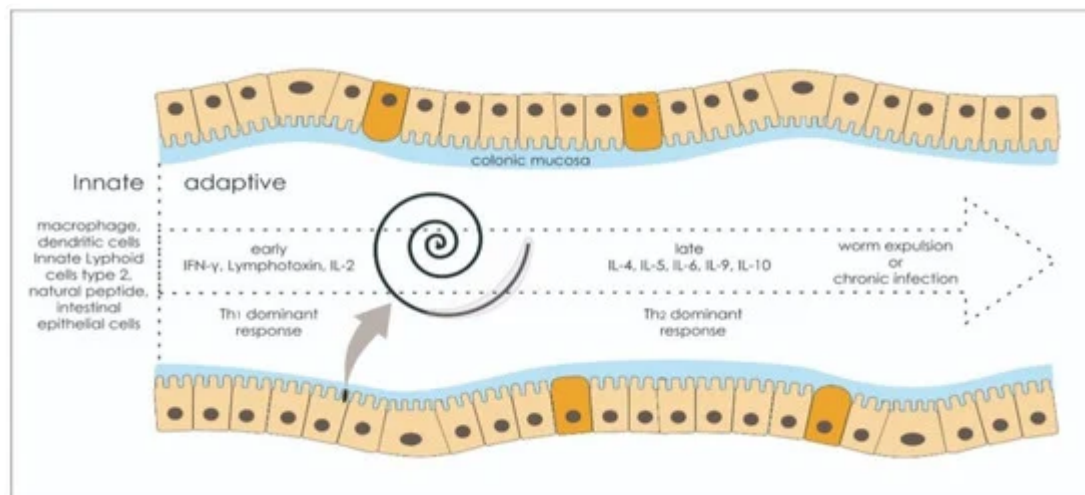
Figure 1. The fate of the immunological response against *Trichuris* sp. infection. There are two critical factors associated with the successful worm expulsion: The host inflammatory genotype and infection burden. The innate immune response must mount Th2-type cytokines.

In the end, the complex framework between innate and adaptive immune response is a continuation of different immune activation and regulation processes. The amalgamation of functions among immune cells is responsible for leading to worm expulsion by increasing intestinal epithelial cell turnover and mucin secretion. Specifically, IL-4 induce smucin production from enterocytes while IL-13 triggers goblet cell hyperplasia. Both cytokines promote smooth muscle contraction, which ultimately expedites worm expulsion, but cytokine activities might also be independent of the adaptive immune responses [27][28].

1.2. Antibody-Dependent Cell-mediated Cytotoxicity (ADCC): Is It Reliable for Trichuriasis?

In another perspective, antibody-dependent cell-mediated cytotoxicity (ADCC) has become an alternative route to eradicate whipworm due to the inability of phagocytic cells to ingest macropathogens [29][30]. The definition of ADCC refers to the immune killing method through the opsonization of antigens using antibodies mediated by cross-linked Fc receptors found in effector cells, such as macrophages, natural killer cells (NK cells), neutrophils, and eosinophils [29]. IgG, IgA, or IgE coat antigens and activate the complement system to finalize the cytotoxic response. In the end, effector cells release granules and lysosomal content and form an identical immunopathology with a "granulomatous appearance" in certain parasitic infections implicated by ADCC, which is highly dependent on sensitized CD4+ T lymphocytes [31][32].

It has long been documented that cytotoxicity represents the essential immune response against *Trichuris* sp. infection, but the role of antibodies has also been notable in some studies. Moreover, some reports have concluded that the role of one of the cytotoxic cell effectors, eosinophil, has been disputed in terms of its protective function during ADCC and its intrinsic function during infection [33][34][35]. The study demonstrated that the worm expulsion or resistance state also continued in the absence of eosinophil and mast cells, while other immune cell subsets

affected the regulation [35]. Nevertheless, ADCC might still occur as an innate immune response against helminth larvae, but it could be an inefficient way to generate adult worm expulsion [36].

1.3. Adaptive Immune Response: Worm Expulsion versus Chronic Infection

The investigation of the adaptive immune response against *T. trichiura* is incomplete, and several hypotheses and deviant responses have also been proposed during the infection. Early studies divided the terms of "responders," referring to mice that achieved worm expulsion, and "non-responders," referring to mice with no immune response against *Trichuris* sp., resulting in chronic infection [37]. Nevertheless, recent studies have disputed the terms because there is still significant immunity established following infection in both groups but inadequate responses among non-responders. Therefore, "resistant" and "susceptible" have been proposed to reflect immune reactivity against *Trichuris* sp. infection. In other words, resistant mice will generate a predominantly Th2-type response, resulting in worm expulsion [38].

Susceptible hosts experience chronic infection and Th1 polarization that is ineffective and even increases immunopathological abnormality [15]. Many studies have supported the fact that Th2-type response predominance against *T. trichiura* quickly results in worm expulsion [5][10][11][17][18][39]. A study discovered that *Schistosoma mansoni* coinfection with *T. muris* caused spontaneous infection resolution [40]. This resistant host phenotype relied on Th2-associated cytokine and antibody isotypes previously produced by the antigenic exposure to the *S. mansoni* egg.

2. Immunomodulation Properties of *Trichuris* sp. and Clinical Implications: Focus on the Role of Excretory/Secretory (ESPs) and Soluble Products (SPs)

Drawing the theoretical background regarding how helminths, particularly *Trichuris* sp., produce chronic infection is not a simple task. During this period, helminth infection deliberately invades the gastrointestinal mucosa and produces a supportive niche for its sustainability. Nevertheless, the infection process only triggers a subtle inflammatory response, frequently flawed Th2 response, or a predominant Th1 immune response. The latest investigation demonstrated one of the remarkable features of *Trichuris* sp.—that it could transform the immune response into favorable states through the secretion of excretory/secretory products (ESPs)—as we elaborate in the following discussion.

ESPs are a group of molecules released from helminths, bearing immunomodulation features during the host–parasite interaction consisting of some uncharacterized substances, proteases, glycolytic enzymes, protease inhibitors, chaperones, miRNA, and antigen homologs or metabolites [41][42][43]. Whipworms organize the substances for survival and modulate the immune response through two primary mechanisms. First, ESPs can manipulate the expression of PRRs or act as cytokine homologs, affecting downstream signaling pathways [44]. Second, immunomodulation features can also trigger several changes in the response to the regulation and polarization of immune cells that could blunt inflammatory responses via anti-inflammatory cytokine secretion, such

as IL10 and transforming growth factor β (TGFβ). In a study, the direct effect of the presence of ESPs reduced IL-1β, TNF-α, and NO-2 as secreted products of macrophages in the large intestine [4]. However, whey acidic protein (WAP), as an abundant type of EPs found in *T. muris*, induces induce type-2 immunity that eventually promotes worm expulsion [45].

2.1. Secreted Products Modulate Pattern Recognition Receptor (PRR)

ESPs impair the function of PRR, which is an essential part of the innate immune response for antigen recognition. There are several types of PRRs, such as retinoic-acid inducible gene (RIG)-like receptors (RLRs), NLRs, CLRs, and toll-like receptors (TLRs), contained by future antigen-presenting cells (APCs), such as macrophages and dendritic cells (DCs). By modulating the activation of PRRs, the ESPs of *T. suis* were shown to prevent lipopolysaccharide-induced TLR4 sensing in human dendritic cells (DCs) in a study, suppressing downstream signaling pathways [46]. It was also evident that *T. suis* SPs transform macrophages into a more anti-inflammatory phenotype by inhibiting P2RX7, a receptor involved in the stimulation of immune cells such as macrophages, dendritic cells, and lymphocytes, concurrent with reduced IL12B, CCL1, and CXCL9 expression [47]. This interaction reduced the expression of proinflammatory cytokines via Rab7b overexpression, a small GTPase-degrading TLR4 [48][49]. Both pathways related to TLR4 for myeloid differentiation would undoubtedly also be impaired. Reductions mainly involve MyD88-dependent mediated TLR4 responses, finally reducing the level of proinflammatory cytokine genes, reactive oxygen species (ROS), and eicosanoids [48]. ESPs also affected the remaining TLR4 signaling pathway in a TIR-domain-containing adaptor protein-inducing, interferon-β (TRIF)-dependent manner, by reducing IFN α/β production, finally resulting in the scarcity of expression of type I IFNs [50]. *Retinoic acid*-inducible gene (RIG)-I-like receptors also disintegrate following ESP administration, downregulating several essential signaling proteins such as Irf7, Ddx60, and Dhx58 [51]. Thus, there is a decreased downstream signaling for proinflammatory cytokines, and the threats for type-I IFN production become more prominent [52].

Impairing TLR4 activation prevents the surge of proinflammatory cytokine secretion, which eventually results in several clinical implications for other conditions. In sepsis, the hyperactivation of TLR4 and TLR2 is concurrent with the overload of systemic inflammation and organ dysfunction and could produce poor outcomes in animal models [53]. *Trichuris* infection prevents TLR4 activation by downgrading its receptor and signaling pathway, thus reducing the repercussions of proinflammatory cytokine upregulation [47]. Additionally, the immunomodulation properties of *Trichuris* could also increase insulin sensitivity [54]. Dietary fatty acids and enteric lipopolysaccharides (LPS) can activate TLR4 and provoke proinflammatory responses to behave as insulin resistance inducers [55][56]. Therefore, preventing TLR4 signal activation could be the novel target to increase insulin sensitivity.

Glycan-based components in *Trichuris* sp. SPs bind the mannose receptor, a CLR, and increase its expression in monocytes and dendritic cells, inducing protein kinase C (PKC) phosphorylation, specifically PKC δ, and shift the monocyte behavior to an anti-inflammatory phenotype [57][58]. Most novel PKC activation implications remain unknown, but CC chemokine receptor (CCR) 2 and lymphocyte function-associated antigen (LFA) 1 expression are upregulated following PKC activation [59][60]. In IBD, a disease characterized by gut physiology resembling *T. muris* infection, breaking mucosal integrity becomes the basis of pathogenesis, which is perpetually insulted by the

expression of proinflammatory cytokine and oxidants caused by the PKC downstream signaling pathway [61]. Moreover, PKC inhibitors were found to attenuate tissue injury in a mice model for colitis [62]. The same study also suggested a breakthrough in advancing qualities for managing several autoimmune diseases with T cells and the autoreactivity of monocyte-derived macrophages using *Trichuris* sp.-secreted products, such as multiple sclerosis and IBD [57].

Cytosolic PRR or the inflammasome have demonstrated several pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) [44]. The presence of ESPs and other extracellular vesicles released from *Trichuris* also affects the function of NOD-like receptor protein 3 (NLRP3), a well-known inflammasome that has pivotal roles during the initiation and amplification phases of both the innate and adaptive immune response [63]. *Trichuris* exosomes encourage pro-helminthic immunity by upregulating IL1β and IL18 via the NLRP3-dependent pathway [63][64]. IL18 appears to be a driving force for the different outcomes since it has a diverse function that could initiate a resistant or susceptible type of immune response. IL18 used to be known as IFNϒ-inducing factor (IGIF) and is involved in the vast signaling pathway for Th1 and NK cell activation, but in vivo studies have suggested that IL18 undermines anti-helminth immunity through an IFNϒ-independent pathway. In other studies, NLRP3 activation triggered downstream signaling pathways of the Th1-type response, making the host susceptible to chronic infection [63]. In contrast, infecting NLRP3-deficient mice with helminths augmented early innate immune cell recruitment, eosinophilia, and neutrophilia, as well as type-2 cytokine responses, while the presence of NLRP3 attenuated immunopathological changes in the tissue environment [65].

2.2. Secreted Product Skewed Innate Immune System

Trichuris ESPs and SPs have also become key to developing the innate immune system by shifting the response of classical (inflammatory type) into nonclassical monocytes after *Trichuris* SPs administration. This type of monocyte has no expression of CCR2 and CD14 but has a higher expression of CX3CR1. A group of proinflammatory cytokines (a marker of classical monocytes), including IL-10, TGFβ, TNFα, IL-6, and ROS, was first secreted during early observation. However, transition occurred following 16 h of SPs treatment with prominent anti-inflammatory cytokine expression, showing that classical monocytes were largely impacted by the presence of SPs [57].

Monocyte hypermotility, mediated by the activity of small Rho GTPases such as Rho, Rac, and Cdc42 on the actin cytoskeleton, was also notable and reduced adhesion to endothelial cells following *Trichuris* ESPs treatment [57]. A high-saturated prostaglandin E2 content of EPs and SPs also manipulated dendritic cells by skewing proinflammatory features by upregulating RAB7B [49]. PGE2 synthesis by *T. suis* was independent of cyclooxygenase activity in the study. SPs modulate DCs through a mechanism that predominantly involves the overexpression of PGE2, although its effect differs based on its concentration and bound receptors [43]. This could resolve inflammation to accommodate immunopathological repair. However, the glycan component of SPs was also found to interact with CLRs in human DC, with the final result of modulating DCs to suppress proinflammatory responses, but this is a concentration-related effect.

2.3. Secreted Product Produce Deviant Cytokine Response

ESPs influence proinflammatory cytokine expression. However, higher levels of IL10 and other regulatory cytokines, TGFβ and IL-35, are associated with the administration of *Trichuris* ESPs. This also suggests that this cytokine concoction yields the main immunomodulation properties of ESPs. The regulatory function of IL10 cannot be described solely as pro- or anti-inflammatory cytokines because of the pleiotropic features caused by heterogeneous receptors IL10Rα, IL10Rβ, IL22Rα, and IL28Rα with diverse implications. Nevertheless, IL10 still augments the Th2-type immune response against acute *Trichuris* infection via IL10Rα activation [66]. It also plays a vital role in protecting the intestinal barriers, preventing other bacterial invasions, and constraining the systemic inflammatory response against *Trichuris* infection. Conversely, several significant findings regarding tissue rupture are caused by *Trichuris* invasion promoting bacterial translocation through the lesion. In two separate studies, the response of *T.suis* inoculation was clearly found to lead to macro-pathological changes associated with bacterial infiltration and the suppression of local immunity to the *Trichuris* sp. site of infection [4][67].

In contrast, it was observed that Alzheimer's transgenic mice infected with *Trichuris* were more vulnerable to suffer from exacerbations caused by neuroinflammation and larger microglia size, suggesting that a systemic response also developed during overwhelming IL10 secretion [68]. Nevertheless, IL10 upregulation following ESP treatment showed positive implications in other pathological conditions, including IBD. IL10-deficient mice developed chronic inflammation, resulting in the significant immunopathology caused by an incessant immune response against normal intestinal flora [69]. Meanwhile, the reduction of airway responsiveness and IgE production dependent on IL10 was also evident in the mice model for allergic disease, showing the immunoregulatory function of IL10 [70]. Concerning this evidence, ESPs ultimately reduces the inflammatory response and its immunopathology by promoting IL10 secretion.

The administration of ESPs also thwarts Th2 immune cell polarization via the direct activity of ESPs modulating IL4 and IL13 expression, which are useful in different pathways for Th2 immune maintenance [71][72]. This recent finding shows that the protein component of ESPs secreted during chronic *T. muris* infection, called p43, acts as a homolog for IL13 receptor α2 (IL13Rα2) and thrombospondin type 1 [72]. This protein binds into the IL13 active site, inhibiting downstream activation, thus resulting in susceptibility and failed worm expulsion. In predominant eosinophilic diseases, IL13 plays a crucial role in eosinophil priming and proliferation, causing more damage to the tissue environment. Since ESP mimics IL13Rα2, it could halt the vicious pathological changes mediated by IL13 activity, such as airway hyperresponsiveness and goblet cell proliferation, as well as mucus secretion. Therefore, it might be beneficial for asthma, atopic dermatitis, and chronic rhinosinusitis with nasal polyps.

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