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Role of Macrophage Cell in Lymphatic Filariasis

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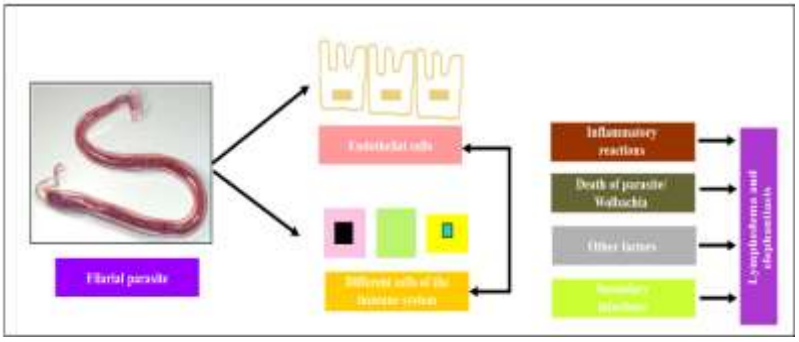
Graphical abstract



Highlight

- Filarial parasite is infected in endothelial cells, and different cells involved in immune systems.
- It creates inflammation and other secondary infections.
- External appearances like lymphedema, lymphangitis, and elephantitis.

ABSTRACT

Lymphatic filariasis (LF) is a chronic, neglected nematodan parasitic disease.It is belonging to the group of rare neglected tropical diseases (NTDs). After malaria, it is the leading infectious disease and Causative organisms *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori* belong to the phylum Nematode. They were asymptomatic, but now a day few symptoms have been observed such as lymphedema, elephantiasis and hydrocele. This disease shows close communication with humans by interacting with host immune systems. They disrupt monocytes/macrophages, dendritic cells, granulocytes, eosinophils, basophils, and Toll-like receptors. This review demonstrated macrophage cells' (mϕs) role and their therapeutic approaches. Due to this infection several immune systems hampers in host bodies. Among them, macrophage cells which are originated from monocytes play crucial roles against filariasis. They are produced several cytokines, chemokines, pro-inflammatory factors, and enzymes which prevent this disease from further activation.

KEYWORDS: lymphatic filariasis, neglected tropical disease (NTD), immune system, macrophage cells (mϕs), Toll-like receptor

1. I INTRODUCTION

Helminth parasitic worm infections infect most of the world's population.[1-2] Parasitic LF infections are considered a Negligible Tropical Disease (NTD) classified by the World Health Organization (WHO), in 2017 total of 14.6 million people were infected with onchocerciasis and around 1.15 million people suffered vision loss (WHO. 2022). It is the third most causative parasitic disease around the globe. Causative organisms by nematodes such as – *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*, with symptoms like elephantiasis, hydrocele and lymphedema. In Asia, Europe and North America canine filariasis is a major threat that causative agent by *Dirofilaria repens* and *Dirofilaria immitis*.[3] These parasites showed the animal-to-human cycle i.e. they are known as zoonotic potential in nature, which increases the rate of infections in humans has been documented.[4-5] The life cycle comprises these filarial parasites vector mosquitoes such as *Culex* species and human stages. In another way, a pathogenic form of L3 of *W. bancrofti* enters the host system through vector-dependent spreading via the blood flows during the night (nocturnal) that interactions with different immunological cells like- monocytes/macrophages, dendritic cells, granulocytes and also various life stages of the filarial parasitic worms (microfilaria, L3 larvae and also adult stage)[6] (Figure 1). In tropical regions around the globe, causative organisms of *Wuchereria bancrofti* and *Brugia malayi* create drastic problems for 859 million people in 50 countries around the globe and reported that 51 million people are still now infected, according to the WHO (WHO, 2022). The vaccine development against filarial parasites is still ongoing.[7] In, *D. immitis* affects dogs and it is also a causative pathogen of heartworm disease.

Treatments are useful against adult worms, such as diethylcarbamazine (DEC),[8] and also observed microfilaricidal activity like ivermectin.[9-10] Current evidence shows that tetracyclines have both macro and microfilaricidal effects against filariasis.[11-13]

Filarial nematodes prefer to migrate Mf through the blood circulatory system and also in lung capillaries during their periodicities which, helps permanent interactions between Mf and host endothelial cells.[3] The highest peak of Mf concentration in the peripheral blood systems is during hours when mosquitos are likely to feed.[14] In another finding, Mf of *D. immitis* prefers phototaxis movement towards infrared light.[15]

Helminth parasites downregulate the host immune mechanisms that help regulate the host body's immune dysfunction.[16] The LF host parasitic interaction shows a chronic infection and dysfunction of the innate and adaptive immune system.[6] Generally, the response of Th2 cells can down-regulated host immune mechanisms.[16-18] Th2 is critical for protection while IL-8 plays a vital chemokine that leads to the pathogenesis of filarial diseases,[19] anti-inflammatory cytokines like IL-10 regulate inflammatory responses such as allergies and auto-immune disorders.[20] This study, discussed macrophage cells secrete some enzymes, important chemokines, that fight against LF.

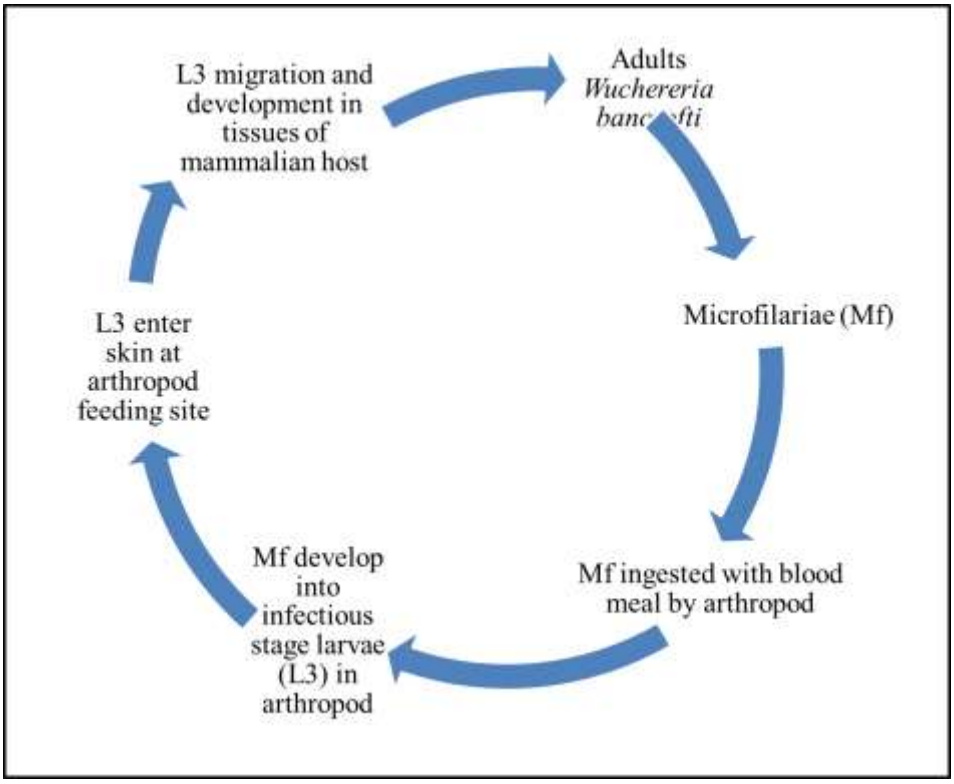


FIGURE 1 The life cycle of *Wuchereria bancrofti*.

2. Macrophages act as effector cells

2.1 Parasitic worm killing via macrophages

Macrophages are important for killing the infective L3 stage of filarial worms. In residence, macrophages were observed to kill *Acanthocheilonema vitae* microfilaria (MF) in the presence of such an immune system.[21] Adherent macrophages (mϕs) are capable to kill MF in the presence of anti-micro-filarial therapy.[22] Two other groups have been shown MF of *B. malayi* to be killed with the help of IFN-γ and which helps to activation of macrophages that help immediately least part of NO.[22,25] In another way, the appearance of a little bit of H_2O_2 effect *Brugia* sp. but it does not harm *Onchocerca*.[23-24] Activated macrophages can kill the filarial nematode parasites in the vitro process.[25] In the adult stage, macrophage-mediated damage is more resistant than in the larval stages,[25] during the presence of antioxidant enzymes.[26] Currently, filarial parasites show several attributes that fight against oxidative attack highlighting the significant ROSs levels that attack the immune system.[27] In the bioprocess, activation of macrophages by the help induction of *B. pahangi* larval stage (L3) in the peritoneal cavity of jirds. These macrophages show dual roles like phagocytic and also microbial activity.[28] In filariasis, in the peritoneal cavity of jirds, dominant mϕs dependents with granulomatous lesions form adult parasitic worms and also microfilaria, presence of these cells on the adherent portion of the parasitic surfaces.[29] Evidence showed macrophages play a major role to resist infection.[30] Currently, sex and age-wise data observed susceptibility in mice and they also demonised when mϕs activation is inhibited by carbon (C) particle injection. [30] Macrophages and granulocytes are important for the destruction of the parasite.

2.2 Macrophages in filarial pathology

In this review, macrophages activate to kill filarial parasitism and the cells can be an important few in the pathological association with LF.[31] Pathological ways, which help around dying parasites are abundant in macrophages and eosinophils.[32,33] Activation of macrophages in case of parasitic infection may cause damage to host tissue. This study,[34] showed that intracellular, gram-negative bacteria (*Wolbachia*) presence plays a central role in the inflammatory pathology of *Brugia malayi*. *Wolbachia* protein found in the debris of *B. malayi* can stimulate macrophage cells to increase cytokines like - tumour necrosis factor (TNF), interleukin-1 (IL-1) and NO. Macrophages lack surface CD14, they were defective in binding lipopolysaccharides (LPS) on their surface, and also mouse strain had a mutation in TLR4. Dying worms release LPS. [34]

2.3 Macrophages in natural resistance

Macrophage cells play a crucial role to control filarial infection. In *xid* mice strain of CBA/N that defects in the Bruton's tyrosine kinase (*Btk*) gene. In this strain, they are capable to clear of MF that are more susceptible to causing infection with vector-borne larval forms that comprise wild-type CBA/J mice.[35-38] Due to the defect in the *Btk* gene, also observe defective B cell signalling and development. In myeloid origin, the *Btk* gene is expressed in antigen-presenting cells (APCs) and also B cells.[35] In this study,[39] CBA/N mice show significant alternatives function of macrophages that can help in the vital role of filarial pathogenesis. These mice macrophage cells have been able to decline the production of NO, but it also enhanced the IL-12 concentration levels that downregulate the induction effects of NO and IL-12.[39] Adoptive transfer experiments are different cytokine that regulates macrophages rather than B cells.[37] B cells are capable of resisting filarial infection in mice.[38,40] Due to defective B cell function, *xid* mice are unable to rapidly clear their mf.

3. Macrophage supresses LF infection

In humans,[41-43] key findings have been observed and also in animals,[33,42,44-46] shows individuals infected with filarial parasite causes defective lymphocyte proliferation occurs. An experimental model of jird,[45,46] demonstrated that the removal of adhesion cells community was able to reverse the proliferative defect. The finding showed that in human peripheral blood, the system adheres to phagocytic cell proliferation.[47] Macrophages or monocytes play a strongly implicated immune suppressor observed over the entire course of filarial infection. The chronic infection of *B. pahangi* leads to the inactivated role of macrophages.[47] Due to measuring the capability to kill *Toxoplasma* sp. and secretes TNF. The present study in jird showed that inactivated macrophages conjugate with a decline in the inflammatory response in systemic granulomatous. These data opined, that anti-inflammatory macrophages can down-stimulate immunopathology. Macrophages produce down regulatory cytokines, known as IL-10 and lymphocytes which can directly interact with the pro-inflammatory effects of IFNY. Blood mononuclear cells have been produced with the help of IL-10. The implication in the down-regulate of T-cell response in the cause of human filarial pathogenesis,[48] and rapid secretion of the highest concentration of IL-10 by adhering mononuclear cells that assembled for the hyporesponsive state.[49] As per this study,[50] IL-10 secretes an adherence to splenocytes and dysregulates T cell proliferative levels in *B. pahangi* infected mice. Production of macrophages with the help of IL-10 and in filarial infection must regulate the immune responses.

3.1 IL-4-dependent anti-proliferative cells in the mouse

As previously studied, the determination of the filarial parasitic worms in APC function could be defective in antigenic T cell proliferation associated with infection.[51] APC was even able to block transformed cell line proliferation.[51] Initially, mf induces IFN-Y while L3 forms and adult form induces high IL-4 levels that were located previously.[52,53] As per available literature, IL-4 required the induction of suppressor cells. By using IL-4 it is neutralizing antibodies that decline the IL-4 levels and are easy to deliver growth of the antiproliferative cells necessary for host IL-4.[54] Studies showed that neutralized antibodies like IL-10 and TGF-ß that are resistant to NO, prostaglandins or H_2O_2 also were not capable of reversing the proliferative defects.[51] The antiproliferative effect of IL-10 is more valuable evidence that down-regulates the effect.[50,55] Another study of cell type responsible for the suppressive effects of macrophages.[56]

3.2 A balance of cytokines and macrophages

Th1/Th2 cell helps to play a central role to plays the immune responses. A recent study showed that cytokines have opposing effects on macrophages. Firstly, IFNY is activated with the help of macrophage cells and IFN-Y is lost intracellular causing pathogens by the production of pro-inflammatory conjugates such as NO[57,58] (Figure 2). IL-13 and IL-4 are two cytokines that are activated with the help of macrophages, it helps in the development of a distinct phenotype. [59-61] The cells are known as “alternatively activated macrophages” (AAMϕ) to differentiate them from macrophages “classically activated macrophages” (CAMϕ) by IFN-Y or LPS.[61] Thus macrophages are similar to T cells and dendritic cells (DCs).[62,63] This developmental pathway is dependent on the cytokine microenvironment.

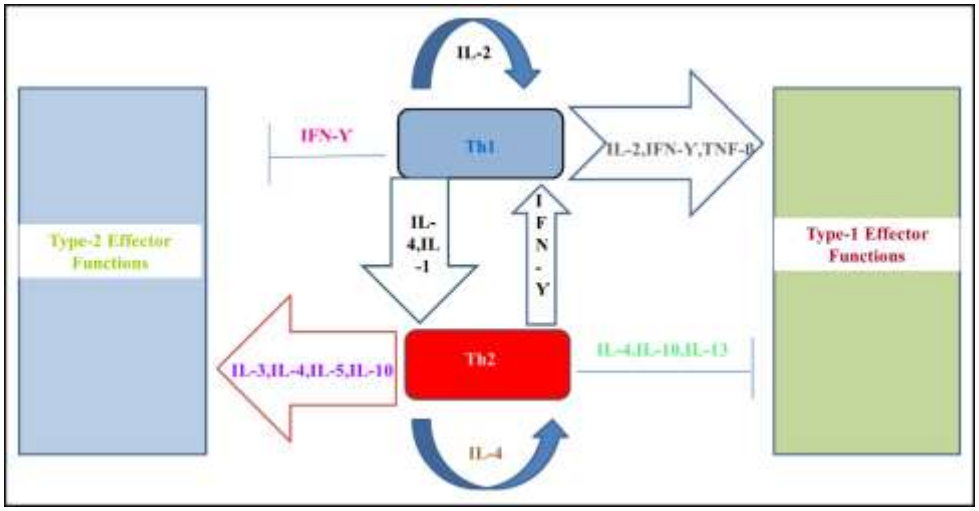


FIGURE 2 Cytokine mediated pro-inflammation (Th1) and anti-inflammation (Th2) of immune Cells.

3.3 Arginase-1 versus iNOS

CaMϕs have enough potential to eliminate intracellular pathogens. Nitric oxide (NO) shows antimicrobial actions and releases peroxynitrite which occurs from the NO reaction. L-arginine produces NO with the help of an inducible isoform of the Nitric Oxide Synthase (iNOS) enzyme.[61] iNOS stimulates several kinds of cytokines like IL-12, TNF-α and IFN-Y to get induced macrophages.[64] In CaMϕs, type 2 cytokines such as IL-13 and IL-4 stimulate arginase-1 which helps to express in macrophages (Figure 3),[65] an alternative activation marker in mouse macrophages.[66] "Alternatively activated" macrophages indicated IL-13 and IL-4 that enhance macrophages,[66] factors like TGF-ß or IL-10 (Figure 2),[67] and phagocytosis of apoptosis of apoptotic cells.[68] AAMϕs have been identified as being involved in inflammation such as in the lung and placenta.[69,70] Increasing concentration of arginase inactivates in the blood systems of pregnant women.[71] In minute and severe inflammatory responses, macrophages show psoriasis and rheumatoid arthritis.[72,73] Hence, AAMϕs help to maintain homeostasis. During different causative pathogens infections, IL-13/IL-4 dependent AAMϕs limiting CaMϕs depends on clearing parasites and also help parasitic worms proliferation.[74,75] Successfully eliminated an infectious disease to the existence of temporary regulation of signals that helps to activation of macrophages.

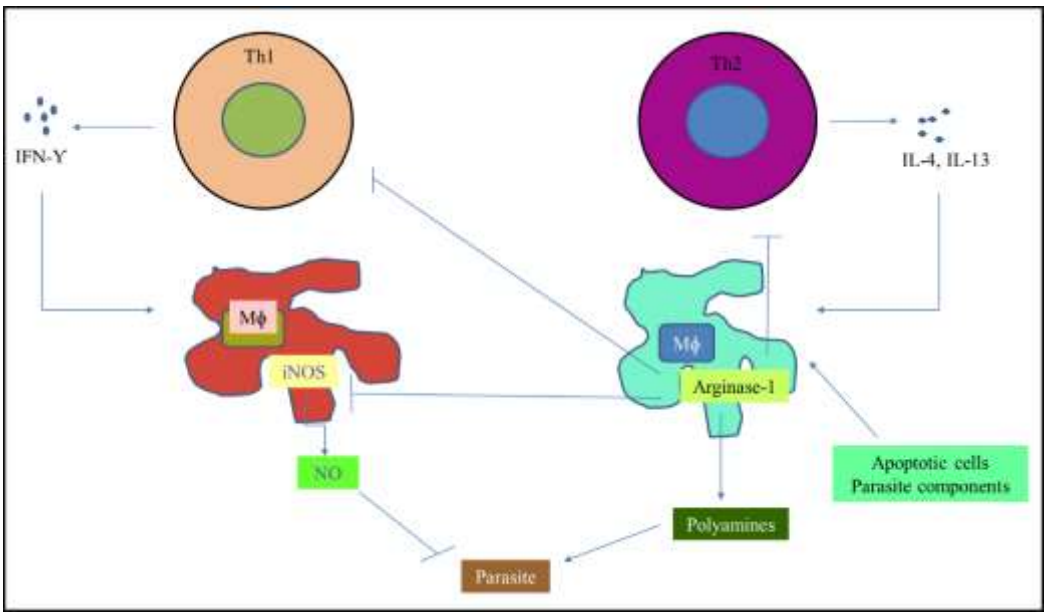


FIGURE 3 Type 1 cytokine-dependent proinflammatory response enhances NO and several other products. In type 2 cytokine-dependent systems arginase-1 suppresses T-cell responses that promote parasitic proliferation and survivability.

3.4 Roles of arginase-1 in macrophages

IL-13 and IL-4 show protection against helminth-dependent infection. Th2 cytokine (Figure 3) recruits AAMϕs in the chronic stage of infection, which elicits T-cell suppression and also fibrosis.[76-79] In *B. malayi* infection shown that IL-4-dependent macrophage activation controls the proliferation of

lymphocytes.[80] Infection of *Schistosoma mansoni* shows the development of Th2 cell response. Brunet and colleagues demonstrated that IL-13 and IL-4 are critical players in the survival of Th2-dependent immune response during *S. mansoni* infection.[81] The conclusion shows that elicits in the NO and TNF-α levels indicate the severity of infection. Th2 response in chronic infection shows highly harmful hepatic fibrosis and portal hypertension.[82] Th2 accumulates arginase-1, which is also expressed in macrophages, it is surrounded by arginase-1, and also granulomas. It helps in the expression of peritoneal cavity macrophages that also activate circulating polyamines.[83] Arginase-1 expresses macrophages promoting the deposition of collagen and also in the fibrosis h proline synthesis mediated by arginase-1. According to this study,[84] AAMϕs (*Il4ra*$^{-/flox}$*; LysMcre*) activation is vital during schistosomiasis and downregulates Th1 responses and immunopathology. Macrophage-directed arginase-1 helps in anti-inflammatory activities via the Th2-dependent inflammatory response elicited by *S. mansoni*, and it is also the resolution of schistosomiasis by inhibiting CD4+ T cells.[85,86] Pesce and colleagues demonstrated that arginase-1-expressing macrophages mediated immune down-modulation in chronic schistosomiasis.[85] AaMϕ expresses resistin-like molecule (RELM)α, which is involved in Th2-dependent cytokine falls during the inflammation in pulmonary have been taken place in schistosomiasis.[87] The infective larval stage is an arginase-dependent pathway, that leads act as the massive exposure of adult worms.[88] Gut contractibility and luminal fluid secretion lead to Th2 responses that cause worm expulsion.[89,90] Arginase activity inhibition shows in intestinal nematode parasitic worms *Nippostrongylus brasiliensis* infection of smooth muscle contraction and relaxation that partially protects the immune system of the host body.[64] Widely induced by arginase-1 expression of macrophages in helminth infection.

3.5 Mechanism of proliferative suppression

Cytotoxic activity signifies NO produced by CAMϕ, in a nontoxic manner it also inhibits cellular proliferation. During the presence of NO synthesis inhibitors or the absence of iNOS, proliferative T cells that lead to the enhancement of inflammatory cytokines increase significantly.[91] The demonstration shows that activated "suppressor" macrophages in models of mouse African trypanosomiasis infection in *Trypanosoma brucei* (*T. brucei*) elicit generation of macrophages inhibited T cell enhancement via prostaglandins and NO.[92-94] The primary function of CAMϕ is microbial destruction. The primary function of AAMϕ is damaging the downregulation of the immune system. Anti-inflammatory cytokines that lead to key features of APC activate under type 2 conditions.[95] AAMϕ mediated suppression is involved in IL-10 and TGF-ß.[95] Human macrophages co-cultured involved IL-4 and glucocorticoids that suppress the proliferation of T cells independently of IL-10, NO or prostaglandins.[96] Higher consistent suppression of induced macrophages by a filarial infection helps out these potential mediators.[50] When fixed with paraformaldehyde AAMϕ can inhibit cellular proliferation.[55] Macrophage cells are induced not only on murine lymphocytes but also inhibit human tumour cell line proliferation.[55] Similarity study of macrophages that uses an aerosol challenge in transgenic mice system and is also capable to produce Th1/Th2 cytokines.[97] Th2 responses way of activation/differentiation of a macrophage population.

3.6 Th2 cell induction by AAMϕ

An immune suppression study suggested that AAMϕ is a similar type DCs, which could induce naive T cells that differentiated into Th2 cells.[86,95] The study showed that AAMϕ induction can live in adult *B. malayi* that drive differentiated Th2 cells that are isolated from pigeon cytochrome c (PCC) specific TCR transgenic (PCC-Tg) mice.[98] Dendritic cells (DCs) can stimulate and differentiate naive T cells, and stimulants of macrophages can differentiate Th2 cells.

3.7 Different Roles of Macrophages in filarial infection

At the time of infection, it makes an equilibrium population of two macrophages that determines the severity of the disease associated with infection. In the daily injection basis study, excretory materials (ES) showed that in adults it generated AAMϕ but cannot be generated dead parasites implantation.[99] The macrophages release pro-inflammatory mediators to endeavour dying worms.[32] This suggests us in the lymphatic system live adult parasites live, where ES products are also secreted into the afferent lymphatic systems. Immunomodulatory ES molecules induce Th2 responses and recruitment of AAMϕ.[99] LPS from the intracellular bacteria is released, when parasites were a death that leads to the activation of CAMϕ. CAMϕ produced cytokines that would drive the development of Th1 cells and induce inflammatory-mediator damage to the around tissues. Bacterial LPS-induced inflammatory responses create an inflammatory response that leads to chronic infection. The granulomas formed surrounding the egg's surface of the schistosome. Macrophages with an activated phenotype appear alternatively, that is rapidly down-regulated inflammatory systems. The proposal of this study is a balance between cytokines that creates a balance between the two populations of macrophage.

4. Macrophage-dependent therapies

Activation of macrophages plays a crucial role in the balance of tissue homeostasis and resolving inflammation of many diseased processes. It acts in a signal and tissue-specific manner and it also helps in several activation patterns that lead to growing specific functional attributes (Figure 4).[100,101] Current studies on airway hyperactivity have been local macrophages acquired AAMs, that regulate inhibition of the development pathway of induces antigen-dependent $CD4^+$ $FoxP3^+$ T regulatory (Treg) cells.[102] Many immune systems are involved in helminthiasis that activates with Tregs, which regulates B (Bregs) cells and presents AAMs as key regulators of pathogenesis.[103] Macrophage-directed therapies are useful for diabetes, inflammatory diseases and renal disease. The chronic inflammatory response causes renal disorder polarization of macrophages in vitro with IL-13 and IL-4 in improved patients who are prone and injured after transfer into the mice for disease.[104] During helminth infection, macrophage immunoregulatory phenotypes that diverge induce host tolerance, parasitic survivability and repair of the injured tissue that causative agent by eggs and larvae.[105,106] Neutrophil helps develop M2

macrophages, they can bind in helminth larvae, which leads to enhances mortality and macrophages to transfer protection of naïve hosts.[107] In *B. malayi* infection, M2 marker express monocytes, which recapitulated the response of human monocytes in filarial antigen or live microfilariae.[108-110] Macrophages induce specific phenotypes that have been made helminth products with therapeutic potential.[111] An example of filarial molecule ES-62 from *A.viteae* shows specific repression of IL-12 in cells exposed to LPS and IFN-Y.[112,113] In A. *viteae* a cysteine (AvCystatin) protease inhibitor that recognized and takes macrophages that induces phosphorylation of the mitogen-activated protein kinase (MAPK) signalling diagram ERK1/2 and p38, the result shows IL-10 production.[114] The macrophage leads to activate arg-1, PD-L1 and PD-L2, (Figure 5) which helps in IL-10 production and also $CD4^+$ T cells help in a cell contact-dependent manner.[115]

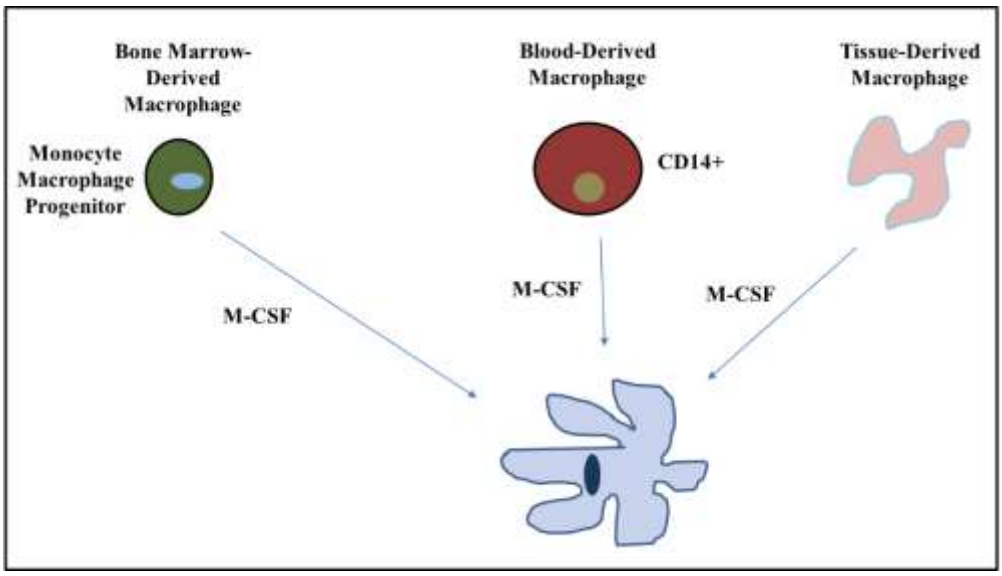


FIGURE 4 Origin of human macrophages.

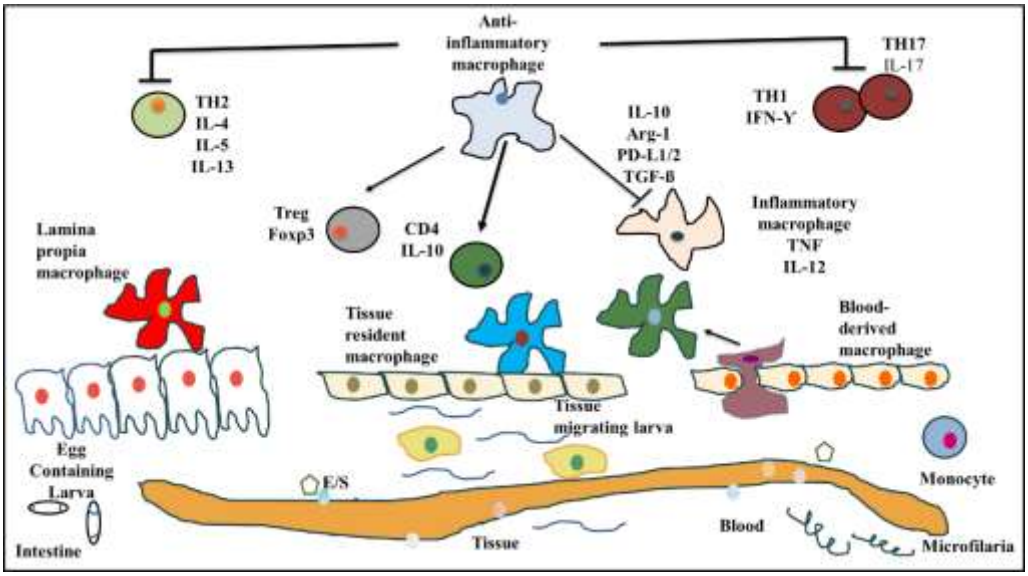


FIGURE 5 Anti-inflammatory macrophages are conjugated from of the intestine, tissue or blood profile, enhances by helminths or their products and their mechanism of action.

5. Conclusion and future aspects

Parasitic nematodes closely communicate with the host and pathogen which is a key event for activation of immune modulation that grows for tolerance to establishing chronic infection that continues for long time. Still, 52 countries in 880 million are showing threats of LF infection and 40 million people are showing chronic infections that have no significant signs and symptoms. In the immune-modulatory system, specifically antigen-presenting cells (APCs) function aborted, which leads to signs of chronic filarial infections. In the case of the life of their effect on human APCs, function affected host T cell response to the filarial infection.[116-120] Interactions of the dendritic cells (DCs) in filarial nematodes secrete such immune responses that inhibit massive inflammation that helps in prolonged survival rate in the host body.[86,102,121] In chronic infection high levels of anti-inflammatory or anti-allergic

type of responses.[122] Releasing of cytokines that help in Th1 releases. Targeting the immunomodulatory pathway that helps in subsequent abortion from the host body does not hamper the host immune mechanism for novel anti-filarial treatments.

Table. 1 Role of Immune cells in Lymphatic filariasis (LF)

Serial No.	Name of Cells	Role
1.	TLR (Toll-like receptor) 2	It activates macrophages that lead to the production of pro-inflammatory cytokines.[6]
2.	Th2 cells	It helps in response to type 2 innate lymphoid cells (ILCs), which suggested the expression of IL-10 that produces $CD4^+$ T cells and Tregs.[119,123-126]
3.	Macrophage cells (Mϕs)	It conjugates to dead larvae and releases myeloperoxidases, nitric oxide (NO) that help kill infective larval (L3) forms of parasitic worms.[127]
4.	IgE	After exposure to the L3 stage, filarial larvae show an increasing level of IgE.[128]
5.	Dendritic cells (DCs)	In the presence of Th2 responses, IL-12 downregulates their capability to activate $CD4^+$ T cells.[86,129]
6.	Eosinophil	It helps in cell density changes, increasing cellular cytotoxicity that releases proteins, cytokines, chemokines, leukotrienes, and other inflammatory mediators.[130]
7.	Basophil	It produces a large amount of IL-4, which plays a major role in various stimuli.[131]
8.	C-Type Lectin Receptors (CLRs)	DCS activate CLRs that lead to Th2-dependent immune responses.[131]

AUTHOR CONTRIBUTIONS

Souvik Dhar: Overall designing the work and drafting the manuscript.

Chiranjeeb Dey: Overall designing the work and drafting the manuscript.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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