Review Article

Cell Type-Specific Immunomodulation Induced by Helminthes: Effect on Metainflammation, Insulin Resistance and Type-2 Diabetes

Vivekanandhan Aravindhan^{1*†} and Gowrishankar Anand^{2†}

¹Department of Genetics, Dr ALM PG IBMS, University of Madras, Chennai, India; ²AU-KBC Research Centre, MIT Campus of Anna University, Chennai, India

Abstract. Recent epidemiological studies have documented an inverse relationship between the decreasing prevalence of helminth infections and the increasing prevalence of metabolic diseases (“metabolic hygiene hypothesis”). Chronic inflammation leading to insulin resistance (IR) has now been identified as a major etiological factor for a variety of metabolic diseases other than obesity and Type-2 diabetes (metainflammation). One way by which helminth infections such as filariasis can modulate IR is by inducing a chronic, nonspecific, low-grade, immune suppression mediated by modified T-helper 2 (Th2) response (induction of both Th2 and regulatory T cells) which can in turn suppress the pro-inflammatory responses and promote insulin sensitivity (IS). This article provides evidence on how the cross talk between the innate and adaptive arms of the immune responses can modulate IR/sensitivity. The cross talk between innate (macrophages, dendritic cells, natural killer cells, natural killer T cells, myeloid derived suppressor cells, innate lymphoid cells, basophils, eosinophils, and neutrophils) and adaptive (helper T [CD4⁺] cells, cytotoxic T [CD8⁺] cells and B cells) immune cells forms two opposing circuits, one associated with IR and the other associated with IS under the conditions of metabolic syndrome and helminth-mediated immunomodulation, respectively.

INTRODUCTION

Immunometabolism, the interface between two historically distinct disciplines namely immunology and metabolism, is a fast emerging field of investigation. Accelerating interest in this area is being fuelled by the increasing epidemic of obesity and diabetes, collectively called as diabetes.¹ Studies examining the interface between infections and metabolic diseases provide an intriguing new dimension to the commonly held “hygiene hypothesis.” Can the increasing incidence of metabolic diseases, such as the prevalence of obesity, diabetes, and hypertension, be exuberated by the absence of certain infections?

METAINFLAMMATION, -INSULIN RESISTANCE (IR), TYPE-2 DIABETES (T2DM)

Inflammation has long been recognized as a major etiological factor for metabolic diseases.² The inflammation in metabolic diseases is chronic and low grade and was long thought to be nonantigen specific; however, few recent reports have suggested that autoantigens to fuel this inflammation. Chronic inflammation leading to IR has now been identified as a major etiological factor for a variety of metabolic impairments other than obesity and T2DM.³ This is now being addressed as metabolic inflammation or metainflammation and plays a pivotal role during both early and late stages of T2DM and also serves as a link between T2DM and coronary artery disease (CAD).⁴ IR typically starts as an organ-specific inflammation affecting the major organs of insulin action, namely, adipose tissue (AT), skeletal muscles, and liver. With disease progression, the inflammation becomes more systemic and starts affecting the blood vessels, leading to

endothelial dysfunction—a prestage for vasculopathies.^{5,6} In fact, the inflammation associated with macrovasculopathies, such as cardiovascular diseases, cerebrovascular diseases, and perivascular diseases, seems to be different from microvasculopathies, such as diabetic retinopathy, nephropathy, and neuropathy.^{5,6} The exact cause of inflammation in IR is not clearly known even though dietary, genetic, and a variety of environmental factors have been implicated.^{7–9} Infections serve as an important source of inflammation especially in tropical countries, and inflammation itself can serve as a link between infections and metabolic diseases. In general, infections which promote inflammation are thought to augment metabolic diseases, whereas those which dampen inflammation by immunomodulation can confer protection against metabolic diseases.¹⁰ The multilevel interactions between the metabolic and immune systems suggest pathogenic mechanisms that may underlie many of the downstream complications of IR and offer substantial therapeutic avenues. This article will summarize the recent advances in helminth-mediated immunomodulation against IR and diabetes, with a focus on filarial nematodes.

IMMUNOMODULATION BY HELMINTHS

At least in mice, there is evidence to show that helminthic infection can prevent Type-1 Diabetes (T1DM).^{11–13} Recently, the same immunomodulatory effect was found to dampen inflammation and protect against T2DM in mice models.^{14–16} Previously, we have shown decreased prevalence of filariasis among both T1DM¹⁷ and T2DM subjects.¹⁸ Furthermore, serum cytokine profiling revealed the downregulation of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and granulocyte-macrophage-colony stimulating factor (GM-CSF) and upregulation of tumor growth factor-beta (TGF-β) in filarial-positive compared with filarial-negative diabetic subjects.¹⁸ Interestingly, this effect was specific only to T1DM and T2DM and was not seen among subjects with CAD.¹⁹ In another cross-sectional study conducted in Indonesia,

* Address correspondence to Vivekanandhan Aravindhan, Department of Genetics, Dr ALM PG IBMS, University of Madras, Taramani, Chennai, Tamil Nadu 600113, India. E-mail: cvaravindhan@gmail.com
† These authors contributed equally to this work.

infections associated with soil-transmitted helminthes (STH) were associated with a modest improvement of insulin sensitivity (IS), which was not accounted for by STH effects on body mass index (BMI).²⁰ Even though these were cross-sectional studies, they indicate probable immune-mediated protection against both T1DM and T2DM by prior filarial infection. One way by which helminth infections such as filariasis can modulate diabetes is by inducing a chronic, nonspecific, low-grade, immune suppression mediated by Th2/regulatory T cells (Tregs) (modified Th2) response which in turn can suppress the proinflammatory responses in obesity/diabetes.¹⁴ Filarial antigens are also capable of inducing IL-10 by dendritic cells (DC) and B cells, inducing “alternatively activated macrophages” (AAM) and invariant natural killer T (iNKT) cells, and interfering with Toll-like receptor (TLR) signaling.^{14,21,22} Thus, based on circumstantial data, we think that childhood filarial infection may somehow limit the inflammation, thereby conferring protection against IR in adult life.²³ If this is true, the decreasing incidence of filariasis (due to mass drug administration programs) can have a serious impact on the incidence of diabetes in future. Recently, three rounds of antihelminthic treatment was found to decrease the worm burden (soil-transmitted helminths) and increase IR among infected individuals in an Indonesian island.²³ Thus, childhood infection can have either a beneficial or a harmful role in determining the susceptibility to T2DM depending on the nature of immune training induced (“metabolic hygiene hypothesis”).

CROSS TALK BETWEEN INNATE AND ADAPTIVE IMMUNE CELLS

In the recent review, the various parasitic excretory-secretory products and their effects on metabolic syndrome (MS) have been extensively reviewed.²⁴ In the present review, we would restrict ourselves to the various immune cell types and their cross talks that mediate helminth-mediated immunomodulation of IR. Traditionally monocytes/macrophages, DC, natural killer (NK) cells, and granulocytes (neutrophils, eosinophils, and basophils) together form the cellular arm of innate immunity because they recognize pathogen and damage-associated molecular patterns (PAMs and DAMs).^{25,26} T and B lymphocytes together form the cellular arm of adaptive immunity because they recognize antigens/epitopes and have immunological memory.^{25,26} During an immune response, monocytes/macrophages, and DC, which are the major antigen presenting cells (APCs), recognize PAMs and DAMs through various innate immune receptors (TLRs, NOD-like receptors, RIG-1-like receptors, and C-type lectin-like receptors), and get activated. Most of these cells take up the cargo, process them, and present them to the T cells within the context of major histocompatibility complex (MHC).^{25,26} The T cells which recognize these MHC-epitope complexes through their T-cell receptors (TCRs), get activated, and secrete cytokines. These cytokines in turn activate the APCs completing the positive feedback loop.^{25,26} Thus, antigen processing and presentation and subsequent cytokine secretion are the cross talks between innate and adaptive immune responses which finally determine the magnitude and nature of the immune response. Even though under certain conditions even granulocytes are capable of antigen processing and presentation, their direct contribution to the overall cross talk between innate and adaptive immune response

remains minimal.²⁷ However, by means of degranulation and secretion of cytokines/chemokines, they can greatly modify the milieu in which APC-T cell interaction takes place and can thereby modulate T-cell responses.²⁷

ROLE OF INNATE IMMUNE CELLS IN IR AND IMMUNOMODULATION

The innate immune cells include macrophages, DC, NK cells, neutrophils, eosinophils, and basophils which play an important role in both IR and immunomodulation.

Macrophages in IR and immunomodulation. Of several immune cell types, macrophages were the earliest to be associated with IR.²⁸ Macrophages are phagocytic cells and exhibit two distinct phenotypes which are interchangeable because of their cellular plasticity: M1 (classically activated) and M2 (alternatively activated), which differ in their cytokine secretion and function.^{29,30} The infiltration of macrophages into AT under conditions of obesity-associated inflammation was reported as early as 1976, which was closely paralleled by the appearance of IR.²⁸ However, recent studies have indicated proliferation and/or polarization of local AT macrophages to be more associated with IR.³¹ Classically activated or CD11c⁺CD206⁻ M1 macrophages were found to be elevated in visceral adipose tissue (VAT) of diet-induced obese mice with elevated proinflammatory cytokine TNF- α , IL-1 β , and IL-6 secretion³² (Figure 1). Transcriptional profiling of AT from Ob/Ob mice revealed the upregulation of 1,304 transcripts which significantly correlated with the BMI. Of the top 100 genes which were differentially expressed, 30% coded

FIGURE 1. Innate and adaptive immune cross talk in insulin resistance (IR). Infiltration of classically activated/M1 macrophages into adipose tissue sets in redox stress and inflammation, which leads to IR (1). The Th1, Th17, and CTLs get recruited before macrophage entry and promote macrophage recruitment/polarization. (2) Pathogens such as viruses and bacteria activate dendritic cells (DCs) and promote Th1 and Th17 differentiation. (3) Neutrophils (N0), basophils (B0), and B cells get recruited into AT and promote inflammation (4).

for proteins specific for macrophages.³³ VATs from both obese mice and obese humans were found to express macrophage markers. Interestingly, lean individuals expressed less macrophage markers compared with obese subjects.³³ Resident AT macrophages in lean mice expressed macrophage galactose-binding C-type lectin (MGL1) along with other genes associated with M2 macrophages (Ym1⁺, CCR2⁻, arginase-1 [Arg-1]⁺, and IL-10) (Figure 2). With diet-induced obesity, a new population of Ym1⁻, MGL-1⁻, CCR2⁺, iNOS⁺, and M1 macrophages was recruited which cluster around the necrotic adipocytes forming crown-like structures (CLS). Whereas the M1 macrophages are associated with IR, M2 is more associated with IS³⁴ (Figures 1 and 2). The exact mechanism of macrophage infiltration is not completely known even though adipocyte hyperplasia/hypertrophy followed by hypoxia-induced necrosis has been postulated.³⁵ The macrophages which can phagocytose the necrotic adipocytes fuse to form large lipid-laden multinucleated syncytia, which surround the adipocyte cellular debris forming CLS.^{35,36} These macrophages are known to secrete proinflammatory cytokines, such as TNF- α , IL-1 β , IL-6, and MCP-1, which amplify the inflammatory response and inhibit adipocyte insulin signaling.³⁷ Even the residential M2 macrophages have been known to “switch” to M1 phenotype during the state of overnutrition.^{32,38} Mice lacking CCR2, which is required for the trafficking of inflammatory monocytes and macrophages into AT were shown to have less obesity-induced macrophage infiltration, inflammation, and IR.³⁹ Selective depletion of the CD11c⁺ classically

activated macrophages (CAM), reduced AT inflammation, and improved IS without having a significant impact on obesity.⁴⁰

With respect to helminth infection, despite the central role played by CD4⁺ T cells and DC, the role played by macrophages in both pathology and protection cannot be waived off^{41–43} (Figures 1 and 2). Macrophages coordinate fibrosis and wound healing and suppress the inflammation caused by the effector T cells.^{43,44} The main cytokines activating the M2 macrophage are IL-4 and IL-13 produced by Th2 cells.^{45,46} The macrophages that are activated by helminths are known to express chitinase 3-like 3 (YM1), chitinase 3-like 4 (YM2), and resistin-like molecule alpha and other markers of M2 phenotype and produce IL-10 which maintains the anti-inflammatory milieu.⁴² The overall function of the macrophages in helminth infection seems to maintain the anti-inflammatory network and promote wound healing. In a recent study, chronic infection with *Schistosoma mansoni*, as well as treatment with its egg antigen, protects against metabolic disorders in a diet-induced obesity mice model.¹⁴ Analysis of immune cell composition at the cellular level showed increased levels of eosinophils and Th2 cells, and liver and M2 polarization in VAT.¹⁴ In another study, infection of diet-induced obesity mice with *Nippostrongylus brasiliensis* decreased weight gain and was associated with improved glucose metabolism, which was associated with M2 polarization of AT macrophages.¹⁶

DC in IR and immunomodulation. DCs are the major APCs, which play a crucial role in linking the innate and adaptive immunity. DCs can interact with both T cells and B cells. Animal studies focusing on the role of DCs in IR are limited. The CD11c⁺ myeloid DCs (mDCs) were significantly increased in the AT of obese mice.⁴⁷ This suggests that DCs might be involved in T-cell polarization and activation of macrophages, thereby playing an important role in AT inflammation/IR (Figure 1). In the AT of the diet-induced obese mice, there was a significant increase in the percentage of DCs which was associated with CLS.⁴⁷ Mice lacking DCs, (Flt3^{-/-}) had reduced number of AT and liver macrophage content, whereas DC replacement in DC-null mice increased liver and AT macrophage infiltration. Furthermore, transfer of bone marrow-derived DCs to lean wild-type mice increased the AT and liver macrophage infiltration.^{48,49}

In helminth infections, DCs are arrested in an immature state characterized by an absence/moderate expression of costimulatory molecules along with reduced proinflammatory cytokine secretion. This feature might presumably induce the development of a Th2 immune response.⁵⁰ Many studies have shown that activation of TLRs on DCs with helminth products can induce an anti-inflammatory response.^{51,52} However, the exact mechanism is not clearly known. Interestingly, not all the costimulatory molecules are downregulated in DCs exposed to helminth products. For example, OX40L, a molecule important for Th2 polarization, is upregulated in the presence of helminth products.⁵³ Recently, thymic stromal lymphopoietin (TSLP), IL-25, and IL-33 have been identified as upstream mediators involved in this process.⁵⁴ Whereas decreased serum levels of IL-33 in T2DM have been reported,⁵⁵ the levels of the other two cytokines under this condition are not clearly known. Helminth-educated DCs promote both Th2 and Treg responses.⁵⁶ However, how they exactly do so is less well understood, although helminth products are known to alter the function and maturation of DCs⁵⁷ and impair their ability

FIGURE 2. Innate and adaptive immune cross talk in insulin sensitivity (IS). IS in the adipose tissue is maintained by the resident M2 macrophages, which are maintained in their “alternatively activated” state by the resident eosinophils (E0) (1). The resident innate lymphoid cells 2 (ILC-2) promote eosinophil recruitment and activation (2). During helminth infection, tolerogenic and myeloid dendritic cells (mDCs) get activated (3) which in turn promote Tregs and Th2 differentiation (4). Th2 and Tregs also aid in M2 polarization (5). The role played by invariant natural killer T cells (iNKTs) in IS is not clearly known (6).

to respond to TLRs.⁵⁸ It is speculated that modulation of DCs by the helminth parasite is one of the major immune evasive strategies for their survival.⁵⁰ Incidentally, the same strategy might confer protection against T2DM (Figure 2).

NK cells in IR and immunomodulation. NK cells are an important component of the innate immune response to viral infections and tumors. They have the ability to provide an early source of both innate (IL-6 and TNF- α) and adaptive (interferon- γ [IFN- γ], IL-4, IL-5, and IL-13) immune cytokines and lyse their target cells through the perforin/granzyme-mediated cytolytic pathway. Although the role of NK cells in infections and malignancies has been well documented, very little is known about their role in adiposity and IR. Stromal vascular fraction from VAT obtained from obese subjects was found to have an increased frequency of IFN- γ -expressing NK cells.⁵⁹ Both human and animal studies together strongly suggest that obesity elevates NK cell numbers. These NK cells along with Th1 and cytotoxic T cells (CTLs) are responsible for polarizing AT macrophages to M1 phenotype,⁵⁹ suggesting that NK cells participate in the regulation of obesity-induced IR at the late stage of obesity.⁶⁰ However, this simplistic view of NK-mediated adipose inflammation was challenged by a recent study wherein overexpression of NKG2D (an activating receptor of NK cells) or its ligand in AT had no effect on CTL recruitment or IR.⁶¹ The role played by inhibitory receptors NKG2A/C/E or KIR2DL3 in AT inflammation is not known.

Compared with other cell types, the role played by NK cells in helminth-mediated immunomodulation is intriguing. Co-culture of fresh peripheral NK cells with filarial larvae brought about early cellular activation, secretion of IFN- γ and TNF- α and significant alterations in the expression of NK-cell receptors. This activation is dependent on the presence of monocytes, IL-12, and direct contact with the live parasites.⁶² Infection of BALB/c mice with *Litomosoides sigmodontis* suppressed the activation of inhibitory receptors but promoted the induction of activating receptor on NK cells.⁶³ Thus, the NK cell–parasite interaction is complex, with filarial parasites inducing premature apoptosis, which may aid the parasite and also confer protection against IR.

Neutrophils in IR and immunomodulation. Neutrophils are short-lived phagocytic cells that remove and destroy invading microorganisms, and are a vital component of the innate immune system, and play a crucial role in host defense.⁶⁴ In diet-induced obese mice, increased infiltration of neutrophils into AT was reported. Consequently, it is possible that neutrophils could have a role in initiating the inflammatory cascade in response to obesity⁶⁵ (Figure 1). In addition to host defense, neutrophil-derived serine proteases, such as neutrophil elastase, have been implicated in sterile inflammation.⁶⁵ Treatment of hepatocytes with neutrophil elastase induced IR (by IRS-1 degradation), whereas deletion of neutrophil elastase in diet-induced obesity mice restored IS associated with less inflammation and improved glucose tolerance.⁶⁵ Taken together, neutrophils can be added to the extensive repertoire of immune cells that participate in inflammation-induced IR.

Because neutrophils are known for their role in phagocytosis of microbial pathogens, despite their nature of rapid activation and recruitment at the sites of infection, they are seldom studied in helminth infection.⁶⁶ In recent times, like macrophages, neutrophils were shown to get polarized either toward either classically activated or alternatively activated

phenotypes after bacterial infections.⁶⁷ Whether such polarization takes place during helminth infections is not clearly known. Neutrophils are increasingly being recognized as important components of the Th2-type response elicited during helminth infections. Recently, a 55-kDa secretory–excretory glycoprotein was identified in *Haemonchus contortus*, which was capable of binding to CD11b/CD18 integrin and inhibiting neutrophil activation.⁶⁸ Bm-SNP-2, a serpin secreted by the helminth *Brugia malayi*, was found to neutralize at least two neutrophil enzymes, namely, Cathepsin G and elastase.⁶⁹ Furthermore, live *B. malayi* was found to inhibit trans-endothelial migration of neutrophils⁷⁰ via Th2 cytokines IL-4 and IL-13.⁷¹ Because accumulation of activated neutrophils in the VAT is a major event associated with IR, inhibition of neutrophil migration/activation could be a major factor contributing to helminth-induced inhibition of IR.⁶⁸

Eosinophils in IR and immunomodulation. Eosinophils are mainly associated with evoking allergic responses in parasitic infections.⁷² Whereas IL-5 serves as the main growth factor for eosinophil development, eotaxins (CCL11 and CCL26) serve as its major chemotactic factors.⁷³ Activation of eosinophils results in the release of its granular content on to the target cell.⁷⁴ Eosinophilic granules are primarily composed of cytotoxic cationic proteins including major basic protein, eosinophil peroxidase, eosinophilic cationic protein, and eosinophil-derived neurotoxin.⁷⁵ Eosinophils in adipose tissue (ATEs) have been implicated in metabolic homeostasis and in the maintenance of AAM (Figure 2). The absence of eosinophils can lead to adiposity and systemic IR in diet-induced obesity mice.⁷⁶ Galectin-10, one of the major components of primary granules of eosinophils, was found to promote adipocyte differentiation, prevented lipolysis, reduced IR, and improved glucose tolerance.^{77,78} In diet-induced obesity mice, IL-5 deficiency had a profound impact on ATE accumulation and resulted in increased adiposity and IR when placed on high-fat diet.⁷⁹ ATEs were shown to be the major source of IL-4 in VAT which was required for maintaining the M2 phenotype of AT macrophages.⁷⁶ The absence of Th2 cytokines such as IL-4, IL-5, or IL-13 resulted in reduced ATE content of VAT and promoted macrophage invasion and IR.^{79,80}

Clinically, helminth infections are the most common cause of persistent eosinophilia wherein eosinophils play the most pivotal role in killing and eliminating the pathogen. Ligation of parasite-specific Ig to Fc receptors or ligation of TLRs by helminth products leads to activation and degranulation of eosinophils.⁸¹ Activated eosinophils bring about worm expulsion by two ways: 1) direct killing of the worm by depositing cytotoxic granules along with reactive oxygen species on to the worm membrane and 2) expulsion/encystment of the dead worm by coordinating with other immune and nonimmune cells.^{82,83} However, recent evidence have indicated that the activation of eosinophils against helminthes is an immune-evasive strategy by the helminthes.^{84,85} Eosinophils may influence the immune response in a manner that would sustain chronic infection and ensure worm survival.^{84,85} Recently, in a high fat–diet mice model, animals infected with the migratory helminth *N. brasiliensis* showed sustained metabolic control characterized by decreased fasting glucose and improved IS, and glucose tolerance associated with decreased perigonadal AT weight and increased eosinophil content.^{76,86} IL-33 produced by adipocytes activated resident innate

lymphoid cells (ILCs) 2 or neocytes to secrete IL-5, which in turn promoted eosinophil recruitment and activation. The activated eosinophils in turn secreted IL-4 and IL-13, which in turn promoted M2 macrophage polarization and promoted IS¹⁴ (Figure 2). Thus, recruitment and activation of eosinophils by helminthes might aid adipose homeostasis and result in improving IS.

Basophils and mast cells in IR and immunomodulation.

Basophils are polymorphonuclear granulocytes, mainly found in the blood and peripheral tissues, representing less than 1% of total leukocytes in the blood and spleen. Basophils are characterized by the presence of basophilic granules and the surface expression of high-affinity FcεRI receptor, which binds IgE and receptors for cytokines, chemokines, complement proteins, and lipid mediators.⁸⁷ Basophils can be activated through an IgE-dependent or IgE-independent mechanism wherein they release chemical mediators, such as leukotriene C4 and histamine, and Th2 cytokines such as IL-4, IL-13, and TSLP (degranulation).⁸⁸ Although mast cell and basophils function classically in allergic responses, recent studies indicate that these cells contribute to other diseases such as obesity and diabetes^{89,90} (Figure 1). VAT from obese humans and mice had more mast cells than those from their lean counterparts.⁹¹ Mast cell deficiency or pharmacological stabilization of mast cell granules in mice resulted in reduced weight gain, decreased serum inflammatory markers, improved glucose homeostasis, and promoted energy expenditure.⁹² Mechanistic studies revealed that mast cells worsen adipose inflammation by augmenting cathepsin (B, L, and S) activity through IL-6 and IFN-γ.⁹³ Measurement of food and water intake, fecal and urine production, O₂ consumption, and CO₂ production showed that mast cell-deficient mice and mast cell stabilizer-treated wild-type mice had an increased resting metabolic rate, illustrated by significantly greater O₂ consumption and CO₂ production than untreated mice,⁹² and these mice had higher brown fat UCP1 expression, a marker of energy expenditure. Mast cell-stabilizing agents were also able to reduce diet-induced weight gain and improved glucose tolerance even under preexisting obesity/diabetic condition.^{92,94}

One of the hallmarks of helminth infections is the elevated levels of IgE and eosinophilia during the acute phase response.⁹⁵ This might be helping the host to kill and expel the parasite and ensure its clearance. However, helminthes have evolved an escape mechanism to evade this process by producing nonspecific IgE polyclonal antibodies which may be able to act as competitive inhibitors for antigen-specific IgE.^{96,97} Eosinophils and basophils were found in large numbers in the lamina propria of the small intestine in *N. brasiliensis* infected wild-type and mast cell-deficient c-Kit^{W^{sh}} mice.⁹⁸ Basophils are rapidly recruited into the bone marrow, small intestine, blood stream, and other tissues during helminth infections and perform a variety of functions including degranulation of soluble mediators, secretion of Th2 cytokines, recruitment of eosinophils, and neutrophils via eotaxins and more recently as a Th2-promoting APC-like function.⁹⁹ Both resting and activated basophils express MHC and B7-1 molecules, produce IL-4, and are capable of forming immunological conjugates with T cells.¹⁰⁰ These suggest a role for basophils in Th2 differentiation of naive CD4⁺ T cells during helminth infection,¹⁰¹ although the extent to which they do so in vivo remains unknown.

Myeloid-derived suppressor cells (MDSCs) in IR and immunomodulation.

MDSCs represent a heterogeneous and metabolically plastic population of immature myeloid cells in different stages of differentiation, having in common the capacity to inhibit active immune responses and to accumulate at the site of inflammation. In the steady state, MDSCs are predominantly present in the bone marrow and participate in myelopoiesis. However, under inflammatory conditions, the proinflammatory factors induce rapid expansion of MDSCs that will accumulate in peripheral lymphoid organs and blood, wherein they actively inhibit CD4⁺ and CD8⁺ T-cell responses.¹⁰² Xia et al.¹⁰³ showed that MDSCs were highly enriched in peripheral tissues (i.e., liver tissue and AT) during obesity, and antibody-mediated depletion of these cells in diet-induced obese mice significantly increases inflammation and impairs IS, whereas elevation of these cells via adoptive transfer had opposite effects. Mechanistically, these cells suppressed the proliferation, induced the apoptosis of CTLs, and were capable of polarizing macrophages toward the M2 phenotype.¹⁰³ Taken together, MDSCs counter proinflammatory immune cells in the liver and AT during obesity to prevent IR.

Even though MDSCs play a pivotal role in tumor immunosuppression, the role played by these cells in helminth-induced immunomodulation is poorly understood. In a murine model of *Taenia crassiceps* infection, MDSCs were found to expand in an IL-4/IL-13-dependent manner and were found to impair T-cell proliferation.¹⁰⁴ The suppressive activity was dependent upon the expression of Arg-1 and 12/15-lipoxygenase.¹⁰⁴ In a recent study, soluble egg Ag and schistosome worm Ag of *Schistosoma japonicum* were found to enhance the accumulation of MDSCs. Ag-induced MDSCs showed more potent suppressive effects on T-cell responses compared with control MDSCs under both in vivo and in vitro conditions.¹⁰⁵

Innate lymphoid cells (ILCs) in IR and immunomodulation.

ILCs are a growing family of immune cells that are considered as innate counterparts of T-helper (Th) cells.¹⁰⁶ However, in contrast to T cells, ILCs do not express antigen receptors or undergo clonal selection/expansion. Instead, they react to innate immune stimuli and produce adaptive immune cytokines that direct the development of the immune response.¹⁰⁶ Like helper T lymphocytes, ILCs are classified into three groups with a distinct cytokine profile and function: 1) group 1 ILCs (ILC-1)—they secrete IFN-γ and TNF-α in response to IL-12, IL-15, and IL-18 and bring about M1 macrophage polarization; 2) group 2 ILCs (ILC-2)—they secrete IL-4, IL-5, and IL-13 in response to IL-33, IL-25 and TSLP and bring about M2 macrophage polarization and are involved in thermoregulation; and 3) group 3 ILCs (ILC-3)—they secrete IL-17, IL-22, and GM-CSF in response to IL-1β, IL-6, and IL-23 and bring about epithelial cell proliferation.¹⁰⁶ In AT, they regulate thermogenesis and prevent local inflammation that may lead to IR.¹⁰⁷ ILC-2 upon stimulation with IL-33 secrete high levels of IL-5 and IL-13. IL-5 recruits eosinophils and induces the secretion of IL-4, which in turn acts on macrophages and brings about M2 polarization.¹⁰⁷ The IL-13 secreted by ILC-2 can directly act on macrophages and can bring about M2 polarization.¹⁰⁷ Furthermore, Met-enkephalin secreted by ILC-2 can act directly and induce browning of AT.¹⁰⁷ Recently, ILC-1 cells were found to accumulate in the VAT in diet-induced obesity mice and were found to promote IR via IFN-γ and TNF-α.¹⁰⁸

Helminth infections, in general, induce Th2 immune response characterized by high levels of serum IgE and eosinophilia. Whereas IL-12 secreted by mDCs polarize native CD4⁺ T cells toward a Th1 phenotype, corresponding polarizing cytokine and instructor cell type for Th2 cells remained elusive for a long time. Studies carried out with the intestinal helminth *N. brasiliensis* led to the identification IL-25 and IL-33 as the master polarizing cytokines and ILC-2/nuocytes as the major instructor cells for Th2 polarization.¹⁰⁹ Treatment of diet-induced obesity mice with recombinant *S. mansoni* egg-derived ω 1 antigen induced weight loss and improved glucose homeostasis which was largely dependent on the IL-33/ILC-2 axis.¹¹⁰ In another recent study, infection of diabetic mice with *L. sigmodontis* or treatment of these animals with its antigen significantly improved IS without affecting obesity, which was largely mediated by the Th2-type immune response (whereas Tregs were dispensable).¹⁵ Moreover, the increased frequency of ILC-2 may drive browning of AT, as shown by few recent studies.^{107,111} Whether *L. sigmodontis* infection or administration of its antigen leads to browning of fat needs further investigation.

ADAPTIVE IMMUNE CELLS IN IR AND IMMUNOMODULATION

Adaptive immune cells include T cells, B cells, and natural killer T (NKT) cells which play an important role in both IR and immunomodulation.

Th cells in IR and immunomodulation. T cells are lymphocytes which mature from the thymus and are the major components of the adaptive immune system. Based on the physiological requirement, T cells perform three major functions: 1) as Th cells—they activate B cells, macrophages, DCs, and other T cells; 2) as cytotoxic T cells (Tc)—they specifically target and kill tumor and pathogen-infected cells; and 3) as Tregs—they maintain immunological tolerance by secreting IL-10 and TGF- β . Th cells are further classified based on their distinct cytokine profile (Th1-IFN- γ , IL-2, and TNF- β and Th2-IL-4, IL-5, and IL-13) and the arms of the immune system that they activate (Th1-cellular and Th2-humoral). T cells are also major participants in VAT inflammation, with pro-inflammatory CTLs and IFN- γ -producing Th1 cells contributing to inflammation (Figure 1). On the contrary, VAT-resident Tregs and Th2 cells tend to suppress inflammation^{112,113} (Figure 2). Notably, the clonal diversity of VAT T cells is highly restricted, with a dominating adaptive immune response resulting in a population of potentially autoimmune T cells.¹¹⁴ Obese IFN- γ -deficient mice had significantly reduced expression of TNF- α and MCP-1 and decreased inflammatory cell accumulation in the VAT with better glucose tolerance compared with wild-type mice.¹¹⁵ Genetic ablation of IL-13 in mice resulted in hyperglycemia, which progressed to hepatic IR and systemic metabolic dysfunction.¹¹⁶ Adipocyte-derived Th2 cytokines, improve the insulin signaling via M2 polarization.¹¹⁷ The Th2 cytokines such as IL-4 and IL-13 are thought to help in the activation of peroxisome proliferator-activated receptors (PPARs) in macrophages and stabilization of the M2 phenotype.¹¹⁸ In high-fat diet mice, the expression of Th2-regulating transcription factor GATA-3 was significantly reduced in VAT, whereas T-bet, the master controller of Th1 polarization, was augmented.^{32,119} However, studies conducted in our laboratory on serum cytokine levels in subjects with MS showed a mixed Th1–Th2

response with increased systemic levels of IL-12, IFN- γ , IL-4, IL-5, and IL-13.¹²⁰ The role of recently discovered IL-17–producing Th17 in VAT inflammation is still an enigma. Some studies have shown a strong proinflammatory phenotype for these cells in inducing IR, whereas our study showed a decline in serum IL-17 levels in subjects with MS¹²¹ (Figure 1). It was interesting to note that even though the MS subjects had increased serum levels of IL-6, TNF- α , and TGF- β , their IL-17 levels were significantly reduced. The Tregs in VAT have a unique function of maintaining immune-hemostasis and improving insulin signaling by PPAR-g activation.^{113,122,123} Depletion of Tregs was shown to worsen IR, whereas adoptive transfer of Tregs into diet-induced obesity mice improved IS and glucose tolerance¹²⁴ (Figure 2). The role of other recently identified Th cell subtypes, such as Th22 and Th9, in T2DM is not clearly known.

T-cell immune responses during filariasis depend on the phase of the infection: 1) the acute phase is skewed toward Th2 (IL-4, IL-5, and IL-13) response,¹²⁵ 2) the chronic phase is skewed toward modified Th2 response with Tregs (IL-10 and TGF- β) playing a more prominent role followed by Th2 cells, and 3) the chronic pathology phase, characterized by a shift from modified Th2 to Th1/Th17 (IFN- γ , IL-2 and IL-17) response, which happens only in those who develop clinical pathology.¹²⁶ Stimulation of purified T cells from filarial-infected individuals with *B. malayi* antigen induced a significant impairment in Th1 response with decreased expression of T-bet, suppressor of cytokine signaling-1 (SOCS-1), SOCS-5, and SOCS-7.¹²⁷ Furthermore, in vitro culturing of peripheral blood mononuclear cells from infected individuals with live larval stage-3 (L3) and microfilarial (mf) worms had revealed impaired expression of T-bet and GATA-3 but augmented expression of Foxp3 compared with uninfected individuals.¹²⁸ Expression levels of IL-10 were significantly elevated in infected individuals compared with those with clinical pathology.¹²⁹ At least under in vitro conditions, parasite-secreted protein, termed *Heligmosomoides polygyrus* excretory–secretory antigen, has shown to induce de novo expression of Foxp3 in naive T cells and converted them into functional Tregs.¹³⁰ In addition, ES-62, a filarial glycoprotein and a PAMP was shown to elicit a Th2 immune response.^{131,132} Thus, the immunoregulatory network maintained during helminth infections might be helpful in alleviating systemic inflammation in T2DM via secreted helminth products.

CTLs in IR and immunomodulation. Cytotoxic (CD8⁺) T cells are one of the effector cells in T-cell-mediated immunity, which directly kill the target cells (virus- or bacteria-infected cells and tumor cells). CD8⁺ T cells were found to migrate into the AT much before the accumulation of macrophage in the diet-induced obesity mice model.¹¹⁷ It is speculated that IFN- γ production by CTLs might promote the recruitment and polarization of M1 macrophages (Figure 1). This results in worsening of the AT inflammation and IR. In the high-fat diet mice model, there was an increased infiltration of CTLs into the AT around the 22nd week after the initiation of high-fat diet.^{133,134} Antibody-mediated or genetic depletion of CTLs had lowered the macrophage infiltration and AT inflammation, consequently ameliorating systemic inflammation and IR.¹³⁵

When compared with Th cells, the amount of literature available on the role of CTLs in helminth infection is limited. In clinical studies, LF infection was shown to upregulate

HLA-A, thereby activating CTLs.¹³⁶ However, these activated CTLs showed poor proliferative response under in vitro conditions.^{137,138} The CTL activity was largely seen during lymphedema development, rather than acute/modified immune response to helminths.^{126,139} Furthermore, these activated CTLs seem largely to be immunomodulatory rather than proinflammatory in nature. It would be interesting to see whether these activated immunosuppressive cells are in fact the recently discovered CD8(+) Treg population.¹⁴⁰ At least in mice models, helminth infection significantly reduced the frequencies of CTLs and inhibited IFN- γ and TNF- α secretion and cytotoxicity.^{141–143}

B cells in IR and immunomodulation. B cells form a major component of adaptive immunity and perform two vital functions: 1) antigen presentation which links innate and adaptive immunity and 2) production of antibodies which possess the effector functions. In the context of development of IR, B cells were found to migrate into the AT shortly after the initiation of high-fat diet in mice¹⁴⁴ (Figure 1). Increased activation of B-cells has been observed in subjects with obesity and/or T2DM.¹⁴⁵ The initial signal for B cell activation was found to be provided by the stressed adipocytes by releasing the self-antigens in the VAT.^{146,147} The activated B cells then induce the activation of proinflammatory macrophages and T cells and production of autoantibodies, inducing VAT inflammation. Correspondingly, increased IgG production (predominantly of IgG2c subtype) and increased IgG⁺ B cells were seen in the VA0054 of high-fat diet mice.¹⁴⁸ B-cell null mice showed that reduced immune cell activation and IR in VAT and transfer of IgG antibodies from high-fat diet wild-type mice to diet-induced obesity B^{null} mice worsened glucose tolerance. The recipient mice were found to secrete higher levels of TNF- α in VAT stromal vascular cultures and also showed augmented M1 polarization.¹¹⁴ They also had elevated levels of serum MCP-3, IL-6, and GM-CSF.¹⁴⁵ The IgG antibodies, apart from promoting B-cell-mediated AT inflammation, can also bind to Fc γ Rs on macrophages through their Fc portion and directly induce macrophage oxidative burst, cytotoxicity, and proinflammatory cytokine production.^{149,150} This activity further worsens the IR.

The function of B cells in helminth infection is largely restricted to the protective Th2 response. IL-4-mediated activation, class switching, and affinity maturation of B cells are responsible for the elevated levels of IgE antibodies in infected individuals.¹⁵¹ IgM production by B cells is also important for activating macrophages during the protective Th2 response. However, during the modified Th2/Treg response, there is a shift from IgE to IgG4 secretion by B cells. IL-10-producing B cells, also termed as regulatory B cells (Bregs), can dampen inflammation under conditions of autoimmunity.^{152–154} The regulatory function of B cells is thought to maintain the state of immune tolerance in chronic infections by enhanced secretion of IL-10.¹⁵⁵ During chronic schistosome infection in mice, blockade of IL-10 receptor in vivo by administration of anti-IL-10 receptor mAb was shown to promote loss of B cells from the liver.¹⁵⁶ IL-10R blockade also precipitated the development of portal hypertension and the accumulation of parasite eggs in the lungs and heart.¹⁵⁷ Thus, B cells play contrasting roles in insulin resistance and helminth infections: In the context of helminth infections, they orchestrate regulatory immune responses via IL-10, whereas in IR, they induce the AT inflammation via autoantibodies.

NKT cells in IR and immunomodulation. NKT cells are a subpopulation of lymphocytes that serve as a link between the innate and adaptive immunity. They are a heterogeneous group of T cells that share properties of both T cells and NK cells. Many of these cells recognize self and foreign lipids and glycolipids bound to the nonpolymorphic CD1d molecule. They constitute only approximately 0.1% of all peripheral blood T cells. NKT cells should not be confused with NK cells. They are divided into two major subsets: 1) the iNKT cells, which express exclusively an invariant TCR alpha chain (V- α 14 and J- α 18 in mice), and 2) the non-iNKT cells, which express more diverse TCRs. NKT cells can quickly produce Th1- and/or Th2-type cytokines followed by stimulation with glycolipid antigen galactosylceramide (GalCer) and, through this property, play important immunoregulatory roles in autoimmune diseases, cancer, and infection.¹⁵⁸ The role of iNKT cells in the regulation of metabolism is just emerging, although it has previously been described that ATs and liver of both mice and humans contain a population of iNKT cells, which decreased with increasing adiposity and IR¹⁵⁹ (Figure 2). In fact, this coincides with the infiltration of macrophages and T cells into the AT. Treatment of high-fat diet mice with GalCer, an activator of iNKTs, ameliorated inflammation and IR by polarizing AT macrophages toward the M2 phenotype.¹⁶⁰ Mantell et al.¹⁶¹ showed that deletion of NKT cells (CD1d^{-/-}), in the absence of CTLs, had no effect on weight gain and IR, whereas Lynch et al.¹⁶² noted that high-fat diet mice lacking iNKT cells (V α 14^{-/-}) had enhanced weight gain, larger adipocytes, fatty liver, and IR, thus documenting the negative role of NKT cells in IR. NKT cells during helminth infections were shown to produce IL-4 as an immunoregulatory cytokine when exposed to the nematode glycolipids.^{163,164} Helminthes activate both iNKT and non-iNKT cells in vivo, enabling them to differentially influence the Th1/Th2 balance.¹⁶⁵ NKT cells were known to be the early source of IL-4 in the spleen within 24 hours of infection with L3 *Brugia pahangi* in mice.¹⁶⁶ Thus, helminth infection seems to augment NKT cell activity and thereby ameliorate IR.

CONCLUSION

AT, which was once considered an inert storage organ, is increasingly being recognized as an active endocrine gland (in secreting adipokines) and a tertiary immune organ (with respect to generating/amplifying active immune responses).^{167,168} Even though both antihelminth immunity and inflammation-induced IR are well studied, the link between these two conditions have only now started to emerge. At this point, the role of immune response in IR seems to be bidirectional: Inflammation leads to IR/T2DM, which in turn compromises immunity to infections and accounts for the increased susceptibility of diabetic subjects to infections. A much higher level of complexity is brought about by the recently identified helminth-induced immunomodulation in conferring protection against inflammation/IR. As can be seen in this review, with respect to immune cells, at least two different paradigms can be identified: 1) those associated with IR (CAMs or M1 macrophages, mDCs, Th1, Th17, neutrophils, basophils, CTLs, and B cells) (Figure 1) and 2) those associated with IS (AAMs/M2 macrophages, MDSCs, Th2, Tregs, nuocytes, and eosinophils) (Figure 2). However, the exact spatiotemporal order in which these cells traffic the AT and whether these cells form a single complex circuit or multiple parallel pathways with overlapping functions are largely

unknown. Furthermore, the exact role played by NK cells in these circuits remains to be elucidated, whereas the role of NKT cells in these circuits remains highly controversial, at this time point. With respect to helminth-mediated protection against IR via immunomodulation, at least there is direct proof for the involvement of AAMs, eosinophils, and nuocytes, but the role of other cells is more circumstantial.

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Authors' addresses: Vivekanandhan Aravindhan, Department of Genetics, University of Madras, Taramani Campus, Chennai, Tamil Nadu, India, E-mail: cvaravindhan@gmail.com. Gowrishankar Anand, Department of Molecular Immunology, Anna University-KB Chandrasekhar Research Centre, Chennai, Tamil Nadu, India, E-mail: anandgshankar@gmail.co.

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