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Helminth Induced Immunomodulation against Metainflammation and Insulin Resistance

Vivekanandhan Aravindhan and Sibi Joy Manohar

Abstract

Filariasis mediated immunomodulation against metabolic diseases is a recently identified novel phenomenon. There seems to be an inverse relationship between filarial infections and type-2 diabetes. Rapid elimination of filarial diseases, due to mass drug administration has somehow fueled the sudden and rampant increase in type-2 diabetes, at least in certain tropical countries, like India and Indonesia. Filarial infections are in a way unique, since they bring about immunomodulation, in contrast to inflammation which is triggered by viral and bacterial infections. This dampens immunity and confers better survival for the pathogen. However, this also attenuates chronic inflammation and insulin resistance and thereby confers protection against type-2 diabetes. This chapter elucidates the various immune mechanisms involved in immunomodulation against insulin resistance and type-2 diabetes induced by helminth infection.

Keywords: Metainflammation, Insulin Resistance, Immunomodulation, Helminth infections, Metabolic diseases

1. Introduction

1.1 What is metainflammation?

Chronic inflammation has long been recognized as a major etiological factor for metabolic diseases [1]. The inflammation in metabolic diseases is chronic, low grade and non-antigen-specific but differs from one condition to other [2]. This is different from those seen in infectious diseases and has been named “Metainflammation”. Meta inflammation leads to insulin resistance (IR) wherein the target organs of insulin become resistant to insulin action [2]. IR has now been identified as a major etiological factor for a variety of metabolic diseases, apart from obesity and Type-2 diabetes (T2DM) [2]. Meta inflammation typically starts as an organ-specific inflammation affecting the major target organs of insulin namely adipose tissue, skeletal muscles and liver [2]. With disease progression, it becomes more systemic and starts affecting the blood vessels leading to endothelial dysfunction called vasculopathy [2]. The exact cause of inflammation in IR is not clearly known even though dietary, genetic and environmental factors have been implicated [2].

1.2 Helminth infection as an immunomodulation strategy

Infections serve as an important source of inflammation especially in tropical countries and can serve as a link between infections and metabolic diseases [3]. The link between infections and metabolic diseases is less well explored and in recent years has gained tremendous interest [3]. Changes in the lifestyle of people living in industrialized countries have led to a decrease in the infectious burden and an increase in the prevalence of allergic and autoimmune diseases [4]. The leading idea is that some infectious agents – notably those that co-evolved with us – are able to protect us against a large spectrum of immune-related disorders [5]. The strongest evidence for a causal relationship between the decline of infectious diseases and the increase in immunological disorders originates from animal models and a number of clinical studies, suggesting the beneficial effect of infectious agents or their components known as immunomodulators [5]. Immunomodulators are drugs or molecules (Thalidomide, Macrolide antibiotics, and curcumin) that modify the dangerous immune response to prevent the inflammatory damage, while leaving the protective immune response intact [6]. It is speculated that infections as such are important in keeping the immunoregulatory network active and, in the absence of such infections, the immune system gets hyperactivated, resulting in allergies and autoimmunity [5]. In this regard, the helminth infections need a special mention since they were found to be alleviating numerous autoimmune disorders like atopic disorders, systemic lupus erythematosus, multiple sclerosis, sepsis, inflammatory bowel diseases [7].

Not all infections promote inflammation. While in general, viral and bacterial diseases induce inflammation, helminth infections are largely immunosuppressive in nature [3]. The link between fungal and protozoan diseases, with systemic inflammation, is not known. In general, infections which promote inflammation are thought to augment metabolic diseases while those which dampen inflammation by immunomodulation can confer protection against metabolic diseases [3]. Previously, we have shown a decreased prevalence of filarial infection (not disease) among both T1DM [8] and T2DM subjects [9]. Further, serum cytokine profiling revealed the downregulation of Interleukin-6 (IL-6), Tumour Necrosis Factor-alpha (TNF- α) and Granulocyte-Macrophage-Colony Stimulating Factor (GM-CSF) and upregulation of Tumour Growth Factor-Beta (TGF- β) in filarial positive, compared to filarial negative diabetic subjects [9]. Interestingly, the immunomodulatory effect of helminth infection was seen only in T1DM and T2DM subjects but not among the coronary artery disease (CAD) patients [10]. Even though these were cross-sectional studies, they indicate probable immune-mediated protection against both T1DM and T2DM by prior filarial infection. This also indicates some degree of overlap in the disease pathology between these two seemingly different forms of diabetes, which the helminth infection is able to target [3, 11]. If this is true, the decreasing incidence of filariasis (due to mass drug administration programs) which is being carried globally, can fuel diabetic pandemic in future [3, 11]. Thus, childhood infection can either have a beneficial or harmful role in determining the susceptibility to T2DM depending upon the nature of immune training-induced [3, 11].

2. Role of innate immune cells in insulin resistance and immunomodulation

Traditionally monocytes/macrophages, dendritic cells, Natural killer (NK) cells and granulocytes (neutrophils, eosinophils and basophils) together form the

cellular arm of innate immunity, since they recognize the pathogen and damage-associated molecular patterns (PAMPs and DAMPs) [2]. T and B lymphocytes together form the cellular arm of the adaptive immunity, since they recognize antigens/epitopes and have immunological memory [2]. During an immune response, cells of innate immunity recognize PAMPs and DAMPs through various innate immune receptors like Toll-like Receptors (TLRs), NOD-Like Receptors (NLRs), RIG-1 Like Receptors (RLRs) and C-Type Lectin Like Receptors (CLRs), etc. and get activated. Most of these cells take up the cargo, process them and present them to the T cells within the context of MHC [12]. B cells on the other hand take up antigens by antibody-mediated endocytosis, process them and present them to the T cells [12]. The T cells which recognize these MHC: epitope complexes through their T Cell Receptors (TCRs), get activated and secrete cytokines and chemokines [12]. These cytokines and chemokines in turn activate and attract more number of antigen-presenting cells (APCs), completing the positive feedback loop [12]. Thus, antigen processing and presentation and subsequent secretion of cytokines and chemokines establish the cross-talks between innate and adaptive immune responses, which finally determine the magnitude and nature of the immune response [12]. Next, we will look at the role played by specific cell-types in IR and immunomodulation.

2.1 Macrophages in insulin resistance and immunomodulation

Out of several immune cell types, macrophages were the earliest to be associated with IR [13]. Macrophages are phagocytic cells that serve as the first line of defence mechanism against infections [14]. They are of two types: M1 (classically activated) and M2 (alternatively activated), which differ in their cytokine secretion and functions [14]. The infiltration of macrophages into adipose tissue under conditions of obesity-associated IR was reported as early as 1976 [13]. Classically activated or CD11c⁺CD206⁻ M1 macrophages were found to be elevated in visceral adipose tissue (VAT) of diet-induced obese (DIO) mice which secrete increased levels of pro-inflammatory cytokines like TNF- α , IL-1 β and IL-6 (**Figure 1**) [15]. Transcriptional profiling of adipose tissue from leptin knock-out mice revealed the upregulation of 1,304 genes which showed a strong correlation with the body mass index. Of the top 100 genes which were differentially expressed, 30% were specific for macrophages [16]. Resident macrophages in lean mice expressed Macrophage Galactose-binding C-type lectin (MGL-1) along with other genes associated with M2 macrophages

Figure 1. Model explaining “Metabolic Hygiene Hypothesis”. Chronic inflammation serves as a link between infections and type-2 diabetes. During early stages of the disease, the inflammation is more tissue restricted and primarily affects pancreas and target organs of insulin namely skeletal muscle, adipose tissue and liver. This in turn leads to pancreatic beta cell loss and insulin resistance, respectively. During latter stages, the inflammation becomes more systemic and affects the blood vessels leading to vasculopathies. If small blood vessels are affected, it results in microvasculopathies. If larger blood vessels are affected it results to macrovasculopathies. While most viral and bacterial infections, can trigger chronic inflammation, helminth infections are unique in attenuating inflammation, by means of immunomodulation. Thus, a drastic decrease in helminth infections due to mass drug administration can fuel epidemic increase in metabolic diseases.

(Ym1⁺, CCR2⁻, Arg-1⁺ and IL-10, 15, 16]. With diet-induced obesity, a new population of Ym1⁻, MGL-1⁻, CCR2⁺, iNOS⁺ M1 macrophages were recruited which cluster around the necrotic adipocytes forming crown-like structures. While the M1 macrophages are associated with IR, M2 is more associated with insulin sensitivity (**Figure 1**) [15–17]. In general, peripheral macrophages in newly diagnosed diabetic patients are hyporesponsive to inflammatory signals due to the downregulation of TLRs [18]. In contrast, macrophages from chronic diabetic patients show chronic activation due to constitutive upregulation of B7-1 molecules [19].

With respect to helminth infection, despite the central role played by lymphocytes and dendritic cells, the role played by macrophages in both pathology and protection cannot be undermined [20]. Helminth products are known to polarize macrophages into M2 phenotype which orchestrate fibrosis and wound healing [21]. Helminth infected macrophages are also termed as nematode-elicited macrophages that express a peculiar M2 phenotype [21]. The master cytokines involved in M2 polarization are IL-4 and IL-13. The macrophages which are polarized by helminth infection express YM1, YM2, Resistin-Like Molecule alpha (RELM α) and other markers of M2 phenotype and produce IL-10 [21]. Diet-induced obese mice treated with *Litomosoides sigmodontis* (Ls) antigen showed an increased number of M2 macrophages in the epididymal adipose tissue (EAT) inducing a type-2 immune response which improved glucose tolerance (**Table 1**) [22]. Recently, *Heligmosomoides polygyrus* infected high-fat diet mice showed M2 polarization of adipose macrophages which reduced IR [27]. Mice injected with *Schistosoma mansoni* antigens showed significant improvement of metabolic control and increased frequency of M2 in HFD mice [28]. HFD mice infected with *Nippostrongylus brasiliensis* had decreased weight gain and improved glucose tolerance which was largely due to the polarization of adipose macrophages into the M2 phenotype (**Table 1**) [23].

2.2 Dendritic cells in insulin resistance and immunomodulation

While macrophages are major phagocytic cells, Dendritic cells (DCs) are the major antigen-presenting cells that play a crucial role in linking innate and adaptive immunity. DCs can interact with both T cells and B cells. Animal studies looking at the role of DCs in IR are limited. The CD11c⁺ myeloid DCs were significantly increased in the adipose tissue of obese mice [29]. This suggests that DCs might be involved in T cell polarization and activation of macrophages thereby playing an important role in adipose inflammation and IR [29]. In the adipose tissue of obese mice, there was a substantial increase in the percentage of DCs which was associated with crown-like structures [30]. Mice lacking DCs (Flt3^{-/-}) had reduced number of adipose and liver macrophage content, whereas DC replacement in DC-null mice increased liver and adipose macrophage infiltration and IR [30]. Both myeloid DCs and plasmacytoid DCs from chronic diabetic patients show upregulation of lineage markers due to high levels of circulating GM-CSF [31].

In helminth infections, DCs are arrested in an immature state characterized by an absence/moderate expression of co-stimulatory molecules along with reduced pro-inflammatory cytokine secretion [32]. This feature might presumably induce the development of a Th2 immune response [33]. While Toll-Like Receptor-mediated activation brings about DC maturation in general, helminth products have evolved alternate pathways of activation which can induce an anti-inflammatory response [34]. Helminth antigen treated dendritic cells produced increased levels of IL-4 and IL-10 [35]. Also, human monocyte-derived dendritic cells (mDCs) when infected with live *Brugia malayi* microfilariae showed downregulation of TLR3 and TLR4 expression and diminished production of pro-inflammatory

S. No	Filarial antigen	Organism/ species	Disease condition	Immune cells involved	Mechanisms	Outcome	Ref.
1	<i>Litomosoides sigmodontis</i> (L.s) antigens	C57BL/6 J DIO mice and C57BL/6 J DEREG mice	Diet induced obesity and glucose intolerance	Eosinophils, macrophages, innate lymphoid cells	Increased number of eosinophils, M2 macrophages, ILC-2 and Tregs in AT	Increased insulin sensitivity and glucose tolerance	[22]
2	<i>Nippostrongylus brasiliensis</i> (L3)	C57BL/6 J mice	Diet induced obesity and glucose intolerance	Macrophages	Increased M2 macrophages and increased expression of IL-13.	Reduced body weight and improved glucose metabolism	[23]
3	<i>Brugiamalayi</i> adult soluble (Bm A S) or microfilarial excretory-secretory (Bm mf ES) or microfilarial soluble (Bm mf S) antigens	BALB/c mice	STZ induced T1D	Antibodies	Increased IgE levels and sub- isotype switch of anti-insulin antibodies from IgG2a to IgG.	Improvement in glucose metabolism	[24]
4	Filarial proteins rWbL2(recombinant <i>Wuchereriabanc rofti</i> 1.2) or rBmALT-2 (recombinant <i>B. malayi</i> abundant larval transcript 2)	Female Balb/c mice	STZ induced T1D	Antibodies	Inhibition of TNF- α and IFN- γ secretion and augmentation of IL-4, IL-5 and IL-10 secretion. Production of insulin specific IgG1 and antigen-specific IgE antibodies	Improvement in glucose metabolism	[25]
5	rDiAg (Recombinant <i>Dirofilaria immitis</i> antigen)	NOD/shi female mice	Autoimmune T1D	Antibodies	Reduced level of anti insulin autoantibodies. Th1 to Th2 shify. Elevated IgE levels	Prevention of insulinitis	[26]

Table 1.
Effect of filarial antigen treatment on glucose metabolism and insulin sensitivity in Type-2 diabetic mice models.

cytokines following TLR challenge [36]. Recent research shows that priming of DCs with helminth products brings about Th-2 polarization and improves metabolic dysregulation [37].

2.3 Neutrophils in insulin resistance and immunomodulation

Neutrophils are microphages which are short-lived phagocytic cells that remove and destroy invading microorganisms and also cellular debris [38, 39]. In diet-induced obese mice, increased infiltration of neutrophil into adipose tissue was reported during weight gain and was associated with IR. In addition to host defence, neutrophil-derived serine proteases, such as neutrophil elastase, have been implicated in sterile inflammation [40]. Treatment of hepatocytes with neutrophil elastase-induced IR (by IRS-1 degradation) while deletion of neutrophil elastase in obese mice restored insulin sensitivity [40]. Taken together, neutrophils can be added to the extensive repertoire of immune cells that participate in inflammation-induced IR.

Compared to macrophages the role played by neutrophils in helminth infection is well studied [41]. In recent times, like macrophages, neutrophils were shown to get polarized either towards classically activated (N1) or alternatively activated (N2) phenotypes, following bacterial infections [42]. Whether such polarization takes place during helminth infections is not clearly known. Neutrophils were found to provide resistance to *H. polygyrus* infection *in vivo* and were able to kill the worm under *in vitro* conditions [43]. More recent reports indicate an important role for neutrophils in killing the larval stages of *Strongyloides stercoralis* [44]. Thus there is a possibility of neutrophils polarization during helminth infection which might aid host metabolism. *Haemonchus contortus*, a gastric parasite, secretes a 55 kDa secretory glycoprotein (gp55) which binds to CD11b/CD18 integrin present on neutrophils and inhibits its action [45].

2.4 Eosinophils in insulin resistance and immunomodulation

Eosinophils are generally associated with allergic responses as seen in parasitic infections [46]. While IL-5 serves as the main growth factor for eosinophil development, eotaxins (CCL11, CCL24 and CCL26) serve as its major chemotactic factors [46]. Activation of eosinophils results in its degranulation on to the target cells [46]. They carry eosinophilic granules which are rich in cytotoxic cationic proteins including major basic protein (MBP), eosinophil peroxidase (EPO), eosinophilic cationic protein (ECP) and eosinophil-derived neurotoxin (EDN) [46]. Adipose tissue eosinophils are needed for metabolic homeostasis and are involved in the maintenance of alternatively activated macrophages (AAMs) (**Figure 1**) [47]. They serve as the major source of IL-4 which polarizes the macrophages into the M2 phenotype. Absence of eosinophils can lead to adiposity and systemic IR in obese mice [47]. In these animals, IL-5 deficiency leads to loss of eosinophil accumulation in the adipose and increased IR [48].

Clinically, helminth infections are the most common cause of persistent eosinophilia, wherein they play a vital role in parasitic killing and elimination [49]. Ligation of parasite-specific Ig to Fc receptors or direct binding of helminth products to TLRs leads to eosinophil activation and degranulation [49]. Activated eosinophils bring about worm expulsion in 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 non-immune cells [49]. However, recent evidence has indicated eosinophil activation during helminths infection is an immune evasive strategy

favouring the parasite [50]. Eosinophils may influence the immune response in a manner that would sustain chronic infection and ensure worm survival [50]. Recently, in a high-fat diet mice model, animals infected with *Nippostrongylus brasiliensis* showed sustained metabolic control characterized by decreased fasting glucose and improved insulin sensitivity, which was associated with increased eosinophil content in the adipose tissue (**Figure 1**) [51]. Obese mice injected with *Litomosoides sigmodontis* (Ls) antigen showed an increased number of eosinophils in the epididymal adipose tissue which normalized glucose intolerance (**Table 1**) [22].

2.5 Basophils and mast cells in insulin resistance and immunomodulation

Basophils and mast cells are known for their involvement in allergies and airway inflammation [52]. Both cell lineages share a common ancestry: while basophils circulate; mast cells remain resident in tissues under normal conditions [52, 53]. As like other immune cells, recent studies have implicated them in glucose homeostasis and adipogenesis [54]. VAT from obese mice as well as humans contained a significant amount of mast cells [54]. Mast cell-deficient mice showed better glucose homeostasis with increased metabolic rate [55]. Leptin deficient Ob/Ob mice have an increased mast cell content in their adipose tissue and were found to secrete an increased amount of TNF- α [56].

Like eosinophils, basophils also serve in the first line of defence mechanism against helminth infection [57]. However recently, this concept has been challenged for certain helminth infections [58]. The cross-linking of surface IgE on basophils by helminth antigens induced IL-4 secretion [59]. Thus, the anti-inflammatory Th-2 response is augmented by basophils and mast cells [60]. During helminth infections, eosinophils, neutrophils and basophils directly participate in the parasite killing and expulsion [61]. Basophil deficient mice, infected with L3 larvae of *Brugia malayi* showed decreased eosinophil count, decreased titers of parasite-specific IgE, reduced CD4⁺ T cell proliferation and decreased antigen-specific IL-4 production demonstrating the importance of basophils in the amplification of type-2 immune response [62]. Helminth infected mice have an increased number of basophils which were capable of priming of Th-2 response [63].

2.6 NK and NKT cells in insulin resistance and immunomodulation

Natural killer (NK) cells are an important component of the innate immune response to viral infections and tumours [64]. They have the ability to provide an early source of both innate (IL-6 and TNF- α) and adaptive (IFN- γ , IL-4, IL-5 and IL-13) immune cytokines and can also lyse the target cells through perforin-granzyme-mediated cytolytic pathway [64]. Natural Killer T (NKT) cells are sub-population of lymphocytes that serve as a link between the innate and adaptive immunity [65]. They are a heterogeneous group of lymphocytes that share the properties of both T cells and NK cells. Many of these cells recognize self and foreign lipids and glycolipids bound to the non-polymorphic CD1d molecule [65]. Very little is known about the role played by NK and NKT cells in metabolic homeostasis [66]. VAT obtained from obese subjects was found to have an increased frequency of IFN- γ expressing NK cells [67]. The role of iNKT cells in the regulation of metabolism is just emerging. Previously, it was found that adipose tissues and liver of both mice and humans contain a population of iNKT cells, which decreased with increasing adiposity and IR (**Figure 2**) [68]. In fact, this coincides with the infiltration of macrophages and T cells into the adipose tissue.

Compared to other cell types, the role played by NK cells in helminth mediated immunomodulation is intriguing. NK cells were found to express IL-4 and IL-13

Figure 2.

Myeloid cell network in Insulin Resistance (IR) and immunomodulation. Helminth infections can bring about macrophage polarization from the pro-inflammatory M1 phenotype to anti-inflammatory M2 phenotype. They also polarize neutrophils from pro to anti-inflammatory phenotype. They augment both eosinophils and basophils which attenuate IR. They induce tolerogenic dendritic cells and myeloid derived suppressor cells which inhibit Th1 immunity.

in response to microfilaremia but not L3 infection [69]. The early activation of NK cells led to apoptosis in response to live L3 exposure, but not to live microfilaremia infection [69]. Impairment of NK cell function had a profound effect on worm burden and delays the clearance of the parasite. Infection of BALB/c mice with *L. sigmodontis* was shown to suppress the activation of inhibitory receptors but promoted the induction of activating receptor on NK cells [70]. NKT cells during helminth infections were shown to produce IL-4 as an immunoregulatory cytokine when exposed to the nematode glycolipids [71]. Helminths activate both iNKT and non-iNKT cells *in vivo*, enabling them to differentially influence the Th1/Th2 balance [71]. NKT cells were known to be the early source of IL-4, in the spleen, within 24 h of L3 *B. phangi* infection in mice [71].

2.7 Other innate immune cells in insulin resistance and immunomodulation

Myeloid-Derived Suppressor Cells (MDSCs) are heterogeneous immature myeloid cells which were first discovered in the tumour stroma wherein they were found to suppress anti-tumour immune response [72]. Recently, MDSCs were shown to alleviate insulin resistance and confer protection against diabetes [73]. Adoptive transfer of MDSC cells into HFD mice showed better glucose tolerance [74]. Loss of these cells in obese animals aggravated IR [74]. Within the adipose tissue milieu, these cells were found to suppress Th1 activation [74]. During helminth infection, anti-proliferative MDSCs emerge which inhibit T cell proliferation using eicosanoids generated through 12/15 lipoxygenase pathway [75]. Similarly, *Schistomes* soluble egg antigens were shown to prime MDSC cells which strongly inhibited T cell activation [76].

Nuocytes or Innate lymphoid cells (ILC) are recently discovered innate lymphoid cells capable of augmenting other immune cells like helper T cells [77]. ILCs are primarily tissue-resident lymphocytes, found in both lymphoid (immune-associated), and non-lymphoid tissues, and rarely in the peripheral blood (<1%) [77, 78]. They are particularly abundant at mucosal surfaces controlling mucosal immunity and homeostasis [77, 79]. They differ from other immune cells by the absence of regular lymphoid morphology, TCR and BCR rearranged, and expression of myeloid-specific CD markers [77]. Based on the difference in developmental pathways, phenotype, and cytokine secretion, in 2013, ILCs were divided into three groups: 1. ILC-1 cells upon priming with IL-12, IL-15 and IL-18 secrete IFN- γ and TNF- α ; 2. ILC-2 cells upon priming with TSLP, IL-25 and IL-33 secrete IL-4, IL-5 and IL-13; 3. ILC-3 cells upon priming with IL-1 β , IL-23 and IL-6, secrete IL-17 and IL-22 [77]. ILC-1 recruitment into the adipose tissue is directly linked to fat accumulation and exacerbates IR [80], while ILC-2 cells are involved in browning of visceral adipose tissue [81]. During helminth infection, the early source of IL-13 was from nuocytes, through IL-25 and IL-33 dependant priming [82]. Administration of *Schistosoma mansoni* egg-derived ω 1 antigen into diabetic mice induced Th-2 response, which correlated with increased frequency of ILC-2 in adipose tissue, which in turn increased the metabolic homeostasis [83].

3. Adaptive immune cells in insulin resistance and immunomodulation

The adaptive immune cells include T cells and B cells which play an important role in both IR and immunomodulation.

3.1 T-helper cells in insulin resistance and immunomodulation

T cells are lymphocytes which mature from the thymus (and hence the name) and are the major components of the adaptive immune system [84]. They perform three major functions: 1. Helper T cells (Th) activate B cells, macrophages, DCs, other T cells and other immune cells, 2. Cytotoxic T cells (Tc) directly kill tumour cells and pathogen-infected cells and 3. Regulatory T cells (Tregs) maintain immune homeostasis [84]. The Th cells are distinguished by their CD4⁺ phenotype and are further classified based on their cytokine profile as 1. Th1 (IFN- γ , IL-2, and TNF- β), Th2 (IL-4, IL-5 and IL-13), 3. Th17 (IL-17 and IL-17F), 4. Th9 (IL-9 and IL-10), 5. Th22 (IL-22), etc. [84]. T cells in coordination with macrophages and DCs fuel VAT inflammation [85]. Both pro-inflammatory cytotoxic T cells (CTLs) and interferon- γ (IFN- γ)-producing Th-1 cells contribute to inflammation (**Figure 2**) [86]. On the contrary, VAT-resident Tregs and Th2 cells tend to suppress inflammation (**Figure 2**) [87]. Obese IFN- γ -knockout animals, compared with obese wild-type mice, showed modest improvements in insulin sensitivity, decreased adipocyte size, and an M2-macrophage phenotype and cytokine expression [88]. Genetic ablation of IL-13 in mice resulted in hyperglycemia, which progressed to hepatic IR and systemic metabolic dysfunction [89]. However, studies conducted in our lab on serum cytokine profiles in subjects with metabolic syndrome (MS) showed a mixed Th1-Th2 response with increased levels of IL-12, IFN- γ , IL-4, IL-5 and IL-13 in the serum of subjects with metabolic syndrome (a precondition of diabetes, if not already present) [90]. The role of recently discovered Th17 in VAT inflammation is still an enigma. Some studies have shown strong pro-inflammatory phenotype for these cells inducing IR [91], while our study showed a decline in serum IL-17 levels in subjects with MS (**Figure 2**) [92]. The Tregs in VAT has a unique function of maintaining immune-homeostasis and improving insulin signalling by PPAR-g

activation [93]. The role of other recently identified Th cell subtypes like Th22 and Th9 in IR is not clearly known. In general, type-2 diabetic subjects show a mixed Th1-Th2 response which becomes more Th1 polarized as the diabetic subjects develop microvascular [94] and macrovascular complications [95]. Serum IL-17 levels are generally low in patients with diabetic nephropathy [96].

T cell-mediated immune responses during filarial infection depend on the phase of the infection: 1. The acute phase is skewed towards Th2 (IL-4, IL-5 and IL-13) response, 2. The chronic phase is skewed towards “modified Th2 response”, with Tregs playing a more prominent role compared to Th2 cells and 3. The third phase is chronic pathology phase, which is characterized by a drastic shift from “modified Th2” response to Th1/Th17 (IFN- γ , IL-2 and IL-17) response, which happens only in those who develop lymphatic pathology [97]. Thus, the differential immune response seen during various phases of the filarial infection is paralleled by the life cycle of the parasite: 1. Microfilaremic stage-predominant Th2 response, 2. Adult worm stage- modified Th2-Treg response and 3. Chronic pathology stage- Th1/Th17 response [97]. Infection of HFD induced obese mice with *Heligmosomoides polygyrus*, an intestinal nematode parasite, resulted in significantly attenuated obesity with marked upregulation of uncoupling protein 1 (UCP1), a key protein involved in energy expenditure in adipose tissue [98]. Further suppression of glucose and triglyceride levels and alteration in the expression of key genes in the liver involved in lipid metabolism were also seen [98]. An augmented helminth induced Th2/Treg response and M2 macrophage polarization was characteristic of this attenuated obesity [98].

3.2 Cytotoxic T cells (CTLs) in insulin resistance and immunomodulation

Cytotoxic (CD8+) T cells are one of the effector cells in T-cell mediated immunity which directly kills the target cells (virus or bacteria-infected cells and tumour cells). CD8+ T cells were found to migrate into the adipose tissue much before the accumulation of macrophage in obese mice [99]. IFN- γ produced by CTLs promotes the recruitment and polarization of M1 macrophages (**Figure 1**) [99]. This results in adipose tissue inflammation and IR [99]. In the obese mice, increased infiltration of CTLs into the adipose tissue around 22nd week after the initiation of a high-fat diet was seen [99]. Antibody-mediated or genetic depletion of CTLs lowered macrophage infiltration and adipose inflammation, ameliorating IR [99].

When compared to T-helper cells, the amount of literature available on the role of CTLs in helminth infection is limited. At least in mice, there is evidence to show that CTL population is dispensable for anti-helminth immunity [100]. In clinical studies, LF infection was shown to upregulate HLA-A thereby activating CTLs [101]. However, these activated CTLs showed poor proliferative response under *in vitro* conditions [101]. The CTL activity was largely seen during lymphedema development, rather than acute/modified immune response to helminths [101]. Further, these activated CTLs were largely immunomodulatory rather than pro-inflammatory in nature [101]. It would be interesting to see whether these activated immunosuppressive cells are in fact the recently discovered CD8(+) Tregs population (**Figure 3**).

3.3 B cells in insulin resistance and immunomodulation

B cells form a major component of adaptive immunity and perform two vital functions namely: 1. Antigen presentation to T cells which links innate and adaptive arms of the immune response and 2. Production of antibodies which perform the effector functions. In obese mice, B cells were found to migrate into the adipose

helminth infections; in the context of helminth infections, they orchestrate regulatory immune responses via IL-10, whereas in IR they induce adipose inflammation via autoantibodies.

4. Conclusion and future directions

A decrease in helminth infections (like lymphatic filariasis) could potentially account for the increased prevalence of metabolic diseases in the western world. The same immunomodulatory effect can have an impact on type-2 diabetes, as was seen in tropical countries. Recently, several helminth antigens were shown to confer significant protection against obesity, insulin resistance and diabetes, in animal models. The implications of helminth induced immunomodulation are thus twofold: Mass drug administration in populations which are highly susceptible to type-2 diabetes has to be carried out with care; Secondly, more research is needed in identifying and characterizing novel helminth antigens with a strong immunomodulatory effect which can later be developed into diabetes vaccines.

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