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Parasites, nutrition, immune responses, and biology of metabolic tissues

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Abstract

Nutritional immunology, immunometabolism, and identification of novel immunotherapeutic targets, are areas of active investigation in parasitology. There is a well-documented crosstalk among immune cells and cells in metabolically active tissues that is important for homeostasis. The numbers and function of these cells are altered by obesity leading to inflammation. A variety of helminths spend some part of their life cycle in the gastrointestinal tract and even entirely enteral nematode infections exert beneficial effects on glucose and lipid metabolism. The foundation of this review is the ability of enteric nematode infections to improve obesity-induced type 2 diabetes and the metabolic syndrome, which are significant health issues in developed areas. It considers the impact of nutrition and specific nutritional deficiencies, which are occur in both undeveloped and developed areas, on the host's ability mount a protective immune response against parasitic nematodes. There are a number of proposed mechanisms by which parasitic nematodes can impact metabolism including effects gastrointestinal hormones, altering epithelial function, and changing the number and/or phenotype of immune cells in metabolic tissues. Nematodes can also exert their beneficial effects through Th2 cytokines that activate the transcription factor STAT6, which upregulates genes that regulate glucose and lipid metabolism.

Helminth Infection and Metabolic Diseases

It is estimated that one third of the world's population is infected with parasitic helminths with the greatest burden in underdeveloped nations particularly Nigeria and the Congo (1). Nutrients are cofactors and activators for the developing immune system (2) and malnutrition as well as bacterial co-infections are frequent in these developing areas and promote the chronicity of helminth infection. There is also increasing recognition that specific deficiencies in vitamins and/or minerals can contribute to the severity of parasitic infections in endemic areas. Alternately, well developed urban areas with the lowest worm burden have a much greater incidence of metabolic diseases including obesity-induced type 2 diabetes (T2D) and the metabolic syndrome. Increasing evidence suggests that helminth

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infection regulates food intake and appetite, reduces body weight, and improves the symptoms of the metabolic syndrome and T2D (3).

There is a well-documented crosstalk among immune cells and cells in metabolically active tissues that is important for homeostasis. Parasitic nematodes or their products can impact cellular metabolism by a number of mechanisms including direct effects on hematopoietic and non-hematopoietic cell function or indirect effects mediated by downstream activation of genes that regulate production of metabolically active factors. There are a variety of helminths, including parasitic nematodes, which spend a large portion of their life cycle in the gastrointestinal (GI) tract. Their presence in the lumen initiates, extends, or amplifies signals that are critical to host defense against parasites. The GI tract provides a starting point for this review focused on the known and proposed mechanisms by which the nutritional status impacts host defense against parasitic nematodes and by which worm infection impacts host nutritional status and metabolism.

THE IMPACT OF NUTRITION ON HOST DEFENSE

For most of human history, malnutrition was common, and the effect of malnutrition on immunity, especially cellular immunity, has been studied extensively (4). A systemic review of the effects of malnutrition in children reported reduced gut barrier function, atrophied lymphatic tissue, and polarized cytokine production toward a Th2 response (2). The skewing of cytokine production toward a Th2 response; however, does not necessarily translate into improved resistance to nematode infections. Mice fed diets with reduced protein content showed delayed expulsion of primary *Nippostrongylus brasiliensis* (*N. brasiliensis*), *Trichinella spiralis* (*T. spiralis*) and *Trichuris muris* (*T. muris*) infections (5) and the Th2 response to a secondary *Heligmosomoides polygyrus bakeri (H. polygyrus bakeri)* infection was impaired resulting in increased worm burden (6). Similarly, mice infected with *H. polygyrus bakeri* and fed a diet with adequate protein and nutrient levels, but reduced caloric content, showed impaired lymphocyte proliferation, reduced Th2 cytokine production with lower levels of IgE, parasite-specific IgG1, and eosinophils, resulting in higher worm burdens and fecundity (7). In a recent study using multiple small (trickle) infections with *H. polygyrus bakeri* to mimic natural infections, the tolerance to infection, as measured by intestinal barrier function, was decreased by protein malnutrition (8). These results indicate that both sufficient protein and calories are required for optimal resistance to parasitic nematode infections.

In the twentieth and twenty-first centuries, consumption of “Western diets” has led to excessive caloric intake, increased consumption of highly refined foods, and decreased consumption of fruits and vegetables that may lead to deficiencies in at-risk populations including the elderly, the economically disadvantaged, or those with diseases that contribute to impaired absorption including Crohn’s disease, ulcerative colitis, and parasitic infections (9, 10). In particular, both gastrointestinal diseases and parasitic infections have been shown to impair micronutrient absorption. Several of these micronutrients, including vitamin A, selenium and zinc, play critical roles in immune function and resistance to parasitic infections.

The Role of Vitamin A in Resistance to Parasitic Infections

The role of vitamin A in immunity is highly pleiotropic. The effects are dose-, receptor form-, cell type-, and environmentally-dependent (reviewed in (11)). Dietary vitamin A or retinol is converted to retinaldehyde by ubiquitous alcohol dehydrogenases and then irreversibly acted on by cell-specific retinaldehyde dehydrogenases to generate its active metabolite, retinoic acid (RA), which binds to the RAR and RXR nuclear receptor families and function as transcription factors (11). RA can be produced locally by migratory $CD103^+$ dendritic cells and macrophages in the lamina propria, and by stromal cells in the mesenteric lymph nodes and bone marrow (12, 13). In addition, RA is elaborated by intestinal epithelial cells that, in turn, promote gut-homing of IgA secreting B-cells (14), $CD4^+$-, and $CD8^+$ T cells (15, 16), a process that is impaired in vitamin A deficient mice (15, 17). B-cell development and antibody production are also vitamin A dependent [reviewed in (18)].

RA can act as a suppressor or activator of an inflammatory response depending on the circumstances. RA provides a critical signal for iTreg cell differentiation and iTreg cells can inhibit Th1- and Th17-type inflammatory responses (19–21). iTreg cells are decreased in vitamin A deficient mice leading to impaired oral tolerance (22). Differentiation of $CD4^+$ T-cells is dependent on both vitamin A and RARα. Production of IFN-γ and IL-17A is decreased in T-cells lacking RA signaling and Th17 cells are severally reduced in vitamin A deficient mice (23). RA is important for maintenance of polarized Th1 cells and preventing conversion of Th1 cells to dual IFN-γ/IL-17-expressing Th17 cells (24). In contrast, RAR signals favor Th2 differentiation in naïve T-cells (25), is mediated via cytokine production by APC (25), and can impact resistance to parasitic infections which are classic inducers of Th2 immunity. This is important as the WHO showed that regions where soil-transmitted helminthiasis is most prevalent, Central America, especially Mexico, Central Africa, and Southeast Asia, are also areas of endemic vitamin A deficiency. Both low and high doses of RA increased localized Th1, Th2, Treg, and inflammatory responses in the liver and lung of *Ascaris suum*-infected pigs as well as increased BAL eosinophilia that may be related to enhanced induction of eosinophil chemokine activity by alveolar macrophages (26). The increase in type 2 innate lymphoid cells (ILC2) cells in vitamin A deficient mice was associated with increased resistance to a *T. muris* infection (23) that was dependent on fatty acid oxidation (27). This finding extends earlier work where egg excretion decreased more rapidly in *Trichuris suis*-infected, vitamin A deficient pigs than in vitamin A sufficient pigs (28), but contrasts with the increased parasite burden in *Litomosoides carini*-infected, vitamin A deficient cotton rats (29). Although worm expulsion was only slightly reduced in *T. spiralis* infected vitamin A deficient mice, differences in the immune response between sufficient and deficient mice were observed including higher IFN-γ and lower IL-4 production in MLN of infected deficient mice (30). Mice with a chronic infection of *T. muris* have reduced enzyme activity of and cell percentage staining for retinal dehydrogenase in lamina propria-derived dendritic cells and macrophages that did not rebound until the infection was cleared, indicating that chronicity may be related to decreased local RA levels (31) and impaired immune responses. The cause of this reduction was not identified, but may be a regulatory mechanism used by the parasite, or may result from reduced vitamin A absorption (32). These studies demonstrate that the ability of

vitamin A to enhance or impair immunity to parasitic infections is at least partially parasite specific and additional studies are required to further clarify this dependency.

Selenium and Zinc are Key Minerals Required for Immune Function and Resistance to Infection

Selenium (Se), via its incorporation into selenocysteine-containing proteins (Sels), has substantial effects on immune function. There are 25 Sels identified in humans and 24 in mice with only partially characterized function. Selenium is important for both humoral and cell-mediated responses including cytotoxic T-lymphocytes and natural killer cells (33), chemokine and cytokine responses to viral infections (34, 35), respiratory burst (36), and for protection against LPS-induced oxidative stress (37). Many of the immune modulating effects of Se are due to its role in regulating activation of important transcription factors including NF-κB (38, 39), p38 MAPK (39), ERK (40), JNK (41) and AP-1, at least in part, by modulating redox status (42).

Specific Sels have been implicated in immune function. Both glutathione peroxidase 1 (GPx1) and glutathione peroxidase 2 (GPx2) are important for controlling Th2-dependent allergen-induced airway inflammation (43) with knockout of GPx1 shifting the Th cell bias toward Th1 and suppressing development of Th17 cells (44). Thioredoxin reductase maintains thioredoxin in its reduced state and thioredoxin is important for immune function and cell survival (45). Selenoprotein K KO mice exhibit aberrant calcium signaling in immune cells and an impaired immune response (46). Selenoprotein S is linked to regulation of inflammation (47). Selenoprotein P is also important for intercellular transport of Se, especially to the brain, and in controlling inflammation, and colitis-induced tumorigenesis (48–50).

Se status affects the immune response to parasitic infections. Selenium deficiency resulted in delayed expulsion of *H. polygyrus bakeri* (51, 52) due at least, in part, to decreased Th2 responses and production of Relm-β, a goblet cell protein critical for worm expulsion (53). Similarly, Se deficiency impaired clearance and reduced the Th2 response to *N. brasiliensis* infection in mice, an effect also observed in mice with conditional knockout of selenoprotein expression in macrophages (54). This effect of *N. brasiliensis* infection was attributed to the reduction in the transcription factor proliferator-activated receptor-γ (PPAR-γ)-mediated switch from a classically activated (M1) to an alternatively activated (M2) macrophage phenotype (55). This change was dependent on prostaglandin D_2 synthase and 15-deoxy-$\Delta^{12,14}$-prostaglandin J2 (15d-PGJ_2) (55–57), highlighting a role for Se in regulating prostaglandin synthesis (56) and promoting the development of M2.

Many aspects of immunity are dependent on zinc. Zinc deficiency leads to atrophy of the thymus, a reduction in leukocytes, as well as in antibody-mediated, cell-mediated, and delayed-type hypersensitivity responses (58). In addition, NK cell activity is decreased in neutrophils, and macrophages have reduced levels of phagocytosis and respiratory burst in zinc deficiency (59). Production of the Th1 cytokines IL-2 and IFN-γ is attenuated by zinc deficiency resulting in a shift toward a Th2 response (60). Basal levels of pro-inflammatory cytokines are elevated in zinc deficiency, but production is ablated upon stimulation (61). Decreased cytokine production may result from decreased NF-κB activation in zinc

deficiency (62, 63). Both immature and mature B-cells are reduced by zinc deficiency (64) as is antibody production (65). Zinc was found to increase Treg cell numbers in allergen-stimulated cells from atopic subjects and in mice with experimental autoimmune encephalitis (66, 67). Significantly, moderate zinc deficiency (3 mg/kg diet) in rats delayed expulsion and increased worm burden of *T. spiralis,* egg excretion, but not worm burden of *N. brasiliensis*, and delayed clearance of *Strongyloides ratti* (68). Moderate and severe (0.75 mg/kg), but not marginal (5 mg/kg) zinc deficiency, impaired the Th2 response to *H. polygyrus bakeri* and prolonged worm survival in primary *H. polygrus bakeri*-infected mice while in a challenge infection, only severely deficient mice had an impaired Th2 response and increased worm burdens (69). These data indicate that zinc deficiency impairs the Th2 response to parasitic infections and that zinc is important for Th2 immunity to parasitic infections. Supplementation may be indicated for at-risk or infected populations where inadequate dietary intake or malabsorption is present.

The impact of malnutrition and micronutrient deficiencies was focused for many years on developing nations. In areas of endemic infection, parasitic helminths that have evolved strategies that favor chronic infection are common (1) and the adverse effects of nutritional deficiencies to host defense further compound chronicity. Despite the epidemic of obesity and the metabolic syndrome in the United States and across the world, obese patients are often malnourished and exhibit similar deficiencies in micronutrients (70). The World Health Organization (WHO) estimates that 39% of adults aged 18 years and over were overweight in 2014, and 13% were obese in the world. The nutritional status of obese populations in developed nations merits equal attention as these conditions increase mortality, morbidity, and the economic costs of health care.

THE IMPACT OF PARASITIC NEMATODES ON HOST METABOLISM

There is little information on the impact of obesity on type 2 immune responses. Obesity prone mouse strains however, are more susceptible, while lean mouse strains were more resistant, to parasitic nematode infection (71). Obesity induces a wide variety of inflammatory and stress responses in metabolic tissues and higher concentrations of circulating inflammatory markers. This results in chronic, low grade inflammation termed “metaflammation” (72) which is central to insulin resistance and disruption of insulin receptor signaling (73), and requires the participation of both immune and non-immune cells. This has fostered the emerging field of immunometabolism that is focused on investigating the pro-inflammatory cytokines and mediators of obesity, the metabolic syndrome, and T2D (74). Parasitic infections, even those restricted to the intestine, increase circulating levels of IL-4, IL-5, and IL-13 which may act to blunt or reverse the Th1-induced inflammation in metabolic tissues.

Nematode Infection Alters Intestinal Barrier Function and the Intestinal Microenvironment

The surface epithelial cells that line the GI tract form the first line of defense in the gut and include the absorptive enterocytes, the mucus-producing goblet cells, and the hormone-secreting enteroendocrine cells (EEC). Along with immune cells, epithelial cells transduce specific pathogen-derived signals into effector functions; however, the mechanisms by which

a wide variety of helminths induce a Th2 response remain to be elucidated. A confounding issue is that helminths elaborate antigens and excrete and secrete (E/S) a variety of products that may be involved in the initiation and maintenance of the type 2 immune response. How the cells respond to E/S products is also unclear, but highly implicated are pattern recognition receptors (PRR) and membrane-associated toll like receptors (TLR) that recognize conserved features of pathogens. There is also evidence that enteric parasitic nematodes elaborate trypsin-like serine proteases that activate protease activated receptors (PAR) such as PAR-2 on epithelial cells (75).

Worm-derived proteases may play a role in transducing the density and location of nematodes in the intestinal lumen (76). PAR-2 expression is ubiquitous along the GI tract and is expressed by epithelial cells, enteric nerves, and smooth muscle cells as well as by a variety of immune cells, including mast cells, macrophages, and T cells (77). Activation of PAR-2 on enterocytes increases epithelial permeability and fluid secretion from enterocytes and also enhances the nerve sensitivity of visceral afferent nerves (76), effects that are important for worm expulsion (78–81). Of interest is that in functional GI disorders, such as IBS, these effects are amplified and/or unresolved (82, 83). The reduced barrier function also facilitates the passage of E/S products across the intestinal barrier where they interact with resident immune cells to initiate and maintain the type 2 immune response. Activation of PAR-2 on macrophages also promotes development of the M2 phenotype (84).

The magnitude and duration of the effect of proteases is determined by the level of proteases and the number and availability of PARs on the cell surface (85, 86). PARs are “one shot” G protein-coupled receptors that must be continuously replenished from intracellular stores. Of interest is that the exposure to nematode proteases results in loss of surface PAR-2 on enterocytes thereby limiting the duration of their direct effects on epithelial permeability (76). With the loss of protease-mediated permeability, changes in barrier function are maintained during nematode infection by IL-25/IL-13/STAT6-dependent mechanisms (78, 79, 87).

The GI epithelium produces IL-25 and recent studies confirm that doublecortin-like kinase 1 (Dclk1)-expressing tuft cells are the sole epithelial source (88). Tuft cells are a distinct lineage that arise from stem cells in the located in the crypts and comprise approximately 0.4% of epithelial cells (89). The receptor for IL-25 (IL-25R) is a heterodimer consisting of IL-17RB and IL-17RA (90), which is expressed by various tissues/cells, including epithelial cells and immune cells including macrophages (91, 92) and ILC2. IL-25 plays a major role in the promotion and initiation of type 2 immunity, down-regulating pro-inflammatory cytokines, and facilitating development of M2 (91–93). IL-25 increases mucosal permeability through release of IL-13 (92) from resident mast cells and ILC2. Thus, the enhanced permeability during nematode infection is initiated by both worm-derived products and immune-mediated processes (76). Worm proteases and epithelial release of IL-25 facilitate the early passage of intraluminal products that promote the type 2 immune response. The increased permeability is sustained by IL-4, IL-13 working through STAT6-dependent mechanisms, including the influx of mast cells (79, 80, 94).

Parasitic Nematode Infection Regulates Glucose Transport

Obesity and T2D are associated with poor glycemic control as a result of dysregulated control of glucose sensing hormones and insulin resistance. Enteric nematode infection is associated with hypophagia and weight loss with improvement of the metabolic syndrome and T2D (3, 95). The mechanisms for the weight loss and decreased food intake remain unclear, but may be linked to local GI events including changes in intestinal glucose handling (78) or the immune cell phenotypes and the cytokine profile associated with infection (96).

Glucose is absorbed in the small intestine by transcellular pathways utilizing transporters as well as by paracellular pathways through solvent drag, a process that is modulated by changes in intestinal permeability. Enteric nematode infection slows enterocyte glucose absorption by inhibiting the activity of insulin-independent sodium-linked glucose transporter 1 (SGLT1) (97). This high affinity transporter can absorb glucose against a concentration gradient and is considered to be the major mechanism for postprandial glucose absorption in the small intestine (98). The nematode-induced effect on glucose absorption was dependent on M2, as depletion of macrophages during nematode infection restored SGLT1 activity (97). Given the prominent role of macrophages in insulin resistance, manipulation of macrophage phenotype may be a potential therapeutic strategy. Enteric nematode infection also decreased the expression of the insulin-dependent transporter GLUT2 by a mechanism that is independent of STAT6 (97). This is a facilitative transporter located on the basolateral membrane that is also trafficked to the apical side at high luminal glucose concentrations. The inhibited SGLT1 activity and reduced expression of GLUT2 during parasitic nematode infection lower enterocyte intracellular glucose (97, 99). This results in a metabolic stress that induces HIF-1α, leading to STAT6-dependent upregulation of GLUT1, a constitutive insulin independent transporter (97), thereby providing glucose for cellular metabolism.

The enhanced permeability during nematode infection also results in a greater absorption of glucose by the paracellular route and provides nutrients to fuel the high metabolic demands required by activated CD4+ T cells (100). Signaling through the T cell receptor activated mTOR leads to upregulation of GLUT1 and HIF-1α (101). Nematode infection induces an upregulation of GLUT1 in both enterocytes and T cells. Of interest is that GLUT1 is expressed by M1, which preferentially use glucose as an energy substrate, while M2 use free fatty acids (102), showing a preference of immune cells for specific energy substrates. Thus, by shifting the major route of intestinal glucose absorption to the paracellular pathway, parasitic nematode infection effectively bypasses insulin-dependent glucose transporters on enterocytes and fuels activated CD4+ T cell and macrophage metabolism. The increased demands of immune cell metabolism may contribute also to weight loss during nematode infection.

Parasitic Nematode Infection Reduces Appetite/Food Intake

The GI tract is the largest endocrine organ in the body. Comprising 1% of the epithelium, EEC arise from intestinal stem cells, are rapidly turned over, and function to sense the composition of the luminal contents and to coordinate release of hormone based on the

location and type of nutrients detected and play a major role in satiety (103, 104). The numbers of EEC are modulated by diet and respond to the intraluminal nutrient composition through taste/chemosensory receptors that are sensitive to bitter, sweet, and umami compounds (105). Sweet taste receptors play a key role in secretion of GI hormones involved in glucose metabolism as well as the activity and expression of SGLT1 and GLUT2 (105). EEC also respond to products released by commensal bacteria (106), so it is likely EEC "sense" the presence of enteric nematodes or their products. There is now strong evidence of communication between immune cells and EEC (107) with EEC functioning as innate immunity sensors (104).

Recent studies show that *N. brasiliensis* induces an IL-25/IL-13 mediated expansion of the secretory lineage of epithelial cells that includes IL-25-producing tuft cells (108), which also express taste receptors (108). There are changes in the EEC number in *T. spiralis* infection, with increased numbers of cholecystokinin (CCK) positive (+) EEC that are dependent on the presence of CD4+ T cells (109). CCK plays many roles in intestinal, pancreatic, and liver function including a role in glucose metabolism and satiety (110). Both *T. spiralis* and *N. brasiliensis* induced a transient decrease in food intake in mice that returned to normal levels during the course of the infection (95, 111), implying a role for satiety hormones. *T. muris* infection of the colon also increased the number of EEC (112). Thus, enteric nematodes may affect metabolism through changes in the numbers of tuft cells and EEC thereby increasing the expression of taste receptors or by increasing the release of GI hormones that regulate satiety and/or glucose metabolism.

The Metabolic Consequences of Type 2 Immune Response to a Parasitic Nematode Infection Are Mediated by STAT6-Dependent and Independent Effects

Evolution continually refines the interaction between host and parasites resulting in a sufficient response to clear worms while limiting immunopathology. For soil-based nematodes that spend all or part of their life cycle in the gut, worm expulsion is facilitated largely by IL-13-, STAT6- and M2-dependent changes in gut function (81, 113, 114). The presence of worms and their products induces the release of epithelial-derived cytokines such as TSLP, IL-25 and IL-33, which are associated with the transition of innate to adaptive immunity. In particular, binding of these cytokines to receptors on ILC2, macrophages, and mast cells induces release of IL-13, which plays a key role in the metabolic effects of enteric nematode infection (figure 1).

The metabolic benefits afforded by nematode infection have been attributed to their immunomodulatory effects including a shift from a Th1 to a Th2 response, promotion of the M2 phenotype, downregulation of the Th17 response, and development of ILC2 (115). ILC2 are a source of IL-13 and are the most recent cells proposed to regulate metabolic homeostasis in adipose tissue in both humans and mice (116–118). IL-13 binds to type 2 IL-4R located on non-hematopoietic cells and a few immune cells such as macrophages. This receptor is linked to the transcription factor, STAT6, with activation leading to upregulation of genes that control the phenotype and/or function of both hematopoietic and non-hematopoietic cells. Many of the enteric nematode infection-induced stereotypic STAT6-dependent changes in intestinal enterocyte function in the small intestine (78–81) are

mimicked by exogenous administration of IL-13 as well as by IL-33 or IL-25 mediated release of IL-13 (78, 81).

There are several models of obesity-induced T2D and metabolic syndrome including the HFD-induced obesity, the ob/ob mouse, and the RIP2-OPa1 deficient mouse. Induction of obesity using a HFD is one of the most well-documented models of obesity and after 8–10 weeks on the diet, mice have elevated fasting blood glucose levels consistent with type 2 diabetes, insulin resistance, and hepatic steatosis (119). Infection of HFD-induced obese mice with *N. brasiliensis* resulted in weight loss, improved glucose metabolism, increased circulating insulin levels, and decreased adipose tissue masses (120). Of interest is that the weight loss effects of *N. brasiliensis* in HFD-induced obese mice were only partly dependent on STAT6, but fully dependent on IL-13 (95). In contrast, the ability of *N. brasiliensis* infection to reduce epididymal and brown fat was retained in STAT6$^{-/-}$ mice indicating some of the beneficial effects of nematode infection on metabolism are independent of IL-4 or IL-13 (120). Exogenous administration of IL-4 to mice fed HFD resulted in activation of STAT6 in the liver and attenuated adipose tissue inflammation which in turn lead to improvement of insulin action (121). HFD fed mice have reduced expression of IL-25 in the liver, and exogenous administration of IL-25 mimicked the beneficial effects of *N. brasliensis* infection on weight loss and hepatic steatosis in HFD fed mice (118). This effect was dependent on IL-13 and STAT6, as well as the development of alternatively activated Kupffer cells/macrophages. These data show the importance of IL-4, IL-13 and IL-25 in the ability of enteric nematode infection to improve the obesity-induced metabolic syndrome and T2D.

Specific STAT6 dependent genes regulating glucose metabolism

There is little information on the specific STAT6-dependent genes responsible for the beneficial effects of nematode infection on metabolism. M2 play a key role in these effects and up regulation of arginase-1, CD206, and other M2 markers are STAT6-dependent. In addition, there are several products of cells in the intestine, liver, or adipose tissue that have significant impact on glucose metabolism.

A family of four closely related cysteine-rich proteins, Resistin, and resistin-like molecules (RELM) α, β, and γ, (encoded by the genes *Retnla, Retnlb,* and *Retnlg*, respectively) have been identified in mice that share about 70% sequence homology, contain conserved C-terminal cysteine residues, and bind to unidentified receptors (122, 123). Two orthologs have been identified in humans, Resistin and RELM-β (124). RELM-α and γ have not been identified in humans, but the expression pattern of human Resistin is more similar to mouse RELM-α than mouse Resistin (125) and thus may share similar functions. Three of these genes, RELM-α, -β and -γ, are induced by parasite infections, including *T. muris*, *H. polygyrus bakeri* and *N. brasiliensis,* by a mechanism that is IL-4/IL-13 and STAT-6 dependent (126–129).

RELM-β is constitutively expressed in the colon, primarily in goblet cells, and is induced by colonization with commensal bacteria (130). Expression of RELM-β can be induced further by infection with pathogenic bacteria, parasitic nematodes, or dextran sodium sulfate suggesting that induction of RELM-β expression in the colon is a general response to

mucosal insults. In contrast, RELM-β is not expressed constitutively in the small intestine, but is induced by parasite infections. RELM-β has been shown to bind to chemosensory organs on enteric parasitic nematodes resulting in impaired feeding and worm health. It is critical for expulsion of *H. polygyrus bakeri* (53) but may not be as important for expulsion of other parasites including *T. muris* (131) and *N. brasiliensis* (132).

In addition to regulation by commensal bacteria and infections, RELM-β expression is altered by diet and obesity. The circulating levels of RELM-β are increased in obese *db/db* mice and by feeding mice a high-fat diet (133). Furthermore, other dietary factors can alter RELM-α and -β expression. In the intestine, high-protein and high-carbohydrate diets suppressed gene expression of RELM-β while RELM-α expression was decreased in epididymal fat by a high-carbohydrate diet (134). Retnlb$^{-/-}$ mice are resistant to methionine-choline deficient, diet-induced non-alcoholic steatohepatitis (135). In this study, liver Kupffer cells were found to be a source of RELM-β, and expression in both colon and Kupffer cells was increased by the deficient diet and was necessary for full manifestation of the disease.

RELM-β also affects glucose metabolism. RELM-β inhibits SGLT-1 activity while increasing GLUT-2 dependent glucose transport (136). Mice infected with *N. brasiliensis* have increased Relm-β expression and decreased SGLT-1 activity; however, their GLUT2 expression also was decreased by infection (97). These data indicate the inhibitory effects of nematode infection on glucose absorption cannot be attributed fully to Relm-β. Rajala et al. demonstrated that increases in circulating RELM-β stimulated glucose production in the presence of fixed insulin levels (137). These changes were associated with increased activation of and flux through glucose-6-phosphatase. Injection of mice with RELM-β induced insulin resistance (137) and transgenic mice over-expressing RELM-β in the liver exhibit hyperglycemia, hyperlipidemia, fatty liver, and pancreatic islet enlargement when fed a high fat diet but not when fed a normal diet (138). Insulin resistance and glucose intolerance were associated with reduced protein expression of IRS-1 and IRS-2 as well as reduced insulin-induced activation of phosphatidylinositol 3-kinase and Akt. Additional *in vitro* studies with primary cultured hepatocytes demonstrated that RELM-β activated ERK and p38, and to a lesser extent, JNK.

RELM-α expression can also affect glucose metabolism. RELM-α mRNA was reported to be decreased in fasting or *ob/ob* mouse adipose tissue, and increased by hyperglycemia in rat adipose tissue (123). Interestingly, while fasting affected mRNA levels in adipose tissue, expression in lung tissue was unaffected suggesting that RELM-α may be differentially regulated depending on the cell or organ type. Retnla$^{-/-}$ mice have lower baseline levels of the satiety hormone, leptin, but no alterations in insulin levels were observed and mice exhibited similar weight gains on both normal and high-fat diet (139). Baseline glucose levels were also unaffected by normal or high-fat diet in Retnla$^{-/-}$ mice. In addition, when compared to WT mice, the kinetics of glucose clearance were unchanged in Retnla$^{-/-}$ mice. In another study, however, mice injected i.p with RELM-α for seven days had increased insulin resistance (140).

Recently, a tissue-resident CD301b mononuclear phagocyte population in adipose tissue was identified that secretes RELM-α and is required for positive energy balance under normal and high-fat metabolic conditions. Depletion of CD301b cells in mice caused hypoglycemia, increased insulin sensitivity, and weight loss in both lean and obese mice. Exogenous administration of RELM-α to CD301b-depleted mice fed a regular diet restored body weight and normoglycemia indicating that RELM-α was responsible for the altered glucose metabolism. Considering that both RELM-α and -β can decrease insulin sensitivity and increase glucose levels and improve the metabolic syndrome, the role of the high levels of both RELM-α and -β in enteric parasitic nematode infection merits further investigation.

STAT6 dependent genes regulating fat metabolism

Dyslipidemia and hepatic steatosis are common in obese individuals due to abnormalities in lipid metabolism. Hepatic steatosis is caused by lipid accumulation within hepatocytes, mainly due to excessive lipogenesis. There is evidence that enteric parasitic nematodes also induce a STAT6-dependent effect on genes that modulate fat metabolism. *N. brasiliensis* infection ameliorated the HFD-induced enlargement of the liver that was accompanied by increased levels of hepatic triglycerides (95). *N. brasiliensis* infection also downregulated genes encoding key lipogenic enzymes in the liver and epididymal fat, including *Fasn*, *Acly*, and *Acaca*, in both lean and HFD induced obese mice (99).

Cell death activator (CIDEA) is an important regulator of energy expenditure and lipid metabolism (141). CD36 in liver functions as a fatty acid plasma membrane transporter that takes up fatty acid into hepatocytes (142). Hepatic *Cidea* and *Cd36*gene expression were significantly upregulated in obese mice and *N. brasiliensis* infection normalized hepatic *Cidea* expression to levels in lean mice by a IL-13/STAT6 dependent mechanism (95). Exogenous administration of IL-25 also ameliorated HFD-induced hepatic steatosis, and decreased expression of the CIDEs in the livers of HFD-fed mice (118). In contrast, gene expression levels of major hepatic enzymes critical for lipolysis or FA oxidation, including hepatic lipase, carnitine palmitoyltransferase 1a, and hydroxyacyl-coenzyme A dehydrogenase, were not significantly altered by the HFD or infection (99). Thus, enteric nematodes improve hepatic steatosis through STAT6-dependent transcription of specific genes involved in the regulation of energy and lipid metabolism.

CONCLUSIONS

Throughout evolution, parasites have co-existed with humans resulting in an intricate interaction between the host and the parasite. For much of the twentieth century, parasite infections were only viewed as deleterious to the host, but as our understanding of the relationship between host and parasite has improved, it is evident our co-evolution has provided us with unappreciated benefits. It is clear that diet can impact resistance to parasitic infections and dietary interventions may be prudent in regions with endemic parasitic infections. Furthermore, ensuring adequate nutrition may improve any therapeutic interventions based on parasite products. It is also clear that parasite infections have significant effects on host metabolism and especially on energy metabolism, opening the door to new and novel approaches to treating obesity and T2D. In mice fed a HFD, *N.*

brasiliensis infection attenuated body weight gain, improved glucose metabolism, decreased adiposity and hepatic steatosis, and increased M2 macrophages in adipose tissue (95). Further work is needed to determine if the benefits induce acute changes that persist only for as long as the parasite is present or chronic changes indicative of a new homeostasis.

There are inherent difficulties in obtaining regulatory approval for use of live parasites to treat otherwise healthy individuals and this has prompted exploration of alternative approaches. Experimental evidence demonstrated that the Th1 dominant C57Bl/6 mouse strain gains weight more rapidly on a HFD and has higher fasting glucose levels on both NCD and HFD than the Th2 dominant BALB/c mouse (143). Overexpression of IL-13 in fat tissue of C57Bl/6 mice blocked HFD-induced weight gain, improved glucose tolerance and insulin sensitivity and reduced inflammation in adipose tissue (144). Administration of IL-25 has beneficial effects on obesity-induced T2D and associated hepatic steatosis (117, 118). The effects of IL-25 are mediated by its ability to increase the numbers of ILC2, M2 macrophages and eosinophils in adipose tissue (116–118). Studies harnessing the therapeutic potential of parasite products or administration of cytokines that promote restoration of anti-inflammatory Th2 environment in metabolic tissues may prove more amenable to approval.

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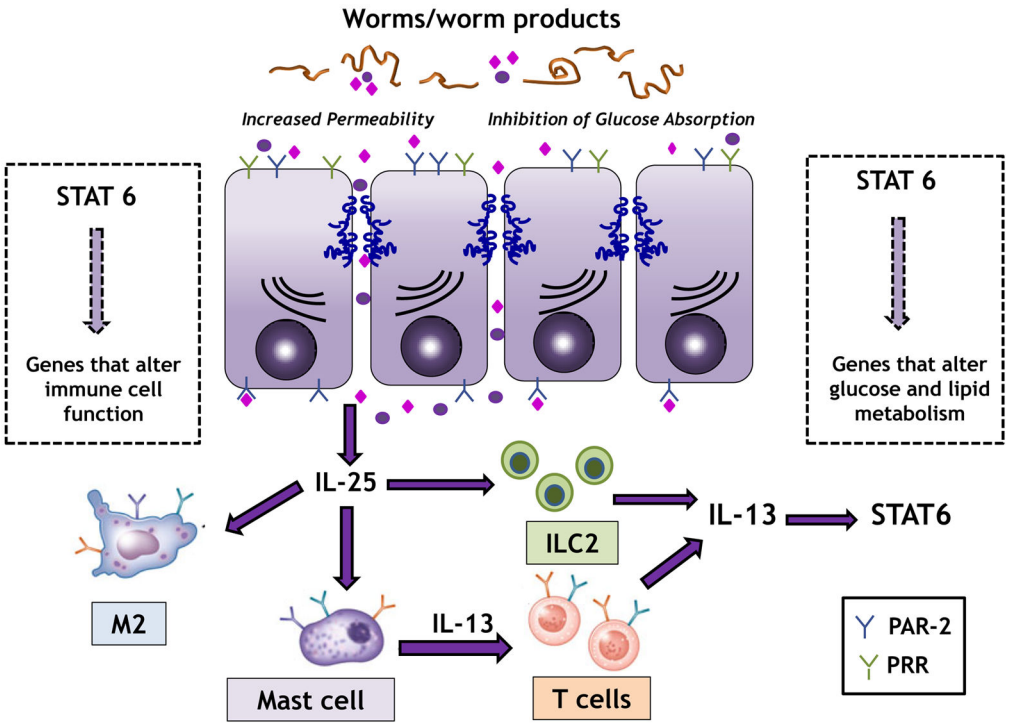

Figure 1.

Worms and worm products induce an increase in epithelial permeability, in part by activation of PAR-2, facilitating passage of these products across the mucosal barrier. Epithelial release of IL-25/IL-33 binds to mast cells and ILC2 leading to release of IL-13. IL-13 binds to the type 2 IL-4R and activates STAT6 on hematopoietic and non-hematopoietic cells. STAT6 u–pregulates genes for markers of alternatively activated macrophages (M2) and M2 play a key role in the STAT6-dependent inhibition of absorption of glucose in enterocytes. IL-13 also activates STAT6 on epithelial cells with upregulation of genes that maintain increased epithelial permeability. In addition, STAT6 activates genes in other cell types leading to alterations in glucose and lipid metabolism.