Review

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A worm of one's own: how helminths modulate host adipose tissue function and metabolism

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Parasitic helminths have coexisted with human beings throughout time. Success in eradicating helminths has limited helminth-induced morbidity and mortality but is also correlated with increasing rates of 'western' diseases, including metabolic syndrome and type 2 diabetes. Recent studies in mice describe how type 2 immune cells, traditionally associated with helminth infection, maintain adipose tissue homeostasis and promote adipose tissue beiging, protecting against obesity and metabolic dysfunction. Here, we review these studies and discuss how helminths and helminth-derived molecules may modulate these physiologic pathways to improve metabolic functions in specific tissues, such as adipose and liver, as well as at the whole-organism level.

Interplay between helminth infection, host metabolism, and immune response

We are ubiquitously colonized by parasites and have coevolved with them over the course of human history. Only in the past half century have human beings in high-income countries succeeded in limiting the rates of parasite infection and other infectious diseases. Concomitant to this decrease in parasitism, the prevalence of the so-called western diseases, such as allergic and autoimmune diseases, cancer, cardiovascular disease, and metabolic syndrome, have spectacularly risen [1]. Humans must contain or eradicate invading pathogens, activating distinct immune responses to appropriately match the pathogen. Infection with virus or intracellular bacteria promote T helper 1 (Th1) immune responses, characterized by elevated interferon (IFN)-γ, whereas parasitic helminth infection drives Th2 allergic immune responses, characterized by the type 2 cytokines interleukin (IL)-4, IL-5, and IL-13. Adaptations of host metabolism may be central to the success of each of these distinct immune responses. Indeed, acute bacterial infections and bacterial sepsis are associated with insulin resistance, promoting abundant serum glucose that is believed to support protective effector immune responses [2,3]. Parasites span a gamut of infectious routes, host responses, and pathology, and therefore likely elicit diverse host metabolic responses. In this review, we focus on the metabolic impact of helminths, which are endemic in low-to-middle income countries, infecting one-third of the world population [4]. Helminths are multicellular eukaryotic worms that remain for months to years in their hosts, eliciting type 2 immune responses that often include significant regulatory elements that limit an excessive immune response [5]. Helminths include three major groups: cestodes (tapeworms), nematodes (roundworms), and trematodes (flukes). Soil-transmitted intestinal nematodes are the most ubiquitous and are comprised of hookworms (*Anyclostoma duodenale* and *Necator americanus*), roundworms (*Ascaris lumbricoides*), whipworms (*Trichuris trichiura*), and threadworms (*Stronglyoides stercoralis*). The outcomes of gastrointestinal helminth infection range from asymptomatic persistence to significant host morbidity, including nutritional and vitamin deficiencies, anemia, growth retardation, and increased risk of other infectious diseases [4,6–8]. In general, these effects have been ascribed to the ability of helminths to directly use host dietary nutrient-derived

Glossary

AAM: alternatively activated macrophage, involved in tissue repair.
BAT: brown adipose tissue, expresses UCP1, generates heat in response to cold.
CD4 Th2: type 2 helper cell, adaptive lymphocyte that responds to specific antigens.
Eosinophil: short-lived granulocyte, potently elicited by helminths.
Hepatic steatosis: excess accumulation of lipids in hepatocytes that can lead to hepatic inflammation and cirrhosis.
ILC2: group 2 innate lymphoid cell, responds to cytokines and damage signals.
IL-33: interleukin-33, a cytokine released with cellular damage that promotes type 2 immune cells and WAT beiging.
Insulin resistance: impaired insulin action on its target metabolic organs/cells.
Lipogenesis: generation of fatty acids and storage trigylcerides (fat), occurring primarily in adipose tissue and liver.
SEA: mixture of soluble molecules extracted from *S. mansoni* eggs.
Type 2 diabetes: metabolic disease characterized by reduced insulin sensitivity and chronic elevated blood glucose.
Treg cell: regulatory T cell, restricts autoimmune and excessive immune responses.
WAT: white adipose tissue, high-energy triglyceride storage site.

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energy and vitamins and promote intestinal mobility. *Schistosoma* flukes (*Schistosoma mansoni*, *Schistosoma japonicum*, and *Schistosoma haematobium*) are also ubiquitous worldwide, residing in the mesenteric and urogenital circulation, and can cause human pathology via egg granuloma generation in the lungs, liver, bladder, and central nervous system [9,10]. Although antihelminthic drugs have provided a great service in treating symptomatic patients, they may have also succeeded in eradicating the bulk of low-level commensal-like helminths, with unclear consequences for global human metabolic health [11,12].

Epidemiologic data are emerging to support the idea of an inverse relationship between helminth colonization, insulin resistance, and type 2 diabetes [13]. However, how helminths modulate host metabolism remains largely unknown [14]. Supported by recent landmark studies in rodents, we propose that the 'silent majority' of helminth infections have significant and prolonged metabolic consequences in the host, notably on white adipose tissue (WAT, see Glossary), but also possibly in the liver and intestine, via their ability to promote regulated type 2 immune responses. By exploring the latest advances in the understanding of type 2 immune cells in the control of adipose tissue homeostasis and whole-body insulin sensitivity, we will provide mechanistic insights on how helminths may affect host metabolism.

Adipose tissue inflammation in metabolic dysfunction

Metabolic syndrome is a cluster of conditions that include high blood pressure (hypertension), abnormal cholesterol levels (dyslipidemia), insulin resistance, and abdominal obesity [15]. In particular, abdominal obesity is highly correlated with insulin resistance and the progression to type 2 diabetes. Over years to decades, type 2 diabetes causes chronically elevated blood glucose (hyperglycemia), resulting in stereotypical damage to the eyes, kidneys, nerves, and peripheral vascular system, and significantly increases the risks of cardiovascular disease and stroke. The World Health Organization currently estimates type 2 diabetes affects 9% of adults worldwide and is a leading cause of morbidity and mortality [16], requiring novel therapeutic approaches.

An emerging paradigm suggests that chronic low-grade inflammation associated with obesity is one of the major contributors to insulin resistance and impaired glucose and lipid metabolism, leading to increased risk for developing type 2 diabetes [17]. Early studies found that inflammatory cytokines such as tumor necrosis factor (TNF)-α [18,19] and IL-6 [20] promoted WAT inflammation and impaired both tissue-specific and whole-body insulin sensitivity. Alterations in WAT macrophage polarization were subsequently reported, with an obesity-induced shift in the balance of anti-inflammatory/reparative alternatively activated macrophages (AAMs), or M2 macrophages, and proinflammatory M1 macrophages [21–23]. Other inflammatory immune cells, including natural killer (NK) cells, CD8 T cells, Th1 CD4 T cells, mast cells, and neutrophils are also implicated in the obesity-induced WAT inflammation and metabolic dysfunction [24–31]. Ultimately, inflammatory cells and cytokines impair liver, adipose, and skeletal muscle tissue insulin signaling, resulting in systemic insulin resistance and further progression to diabetes. This model of obesity-driven WAT inflammation suggests two possible therapeutic approaches that may protect against metabolic disorders: (i) promoting loss of WAT mass; or (ii) limiting WAT inflammation.

The metabolic benefit of helminths infection

Landmark studies using the rodent intestinal nematode *Nippostrongylus brasiliensis* have shown that transient helminth infection promotes long-lasting improvements in insulin sensitivity and decreased adipose tissue mass in high-fat-diet-induced obese mice [32,33]. These effects correlate with prolonged increases in WAT type 2 immune cells [34]. Furthermore, chronic infection with *S. mansoni* and treatment with a mixture of helminth-derived molecules (*S. mansoni* soluble egg antigens; SEAs) promote type 2 immune cells in gonadal and mesenteric WAT of obese mice and improves insulin sensitivity and glucose homeostasis [35]. These studies suggest that helminth infection or helminth-derived products promote WAT type 2 immune responses that may act to limit adipose tissue mass and inflammation and promote metabolic benefit. To understand how helminths promote these changes and their metabolic impacts, we first review the composition and function of type 2 immune cells in normal, uninfected WAT.

The first clue to the presence of type 2 immune cells in healthy adipose tissue was the discovery of adipose tissue AAMs or M2 macrophages [22,23]. These macrophages are traditionally supported via the type 2 cytokines IL-4 and IL-13, and are associated with helminth infections, tissue remodeling, and tissue homeostasis [36]. Subsequently, eosinophils were identified as the primary IL-4-expressing cell in WAT, necessary for optimal AAM maintenance and protection against the development of tissue-specific and whole-body insulin resistance [32]. Eosinophils are short-lived granulocytes that are normal residents in certain tissues, such as the intestine, blood, and adipose; increased eosinophils are a hallmark of chronic helminth infection [37]. In the search for cells that regulate eosinophils, WAT group 2 innate lymphoid cells (ILC2s) were found to be the predominant sources of IL-13 and IL-5, necessary for the maintenance of both eosinophils and AAMs [34,38,39]. ILC2s belong to the recently described family of ILCs [40], and are systemically distributed in mice and humans during development [41]. Although similar to CD4 helper T cells, ILC2s lack the ability to respond to specific antigens, instead responding to cytokines, circadian cues, and damage signals to coordinate type 2 immune responses [41,42]. A unique population of adipose tissue regulatory T (Treg) cells was also identified, which express high levels of ILC2-associated markers, including the transcription factor GATA Binding Protein 3 (GATA3) and the regulated subunit of the IL-33 receptor (T1/ST2, IL1RL1), and are also required for metabolic homeostasis [28,43–45]. Treg cells are the primary leukocytes responsible for limiting excess immune responses and may also contribute to tissue homeostasis and repair [46]. Resting WAT supports an intriguing combination of regulatory and type 2 immune cells, including ILC2s, Treg cells, eosinophils, and AAMs,