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

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Abstract

Parasitic helminths have co-existed 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.

Keywords

helminth; metabolism; adipose tissue; type 2 immunity; diabetes

The interplay between helminth infection, host metabolism and immune response

We are ubiquitously colonized by parasites and have co-evolved 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

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pathogen. Infection with virus or intracellular bacteria promote Th1 immune responses, characterized by elevated interferon-γ IFN-γ, whereas parasitic helminth infection drives Th2 allergic immune responses, characterized by the type 2 cytokines 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*, *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 energy and vitamins and promote intestinal mobility. *Schistosoma* flukes (*S. mansoni, S. japonicum, S. 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 anti-helminthic 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 α (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 (AAM), or M2 macrophages, and pro-inflammatory M1 macrophages [21–23]. Other inflammatory immune cells, including NK cells, CD8 T cells, type 1 helper (Th1) CD4 T cells, mast cells, and neutrophils were 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 (SEA; *S. mansoni* soluble egg antigens) 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 AAM 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 (ILC2) were found to be the predominant sources of IL-13 and IL-5, necessary for the maintenance of both eosinophils and AAM [34,38,39]. ILC2 belong to the recently described family of innate lymphoid cells [40], and are systemically distributed in mice and humans during development [41]. Although similar to CD4 helper T cells, ILC2 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 cells (Treg) was also identified, which express high levels of ILC2 associated markers (GATA3, T1/ST2) and are also required for metabolic homeostasis [28,43–45]. Treg are the primary leukocyte 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 ILC2, Treg, eosinophils, and AAM, which strongly resemble helminth-induced immune responses in the lung and intestine [5,47]. As sterile immunity to helminths is rarely achieved, the ultimate purpose of regulated type 2 immune responses may be to limit tissue damage and promote tissue repair [48,49], functions that are likely conserved in resting WAT (Figure 1). It is fascinating that helminths, most of which reside far from visceral adipose tissue, are able to further amplify this WAT type 2 immune ‘module’, including ILC2, type 2 helper T cells (Th2), AAM, and eosinophils [34,35].

The influence of helminths on other metabolic tissues, such as the intestine, liver, skeletal muscle, or hypothalamic eating centers, remains largely unknown. An increase in eosinophils and Th2 cytokine expression were also observed in the liver of obese mice treated with SEA [35], suggesting that WAT is not an exclusive metabolic target of *S. mansoni* and their derived molecules. Interestingly, IL-4 and IL-13 were reported to contribute to glucose homeostasis by directly regulating hepatic insulin sensitivity and glucose production, respectively [50,51]. The exact contribution of the liver to the whole-body healthy metabolic phenotype induced by helminth infection and/or treatment with helminth-derived molecules remains to be clarified. Of note, both *S. mansoni* infection and SEA administration were also reported to reduce circulating total cholesterol and protect against atherosclerosis in mice [52,53]. ILC2 and eosinophils are also abundant in the intestine at rest, although their metabolic roles in this tissue are poorly understood. Helminth infection promotes robust increases in intestinal ILC2, eosinophils, and mucous producing goblet cells [54], while altering intestinal motility and absorption of nutrients [33]. A recent study found that high-fat diet induces low-grade intestinal inflammation which contribute to WAT inflammation and insulin resistance [55]; by extension, helminth infection could also promote intestinal type 2 immune responses which counteract these inflammatory responses. The intestinal microbiota, which is crucial for maintaining immune and metabolic homeostasis in the host, is also altered by helminth infection [56,57]. This helminth-microbiome interaction remains to be explored in depth, but could be involved in the beneficial effect of helminths on whole-body insulin sensitivity and glucose homeostasis.

Regulation of type 2 immunity in adipose tissue: a role for helminths?

ILC2 appear to be key organizers of the resting WAT type 2 immune module, maintaining eosinophils, AAM, and Treg via production of type 2 cytokines and other signals [34]. After

helminth infection, Th2 helper T cells also increase in WAT [34,35], likely cooperating with ILC2 to orchestrate WAT metabolic alterations. One regulator of this WAT immune unit is the alarmin IL-33, a nuclear bound cytokine that is released with cell stress and death [58]. IL-33 potently activates cells that express the IL-33 receptor T1/ST2, including ILC2, Th2, and subsets of Treg [44,45]. Both ILC2 and Th2 subsets respond directly to IL-33 and produce IL-5 [59]. Mice deficient in IL-33 signaling are more susceptible to diet-induced-obesity and insulin resistance, whereas treating wild-type mice with IL-33 promotes accumulation of adipose tissue ILC2, Treg, AAM, and eosinophils and improves diet-induced metabolic dysfunctions [34,44,60–62]. Both adipocytes and endothelial cells are reported to produce IL-33 in adipose tissue [63,64], although the physiologically relevant source(s) and signals that promote IL-33 production and release are unknown. Whether helminths promote signals in WAT that amplify type 2 immunity, such as IL-33, or instead increase the trafficking or function of type 2 immune cells requires additional studies. Other signals regulate ILC2 and Th2 during helminth infection in the lung or intestine, including thymic stromal lymphopoietin (TSLP), IL-2, IL-9, and IL-25 [49], but their function in WAT of resting animals or after helminth infection is unknown.

In contrast to helminth infection, obesity is associated with a decline in WAT ILC2, Treg, eosinophils, and AAM, particularly in the deep visceral adipose depots; declines in WAT ILC2 and Treg have been confirmed in humans [28,34,62]. Although obesity driven pro-inflammatory cells and cytokines can directly promote insulin resistance, it is also possible that loss of WAT type 2 immune responses contributes to metabolic dysfunction. Adipose IL-33 levels are normal or increased with obesity [44,63], suggesting other signal(s) associated with inflamed obese adipose tissue may actively repress type 2 immune cells. One candidate is IFN-γ, a canonical type 1 inflammatory cytokine produced by inflammatory CD8 T cells, Th1 CD4 T cells, and natural killer (NK) cells, which increases in obese adipose tissue and promotes insulin resistance [65–67]. However, numerous pro-inflammatory immune cells and cytokines have been shown to increase in obese WAT, and further work is required to determine the precise mechanisms and metabolic consequences of a decline in WAT type 2 immune cells. Similar to obesity, it is possible that viral or bacterial infection, normally associated with heightened systemic type 1 immune responses, also tips the balance of WAT immune cells, potentially contributing to the insulin resistance that accompanies such infections. Normal aging is also associated with chronic low-grade inflammation, metabolic derangement, and accumulation of tissue inflammatory T cells [68,69]. Whether aging alters the WAT Th1/Th2 balance is unknown, although recent data highlights the loss of adipose tissue Treg in old mice [70]. Together, the stimuli that may promote adipose tissue Th1- and Th2-associated immune cells are summarized in Figure 1.

A variety of molecules secreted by helminths or their eggs are involved in the type 2 immune responses induced by chronic helminth infection [5]. For example, *S. mansoni*-derived egg antigens (SEA) are enriched in secretory glycoproteins, such as IPSE/α1 and omega-1, that condition dendritic cells for Th2 skewing [71–73]. On the other hand, the whipworm *Heligmosomoides polygyrus* secretes a wide range of products, including a transforming growth factor β TGF-β)-like ligand, that can induce *de novo* Treg induction and dampen excessive type 2 immune responses [47]. Interestingly, both SEA and the synthetic

glycoconjugate lacto-N-fucopentaose (LNFPIII) were recently shown to alleviate hepatic steatosis and insulin resistance in obese mice via both immune-dependent and - independent mechanisms [74]. On one hand, SEA increased the expression of AAM markers in WAT and improved whole-body insulin sensitivity in a IL-10-dependent manner [74]. On the other hand, SEA also reduced hepatic steatosis, at least in part by lowering lipogenesis through a direct effect on hepatocytes [74]. This suggests that helminth-derived molecules could also manipulate metabolic processes by targeting relevant metabolic cells, likely via glycan-mediated interaction with specific receptors [75]. Whether known helminth-derived single molecules, such as IPSE/α1 or omega-1 can directly affect tissue-specific metabolic processes is unknown. Identifying the specific molecules, receptors and underlying mechanisms by which helminths orchestrate their effects on whole-body metabolic homeostasis remain important future objectives.

The evolutionary advantage of helminth-mediated modulation of host metabolism

Helminths are ancient, co-adapted partners with their vertebrate hosts. With this model in mind, we speculate that any metabolic adaptations elicited during helminth infection may represent a mutually beneficial state. Unlike inflammatory type 1 (Th1) skewed immune responses, cells associated with regulated type 2 immunity, such as AAM and Treg, are predominantly dependent on fatty acids rather than glucose metabolism for their energy supply [89]. As such, regulated type 2 immune responses may be promoted by a metabolic response that maintains low blood glucose and intracellular glycolytic flux while possibly promoting fatty acids for energy sources. On the other hand, helminths also utilize fatty acids for energy, particularly for their abundant production of thousands of eggs per day [90], and could benefit from a host with regulated type 2 immune responses that sacrifices worm clearance in favor of limiting tissue damage mediated by inflammatory cells.

Adipose tissue comes in two fundamental flavors: white and brown. White adipose tissue (WAT) constitutes the primary storage site for high-energy reserves in form of triglycerides, whereas brown adipose tissue (BAT) produces heat through UCP1-mediated uncoupling of mitochondrial oxidative phosphorylation, notably in response to cold and dietary intake [76,77]. For a long time, BAT was considered to be solely important in small mammals and young children, serving a primary function of central heat generation [78], but the recent observations of functional BAT in adult humans sheds a new light on this highly active metabolic tissue [76,77]. Indeed, owing to its capacity to dissipate energy and regulate both VLDL-triglyceride [79] and glucose metabolism [80], BAT could be seen as a potential target for the treatment of obesity and metabolic disorders. More recently, it has been shown that WAT can acquire brown-like function, notably in response to cold exposure [81,82]. This WAT conversion occurs predominantly in subcutaneous adipose depots and is termed ‘beige’ or ‘brite’ adipose tissue [82]. Similar to BAT, high expression of UCP1 in beige adipocytes allows energy to be dissipated as heat, sustaining BAT function during cold exposure [81,82]. By contrast, beige fat is poorly innervated by neurons [83,84], suggesting the possibility of alternate means of induction and maintenance. Given the ability of beige

adipose tissue to literally ‘burn’ fat, there is considerable interest in understanding signals that both promote increased beige fat and activate beige fat thermogenesis.

Surprisingly, cells and cytokines associated with helminth-infection also appear to be important regulators of beige fat [85]. AAM were initially implicated in promoting BAT thermal adaptation to cold, requiring IL-4 signaling to produce catecholamines, mobilize fatty acids, and increase energy expenditure [86]. In subsequent work, eosinophils, IL-4/IL-13, and AAM were all found to be required for cold-induced WAT beiging and energy expenditure [87,88]. The muscle hormone (myokine) meteorin-like (Metrnl), which is increased in response to exercise and cold exposure, induces WAT eosinophil activation, AAM induction, and beiging, conferring protection against obesity-induced metabolic disorders [88]. Most recently, two studies have demonstrated that the cytokine IL-33 can also directly promote ILC2 activation and bypass eosinophils and AAM to induce WAT beiging [61,62]. The precise mechanisms by which ILC2 mediate this phenotype differ, with one group proposing ILC2 derived IL-13 promotes adipose precursors to adopt a beige fate [61], whereas the other group suggested ILC2 production of the endogenous opiate methionine-enkephalin mediated the phenotype [62]. Although IL-33 administration drives ILC2 to promote beiging, the roles of IL-33 and ILC2 in beiging during normal physiology, cold adaptation, or helminth infection are unclear. Together, these data suggest that signals such as IL-33 and Metrnl regulate WAT ILC2, eosinophils, and AAM to promote adipose beiging through various mechanisms and may confer protection against obesity-induced type 2 diabetes (Figure 2). As helminths can promote WAT type 2 immune cells and a loss of adiposity, they may be able to induce significant adipose beiging. Helminths and hosts could potentially benefit from increased WAT beiging by promoting host survival in cold climates. Further experimental data carefully documenting the metabolic consequences of helminth infection, particularly in humans, are required to clarify these important points (Box 1).

Concluding remarks

Both helminth infection and helminth-derived productsmay be beneficial for maintaining host metabolic homeostasis, in particular by enhancing type 2 immune responses in WAT, thereby limiting excess type 1 inflammation and possibly promoting increased beige adipocytes. Improved understanding of both immune-dependent and -independent mechanisms by which helminths modulate tissue-specific and whole-body insulin sensitivity, and glucose and lipid homeostasis may offer new insights toward the development of novel therapeutics for the treatment of metabolic disorders and type 2 diabetes.

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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	Regulatory T cell, restricts autoimmune and excessive immune responses
WAT	white adipose tissue, high-energy triglyceride storage site

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Box 1

Outstanding questions

- What are the relevant WAT type 2 immune cells and mechanism(s) that improve whole-body metabolic homeostasis in obese mice?
- Is the helminth-induced type 2 immune response observed in rodent WAT also present in humans?
- What are the exact immune-dependent and -independent mechanism(s) by which helminths and their specific molecules improve whole-body metabolic homeostasis in obese mice?
- What is the contribution of metabolic organs other than WAT to the beneficial effect of helminth infection or helminth-derived molecules on whole-body insulin sensitivity and glucose homeostasis?
- Does helminth nutrient metabolism significantly contribute to parasitism of the host dietary energy intake?
- Does helminthic therapy and/or treatment with helminth-derived molecules hold promise for treatment of metabolic disorders in humans?

Highlights

- Type 2 immune cells are present in healthy adipose tissue and decline with obesity.
- Type 2 immune cells can promote white adipose tissue beiging. Helminths promote adipose tissue type 2 immunity and improve metabolic homeostasis.

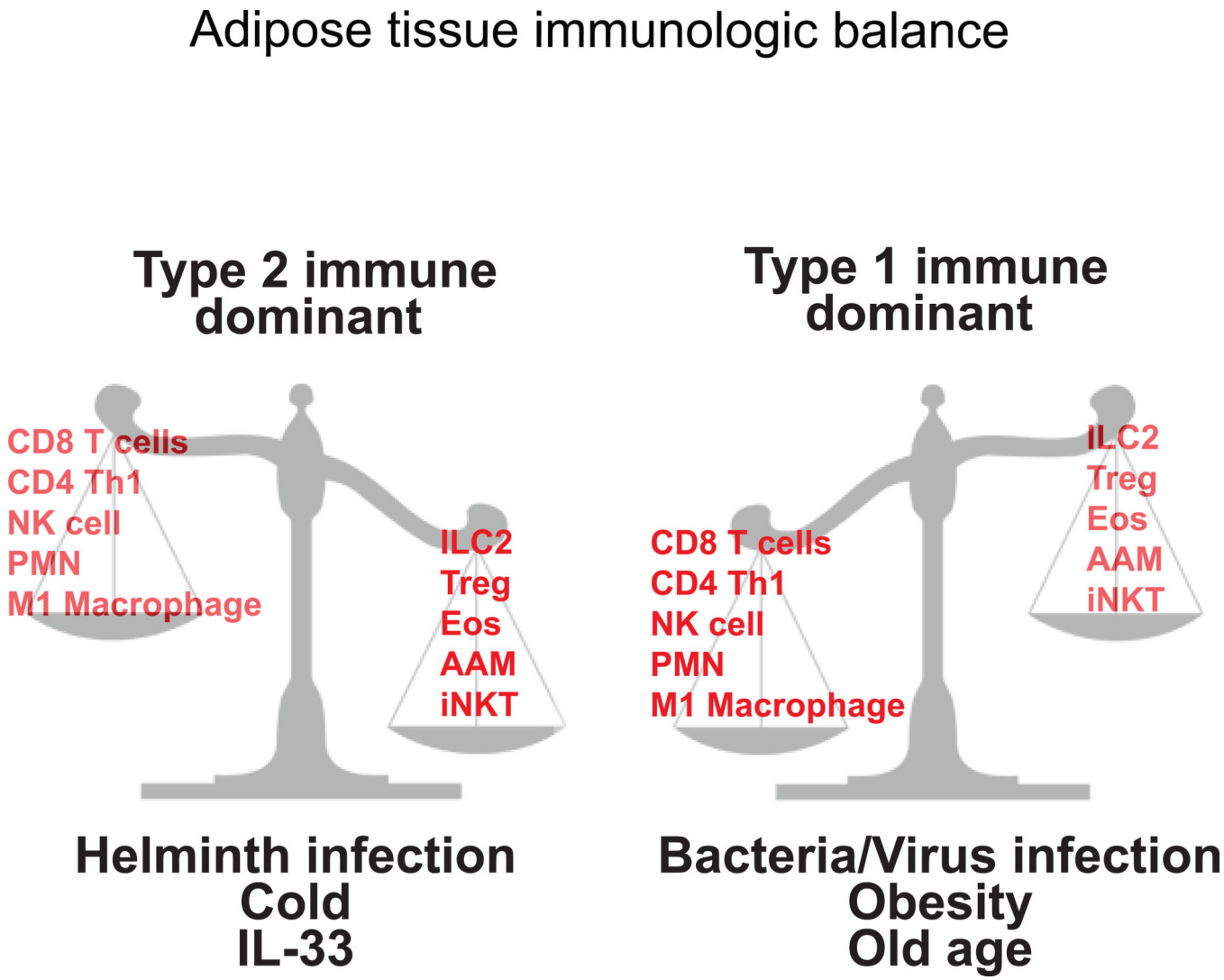

Figure 1. Adipose tissue immunologic balance

In lean adipose tissue (left), immunologic elements associated with a type 2 immune response dominate. These include group 2 innate lymphoid cells (ILC2), regulatory T cells (Treg), eosinophils (Eos), and alternatively activated macrophages (AAM). IL-33, helminth infection, and possibly exposure to cold can each promote these adipose tissue type 2 associated immune cells. In mice and humans, obesity is associated with decreases in each of the type 2 immune cells while promoting type 1 immune cells associated with classical inflammatory responses (right), including neutrophils (PMN), CD8 T cells, CD4 type 1 helper (Th1) T cells, and pro-inflammatory M1 macrophages. We speculate that type 1-associated bacterial and viral infections, which promote systemic insulin resistance, may also promote this pathway in white adipose tissue. Similarly, natural age-related alterations in the immune system, including accumulation of virus-reactive CD8 T cells, may also contribute to this pathway.

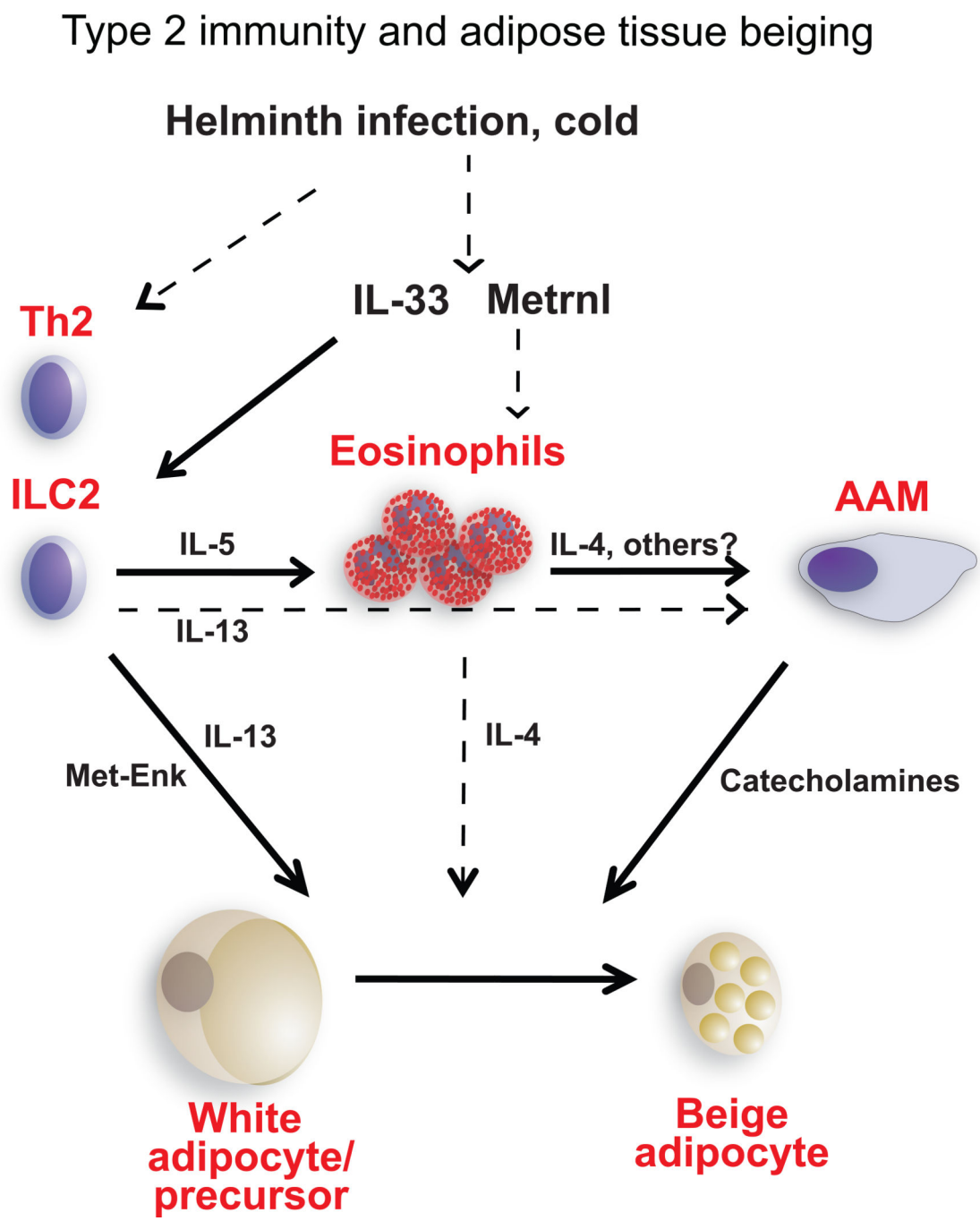

Figure 2. Type 2 immunity and white adipose tissue beiging

A proposed model of how type 2 immune cells impact white adipose tissue (WAT) beiging. In this model, helminth infections promote the accumulation and/or function of group 2 innate lymphoid cells (ILC2) and type 2 helper (Th2) T cells in WAT, possibly via alterations in IL-33 or meteorin-like (Metrnl). ILC2 (and possibly Th2) promote eosinophil accumulation via IL-5 production and alternatively activated macrophages (AAM) accumulation via both eosinophil-mediated IL-4 and possibly via direct effects of ILC2-derived IL-13. AAM can produce catecholamines to activate beige adipocytes to generate

heat, whereas ILC2 and possible eosinophil-derived IL-4/IL-13 can activate adipocyte precursors to adopt a beige fate. Further, ILC2 derived compounds, such as enkephalins (Met-Enk), may further promote these effects. We emphasize how these pathways overlap with adipose tissue adaptation to cold. Dashed arrows represent more speculative interactions, solid arrows published interactions.