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Type 2 responses at the interface between immunity and fat metabolism

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Abstract

Adipose tissue resident leukocytes are often cast solely as the effectors of obesity and its attendant pathologies; however, recent observations have demonstrated that these cells support and effect 'healthy' physiologic function as well as pathologic dysfunction. Importantly, these two disparate outcomes are underpinned by similarly disparate immune programs; type 2 responses instruct and promote metabolic normalcy, while type 1 responses drive tissue dysfunction. In this Review, we summarize the literature regarding type 2 immunity's role in adipose tissue physiology and allude to its potential therapeutic implications.

Introduction

From the time of Leeuwenhoek and Hooke, scientists have noted mammalian tissues' exacting adherence to a defined and reproducible architecture and, over the subsequent three centuries, have layered onto that architecture the twinned significances of function and, later, dysfunction. Despite this intensive study, the ubiquitous and curiously reproducible presence of leukocytes across all tissues was at first overlooked and, more recently, explained away by invoking immune surveillance and host defense. While these explanations are of undoubted validity and importance, they alone fail to explain the suspicious precision with which leukocytes seeded tissues, why this lading was so robustly maintained even in the face of physiologic or experimental perturbation, and why their representation in a given tissue so often seemed disproportionate to potential infectious threat.

Aside from minor evolutions in our understanding of immunity, these questions laid dormant, unanswered, and indeed largely unasked until the relatively recent suggestion that,

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in many tissues, resident leukocytes actively support, regulate, or even directly effect tissue functionality independent of their host defense role [1,2]. With this framework proposed, examples of such functionalities rapidly accumulated. For example, bone marrow resident macrophages regulate and participate in the production of red blood cells, while splenic macrophages mediate their clearance [3]. Similarly, microglia, the resident macrophages of the central nervous system, play important roles in synapse pruning and neural transmission [4]. Indeed, the number of tissues with described ‘functional’ resident leukocyte populations has grown so that it now defines the rule rather than the exception, strongly suggesting that the basic governing principles of mammalian tissue architecture comprise delegation of at least some aspects of tissue function to resident leukocytes [1,2].

While the specific roles shouldered by resident leukocytes and how those roles are executed vary from tissue to tissue, an intriguing pattern has emerged in the literature: most homeostatic functions undertaken by these cells either directly or indirectly involve type 2 immune programs [5–8]. Conversely, a shift in the timbre of the immune bias from type 2 to type 1 is almost invariably followed by some degree of homeostatic dysregulation and dysfunction [9–13]. Indeed, the immune program and tissue homeostasis are so intimately linked that experimental or therapeutic perturbation of one may be (and oft has been) used to control the other. In this Review, we will discuss how this paradigm operates in adipose tissue, its most well studied context. Specifically, we will review the functional roles of resident leukocytes and type 2 responses in white, brown, and beige adipose tissue homeostasis and adaptation and briefly discuss the pathologic consequences of their dysfunction.

White adipose tissue

Adipose tissue may be divided developmentally and functionally into two broad categories: brown adipose tissue (BAT) is a highly catabolic tissue dedicated to thermogenesis, while white adipose tissue (WAT) is an anabolic tissue that serves as mammals’ primary long-term nutrient storage depot [14]. WAT may be further subdivided into visceral and subcutaneous depots, each of which subsume distinct but overlapping physiologic functions [15]. In all WAT, however, nutrient storage remains the primary and most well studied physiologic function. During times of nutrient abundance, such as occur immediately after a meal, WAT scavenges lipids from the blood and stores them as triglycerides in the single dominant lipid globule that gives white adipocytes their characteristic ‘signet-ring’ appearance. Without continued food intake, blood lipid concentrations wane, and nutrient flux into adipocytes slows and, eventually, reverses, as adipocytes begin to liberate stored nutrients as free fatty acids, which are delivered into circulation to provide an alternative fuel source [14]. While its regulation is complex and, to a degree, redundant, acute nutrient flux at both its sinks and sources is predominantly orchestrated by two antagonist pancreas-derived peptides—insulin, which drives the anabolic processes, and glucagon, which promotes the catabolic [16,17].

While the insulin-glucagon axis dominates WAT’s storage function, many other regulatory axes also impinge, including the sympathetic nervous system, sex hormones, and gut-, liver-, and muscle-derived endocrine peptides [18]. More recently, immune mediators, leukocytes, and other physiologic modules traditionally considered exclusive to host defense have

emerged as another major axis of metabolic regulation [11,12,17]]. Initially, immunity's involvement in metabolism was understood only in the context of type 1 responses and their ability to induce/exacerbate metabolic dysfunction such as obesity and type 2 diabetes, and indeed, the bulk of the literature continues to accrue to this paradigm. More recent observations, however, have expanded our understanding of the immune regulatory axis beyond pathologic dysfunction to comprise crucial roles in physiologic homeostasis and adaptation. In this expanded paradigm, type 2 immune programs are responsible for maintaining and tuning tissue function, while type 1 responses represent their disruption, with all attendant pathologic sequelae [10,13,17]. In the following sections, we will discuss these type 2 programs, their cellular and molecular determinants, their functional roles, and allude briefly to the pathologic consequences of their disruption. (For more thorough reviews of type 1 immunity's role in metabolic disease, please see Odegaard et al. and Bresthoff et al.)

Macrophages

Much of the literature surrounding the role of resident leukocytes in WAT physiology centers on the macrophage and for obvious reasons: macrophages are the most populous leukocytes in all adipose tissue depots, are exceedingly sensitive to a wide range of environmental stimuli, and are notoriously effusive in their inflammatory responses there to—indeed, the macrophage is assuredly the favorite *bête noire* of the literature focused on type 1 responses and their metabolic consequences [19,20]. This characterization is only a half-truth, however; these cells are present and functional in WAT under all physiologic conditions and are more properly cast as highly plastic integrators and effectors across these states [17]. In the absence of metabolic dysfunction, for example, they support adipocytes' nutrient storage function by promoting insulin sensitivity directly, through the secretion of IL-10 [21], and indirectly by restraining type 1 responses in other leukocyte populations, sequestering and processing excess iron, safely disposing of dead cells and debris, promoting vascularization and tissue matrix remodeling, *et cetera* [22,23]. Moreover, macrophages also promote and regulate other adipocyte functionalities such as nutrient release (*id est* lipolysis, see brown and beige adipose tissue sections below) and adipokine-mediated endocrine signaling [24,25]. Importantly, all of these functionalities are associated with variations of the type 2, immunoregulatory phenotype—often experimentally defined as CD206⁺CD301⁺IL-10⁺—any disruption of which abrogates the cells' functional roles.

ILC2s and eosinophils

Despite initial suggestions, type 2 macrophage activation does not simply represent a default phenotype enacted in the absence of input; rather, it is highly regulated and maintained by input from upstream innate immune sensors and effectors, most notably type 2 innate-like lymphoid cells (ILC2s) and eosinophils [6]. ILC2s are a recently described innate immune cell lineage related to lymphocytes and natural killer cells but possessed of a distinct ontogeny, phenotype, and function [26,27]. In their canonical host defense role, these cells reside in tissues, poised immediately beneath epithelial barriers, and occupy an important link in the early activation of both innate and adaptive immunity [6,28]. In WAT, in contrast, the role of these cells is quite distinct; they function to promote WAT homeostasis through several defined mechanisms (and likely more yet to be defined). Currently, the most

well studied mechanism involves their regulation of the resident macrophage phenotype; this is accomplished both directly, through the production of IL-13, and indirectly, through the IL-5-dependent maintenance of tissue resident eosinophils, which support macrophage type 2 activation in turn by producing IL-4 [29,30]. Indeed, disruption of ILC2s, eosinophils, or their associated effectors cripples the homeostatic macrophage phenotype and renders the tissue vulnerable to metabolic derangement, while their supplementation, in contrast, is protective [30,31].

In addition to its role in regulating mature adipocyte function, the type 2 immune axis also exerts potent control over general tissue architecture. While this is effected through multiple pathways, the most important mechanism appears to be the regulation of white adipogenesis, where eosinophil- and ILC2-derived IL-4 and IL-13, respectively, drive adipocyte precursor proliferation, differentiation, and fate to control WAT architecture through both development and adulthood [32]. Indeed, these data suggest that this axis controls the balance of hyperplasia and hypertrophy that has been correlated with such dramatically dissimilar metabolic consequences in the context of excess dietary intake.

Interestingly, factors known to regulate the ILC2-eosinophil axis in barrier immunity are also present in the adipose tissue and appear to play active roles in its maintenance [6,28]. IL-33, for example, is a potent mitogen for ILC2s and, to a lesser extent, other type 2 immune cells. Importantly, endogenous IL-33 levels inversely correlate with both rodent and human obesity [33] and animals lacking IL-33 or its receptor, ST2, are more susceptible to metabolic dysfunction [34,35], while exogenous administration of IL-33 is protective [35]. Further complicating this picture is IL-33's unique biology; it is constitutively inactive and localized to the nucleus with no known mechanism of release other than mechanical stress and cellular necrosis/necroptosis [36,37]. How exactly this cytokine then regulates WAT physiology in the absence of demonstrable cell death is unclear.

Regulatory T cells and other immune lineages

Despite their numeric and functional dominance, macrophages are far from the only effector cell types important in WAT homeostasis. Indeed, invariant natural killer, regulatory, and T_H2 T cells have all been implicated in the maintenance of the type 2 immune microenvironment, as have regulatory B cells [10–12]. Interestingly, the IL-33-ILC2 signaling axis has recently been implicated in the maintenance of both regulatory and T_H2 T cell subsets in models focused on host defense [38,39]. While the latter is relatively rare and of unclear significance in WAT homeostasis, regulatory T cells (Tregs) are critical to the maintenance of lean WAT's tolerogenic type 2 microenvironment and are important sources of IL-10 in their own right [40–42]. As such, any link between the IL-33-ILC2 axis and Tregs is potentially of considerable import to WAT homeostasis.

Brown adipose tissue

While the functional significance of WAT is anchored in nutrient storage, brown adipose tissue's *raison d'être* is thermogenesis. To this end, brown adipocytes comprise relatively little stored lipid and instead pack their cytoplasm with mitochondria laden with uncoupling proteins, which allows these cells to generate heat by dissipating the mitochondrial proton

gradients produced by oxidative metabolism [14,43]. In contrast to WAT, BAT is relatively insensitive to nutrient status and endocrine cues and is hardwired by sympathetic nerves for rapid and facile regulation by the central nervous system. As such, the immune regulatory axis has not been shown to significantly influence brown adipocytes directly; however, type 2 immune responses are nonetheless crucial for BAT thermogenesis. Brown adipocytes are highly catabolic and require far more free fatty acids than they contain to fuel their function; these excess fatty acids are supplied by local WAT depots in response to sympathetic stimulation. In contrast to BAT, however, the surrounding WAT is poorly innervated and, thus, unable to respond sufficiently to neural input alone to meet the fatty acid demand [44–46]. To bridge this gap, resident type 2 macrophages respond to sympathetic stimulation by synthesizing and releasing additional catecholamines, thus amplifying and propagating the signal to surrounding white adipocytes, which, in turn, activate lipolysis and release the requisite free fatty acids [25]. Congruently, animals lacking type 2 macrophages or the ability to synthesize catecholamines in macrophages are thus unable to support an effective thermogenic response to a severe cold challenge [25, 47].

Beige adipose tissue

While BAT is mammals' primary adaptation to acute cold exposure, long-term cold exposure activates other programs to recruit additional heat generating capacity to defend core body temperature. Principal among these is the development of true thermogenic capacity within subcutaneous WAT depots, a process defined by the appearance of clusters of histologically and functionally brown-like adipocytes—variably known as 'beige' or 'brite' ('brown-in-white') adipocytes—within the surrounding tissue [48,49]. While a great diversity of factors may influence this process, the dominant physiologic stimulus for both the evolution of beige fat and the activation of its thermogenic function is sympathetic stimulation. Unsurprisingly, type 2 macrophages play a similar role in the activation of WAT thermogenesis as described above in BAT; however, here, type 2 immune responses also participate in beige adipogenesis itself in at least two additional, distinct ways. First, production of IL-4 and IL-13 by eosinophils and ILC2s, respectively, drives adipocyte precursor proliferation, expanding the precursor pool and making cells available for differentiation [32], as described in the WAT section above; however, it also primes these cells for beige differentiation in response to sympathetic stimulation, an effect apparent only in the context of cold-induced sympathetic stimulation [32,47]. Second, IL-33 activated ILC2s produce methionine-enkephalin peptides (MetEnk), which act directly on adipocytes to stimulate beige adipogenesis [34]. Given the similarity between these mechanisms, it is tempting to speculate that type 2 immunity thus regulates beige adipogenesis by first generating and priming adipocyte precursors for beige differentiation via IL-4/-13 stimulation, then promoting that differentiation through MetEnk signaling, and finally supporting thermogenic activation and provisioning through macrophage-derived catecholamines.

Intriguingly, exercise-induced beiging, a well described though mechanistically enigmatic phenomenon, has also been shown to act through this pathway. Here, exercise causes skeletal muscle to release meteorin-like, an endocrine signaling peptide, which induces beige adipogenesis in subcutaneous WAT depots through an eosinophil-, IL-4-, and

macrophage-derived catecholamine-dependent mechanism, congruent with other reports of type 2 immunity's involvement in this process [50].

Therapeutic significance

While this Review has focused on adipose tissue homeostasis, much of the interest in this topic is undoubtedly due to the catastrophic consequences of the current obesity epidemic—indeed, healthy WAT has largely been relegated to a role as foil for obese WAT. As a result, progress towards immune-directed therapies for metabolic dysfunction has been stunted and circumscribed largely by the search for clinically feasible anti-inflammatory agents with acceptable therapeutic indices. Unsurprisingly, the efficacy of this search has been disappointing. By studying and defining immunity's functional roles in health and homeostasis, we hope that a more balanced—and hopefully more effective—approach to anti-obesity therapy might be achieved in which interventions promote and defend adaptive homeostasis rather than simply inhibiting maladaptive dysfunction. Indeed, the material we present above suggests two general approaches that have shown early promise—immunomodulation and thermogenesis.

In general terms, immunomodulation intends to restore the type 2 immune microenvironment in metabolic tissues by promoting type 2 responses rather than inhibiting type 1. Extant approaches to this goal are many and varied, but examples that have shown promise in preclinical studies (and in early clinical studies, in some cases) include the administration of helminths or helminth-derived products [51,52], which potently stimulate type 2 immunity; direct restoration of Treg populations, either by T cell ablation and repopulation or IL-2-mediated Treg promotion [53]; and restoration of healthy gut flora through either ablation and reconstitution or supplementation and competition [54], both of which are associated with promotion of systemic type 2 immune tone [55].

The second treatment paradigm, thermogenesis, involves a simple thermodynamic argument—thermogenic adipose tissue, be it brown or beige, robustly burns fat in cold temperatures and, to a lesser degree, at thermoneutrality [43]. This idea has gained particular traction since the relatively recent description of functional brown and beige fat in adult humans (it was previously thought to be lost early in development) and demonstration of its ability to be activated with relative ease without (importantly) resorting to strenuous exercise (an intervention that, unfortunately, is as unpopular as it is effective) [56–59]. Strategies for increasing the mass and activation status of oxidative adipose tissue are currently being hotly investigated [48,49,60].

Regardless of the outcomes of individual therapeutic investigations or even entire strategies, any approach that effectively combats obesity and its associated metabolic ills is likely to rely on multifactorial invention, including behavioral modification and possibly anti-inflammatory agents in addition to type 2-promoting strategies. Indeed, the only clear and unambiguous lesson so far is that any one of the above is destined to failure.

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Box 1**Types of immunity**

Immune functions may be broadly divided into two categories: Type 1 responses are canonically acute, highly inflammatory programs intended to destroy their targets and often associated with bystander tissue damage. The type 1 response archetype is an acute bacterial infection, which triggers bactericidal neutrophils and macrophages (M1) and, if persistent or recurrent, lymphocytes including CD4⁺ TH1 and CD8⁺ T cells. Type 2 responses, in contrast, are generally more long-lived programs intended to deal with persistent or ineradicable threats—the archetype here being large parasites—and focus on barrier defenses (e.g. mucus barriers, intestinal motility) and the restoration of tissue integrity (e.g. wound healing, fibrosis). These physiologic contexts are generally dominated by type 2 macrophages (M2), eosinophils, and regulatory lymphocytes (e.g. Tregs).

Highlights

- Type 2 immunity plays a crucial role in white, brown, and beige adipose tissue.
- Type 2 immunity acts through ILC2s, eosinophils, Tregs, and macrophages.
- Type 2 immunity supports white adipose tissue's nutrient storage function
- Type 2 immunity provisions nutrients for brown adipose tissue thermogenesis.
- Type 2 immunity drives precursor proliferation and beiging in white adipose tissue

Figure 1. Tissue-resident leukocytes augment beige adipose tissue development and function

Mammals respond to sustained cold stress by increasing SNS input to subcutaneous white adipose tissue (scWAT), which results in commitment of adipocyte precursors to and their subsequent differentiation into beige adipocytes, activation of thermogenic metabolism in those beige adipocytes, and lipolysis in neighboring white adipocytes to fuel metabolic respiration. Due to scWAT's scant sympathetic innervation, however, SNS input alone is insufficient to drive this program. Instead, SNS stimulation requires augmentation by tissue resident leukocytes in 4 primary ways: 1) ILC2-derived IL-13 and eosinophil-derived IL-4 directly stimulate adipocyte precursor proliferation, 2) ILC2-derived Met-Enk and adipose tissue macrophage (ATM)-derived catecholamines promote beige differentiation, and finally, ATM-derived catecholamines activate 3) beige adipocyte thermogenesis, and 4) white adipocyte lipolysis. Abbreviations not used elsewhere: Eos, eosinophils; NE, catecholamines; FFAs, free fatty acids; Met-Enk, met-enkephalin.