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Type 2 responses at the interface between immunity and fat metabolism

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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.

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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, 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•,6–8]. 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 [9,10•,11–13]. 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

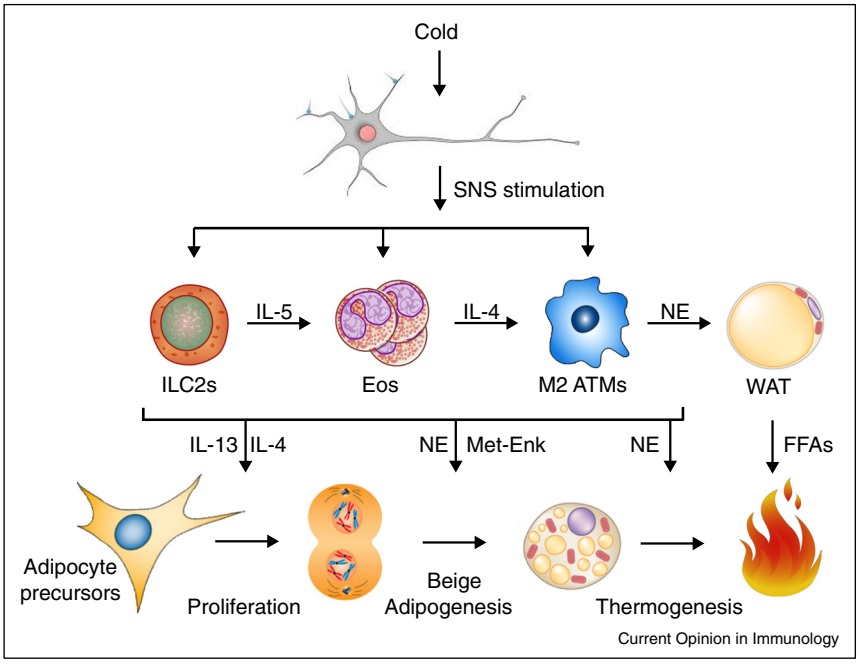
the primary and most well studied physiologic function. During times of nutrient abundance, such as occur immediately after a meal, WAT scavenges lipids from the blood and stores them as triglycerides in the single dominant lipid globule that gives white adipocytes their characteristic 'signet-ring' 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 antagonistic 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.*) (Figure 1).

Macrophages

Much of the literature surrounding the role of resident leukocytes in WAT physiology centers on the macrophage

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.