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The Immune System in Obesity: Developing Paradigms Amidst Inconvenient Truths

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Abstract
Purpose of Review Adipose tissue (AT) houses both innate and adaptive immune systems that are crucial for preserving AT function and metabolic homeostasis. In this review, we summarize recent information regarding progression of obesity-associated AT inflammation and insulin resistance. We additionally consider alterations in AT distribution and the immune system in males vs. females and among different racial populations.
Recent Findings Innate and adaptive immune cell-derived inflammation drives insulin resistance both locally and systemically. However, new evidence also suggests that the immune system is equally vital for adipocyte differentiation and protection from ectopic lipid deposition. Furthermore, roles of anti-inflammatory immune cells such as regulatory T cells, "M2-like" macrophages, eosinophils, and mast cells are being explored, primarily due to promise of immunotherapeutic applications. Both immune responses and AT distribution are strongly influenced by factors like sex and race, which have been largely underappreciated in the field of metabolically-associated inflammation, or meta-flammation.
Summary More studies are required to recognize factors that switch inflammation from controlled to uncontrolled in obesity-associated pathogenesis and to integrate the combined effects of meta-flammation and immunometabolism. It is critical to recognize that the AT-associated immune system can be alternately beneficial and destructive; therefore, simply blocking immune responses early in obesity may not be the best clinical approach. The dearth of information on gender and race-associated disparities in metabolism, AT distribution, and the immune system suggest that a greater understanding of such differences will be critical to develop personalized treatments for obesity and the associated metabolic dysfunction.

Keywords Adipose tissue · Obesity · Innate immunity · Adaptive immunity · Gender · Race · Ethnicity

Abbreviations

Akt	Protein kinase B or PKB
AT	Adipose tissue
ATP	Adenosine triphosphate
BAT	Brown adipose tissue
BMI	Body mass index
Bregs	Regulatory B cell
CCL18	C-C motif chemokine ligand 18
CCL2	C-C motif chemokine ligand 2
CCL3	C-C motif chemokine ligand 3
CCL4	C-C motif chemokine ligand 4
CCL5	C-C motif chemokine ligand 5
CCL7	C-C motif chemokine ligand 7
CD11b	CD11 antigen-like family member B/integrin subunit alpha M

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CD11c	CD11 antigen-like family member B/integrin subunit alpha M
CD14	Cluster of differentiation 14
CD206	Cluster of differentiation 206
CD3	Cluster of differentiation 3
CD301	Cluster of differentiation 301
CD4	Cluster of differentiation 4
CD45	Cluster of differentiation 45
CD69	Cluster of differentiation 69
CD8	Cluster of differentiation 8
cGMP	Cyclic guanosine monophosphate
CLS	Crown-like structures
Col1a1	Collagen type I alpha 1 chain
Col3a1	Collagen type 3 alpha 1 chain
Col6	Collagen 6
Col6a1	Collagen type 6 alpha 1 chain
CRP	C-reactive protein
CVD	Cardiovascular disease
CXCL1	C-X-C motif chemokine ligand 1
CXCL10	C-X-C motif chemokine ligand 10
CXCL8	C-X-C motif chemokine ligand 8
DIO	Diet-induced obesity
F4/80	EGF-like module-containing mucin-like hormone receptor-like 1
FABP4	Fatty acid binding protein 4
FGF21	Fibroblast growth factor 21
Foxp3	Forkhead box P3
GATA3	GATA binding protein 3
GH	Growth hormone
GUCYB3	Guanylate cyclase 1 soluble subunit beta
HbA1C	Hemoglobin A1c or glycated hemoglobin
HFD	High-fat diet
HIF1	Hypoxia-inducible factor 1 alpha subunit
IFN	Interferon
IFNg	Interferon gamma
IL-10	Interleukin 10
IL-13	Interleukin 13
IL-1	Interleukin 1
IL-3	Interleukin 3
IL-33	Interleukin 33
IL-4	Interleukin 4
IL-5	Interleukin 5
IL-6	Interleukin 6
IL-8	Interleukin 8
IL4ra	IL-4 receptor subunit alpha
IMAT	Intermuscular fat
iNKT	Invariant natural killer T cells
IR	Insulin resistance
LDL	Low-density lipoprotein
LPS	Lipopolysaccharide
MCP-1	Monocyte chemotactic protein 1
Myf6	Myogenic factor 6
NK	Natural killer
PAX7	Paired box 7
PKA	Protein kinase A
PPARγ	Peroxisome proliferator-activated receptor gamma
PRKG1	Protein kinase, cGMP-dependent, type I
RANTES	Regulated upon activation, normally T-expressed, and presumably secreted/C-C motif chemokine ligand 5
SAA3	Serum amyloid A3
SAT	Subcutaneous adipose tissue
STAT6	Signal transducer and activator of transcription 6
T2D	Type 2 diabetes
TGF	Transforming growth factor beta
Th1	T helper 1
Th17	T helper 17
Th2	T helper 2
TLR13	Toll-like receptor 13
TLR4	Toll-like receptor 4
TLR7	Toll-like receptor 7
TLR8	Toll-like receptor 8
TNF	Tumor necrosis factor alpha
Tregs	Regulatory T cells
TZDs	Thiazolidinediones
UCP1	Uncoupling protein 1
VAT	Visceral adipose tissue
VEGF	Vascular endothelial growth factor
WAT	White adipose tissue
WHO	World Health Organization
WT	Wild type

Introduction

Obesity is a global epidemic that impacts a broad range of age groups and virtually all races and ethnicities. At an individual level, obesity is a major contributing factor to premature onset of insulin resistance (IR), type 2 diabetes (T2D), and cardiac diseases. Accumulation of adipose tissue (AT) mass is a dominant characteristic of obesity, and it is now well understood that both normal and dysfunctional ATs are an active endocrine organ in addition to being a storage compartment for excess nutrients. Conversion of AT from insulin sensitive in lean subjects to insulin resistant in obesity involves massive expansion of adipocyte volume and remodeling of extracellular matrix components like collagens, elastins, and the associated blood vasculature [1–3]. This remodeling goes hand-in-hand with changes in the secretion of many hormones and adipocyte cytokines, or adipokines, which support and otherwise functionally alter numerous cell types. Failure to remodel AT appropriately in response to over nutrition is detrimental to whole body metabolic homeostasis. Excess lipid and carbohydrate intake in obesity kick-start prolonged uncontrolled inflammation, a process termed "meta-flammation"

(reviewed in [4]), which perhaps results in part from an ability of the nutrient milieu to shift "immunometabolism", or the metabolic programs of immune cells, and thereby immune cell function. In this review, we focus on some of the recent developments in the understanding of the AT immune system and inflammation in the contexts of nutrient milieu, gender, and race. To understand the origin and progression of immune function in AT, we begin with discussing different types of AT and adipocytes before diving deeper into AT expandability and mechanisms of immune malfunction.

Types of Adipose Tissue and Adipocytes

Energy-storing white AT (WAT) constitutes the majority of AT in an adult person, followed by a minority of AT mass contributed by energy-dissipating brown AT (BAT). Depending on anatomical location, WAT is categorized as subcutaneous (SAT) or visceral AT (VAT). SAT lies underneath the skin performing a protective and thermoregulatory function whereas VAT is located in the viscera, enveloping the organs such as the heart (epicardial, pericardial AT [5]), kidneys (perirenal fat), intestines and omentum (mesenteric fat), and liver (hepatic fat). The majority of white adipocytes are $PAX7^{-}/Myf5^{-}$ and are characterized by large unilocular lipid droplets and minimal uncoupling protein 1 (UCP1) expression [6, 7]. These adipocytes constitute almost 90% of WAT volume, but only about 20–40% of the cellular content, depending on the state of obesity [8–10]. WAT in adults also has small numbers of beige adipocytes ($PAX7^{-}/Myf5^{-}$), arising from a lineage that is distinct from white adipocytes [6, 7, 11,12]. WAT-embedded beige adipocytes account for the ability of some WAT to transform phenotypically from white to brown when stimulated with cold, β3-adrenergic receptor agonist, peroxisome proliferator-activated receptor gamma (PPARγ) agonist, FGF21, irisin (reviewed in [13, 14]), or histamine [15].

The second major type of AT, BAT, has the unique ability to upregulate heat production upon cold exposure or in response to certain hormones such as thyroid hormone. BAT consists mainly of brown adipocytes ($PAX7^{+}/Myf5^{+}$) [6, 7] that originate from the skeletal muscle lineage and constitutively express UCP1. Brown adipocytes characteristically contain small multi-locular lipid droplets and higher numbers of mitochondria [7]. Initially it was thought that BAT exists predominantly in the intrascapular region of neonates and infants where it generates heat. However, recent work demonstrated that substantial quantities of UCP1-expressing functional BAT (up to 63 g in one group of subjects) are constitutively present and active in the paracervical and supraclavicular region of 20- to 50-year-old adults [16, 17]. Discovery of BAT and beige adipocytes in adults has led towards accelerated interest in AT research focusing on exploiting these two cell types as new therapeutic targets to burn excess fuel and therefore (at least theoretically) combat obesity and/or metabolic diseases.

Adipose Tissue Expandability and Dysfunction: AT 911

The AT expandability hypothesis states that the most important determining factor of obesity-associated metabolic dysfunction is the capacity of AT to expand in mass to store lipid in a healthy form. A corollary to this hypothesis is that the absolute amount of AT in an individual is relatively superfluous if it remains metabolically healthy [18, 19]. The failure to maintain healthy AT function due to excessive expansion or faulty remodeling results in plasma lipid increases. Ectopic lipids then accumulate in tissues such as the liver, heart, and skeletal muscle. Ectopic lipid deposition accelerates development of metabolic syndrome as measured by high blood pressure, heart disease, hyperlipidemia, insulin resistance, or fulminant T2D. Studies in obese IR individuals suggest that increased lipolysis [20] and impaired storage of dietary fatty acids in the AT [21] can be major contributors of the plasma lipid pool that drives ectopic lipid accumulation. Numerous observations show the importance of proper lipid storage in AT (with little elsewhere) in form of triglycerides. In humans, it is well recognized that metabolically healthy obese people ($BMI > 34.3 \pm 5.5\ kg/m^2$) are protected from IR and its complications [22, 23]. Conversely, individuals who are incapable of storing lipids appropriately due to certain types of lipodystrophy syndrome such as Dunnigan-type familial partial lipodystrophy suffer from IR, dyslipidaemia, and other metabolic complications, even at relatively low BMIs [24]. Further evidence for a disconnect between obesity and metabolic imbalance include outcomes from use of TZDs (thiazolidinediones), a class of anti-diabetic drugs that improve insulin sensitivity despite the tendency to increase body weight [25]. TZDs improve metabolism, at least in part, through an expansion of SAT mass at the expense of decreased lipid in the skeletal muscle and liver [26, 27].

Dysfunctional AT is characterized by many abnormalities: high leptin production, low adiponectin production, cellular hypoxia, accumulation of non-esterified fatty acids in adipocytes, and deposition of excess extracellular matrix components like collagens and elastins. All of these changes can initiate and/or promote immune responses through a variety of mechanisms. For example, uninhibited deposition of extracellular matrix components leads to inefficient vasculature, hypoxia, fibrosis, inflammation, and IR in AT [28, 29]. Alternatively, calorie-stressed AT elicits innate and adaptive immune responses with the aim of digesting lipid laden unhealthy and dead adipocytes. Immune cells are brought in (at least in part) under the guise of dead adipocyte resorption,

but one of the unforeseen consequences of this generally helpful function is that the immune cells persist, pumping out cytokines and otherwise wreaking havoc. The classical pattern wherein immune cells release pro-inflammatory cytokines, followed by anti-inflammatory cytokines and resolution of inflammation in response to and clearance of a pathogen, becomes uncoupled. Immune cells thereby chronically secrete cytokines, with secretion at greater concentrations than the overlapping set of adipokines secreted by AT adipocytes [30].

Triggers of Immune Response in AT

Hypoadiponectinemia

Adiponectin and leptin are adipokines that significantly change in response to obesity. Adiponectin, an insulin sensitizing anti-inflammatory adipokine that exerts favorable effects on lipid and glucose homeostasis via multiple mechanisms, decreases in response to obesity [31, 32]. In contrast, leptin is a pro-inflammatory hormone that physiologically regulates energy balance by inhibiting hunger. Leptin is elevated in obesity, although its ability to decrease food intake can be blunted. Both adiponectin and leptin, along with other obesity-sensitive adipokines, impact the localization and function of a variety of AT-associated immune cells. These include macrophages, B and T cell subsets, neutrophils, mast cells, eosinophils, and dendritic cells, all of which are intimately involved in AT physiology under both lean and obese conditions. Perhaps not coincidentally, in comparison to metabolically unhealthy obese subjects, metabolically healthy obese subjects have more plasma adiponectin and a metabolically favorable inflammatory profile (reduced levels of C-reactive protein and α-1 anti-trypsin), among other measures of metabolic homeostasis [23, 33]. Additional examples of metabolic health despite obesity are mice that overexpress adiponectin (AdTG-ob/ob). These mice maintain a very high body weight but do not exhibit ectopic lipid deposition or IR, in contrast to ob/ob (leptin-deficient) mice that are extremely overweight and become metabolically compromised at an early age [34]. AdTG-ob/ob mice have more SAT, less VAT, and smaller adipocytes compared to the parental ob/ob strain. Recombinant adiponectin treatment of stromal vascular cells derived from obese human SAT leads to decreased expression of inflammatory cytokines (TNFα and MCP-1) and increased expression of mannose receptor, which are all markers of anti-inflammatory macrophages. On the other hand, adiponectin knockout mice compared to WTs had higher amounts of TNFα in AT and plasma together with severe diet-induced IR [35]. Taken together, roles of adiponectin in controlling AT inflammation are clear, but more studies are needed to understand its therapeutic potential (or lack thereof) in humans.

Non-esterified Free Fatty Acids, Hypoxia, and Fibrosis

Adipocytes have an enormous plasticity to accommodate excess lipids either by hyperplasia, hypertrophy, or both. In obese AT, adipocyte hypertrophy, apoptosis, and hypoxia following chronic intake of a high carbohydrate and lipid-rich hyper-caloric diet have been tightly linked to uncontrolled accumulation of most immune cell types. Examples of this phenomenon are studies that maintained mice on a high-fat diet (HFD) for 12 weeks, which resulted in a 150-fold increase in the frequency of hypertrophic and apoptotic adipocytes, accompanied by an increase in the macrophage activation markers CD11c, F4/80, and CD11b [36]. Adipocyte size peaked by 12 weeks of HFD and was followed by increased deposition of collagen, indicative of AT dysfunction. Free fatty acids spilled both locally and systemically by "overwhelmed" adipocytes are powerful ligands for TLR4 receptors present on both adipocytes and immune cells and (entirely predictably) trigger inflammatory responses [37, 38]. Loss of TLR4 protected from such responses in cellular and animal models as follows. Knockdown of TLR4 in 3T3-L1 adipocytes protects these cells from free fatty acid- and LPS-induced IL-6 and TNFα expressions [37]. Likewise, in mice, TLR4 knockdown protects from onset of inflammation and IR caused by an acute 5 h lipid infusion, or a chronic 26 week long HFD administration, further confirming a role for fatty acid receptors like TLR4 in diet-induced metabolic disturbance [38].

Hypoxia is a second potent stimulator of obesity-triggered inflammatory responses. Hypoxia increases expression of HIF1α, the master transcription factor of the hypoxia-protective response that induces expression of proangiogenic genes such as VEGF. In naturally hyperphagic ob/ob mice, the expanding AT becomes hypoxic as early as the fourth week of life as determined by increased HIF1α and decreased VEGF expression. This change is followed by an increase in HIF1α protein on hypoxia response elements by eight week of life [3, 39]. Constitutive overexpression of HIF1α in the AT of ob/ob mice increased expression of Col1a1, Col3a1, Col6a1, and elastin. HNF1α overexpression also increased overall fibrosis, probably by activation of lysyl oxidase and subsequent crosslinking of collagen I and collagen III to form fibrillary collagen. Inhibition of lysyl oxidase activity reduced fibrotic staining and reduced messenger RNA (mRNA) encoding F4/80, TLR13, CCL2, CCL18, SAA3, CD14, and CXCL1 in subcutaneous WAT, indicating reduced inflammation. Fibrosis in turn inhibits further AT expansion to limit non-pathogenic storage of excess calories and thereby accelerate obesity-associated inflammation and metabolic disorder [40, 41]. Similarly, studies on Col6, one of the highly abundant and explored collagens in AT fibrosis, indicated mechanistic links between HIF1α and metabolic syndrome: Col6 knockout mouse on an ob/ob background have improved metabolic profiles and higher Akt

phosphorylation (a marker of insulin action or sensitivity) as early as 10 weeks of age. These mice also weighed less on HFD, and lower expression of F4/80, MCP1, and SAA3, despite larger adipocyte size in VAT, in comparison to WT mice [29].

Innate and Adaptive Responses in AT: Paradigms and Paradoxes

The AT immune response involves activation of cells from both innate and adaptive immune subsets as depicted in Fig. 1. Many of these immune cells recirculate through AT, blood, liver and spleen therefore contributing to systemic inflammation [45••]. Numerous studies describe the individual functions of innate and adaptive immune cells in disturbing and (perhaps paradoxically) maintaining AT and systemic metabolic homeostasis.

We and others have noted that macrophages constitute the majority of innate immune response cells in murine AT. AT macrophages are observed in crown-like structures (CLS) that also contain dead or dying adipocytes, or as isolated macrophages outside the crowns. AT from obese people contains notably fewer CLSs and more T cells than mouse AT, perhaps due to temporal considerations of AT physiology or basic immunological differences between the two species [46–49]. Dominance of macrophages in obese murine AT but higher proportions of T cells in obese human AT (Belkina, unpublished observation) raises the inconvenient truth that standard mouse models may only somewhat model human disease. Regardless, the functional continuum of macrophages in AT from either species can be broadly categorized as M1-like or M2-like. M1-like macrophages express surface F4/80 and CD11c and are pro-inflammatory by nature of secretion of the cytokines IL-6, TNFα, and IL-1β. In contrast, M2-like macrophages express CD206 or CD301 surface markers, are generally anti-inflammatory, and thus guard against the chronic inflammation that characterizes unhealthy AT. HFD triggers a transition of macrophages to a more M1 phenotype in mice, and thereby increases the normally low M1/M2 ratio of tissue-resident macrophages that are crucial for maintaining AT health. The "shift" from an M2 to an M1 phenotype, as well as the mixed M1/M2 phenotype identified in mice by Strissel et al. [36] occur due to multiple mechanisms that likely include macrophage precursor recruitment and macrophage proliferation, with evidence for transdifferentiation from M2 to M1 still speculative [50–53]. Curiously, AT from obese people has fewer M1-like macrophages and a higher preponderance of fibrosis than AT from obese mice [54].

Adipocytes actively secrete chemokines such as monocyte chemoattractant protein 1 (MCP-1) that attracts circulating monocytes to the AT, where the monocytes mature into macrophages, at least by some reports [51]. Overexpression of MCP-1 in lean mice imparts systemic IR by increasing macrophage infiltration and pro-inflammatory cytokine production in WAT [55]. In humans, MCP-1

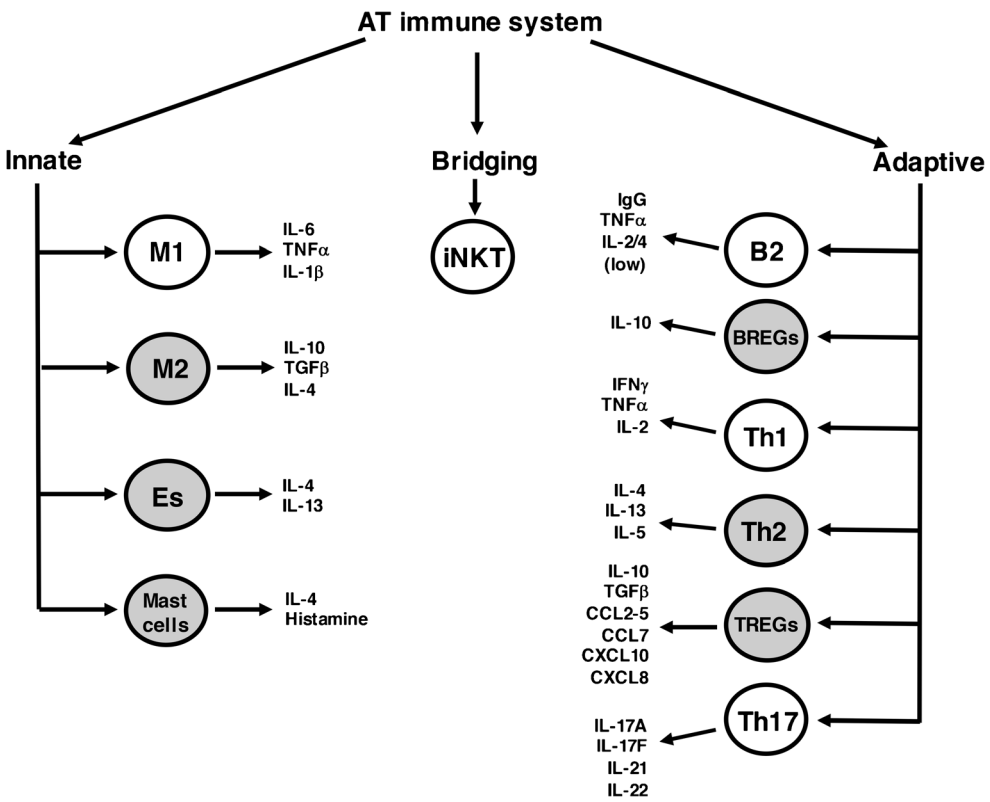

Fig. 1 Schematic representation of innate, adaptive, and bridging immune cells in adipose tissue. Obesity and chronic high-fat feeding the shifts resting immune system in adipose tissue to a pathogenic phenotype that produces a pro-inflammatory cytokine profile. Obese AT contains an increased number of M1 macrophages, B cells, Bregs, Th1 cells and Th17 cells (shown in *open circles*) and a decreased number of invariant natural killer T (*iNKT*) cells, M2 macrophages, eosinophils (*Es*), mast cells, Th2 cells, and Tregs (shown in *gray circles*). The inflammatory role of iNKT cells is debatable and the scientific community has recognized both pro- and anti-inflammatory activities of iNKT cells depending on the conditions [42, 43]. Cytokines, chemokines, IgG, and histamine, which control adipose tissue homeostasis, are listed next to respective cell types [30, 44]

expression in plasma is proportional to obesity, and a 12% weight loss in morbidly obese individuals decreases MCP-1 expression by almost 20% [56]. Apoptotic adipocytes also attract macrophages, a process clearly demonstrated in FAT-ATTAC mice where AT apoptosis is induced by AP21087-mediated caspase 8 activation [57]. Fourteen-day treatment with AP21087 reduced epididymal and inguinal WAT by almost 50% and induced mRNA expression of a mixture of M1/M2 macrophage markers including F4/80, CD11c, CD86, CD206, CD301, IL-10, and TNFα in both WAT depots [57]. These results indicate that macrophage infiltration may be, at least under some scenarios, independent of obesity, and therefore questions the mechanism underlying observations that obesity leads to infiltration, accumulation, and proliferation of M1-like macrophages with a concurrent reduction in the number and proportion of M2-like macrophages [58].

In contrast to the general school of thought that AT inflammation is pathogenic, transient AT inflammation is likely beneficial for maintaining AT health, as evidenced by work showing inhibition of adipocyte inflammation results in systemic inflammation, ectopic lipid accumulation and glucose intolerance [59••]. For these studies, the authors used the adipochaser mouse, in which a small bolus of doxycycline induces β-galactosidase expression in all preexisting adipocytes. The advantage of this mouse is that newly formed adipocytes are negative for blue X-Gal-LacZ staining and are therefore detectable after withdrawal of doxycycline and addition of adipogenic stimulus. Work in this mouse showed that LPS injection induced adipogenesis in the inguinal WAT, suggesting a crucial role for acute inflammation in promoting adipogenesis that is beneficial for maintaining AT homeostasis. LPS-induced adipogenesis in this model echoes results from similar reports by Sadler et al. [60]. Further support for the conclusion that inflammation protects against AT dysfunction, at least under some conditions, are data from mice that express dominant-negative TNFα (dnTNF tg). Such mice are glucose intolerant with reduced adiponectin, even though they are partially protected from diet-induced weight gain and adipocyte hypertrophy [59••]. Outcomes from the dnTNF tg mouse were confirmed by the same authors using a RIDα/β mouse model, in which the host immune response is suppressed by inhibiting TLR4, TNFα and IL-1β signaling.

An additional non-pathogenic role for the AT immune system in AT physiology is indicated by the ability of immune cells to promote AT beiging as a defense against the cold. Two groups independently showed that cold stimulation promoted IL-4 and IL-13 production by eosinophils, which then yielded alternative activation (M2-like) of catecholamine-secreting macrophages that express tyrosine hydroxylase (a key enzyme in catecholamine synthesis). These catecholamines induced lipolytic gene expression in the WAT and thermogenic gene expression in beige adipocytes [61, 62]. Outcomes of this work have been questioned by a very recent study in which authors used mice with adult-onset peripheral deletion of tyrosine hydroxylase in hematopoietic cells [63•] as opposed to mice models with myeloid cell specific deletion of IL4ra and tyrosine hydroxylase [61] or systemically deleted IL4/IL3, STAT6, or IL4ra [62]. Hematopoietic deletion of tyrosine hydroxylase resulted in no differences in browning or energy expenditure in these mice compared to WT controls. Moreover, tyrosine hydroxylase expression was not observed in AT-resident macrophages, which definitively demonstrated that alternatively activated (M2-like) macrophages are incapable of synthesizing catecholamines in these mice. Conceptually similar work with human AT showed that seasonal changes in adipocyte UCP1 expression associated with increased cytokine expression and an increase in mast cell markers in lean subjects [15]. Notably, mast cells express IL-4 to support M2s, and histamine, which can activate adipocyte PKA and induce thermogenesis. Thus, seasonal changes induce a mixture of classically defined pro- and anti-inflammatory features. The paradox that inflammation can promote AT health under some circumstances yet trigger IR under other circumstances remains an inconvenient truth of meta-flammation. Duration and "flavor" of the inflammation alone or in combination with fibrosis, and/or the type of inflammatory stimulus, could play key roles in understanding the balance between the immune system and AT function, as well as the identification of the switch that triggers simultaneous immune and AT pathology.

Adaptive Immune Cells in Adipose Tissue

The adaptive immune system traditionally encompasses B cells and T cells. Immunity conferred by these cells is a more specialized immune response compared to the innate immune response generated by macrophages, neutrophils, eosinophils, and mast cells. Adaptive immune cells mount a highly specific response to epitope structures and form fast-acting memory cells with high specificity for structurally identical epitopes. Both major arms of the adaptive immune system have demonstrated roles in obesity-associated inflammation, although the sequence of neutrophil, macrophage, B cell, and T cell infiltration into the expanding AT in obesity remains controversial. Adaptive/innate immune cell cross-talk is rampant in AT, as indicated by studies showing B cells influence both T cell and macrophage function in VAT [10, 64, 65]. Additionally, comparison of the VAT depot from WT and B cell-null mice on HFD showed the latter have a significantly lower percentage of $CD11c^{+}CD206^{-}$ macrophages and TNFα secretion, the latter of which could initiate from macrophages (as generally assumed) or from T cells. Additionally, B cell-null mice had fewer VAT $CD4^{+}$ T cells. Because bulk changes in $CD4^{+}$ T cells do not define a pro- or anti-inflammatory milieu, more revealing outcomes showed that $CD8^{+}$ T cells and IFNγ secretion (which could be produced by either $CD4^{+}$ or $CD8^{+}$ T cells

but is generally inflammatory) in AT from these mice were also ameliorated in the absence of B cells. B cell-null mice were protected from DIO-associated dysglycemia, and transfer of IgG antibodies (which would arise solely from B cells) isolated from HFD mice then injected into B cell-null mice caused dysglycemia within a week of administration [64, 66]. A distinct group of IL-10-producing B cells in AT, designated regulatory B cells (Bregs), may also play roles in obesity-associated AT inflammation [67, 68]. Despite ongoing controversies surrounding the identification of Bregs as a definite/stable subpopulation, IL-10-producing B cells are absent in the circulation of T2D subjects [69], and B cell-specific deletion of IL-10 causes AT inflammation and IR in mice [67]. Complementary mouse model work showed that transfer of Bregs to DIO mice ameliorates AT inflammation [67].

Much of the work on T cells in AT has focused on $CD4^+$ $Foxp3^+$ regulatory T cells (Tregs) that counter inflammatory response of multiple cell types, including $CD4^+$ T effector cells like Th1s, Th2s, and Th17s. Tregs are abundantly present in VAT from lean mice, but their numbers plummet in murine VAT responding to obesity [70]. Rapid deletion of Tregs using a diphtheria toxin-mediated strategy reduced phosphorylation of the insulin-stimulated insulin receptor in AT, but the reduction was only partial in the spleen of the same animals. Furthermore, expression of TNFα, IL-6, SAA3 and RANTES was higher in VAT of Treg-deleted mice compared to WTs. Follow-up studies on AT Tregs identified an important link between a Treg subset expressing ST2 chain of IL-33 receptor and reduced inflammation. $ST2^+$ Tregs were preferentially housed in non-lymphoid tissue and produced GATA3, IL-5, and IL-13 in response to IL-33. In vitro, these cells diminished $CD4^+$ T cell proliferation via mechanisms partially dependent on enhanced production of anti-inflammatory cytokines IL-10 and TGFβ, but independent of IL-33 [71]. Although obesity specifically reduced the number of $ST2^+$ Tregs in VAT, IL-33 treatment in vivo ameliorated inflamed VAT and an IR phenotype in obese mice [72]. Taken together, IL-33-responsive $ST2^+$ Tregs may have potential as immunotherapy against obesity and metabolic syndrome.

In addition to anti-inflammatory functions, $Foxp3^+$ Tregs may have a secondary function of recruiting neutrophils into the AT [73]. They do so by secreting various chemokines including CCL2–5, CCL7, CXCL10, and CXCL8/IL-8, the latter of which is a potent neutrophil chemoattractant. When expressed ectopically in activated conventional human T cells, transient Foxp3 production results in selective increment of IL-8 production, although other more classical pro-inflammatory cytokines are repressed. Foxp3 expression is also important for function of multiple $CD4^+$ T cell lineages, especially Th17 cells [74]. Upon activation, Th17 cells have a more sustained expression of the Foxp3 gene compared to Th1 cells, and loss of Foxp3 in Th17s increased IFN-γ secretion, a mark of more "pathogenic" Th17s. Work on murine $CD4^+$ T cells in AT that are not Tregs, i.e., effector T cells, arguably culminated with an immunotherapy approach tested for an ability to prevent obesity-induced IR [75]. These investigators used a CD3-specific antibody to block antigen recognition by the T cell receptor/CD3 complex, an important step in T cell activation. This blockade prevented IR despite HFD-induced obesity.

To understand the exchange of adaptive immune cells among tissues and therefore test the importance of parallel and/or independent studies on cells from a variety of tissues, Lynch and colleagues took advantage of a parabiosis approach to investigate exchange of $CD45.1^+$ (host) and $CD45.2^+$ (parabiotic partner) lymphocytes among the blood, liver, spleen, and AT. Subset analysis showed that exchange of total $CD4^+$ T cells, $CD8^+$ T cells, and B cells was significant in the blood, liver, spleen, and AT, suggesting the ability of lymphocytes to recirculate through tissues. However, among the four tissues studied, exchange of Tregs was least in AT, indicating the dominance of tissue resident Tregs over newly recruited cells. Exchange of the lipid sensing innate T lymphocytes, also known as invariant natural killer T (iNKT) cells, was extremely modest in AT, where > 95% of iNKTs were host derived [45••]. Given that iNKT cells are proposed to bridge innate and adaptive immune responses as observed by clusters of iNKT cells and $CD11b^+$ macrophages in AT 3-day post-iNKT stimulation, and that iNKTs protect against diet-induced IR, these data highlight the importance of tissue-resident iNKTs functioning in parallel with recirculating immune populations to determine net AT inflammation [45••].

Data on T cell subsets from human AT broadly support results from T cell analyses from model organism AT. Although $CD8^+$ and $CD4^+$ T cells were observed in both VAT and SAT depots in humans, frequencies of pro-inflammatory T cells (Th1, $CD8^+$ and Th17) were much higher in VAT when compared to SAT [76]. A more comprehensive analysis of T cell cytokines, albeit analyses of circulating T cells, show an ability of cytokines alone to distinguish metabolically healthy and unhealthy obesity in the absence of clinical data from the same subjects [77••]. Multivariate analysis further suggested that a Th17 type inflammatory signature was supported by monocytes in both obese T2D and obese non-T2D subjects, whereas B cells support the Th17 signature only in T2D subjects. This outcome independently confirmed the previous observations in B cell-null mice that B cells promote T cell-mediated inflammation in obesity [10, 64] and perhaps introduce another avenue to pursue as immunotherapy against obesity.

One understudied (and arguably underappreciated) regulator of the AT immune system is the nutritional environment, which has been most thoroughly studied as a regulator of T cell function. Obesity and, to a greater extent, obesity-associated T2D, are characterized by dyslipidemia

and hyperglycemia, even in individuals that meet clinical targets for glycemic and lipid control. All immune cells metabolize a cell-type determined balance of glucose, glutamine, and/or fatty acids, all of which are generally essential to maintain effector functions and memory generation [78–81]. Very early studies showed that stimulated T cells metabolize large concentrations of glucose [82] to maintain functions that are fueled by the rapid ATP generated through anaerobic glycolysis. The importance of anaerobic glycolysis has been more recently indicated by the relatively high expression of the insulin-independent glucose transporter Glut1 on Th1, Th2, and Th17 cells when compared to Tregs, the latter of which more readily utilize fatty acid oxidation via aerobic respiratory pathways to generate ATP [80]. The literature suggests that fatty acid synthesis leads to inflammatory immune responses by Th1 and Th2 T cells, whereas fatty acid oxidation leads to development of $CD8^+$ memory, M2-like macrophages and Tregs (reviewed in [83]). However, the impact of shifts in fuel availability in obesity and obesity-associated T2D, coupled with the reasonably well understood cell-intrinsic differences in immune cells in such subjects, will need additional queries to determine the combinatorial impact of immunometabolism and meta-flammation on T2D pathogenesis with an eye towards drug targets for clinical use.

Gender-Associated Differences in the AT and the Immune System

Differences in the AT-associated immune system between males and females can be two-tiered given gender-determined differences in both AT distribution and the immune response. Evidence from human and mouse studies illustrate that gender, age and sex hormones significantly impact the distribution and function of AT. The earliest differences in AT distribution begin to appear in people post-puberty when males accumulate more VAT compared to females, despite males having a lower volume of total fat mass [84]. Indirect evidence suggests that the process of AT distribution between SAT and VAT is centrally regulated by genetic makeup of an individual and is driven by growth hormone (GH) and glucocorticoids that are disproportionately important for their ability to promote fat redistribution in females. Examples of this phenomenon include supplementation of GH in patients with adult onset GH deficiency [85] or hypopituitarism [86], which reduces the amount of SAT (by 13%) and VAT (by 30%) in both males and females. Similarly, investigators showed prevalence of BAT is gender-dependent in Chinese adults: 5.5% in females and only 1.3% in males. Amount of detectable BAT in these female subjects correlated inversely and independently with age and VAT area, suggesting an association between the amounts of VAT and BAT [87].

In addition to understanding inherent differences in AT distribution, it is imperative to study effects of prolonged HFD on AT distribution and immune cell populations, a goal that is almost impossible to attain in controlled studies with human subjects. In one mouse colony, females were protected from weight gain, hypercholesterolemia, glucose intolerance and systemic inflammation after 14 weeks of HFD. Tregs, which protect against inflammation, increased nearly 6-fold in female VAT in response to HFD but decreased in VAT of male counterparts, perhaps explaining female resistance to metabolic syndrome. In the same study, no gender-associated differences were observed in islet function despite islet cell hypertrophy and hyperinsulinemia in the male mice [88]. Clearly such resistance does not cleanly extend to women who are centrally obese, echoing the inconvenient disconnect between murine and human studies mentioned above. Instead, evidence that sex-associated differences in AT distribution influence whole body inflammation in people can be drawn from studies investigating immune system differences between SAT and VAT, the latter of which expands more commonly in men, who store extra calories in central depots. Obese females can have central adiposity, but "pear-shaped" women with relatively low waist/hip ratios are much more common than pear-shaped men. Notably, expansion of the VAT increases the odds of IR, while expansion of SAT, more typical of pear-shaped people, decreases odds of IR, hypertension and CVD [89, 90]. As adults, women accumulate more gluteofemoral fat (considered as SAT) which is inversely associated with fasting insulin, %HbA1C and metabolic complications [91–94]. Tissue fragments and adipocytes from the VAT secrete more of the pleiotropic (but often considered only pro-inflammatory) cytokine IL-6 compared to SAT [95, 96], consistent with the general paradigm that SAT stores excess calories through less pathogenic mechanisms. Further evidence for a relationship between sex-associated differences in AT distribution and systemic inflammation are demonstrations that serum CRP and IL-6 positively correlate with BMI, waist circumference, and quantity of VAT [97]. Correlation between IL-6 and VAT remains significant despite adjustment with BMI and waist circumference, thus hinting towards global effects of VAT inflammation that are less prevalent in pear-shaped people. VAT from obese compared to lean subjects is enriched in $CD45^+$ (i.e., total immune) cells, NK cells, and $CD11c^+$ macrophages [98]. Interestingly, VAT inflammation can also be partially reflected by blood leukocytes, consistent with demonstrations that the number of classical blood monocytes positively correlate with $CD11c^+$ macrophages in VAT but not in SAT. A recent mouse study mirrors differences in between human VAT and SAT: TNFα secretion from VAT (but not SAT) is higher in HFD fed mice. TNFα inhibited two important aspects of adipocyte biology in these studies: adipocyte differentiation and the adipocyte cyclic guanosine monophosphate (cGMP) pathway

[96]. Additionally, VAT-associated TNFα more robustly activated JNK and NFκB pathways to inhibit the expression of PPARγ, FABP4, PRKG1, and GUCY1B3 genes. In line with this observation, chronic stimulation of the cGMP pathway by sildenafil (an inhibitor of cGMP-specific phosphodiesterase) treatment improves whole body insulin sensitivity and protects from HFD-induced inflammatory imbalance in mice [99].

The immune system is like the AT in that it broadly differs between males and females. In general, females are deemed to have "stronger" immune systems. Two factors determine gender dimorphism in immune responses (physiological and pathogenic or auto-immune): sex hormones and cellular mosaicism due to X-chromosome inactivation in females. X chromosome-dependent differences in innate immune responses include modified expression of various genes like TLR7 (a pattern recognition receptor for single stranded RNA) and TLR8 that are located on the X chromosome and induce type 1 IFN. In such cases, these genes are expressed more robustly in females and occasionally make them more susceptible to auto-immune diseases like systemic lupus erythematosus [100, 101]. The differences also affect immune cells, and may impact preadipocytes and adipocytes from, for example, *ob/ob* or *db/db* mice, which express significantly higher amounts of TLR 1–9 mRNA due to regulation by non-sex determined hormones like leptin [102].

In addition to germline differences, key sex hormones like testosterone and estradiol have opposing effects on adaptive and innate immune responses. Estrogen receptors are present on the entire repertoire of immune cells including B cells, T cells, neutrophils, macrophages, dendritic cells, and NK cells, whereas androgen receptors are present primarily on B and T cells. Furthermore, androgens like testosterone invoke a Th1 response, while estrogens signal a Th2 response, the latter of which ameliorates inflammation under some, but not all, circumstances (reviewed in [103]). Sex hormones may also directly affect the function of innate immune cells. Treatment of macrophages with estradiol in vitro reduces the production of IL-6, IL-1β, and TNFα, suggesting an anti-inflammatory effect of classically defined female hormones [104]. Related work showed that women have an increased number of $CD4^+$ T cells post-puberty [105] and that the T cells proliferate faster with higher IL-17A production and lower IFNγ production (characteristic of non-pathogenic Th17 cells) compared to cells from prepubertal female [106]. Complementary studies showed $CD8^+$ T cells, Tregs, and natural killer (NK) cells to be present in higher numbers in males than in females [107, 108]. Additional sexual dimorphism studies of immune cells showed that percentage of phytohemagglutinin-mediated stimulated NK and total T cells was greater in males, whereas activated T cells ($CD69^+$) generated under the same stimulation conditions were higher in females [109]. Taken together, this work indicates a mixture of pro- and anti-inflammatory differences from immune cells in men and women. These observations support sex-driven distinction in both naïve and activated immune cell populations, a fact that has been conveniently overlooked during extrapolation of male animal-dense research in (especially) obesity to the whole population.

Impact of Race and Ethnicity on AT Distribution and Immunity

Differences in AT distribution among races was a key observation in developing the AT expandability hypothesis detailed above. BMI-matched Asians have increased body fat content when compared to a western population ([110] defines western population) [111]. Similar studies showed that race-associated variances in cardiometabolic risk factors start to appear at an early age in western populations. Comparison of age and BMI-matched obese African Americans and white American adolescents showed that cardiovascular disease risk (measured by increased cholesterol, LDL and triglycerides) was higher in obese African American adolescents despite lower VAT content [112]. With quantity of VAT unable to explain differences in cardiometabolic risk factors among racially defined populations, smaller yet "more pathological" AT depots such as intramyocellular AT (IMAT), located beneath the muscle fascia between muscle groups, have gained attention. IMAT accumulation as a proportion of total AT increase is highest in African Americans compared to whites and Asians, although obesity-associated VAT accumulation is higher in whites and Asians [113]. However, our work on African-American women specifically showed this group had less intramyocellular lipid (predominantly triglycerides) along with lower adiponectin and lower expression of several PPARγ-responsive genes in AT compared to Caucasians [114].

Work on ethnicity, which is defined predominantly by behavioral factors that modify the genetic differences associated with race, complements demonstrations that race influences AT distribution and thus health. Singapore-based studies that initially showed body fat content in Singaporeans are underpredicted based on BMI alone, also showed that body fat distribution differed among the three ethnicity subpopulations of Asians in the study: BMI-matched Indians have the highest body fat content, followed by Malays and Chinese [115, 116]. Even more disheartening, Asians have higher incidence of cardiometabolic disorder at a given BMI. Taken together, these observations suggest that adiposity is less BMI-dependent in Asians (reviewed in [117]) and that a BMI cutoff of 27.5 kg/m^2 instead of WHO suggested 30 kg/m^2 should be used to predict obesity among Asians, irrespective of inputs due to ethnic differences. Importantly, this work supported the conclusion that BMI is no longer considered the best method to define obesity globally.

Although some work has cataloged race- or ethnicity-related differences in metabolic parameters, similarly determined differences in immune responses are relatively unchartered territory. Studies analyzing immune cell populations and inflammatory responses across different populations will allow researchers to pin-point specific targets and mechanisms that may contribute to these differences and perhaps enhance precision-medicine treatments.

Conclusion

Over the past decade, the involvement of the immune system in metabolic syndrome has become clearer. Investigators have begun to understand the crucial tipping point before inflammation turns pathogenic in AT due to (a) the development of new animal models [59••] and (b) identification of metabolically healthy obese human subjects who enabled researchers to characterize immune response differences in metabolic health vs. metabolic dysfunction. Immunotherapy, which is the latest advent in cancer treatment, may be useful weapon in the global fight against obesity-related disorders. In this context, recognition of new obesity-associated immune cell subsets such as $ST2^+$ Tregs [71, 72] and Th17s [64, 77••, 118] and antibodies that can block immune activation [75] may suggest new avenues for immunotherapy as lucrative directions for future studies.

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Compliance with Ethical Standards

Conflict of Interest Madhur Agrawal, Philip A. Kern, and Barbara S. Nikolajczyk declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki Declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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- • Of importance
- •• Of major importance

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