



Immune Cell Activation in Obesity and Cardiovascular Disease

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Abstract

Purpose of Review In this review, we focus on immune cell activation in obesity and cardiovascular disease, highlighting specific immune cell microenvironments present in individuals with atherosclerosis, non-ischemic heart disease, hypertension, and infectious diseases.

Recent Findings Obesity and cardiovascular disease are intimately linked and often characterized by inflammation and a cluster of metabolic complications. Compelling evidence from single-cell analysis suggests that obese adipose tissue is inflammatory and infiltrated by almost all immune cell populations. How this inflammatory tissue state contributes to more systemic conditions such as cardiovascular and infectious disease is less well understood. However, current research suggests that changes in the adipose tissue immune environment impact an individual's ability to combat illnesses such as influenza and SARS-CoV2.

Summary Obesity is becoming increasingly prevalent globally and is often associated with type 2 diabetes and heart disease. An increased inflammatory state is a major contributor to this association. Widespread chronic inflammation in these disease states is accompanied by an increase in both innate and adaptive immune cell activation. Acutely, these immune cell changes are beneficial as they sustain homeostasis as inflammation increases. However, persistent inflammation subsequently damages tissues and organs throughout the body. Future studies aimed at understanding the unique immune cell populations in each tissue compartment impacted by obesity may hold potential for therapeutic applications.

Keywords Obesity · Immunity · Immunometabolism · Cardiovascular disease · Inflammation · Infection

Introduction

For over three decades, scientists have understood that chronic inflammation is a significant contributor to many diseases. This is particularly notable in obesity, where the overall immune phenotype converts from an anti-inflammatory

to a pro-inflammatory state [1]. All types of immune cells, including innate and adaptive, reside in adipose tissue, and the full spectrum of their contributions to adipose tissue homeostasis is not known. Adipose tissue undergoes major remodeling during obesity, including adipocyte hypertrophy, expansion of extracellular matrix, and most notably for this review, extensive changes in the immune cell compartment. Other tissues such as the muscle, liver, pancreas, and brain also have immune-mediated changes during obesity that impact their function. The heart and vasculature contain a diverse network of immune cells that function to maintain homeostasis; respond to ischemic, infectious, and non-infectious injury; and in some instances, inappropriately propagate autoimmune or other pro-inflammatory insults, including chronic inflammation of obesity. In this article, we provide a brief summary of the current literature on how immune cell activation in obesity impacts adipose tissue inflammation, atherosclerotic cardiovascular disease (ASCVD), non-ischemic cardiovascular disease, hypertension, and infectious diseases.

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Adipose Tissue Inflammation in Obesity

Obesity is characterized by an increase in adipose tissue mass, accompanied by chronic tissue-specific and systemic inflammation. In the early 2000s, macrophages were identified as a key contributor to this inflammation in obese adipose tissue [2, 3]. In contrast to lean adipose tissue where macrophages make up 5–10% of total cells, macrophages make up 60% of cells in obese adipose tissue. Additionally, macrophages in obese adipose tissue arrange themselves into crown-like structures surrounding individual adipocytes [4] and exhibit an M1 dominant phenotype [5], secreting tumor necrosis factor alpha (TNF- α) and interleukin (IL) 6. This sustained inflammation is in part due to the interaction between macrophages and CD8⁺ T cells, which infiltrate adipose tissue during the early stages of obesity. CD8⁺ T-cell infiltration into obese adipose tissue precedes recruited monocyte arrival and guides macrophage differentiation, migration, and activation [6]. Obesity research demonstrates that an increase in adiposity is characterized by an infiltration and increase of almost all immune cell populations.

Single-Cell Techniques Reveal Novel Immune Populations

The advent of single-cell sequencing has made it possible to better characterize adipose tissue and highlight contributions from sex, age, environmental temperature, and nutrition. Single-nucleus RNA-seq highlights plasticity in adipose tissue and a shift from a lipogenic population of macrophages to a lipid-scavenging population [7]. Recently, multiple groups have performed single-cell analysis on the immune-rich stromal vascular fraction of white adipose tissue (WAT) from lean and obese humans and mice. Distinct cellular clusters in the stromal vascular fraction were identified, and unsurprisingly, it was determined that as adipose tissue changes from lean to obese, signaling pathways transition from immunoregulatory to inflammatory [8, 9]. In obese WAT, there are increased percentages of endothelial cells, adipose-resident dendritic cells, unconventional T-cells, and myeloid-like, natural killer-like, and innate lymphoid cells [8]. Ligand-receptor analysis in lean WAT indicates that pathways are in place to defend against inflammatory mechanisms resulting from increased adiposity. The number of ligand-receptor pairings increases in cells from obese humans, attributed to accelerated recruitment of myeloid and macrophage populations [8]. Similarly, single-cell RNA (scRNA) sequencing reveals that the immune cell niche is highly variable depending on which adipose depot the immune cells reside in [10].

Other studies have also identified unique macrophage subtypes in obese adipose tissue including lipid-associated macrophages (LAMs), metabolically activated macrophages,

and CD9⁺ adipose tissue macrophages [11, 12, 13]. These macrophages are lipid laden, reside in crown-like structures surrounding adipocytes, and are pro-inflammatory. While the gene signatures of these macrophages are distinct, physiologically, it is likely that these three macrophage populations possess a similar function. A novel marker of this population of macrophages, the triggering receptor expressed on myeloid cells 2 (Trem2), is conserved in the obese adipose tissue of both humans and mice. Loss of Trem2 causes adipocyte hypertrophy [12, 14, 15] and, in some studies, worsened metabolic outcomes [12, 14]. These phenotypic findings suggest that Trem2⁺ macrophages are key metabolic regulators within adipose tissue.

Similarly, scRNA-seq has been used to investigate the impact of a high-fat diet (HFD) on T cells and suggests that after extended periods of overfeeding, T cells become exhausted [16]. Analysis of this data indicates that these T cells are characterized by increased cell surface inhibitory receptors, decreased TCR signaling, and metabolic impairment. Altogether, these data indicate an impaired adaptive immune response which will be discussed later in this review.

T Cell Clonality

CD4⁺ and CD8⁺ T cells play a fundamental role in obesity-induced insulin resistance, and conserved T cell receptor (TCR) sequences have been identified on these cells isolated from obese adipose tissue [6, 17]. Clonal expansion, or the proliferation of T cells with specific TCRs that recognize obese adipose tissue, has been less studied. Previously, we showed that in mice fed a HFD, the number of CD8⁺ T cells was increased, but more importantly, these cells had increased clonality suggesting less TCR diversity than CD8⁺ T cells isolated from lean adipose tissue [18]. Data from the HFD mice indicated that more public clones were present under this dietary condition. The amino acid sequences corresponding to the clonal TCRs were characterized as charged and non-polar. This observation suggests that the tissue microenvironment is composed of compounds that react and influence the increased presence of positively charged, non-polar TCRs. Isolevuglandins are present at high levels in adipose tissue macrophages and have been identified as one of the components of the adipose tissue microenvironment stimulating CD8⁺ T cell proliferation [18].

T Cell Exhaustion

Another expanding area of research is related to the observation that T cell exhaustion, most commonly associated with the tumor microenvironment and viral infections, also increases in obese adipose tissue. Obesity has been implicated in both tumor progression and a transition

from PD-1⁻ CD8⁺ non-exhausted T cells to PD-1⁺ CD8⁺ exhausted T cells [19•]. Furthermore, both CD4⁺ and CD8⁺ T cells in obese adipose tissue have increased expression of the exhaustion marker PD1 on the cell surface [16, 20]. Our group used scRNA-seq analysis of adipose tissue immune cells and revealed that this population of exhausted CD8⁺ T cells exists within adipose tissue from weight cycled and weight loss mice in addition to obese mice [21••]. These CD8⁺ T cells express PD1 and are also characterized by exhaustion markers *Pdcd1*, *Tox*, *Entpd1*, *Tigit*, and *Lag3*. Recent studies have determined that adipose tissue T cells from diabetic humans have an impaired inflammatory phenotype after T cell receptor stimulation, comparable to what is seen in obese diabetic mice [16]. Single-cell sequencing on CD3⁺ epididymal WAT revealed enrichment for exhaustion genes on both CD4⁺ and CD8⁺ cells. These paradigm-shifting results indicate that T cells from obese adipose tissue have an exhausted profile with decreased cytokine production as opposed to an inflammatory one.

Effect of Weight Loss on Immune Cell Populations in Adipose Tissue

It is well established that weight loss improves multiple aspects of cardiometabolic health. However, some evidence suggests that immune remodeling evoked by obesity may not resolve with weight loss and thus may accelerate cardiometabolic disease risk upon weight regain. A recent study placed male mice on a HFD for 12 weeks followed by 2–24 weeks of weight loss. After 8 weeks of weight loss, despite the fact that fat mass was significantly reduced and comparable to control animals, pro-inflammatory CD11c⁺ adipose tissue macrophages (ATMs) remained elevated [22]. Similar to the ATMs, CD8⁺ T cells persist at higher levels post-weight loss as compared to non-diet controls. Our work also confirms the persistence of increased ATMs post-weight loss and shows that these macrophages are characterized by increases in lipid handling (*Cd9*, *Trem2*, *Cd36*), activation/adhesion (*Cd81*, *Cd63*), and co-stimulation (*Cd86*, *Cd40*) genes [21••]. Additional studies support these findings and implicate that obesity contributes to persistent inflammation in adipose tissue even after weight loss. This “obesogenic memory” may contribute to sustained insulin resistance and aberrant glucose metabolism [23].

Inflammation in Cardiovascular Disease

Atherosclerotic Cardiovascular Disease

In the 1970s and 1980s, ASCVD was thought to be driven primarily by hyperlipidemia. As cholesterol-lowering

medications came into widespread use, it became clear that there was a residual risk that was not eliminated even after lipid lowering. Thus, inflammation was explored as an additional compounding factor [24]. With ischemic injury resulting from the rupture of atherosclerotic plaques, there is mast cell degranulation, production of pro-inflammatory cytokines and chemokines by macrophages and cardiomyocytes to recruit additional immune cells, and production of local growth factors by fibroblasts [25]. Endothelial cells lining the heart become activated and express adhesion molecules, further promoting the recruitment of immune cells. Recruited neutrophils and monocytes scavenge dead or dying cells and produce proteolytic enzymes to help in tissue repair. IL-10 production by regulatory T cells and transforming growth factor β (TGF β) and vascular endothelial growth factor (VEGF) production by macrophages further promote tissue repair, fibrosis, and angiogenesis. There is remodeling of both the infarcted as well as the remote or non-infarcted myocardium, and a careful balance of immune responses is needed to avoid development of further cardiac dysfunction such as heart failure or cardiac rupture. Recent clinical trials have shown that anti-inflammatory medications such as anti-IL1 β therapy [the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) [26]] or low-dose colchicine [Colchicine Cardiovascular Outcomes Trial (COLCOT) [27•]] can lead to fewer deaths from ASCVD. However, while deaths from ASCVD were reduced, widespread dampening of the immune system is not ideal and other fatal infections were elevated in the treatment groups in these studies. Thus, the role of inflammation in ASCVD, and the potential to target inflammation more specifically, are important areas of continued research.

Inflammatory Resolution

While much work continues to focus on eliminating pro-inflammatory stimuli, newer studies suggest that enhancing inflammatory resolution may be a superior approach. Inflammatory resolution is a process common in acute infections — with the end goal of tissue repair — but seemingly difficult to achieve with chronic inflammation. Resolution is not passive, but rather an active process involving many mediators, including proteins and lipids. A panel of lipid mediators (lipoxins, resolvins, protectins, and maresins) are derived from arachidonic acid, eicosapentaenoic acid, and docosahexaenoic acid and are generally termed specialized pro-resolving mediators (SPMs). In many animal studies, SPMs have been shown to reduce plaque progression and some human studies also suggest a link between SPMs and ASCVD. A comprehensive review of the contribution of the inflammatory resolution, or lack

thereof, to ASCVD was recently published by Doran [28]. SPMs have specific receptors that can promote inflammation or resolution depending upon the ligand binding to them. In addition to these lipid SPMs, there are also non-lipid cytokines such as IL-10 and pro-resolving gases such as nitric oxide that can promote inflammatory resolution.

Cell Death and Clearance

Several types of cell death have been identified, including apoptosis, necroptosis, autophagy, pyroptosis, and ferroptosis. Under homeostatic conditions, these processes are used to remove damaged, infected, or mutated cells. However, in the context of ASCVD, loss of control over these processes can promote disease [29]. A highly regulated process for the clearance of dead cells, termed “efferocytosis,” is another important aspect of inflammatory resolution and many studies show that enhancing efferocytosis can reduce plaque sizes in mouse models [30]. A new topic of research in this area is the contribution of intracellular metabolism to efferocytic capacity [31••].

Trained Immunity and Metabolic Intermediates

A burgeoning area of research involves understanding how metabolic reprogramming of immune cells in the atherosclerotic environment can contribute to plaque reduction. For example, clearance of dead cells results in the upregulation of oxidative phosphorylation, glucose uptake, and aerobic glycolysis, with a corresponding change in metabolic intermediates. In recent studies, deletion of the glycolytic enzyme pyruvate kinase muscle 2 in myeloid cells enhanced efferocytosis, resulting in decreased ASCVD [32•]. In contrast, deletion of aldehyde dehydrogenase 2 in the hematopoietic compartment impaired efferocytosis, resulting in increased plaque formation [33]. These changes in metabolic intermediates can lead to epigenetic modifications that result in a memory-like response of innate immune cells in a process called “trained immunity” or “innate immune memory” [34]. With relevance to ASCVD, after Western diet feeding of mice, myeloid cells are reprogrammed and retain their responses to innate stimuli, even after mice are switched back to a chow diet [35]. More recently, hyperglycemia has been shown to induce trained immunity in macrophages in a glycolysis-dependent mechanism. This training persists, and when these cells are transferred into normoglycemic hyperlipidemic mice, ASCVD is increased [36•].

Adaptive Immunity

Cells of the innate immune system, such as macrophages, are well known to play a key role in atherogenesis. Macrophages

predominate in the healthy heart, although smaller populations of monocytes, dendritic cells, mast cells, and T and B cells are also present [37]. Within lesions, macrophages become lipid-laden foam cells that can lead to inflammatory cytokine production, an unstable lesion, and plaque rupture. Subsequent studies illuminated the role of the adaptive immune system, where inflammatory cytotoxic T helper 1 (T_H1) cells and B2 B cells were shown to promote atherogenesis [38]. Recent studies on regulatory T cells (T_{regs}) and T_H2 cells also implicated a role for these immunomodulatory cells in protection from lesion formation and progression. The protective role of T_{regs} may be due to their ability to promote macrophage efferocytosis [39] or other pro-resolving plaque remodeling mechanisms [40•].

Other Areas of Research

Other emerging areas of research regarding how inflammation contributes to ASCVD include air and noise pollution, reduced and/or interrupted sleep, and other stressors [28]. These relationships open the door to considering how other methods of lifestyle modification could protect against ASCVD. In addition, identification of somatic mutations in hematopoietic stem cells that increase the development of acute leukemia also increases the risk of CVD [41••]. Thus, pools of immune cells in organs such as the spleen, lymph nodes, and adipose tissue could be considered relevant to atherosclerosis.

Non-ischemic Cardiovascular Disease

In contrast to ASCVD, non-ischemic cardiovascular disease is a broad category of conditions with variable involvement of the immune system. Much less is known about the contribution of the chronic inflammation of obesity to non-ischemic cardiovascular disease, and a brief summary of the current status of the research follows.

Myocarditis

Myocarditis, or inflammation of the heart, can be infectious or sterile and can result in ventricular remodeling, arrhythmias, or heart failure [42, 43]. The immune responses in myocarditis vary depending on the cause of the injury. For example, adenoviruses and enteroviruses are cardiotropic and cause direct myocardial injury by infecting cardiomyocytes; parvovirus B19 is vasculotropic and causes inflammation in the endothelial cells; coronaviruses including SARS-CoV2 may cause indirect cytokine-mediated cardiotoxicity [44, 45•, 46]; and immune checkpoint inhibitors used for cancer treatment cause T cell-mediated injury to unknown, presumably self, antigens [47]. Adipose tissue and systemic immune changes of obesity may contribute to myocardial

injury through soluble mediators that act locally (from epicardial adipose tissue surrounding the myocardium) or at a distance (from visceral adipose tissue within the abdomen) [48–50].

Conductive Disorders

The role of the immune system in conduction disorders of the heart is less understood [25]. There is a higher density of cardiac macrophages at the AV node, and macrophages are known to form connexin 43 containing gap junctions with cardiomyocytes and cells of the conduction system, possibly participating in depolarization and repolarization in the heart. While conductive disorders can occur in inflammatory settings such as sepsis or rheumatoid arthritis, and higher levels of circulating inflammatory markers are found in individuals with conductive disorders, it is unclear if immune dysfunction causally contributes to arrhythmias in humans. A recent study found a correlation between connexin 43 expression in blood immune cells and the inflammatory cytokine IL-6 in humans and demonstrated IL-6-induced downregulation of connexin 43 in vitro, potentially pointing to a mechanism [51].

Endocarditis

Endocarditis, or infections of the heart valves, are most often a result of abnormalities in the valves combined with circulating pathogens in the blood as is seen in bacteremia. It is unclear if resident immune cells at the valves are protective against endocarditis [25].

Heart Failure

Heart failure is a common endpoint of many causes of cardiac injury, including ischemia, myocarditis, valvular disease, and chronic uncontrolled hypertension. In contrast to heart failure with reduced ejection fraction (HFrEF), heart failure with preserved ejection fraction (HFpEF) is a heterogeneous syndrome that is not driven by loss of cardiomyocytes, is closely associated with the epidemic of obesity and metabolic syndrome, and shares cellular and molecular pathologies with these conditions including increased inflammatory responses [52]. In a large, prospective analysis of endomyocardial biopsies in individuals with HFpEF, CD68+ monocyte infiltration was increased in individuals with HFpEF versus controls [53]. Others have reported increased cardiac T cells and circulating monocytes, as well as increased circulating pro-inflammatory markers. Importantly, approximately 80% of individuals with HFpEF are obese, with expansion of the epicardial adipose tissue lining the heart that may contribute to the pathogenesis of heart failure as recently reviewed [54].

Hypertension

While salt retention and renal dysfunction contribute strongly to hypertension, recent work also reveals an immune component. One early event contributing to changes in renal blood flow and sodium transporter expression is an elevation in inflammatory cytokines. In addition, cells of both the innate and adaptive immune systems have been shown to contribute to hypertension.

Innate Immunity

The innate immune system plays an important role in mediating inflammation that accompanies hypertension. Elevated blood pressure leads to increases in damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs), ultimately activating innate effector cells. Under hypertensive conditions, macrophage colony-stimulating factor causes macrophages to release pro-inflammatory cytokines and prompts the adaptive immune system to respond [55]. Recent work has shown that renal tubular epithelial cells of diabetic mice fed a high-fat diet release substantial amounts of IL-1 β that bind to the IL-1R1 receptor on macrophages causing them to take on a pro-inflammatory phenotype. This ultimately drives the production of IL-6 stimulating salt-sensitive hypertension [56]. CD11c⁺ dendritic cells are increased in the spleen and kidneys of salt-challenged mice and can present antigen to both CD4⁺ and CD8⁺ T cells [57]. Natural killer cells (NKs) and neutrophils are two other cell types of the innate immune system that function in response to cardiovascular injury resulting from hypertension. NK cells and neutrophils act as a primary defense against bacterial infection that can capitalize on compromised vasculature [58]. The interaction of these cells with adaptive immune cells such as T_H1 and T_H17 cells promotes further inflammation and damage.

Adaptive Immunity

Salt sensitivity and insulin resistance share characteristics such as vascular dysfunction and immune activation stemming from CD8⁺ T cell stimulation. Impairment in PPAR γ function under both of these conditions may link insulin resistance and hypertension driving changes in the adaptive immune system [59]. In response to high salt environments, T cells become pro-inflammatory and travel via the circulatory system to the brain, heart, and kidneys [60]. These T cells produce pro-inflammatory cytokines damaging organ tissue leading to cardiac, renal, and neurodegenerative damage. Patients with hypertension display an increase in CD8⁺ T cells producing higher levels of perforin and granzyme B. These CD8⁺ T cells have been described as immunosenescent due to repeated antigen

stimulation [60]. B cells are also increased under hypertensive conditions and drive an accumulation of IgG in the aortic adventitia [61].

Sex Differences

An expanding area of interest in the contribution of the immune system to hypertension involves differences by gender. Premenopausal women are protected from hypertension compared with young men; however, after menopause, women are at increased risk of developing hypertension. One explanation for this change is the physiological effect of sex hormones on immune cell function. Although imperfect, animal models can provide some insight. In a rat model of spontaneous hypertension, infusion of the anti-inflammatory cytokine IL-10 reduced blood pressure in male but not female animals [62•]. In a DOCA-salt model, inflammatory T cells were equally increased in male and female mice; however, the female mice had increased T_{regs} compared to males [63••]. Furthermore, depletion of T_{regs} only increased blood pressure in females. For a detailed discussion of sex difference in hypertension, please see these recent review articles [64, 65].

Gut Microbiota

The gut microbiota, consisting of hundreds of species of bacteria, contribute to whole animal physiology by metabolizing food products and secreting molecules, such as short-chain fatty acids, or by synthesizing vitamins, trimethylamines, bile acids, and sterols. Many diseases are now known to be connected to changes in gut microbiota, including hypertension [66]. In humans, there is a positive correlation between *Klebsiella* spp. and *Streptococaceae* spp. with blood pressure [67•, 68]. Strikingly, germ-free mice that receive a fecal transplant from hypertensive people have increased blood pressure compared to recipients from normotensive individuals [69]. Finally, treatment of spontaneously hypertensive rats with losartan to reduce blood pressure concomitantly improved gut dysbiosis [70], suggesting a reciprocal relationship between hypertension and changes in gut microbiota.

Impact of Obesity on the Immune Response to Infectious Disease

Decades of research implicate obesity in infection outcomes [71–76]. Adipose tissue-derived adipokines, including leptin, adiponectin, resistin, and chemerin, are affected by a change from the lean to obese state. Adipokines act directly on immune cells and contribute to the chronic inflammatory state of obesity [77]. This disrupts immune

homeostasis and contributes to the differential immune responses and outcomes in infected obese hosts [78].

Streptococcal Pneumonia

Streptococcal pneumoniae is the most common cause of community-acquired pneumonia and a major cause of morbidity and mortality in the young, elderly, and immune-compromised individuals [79]. A prospective study including 26,429 men from the Health Professionals Follow-up Study and 78,062 women from the Nurses Health Study showed that a gain in 40 pounds or more from baseline was associated with a nearly twofold risk for community-acquired pneumonia [80•]. Leptin deficient *ob/ob* mice infected with *S. pneumoniae* had a fivefold greater burden of bacteria in their lungs compared to lean controls. Though these infected mice recruited a greater number of total leukocytes, comprising mostly polymorphonuclear cells (PMNs), to their lungs as well as achieved higher levels of TNF- α , macrophage inflammatory protein 2 and prostaglandin E2, they did not clear the bacteria effectively [81]. This was partly due to less effective bactericidal killing by PMNs in obese mice. Treatment of *ob/ob* mice with leptin restored PMN bactericidal function with a lower bacterial burden [81]. The effect of leptin on PMNs may be mediated by TNF- α [82].

Influenza Virus

Influenza A (H1N1) is a respiratory viral infection with a higher prevalence and death rate in obese compared to normal-weight individuals [71, 83]. This risk persists even in vaccinated individuals with serologic titers that might be considered protective [84]. CD4⁺ and CD8⁺ T cells from the peripheral blood of obese individuals had lower expression of markers associated with activation including CD69, CD28, and CD40L. Furthermore, ex vivo stimulation of peripheral blood mononuclear cells from obese individuals with live H1N1 virus was notable for lower expression of IFN- γ and granzyme B compared to normal-weight individuals [85]. A similar finding was reported in animals, whereby diet-induced obese mice infected with H1N1 had lower expression of IFN- γ by memory CD8⁺ T cells as compared to lean controls [86, 87].

Lymphocytic Choriomeningitis Virus

In a recent study, lymphocytic choriomeningitis virus (LCMV) grew to high titers in the adipose tissue compartment of infected mice. This preceded the recruitment of virus-specific CD8⁺ T cells [88••]. Mice with diet-induced obesity had a higher proportion of virus-specific CD8⁺ T cells which, upon viral rechallenge, were strongly activated

and led to tissue damage and death. This indicates that worse clinical outcomes in obesity related to viral infections such as LCMV could be due to collateral damage by virus-specific memory T cells in adipose tissue.

Human Immunodeficiency Virus

Individuals infected with human immunodeficiency virus (HIV) on long-term antiretroviral therapy have chronic systemic inflammation. They have persistently elevated C-reactive protein, D-dimer, and IL-6, which are among the inflammatory markers that are linked with the development of cardiometabolic disease [89–93]. Multiple factors may contribute to this persistent inflammation including the virus itself, altered microbiome, antiretroviral toxicities, and co-infections with other pathogens such as cytomegalovirus and hepatitis C [89]. Multiple studies have shown that adipose tissue is an important HIV viral reservoir [94, 95] and that immune changes such as a CD8⁺ T cell predominance seen with obesity [6] are also observed in normal-weight persons with HIV [96, 97]. Changes in adipose macrophage populations in persons with HIV or macaques with simian immunodeficiency virus have previously been limited to the description of M1 and M2 phenotypes, without clear differences from HIV-negative controls [98]. Lipid-associated macrophages, on the other hand, are increased in the adipose tissue of diabetic persons with HIV and are correlated with the adipose tissue CD4⁺ and CD8⁺ T effector memory cells [99]. These studies highlight that adipose tissue is an important HIV reservoir, with immune cells that may contribute to systemic inflammation and other comorbidities.

SARS-CoV2 Virus

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) pandemic has provided additional insights on the role of adipose tissue as a pathogen reservoir. Obese individuals are a high-risk group with increased rates of hospitalization and death [100–103]. Obesity-related changes in the immune system may contribute to these worse outcomes [72]. This could be due to higher SARS-CoV2 titers in obese individuals, partly from the upregulation of the functional receptor, angiotensin-converting enzyme-2, on the adipocytes of obese individuals [104], and/or the upregulation of other receptors such as the glucose-regulated protein 78 (GRP78) that promote binding of SARS-CoV2 [105] and severe infection [106–111].

Conclusions

Obesity and cardiovascular disease are intimately linked and often characterized by inflammation and a cluster of metabolic complications. In obesity, the immune system shifts towards a hyperinflammatory state, contributing to the

plethora of cardiovascular diseases discussed in this article. This heightened inflammatory profile and dysfunctional immune state also increase an individual's susceptibility to worsened health outcomes when faced with an infectious disease. To date, there are no targeted therapies to specifically reduce the inflammation of obesity and improve cardiovascular or infectious outcomes. However, focusing on specific immune cell types may be more beneficial in the future to combat cardiovascular disease. While many immunotherapies have evolved in the past decade, especially in the field of oncology, there are still many cellular and molecular characteristics of inflammation in obesity that need to be defined. Developing therapies specific to tissue and immune cell types important in obesity will be critical for managing long-term cardiovascular and infectious complications of this growing global problem. Lifestyle modifications in combination with immunosuppressants and immunomodulators may serve as effective strategies to combat and treat obesity-associated cardiovascular disease in the future.

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Compliance with Ethical Standards

Conflict of Interest Jamie N. Garcia, Celestine N. Wanjalla, Mona Mashayekhi, and Alyssa H. Hasty declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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