### Title

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# Obesity induced T cell dysfunction and implications for cancer immunotherapy

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## Abstract

Obesity has been shown to increase risk for a number of different disorders, including cancer. In addition, obesity is also associated with immune dysfunction, which could contribute to its strong association with other comorbidities. Recently, the immune system has been found to be heavily regulated by changes in metabolism. In particular, T cells are able to respond to intrinsic metabolic regulatory mechanisms, as well as extrinsic factors such as the changes in metabolite availability. The dysfunctional metabolic environment created by obesity could therefore have a direct impact on T cell responses. In this review, we highlight recent findings in the fields of T cell biology and obesity, with a focus on mechanisms driving T cell dysfunction and potential implications for immunotherapeutic treatment of cancer.

## Introduction

The incidence of obesity has risen drastically over the past few decades, and is reaching pandemic levels in the developed world [1,2]. Approximately 36% of the adult population in the U.S. is obese, and this number is expected to rise over the next decade [2]. Obesity is a major risk factor for a number of other comorbidities including diabetes, kidney disease, liver disease, cardiovascular disease, musculoskeletal disorders and cancer [3]. In addition, obesity has been associated with increased incidence of infectious disease [4]. It is not surprising, therefore, that the impact of obesity on healthcare spending is significant. Some estimates attribute up to $190 billion spent on obesity-related medical care in 2005 alone, or around 20 percent of the total annual U.S. healthcare expenditure that year [5]. Many of the comorbidities associated with obesity have been linked to dysfunction of the immune system [6].

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T cells represent a major component of the immune system, orchestrating and regulating major aspects of an immune response. Recently, they have begun to be appreciated for their dynamic metabolic tuning, that can change depending on activation or availability of different metabolites (i.e. glucose, fatty acids, etc.) [7,8]. In addition, checkpoint blockade therapies aimed at reinvigorating exhausted T cell responses are showing great promise in treating cancer patients in the clinic [9]. T cell exhaustion is characterized as a progressive and hierarchal loss of effector function following chronic antigen exposure and/or inflammation, and has been characterized in cases of viral infection, autoimmunity and cancer [10]. Obesity leads to a state of chronic inflammation, which can augment the T cell pool as well as lead to accelerated thymic aging [11,12]. Therefore, because of the large impact of obesity, and the promise of checkpoint blockade therapy in treating cancer, a better understanding of the effects of obesity on T cells and T cell exhaustion is needed to better utilize these therapies on the growing population of obese patients.

## Effects of obesity on the immune system

Obesity is associated with a state of chronic inflammation, characterized by a number of different changes in the immune system, including increases in serum pro-inflammatory cytokines such as IL-6 and TNFα as well as shifts in the memory to naive ratio of T cells [12,13]. Importantly, a similar phenotype has been characterized not just in mice and humans, but also canines and non-human primates [14–17]. Increases in adipose tissue lead to this inflammatory state, by recruiting different immune cell populations into the adipose tissue, notably macrophages and T cells. The inflammatory state is amplified by M1 macrophage polarization, as well as shifts to Th1/Th17 T cell populations [7,13,18]. An unknown question is the source of antigen(s) driving T cell activation in obesity, with some postulating there is an autoimmune component of obesity due to limited TCR repertoire diversity noted in T cell populations in adipose tissue [19,20].

In general, obesity leads to a state of accelerated immune senescence, similar to what is seen in aged individuals [11,21,22]. This accelerated immune aging phenotype has even been noted in obese children [23]. In line with this, obesity has been found to lead to poor vaccination responses [24,25]. A number of studies have examined the impact of obesity on immune challenge, with conflicting results. Most studies find obesity correlates with dysfunctional immunity. Notably, obesity has been found to lead to defects in memory maintenance following influenza infection, and was even found to be an independent risk factor for increased morbidity/mortality from the pandemic H1N1 infection [26–28]. However, a different study found that obesity did not impact the generation and maintenance of memory T cells following infection [29]. This highlights some of the caveats that come with studying obesity, the primary one being the variability in results due to the large number of variables inherent to obesity studies. Age is a large confounding factor in that it takes time to become obese, and we know that the immune system itself changes with time (age). Another factor is the type of diet or animal model used for obesity. Early studies on obesity relied on mutant mouse models, such as the leptin deficient ob/ob strain. More recently, diet-induced mouse models have become widely used, with both high fat diets and Western diets (i.e. NASH) being heavily reported. The age at which one starts inducing obesity can also have a profound effect on results, with one study reporting significant

changes in the immune phenotype of mice started on a high fat diet at 3 weeks of age that was lost if mice were instead started on the same diet at 12 weeks of age [30]. Intriguingly, caloric restriction has been found to reverse some of the effects of the accelerated immune aging seen in obesity, with reports of delays in T cell senescence compared to ad libitum fed control mice and non-human primates [14,15,31].

## T cell metabolism and obesity

Obesity induces a state of chronic metabolic dysfunction, with altered serum levels of insulin/glucose, leptin/adiponectin, among other hormones and adipokines [32–35]. Many of these same molecules that are important in regulating the metabolic state of an organism, have been shown to have direct effects in regulating immune activation [7,18]. The insulin receptor is upregulated upon T cell activation to support glucose metabolism, and insulin has been shown to polarize toward a Th2 phenotype [36,37]. Adiponectin has been shown to have both pro- and anti-inflammatory properties, as well as direct negative effects on antigen-specific T cell activation [33,34]. The levels of adiponectin have been shown to decline in obesity, thus providing another source of immune dysfunction. Leptin is a hormone involved in regulating satiety, and has effects on many aspects of immune function, primarily stimulating pro-inflammatory responses [32]. It has been shown to promote Th17 differentiation, as well as have a key role in regulating regulatory T cell proliferation [38,39]. More recently, it has been shown to support T cell activation through metabolically reprogramming the T cells [40]. Leptin levels are elevated in obese individuals and could therefore provide a mechanism behind the immune dysregulation found in obese individuals.

In addition, immune cells themselves have recently become more appreciated for the dynamic metabolic shifts that occur during development and activation [7,18]. Naïve T cells remain in a quiescent state, reliant on oxidative phosphorylation for their energy needs. Upon activation, the metabolic signature changes to support increased glycolysis to support the energy needs of the cell. Finally, memory T cell formation is accompanied by another shift to fatty-acid oxidation (FAO). Clearly T cells alter their metabolic profile and needs upon antigen recognition, but what remains unclear is how the metabolic dysfunction caused by obesity might alter the balance in T cell activation. Indeed, Mauro et al. recently showed that a high-fat diet can lead to development of inflammatory effector memory $CD4^+$ T cells [12]. This effect was mediated by inducing metabolic stress using the saturated fatty-acid palmitate. Memory T cells have been shown to be reliant on FAO for development and survival [41]. More recently, the source of fatty acid supporting FAO in these memory T cells was shown to be both exogenously and intrinsically sourced [42,43]. Pan et al. showed that tissue resident memory T cells require exogenous lipid uptake through fatty-acid-binding proteins 4 and 5 (FABP4 and FABP5), and FAO to persist in tissue and mediate protective immunity [43]. In addition, the type of fatty-acid can also have an impact on the type of immune response, with long chain fatty-acids promoting Th1 and Th17 differentiation, and short chain fatty-acids leading to increased regulatory T cell differentiation [44]. Thus, the functional response of a T cell is linked to its metabolic state which can be directly impacted by overall metabolic states of the individual.

## Effects of obesity on cancer

The significance of obesity as a risk factor for cancer incidence has become clear over the last few decades, with some epidemiological studies estimating obesity to surpass smoking as the number one causative agent of cancer [45–47]. Most cancer types have been linked to obesity, but the most significant trends concern cancers of the colon, esophagus, kidney, breast and corpus uteri. In addition, obese patients face a multitude of added complications from diagnosis, to treatment and management [48]. Multiple mechanisms have been proposed for how obesity impacts cancer progression, and it is likely not a solitary factor that drives these effects, but rather a combination of metabolic and inflammatory effects on both the tumor and the immune system [49,50]. Indeed, fasting has been linked to effects on tumor sensitization and subsequent enhancement of chemotherapy as well as direct effects on immune subsets leading to enhanced immunosurveillance [31,51,52]. Brandhorst et al. provide a comprehensive examination of the effects of periodic fasting on multiple aspects of health including metabolism, cognitive function, immune function and bone loss, in yeast, mouse and human [31]. Importantly, they found that period fasting decreased spontaneous tumor incidence in C57BL/6 mice. In addition, diet-induced obese mice were shown to have increased tumor growth and metastasis using multiple strains and tumor models [53–58]. A number of difficulties exist when it comes to treating obese cancer patients, including challenges caused by other comorbidities, difficulty with diagnosis or differences in physiology and pharmacokinetics [48]. Immunotherapies aimed at stimulating the immune system have revolutionized the field of cancer treatment [9]. Being that the immunotherapy field is relatively young, a number of toxicities independent of obesity still persist in patients undergoing treatment and limit efficacy [59,60]. However, Mirsoian et al. showed obese mice undergoing strong immunostimulatory therapy (high dose IL-2 and agonistic anti-CD40) experience rapid and lethal cytokine storm, dependent on macrophage produced TNFα [61]. Interestingly, this phenotype could be reversed with caloric restriction. Based on this and the rising incidence of obesity, more research is needed on the effects of obesity on cancer therapy.

## Obesity and T cell exhaustion

Obesity's effect on the immune system can generally be described as accelerated immune aging, and one of the hallmarks of the immune aging is thymic involution and T cell senescence [62]. Consistent with this, obesity has previously been shown to accelerate thymic aging [11]. This is in contradiction to another report that found obesity lead to increases in thymic weight and cellularity, but this did not translate to significant differences in T cell numbers between lean and obese mice [63]. Therefore, one could argue that obesity lead to defects in thymic output on a per gram basis. Nonetheless, defects in thymic function could account for many of the complications with infection and cancer in obese patients. Most studies examining the functional potential of T cells in obesity find defects in their ability to mount effective immune responses in multiple species and models [14–17,23,26,27,64–66]. On the other hand, some have found enhanced T cell function, leading to exacerbated pathology and disease [67,68]. Differences in the model and experimental design could account for these discrepancies. As mentioned before, the length of time on the

diet and when the diet was started could have a profound impact on the extent of obesity's effect on T cells [30].

Chronic stimulation has been shown to lead to an exhausted phenotype in T cells, characterized by decreased proliferation and production of effector molecules, and increased expression of inhibitory receptors [10]. It is likely the chronic inflammatory environment, combined with the added changes in immune-active metabolites (leptin, adiponectin, glucose) could lead to an exhausted phenotype amongst T cells in obese individuals. TNFα was recently shown to be a critical inducer of T cell exhaustion in chronic viral infection, and obesity leads to increased levels of TNFα [69,70]. In addition, fatty acid mediated activation of T cells adds to this cascade of potential mediators of T cell exhaustion in obesity (Figure 1) [12]. PD-1 expression was even found to be linked to the metabolic status of T cells, dependent on changes in glucose availability in vitro [71]. More recently, PD-1 was shown to augment energy metabolism and mitochondrial biogenesis of exhausted T cells by regulating expression of the key metabolic transcriptional regulator PGC-1α [72]. The authors also showed that early exhausted T cells upregulated expression of Cpt1a, a key regulator of FAO. PGC-1α levels have been previously shown to be decreased in the adipose tissue of obese individuals [73]. Therefore, the constant changes in the metabolic and activation status of T cells that occurs in obesity could lead to a terminally differentiated exhausted T cell phenotype.

The extent of T cell exhaustion or dysfunction could be dependent on the tissue examined as well, as recent work has identified a population of T cells in visceral adipose tissue displaying a senescent phenotype [74]. Shirakawa et al. show that a high fat diet caused an accumulation of $CD4^+$ T cells with an effector memory phenotype, which expressed PD-1 and CD153 in adipose tissue. Other tissue resident T cell populations in the setting of obesity remain to be examined. Organs such as the liver, where large fat deposits are known to occur, or organs known to be adversely affected by obesity would be of interest as potential niches for exhausted T cells. The increased levels of PD-1 expression in adipose tissue, as well as the increased adiposity associated with obesity leads to the question of what effects this could have on immunotherapy treatment of cancer. Checkpoint blockade is an emerging immunotherapy aimed at reinvigorating anti-cancer T cell responses through monoclonal antibody blocking of inhibitory receptors such as PD-1 on T cells [75]. Obese patients who are found to have T cells that express high levels of PD-1 might have a better response to anti-PD-1 treatment. Conversely, due to all of the known toxicities associated with emerging immunotherapies, as well as the known issues with immunotherapy in obese mice, obese patients might be at increased risk for toxicities or complications. More research is needed on the effects of obesity on T cell exhaustion, and the implications for checkpoint blockade therapy.

## Conclusion

It is clear that obesity and the metabolic dysfunctions associated with it can have a profound effect on the status of the immune system. Here, we have highlighted some of the more current findings on this front, with a focus on T cells and implications in cancer immunotherapy. A combination of mechanisms are likely responsible for the T cell

dysfunction noted in obesity (Figure 1). The chronic stimulation T cells experience can lead to an exhausted-like phenotype. It is important to distinguish this from other exhaustion phenotypes as there is no known antigen driving this in obesity, and therefore it is unclear if this is exhaustion or senescence or tolerance. The impact of obesity on human health is massive, with no clear end in sight due to its continued rise. With this in mind, better pre-clinical modeling is needed to more closely represent who is being treated in the clinic, and lead to better outcomes when moving treatments into the clinic.

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## Highlights

- Obesity leads to a state of metabolic and immune dysfunction
- T cells are highly tuned by multiple intrinsic and extrinsic metabolic mechanisms
- Obesity can alter the efficacy of emerging cancer immunotherapies

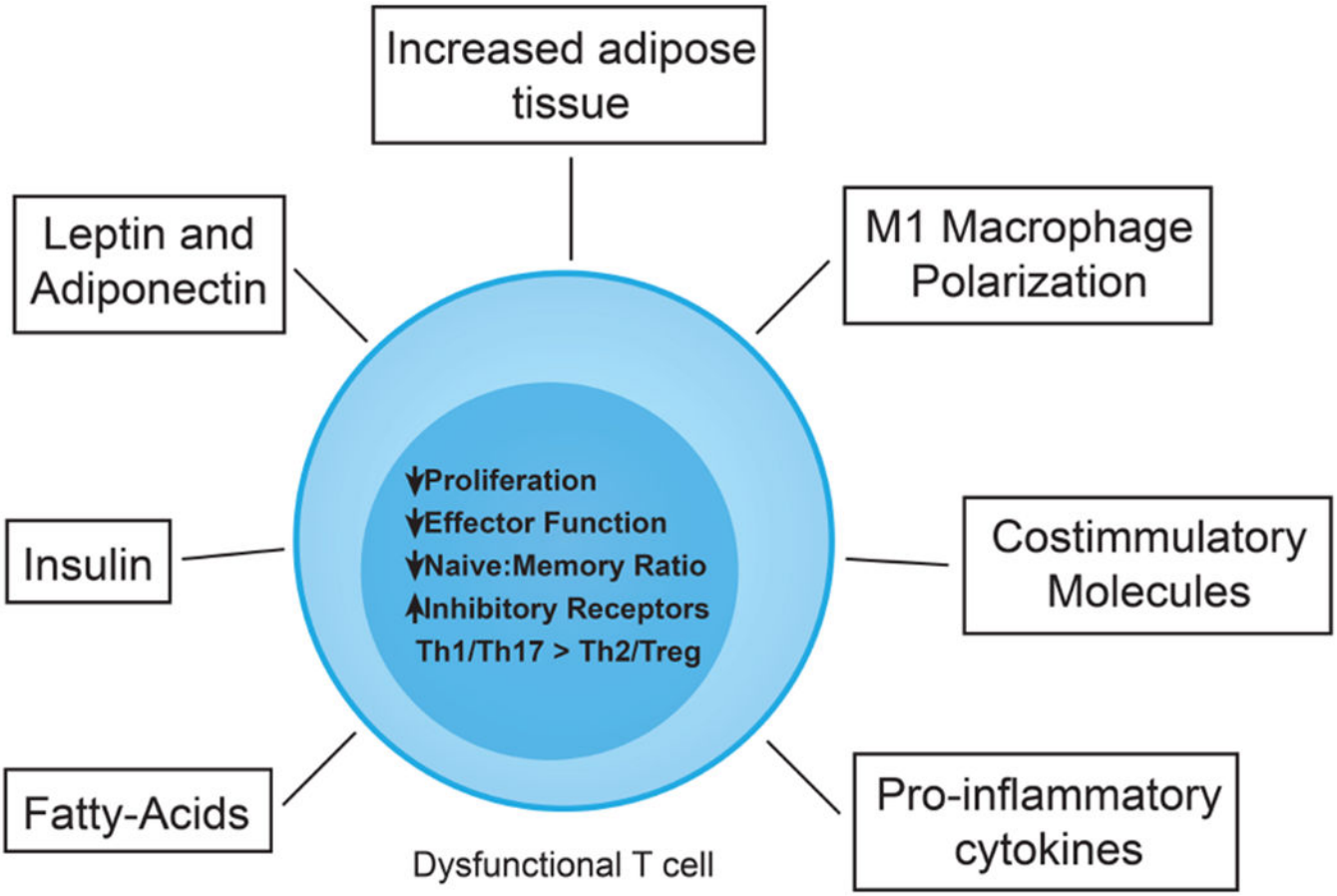


**Figure 1: Mechanisms driving T cell dusfunction in the setting of obesity.**

Increased adipose tissue appears to be the primary driver, producing adipokines such as leptin and adiponectin that have immune regulatory functions, and result in the recruitment of immune cells with altered levels of different metabolites such as fatty-acids, leptin or adiponectin. The local inflammatory environment drives M1 macrophage polarization as well as increased expression of co-stimulatory molecules resulting in T cell activation as well as elevated levels of proinflammatory cytokines. In addition, the altered metabolites (leptin, adiponectin and fatty-acids) can have direct effects on T cell activation. Collectively, they result in a dysfunctional T cell characterized by decreases in proliferation and effector function (i.e. cytokine production), as well as a decrease in the naive to memory T cell ratio. In addition, these changes will be accompanied by an increase in inhibitory receptor expression (i.e.PD-1) as well as imbalances of Th1 and Th17 responses over Th2 and Tregs.