# Obesity altered T cell metabolism and the response to infection

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An epidemic of obesity over the past three decades increases the risk of chronic and infectious diseases for adults and children alike. Within the past few years, obesity has been shown to impair the adaptive immune response to infection through alterations in T cell functioning. Growing evidence suggests that perturbations in T cell metabolism drives this stunted immune response, stemming from nutrient, hormone and adipokine dysregulation in the obese. In this review, recent findings in the fields of obesity and T cell mediated immunity demonstrate a unique relationship between altered mechanisms of T cell metabolic homeostasis and plasticity of adaptive immune responses in the obese setting.

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## Introduction

The immune response to infection involves a complex orchestra of diverse cell types, including dendritic cells, macrophages, natural killer cells, and B and T cells.

As one of the most prominent and critical players in the response to infection, subsets of T cells range in activity from supporting the function and activation of other immune cells, as well as T cells themselves, to producing pro and anti-inflammatory proteins. Cytotoxic T cell subsets are instrumental in the elimination of pathogen-infected host cells. This diversified set of immunologically adaptive immune cells plays a critical and central role in combating pathogens. A number of T cell subset knockout models have demonstrated that removal of T cells during an infectious challenge often results in higher rates of morbidity and mortality. For many years, T cell activation and function was believed to occur from a combination of antigen recognition, subsequent signaling cascades and micro-environmental cues [1,2]. However, recent studies have clearly demonstrated that the cellular metabolism of the T cell is also a key player affecting T cell differentiation, proliferation, function and its ultimate fate [3,4,5•,6–8].

Reports of how metabolic fuels such as glucose, amino acids and fatty acids elicit distinct metabolic profiles depending on cell state (naïve, effector or memory) and subtype (Th1, Th2, Th17, Treg, *etc.*) [4,9–11], has led to a revolution in the understanding of T cell driven immunity. Furthermore, it highlights the metabolic plasticity of T cells to respond to the energetic and biosynthetic demands required to successfully fight infection. For primers on T cell metabolism, refer to the excellent reviews by MacIver *et al.* [4] and Buck *et al.* [5•].

Although T cells respond to antigenic challenge by altering their metabolic state, what is not as well understood is how metabolic conditions may alter their ability to function. One such metabolic condition that may have a profound effect on T cell function is obesity. Obesity has classically been characterized as a state of excess adiposity and is associated with chronic inflammation and metabolic dysfunction such as hyperglycemia, hyperleptinemia and hormone resistance [12]. These uncontrolled metabolic conditions can lead to the development of chronic diseases such as type II diabetes, kidney disease, cardiovascular disease and specific cancers [13]. However, recent data from our lab and others demonstrates a link between obesity and increased incidences of infectious diseases, most likely through impaired cellular immune responses [13,14].

Considering recent findings on how T cell metabolism drives cellular function and survival, understanding how obesity impacts these processes in T cells remains critical. This review examines recent works in the fields of obesity and T cell mediated immunity; exploring possible mechanisms of inflammation, hormone and adipokine regulation, and senescence to understand the altered response to infection in obesity through changes in T cell metabolism.

### T cell metabolism supports cell survival and function

T cells display unique metabolic flexibility unlike other cells in the body. Upon stimulation of the T cell receptor (TCR) and costimulatory receptors, T cells undergo a dramatic metabolic shift from a quiescent to activated

state, highlighted by a change from primarily catabolic to anabolic metabolism (Figure 1) [4]. This shift from oxidative phosphorylation to glycolysis produces ATP and supports the generation of nucleotides and amino acids for the production of daughter cells necessary to mount an effective immune response [15]. Importantly, this glycolytic shift supports effector functions, which varies depending on T cell subtype [3,11,16]. Following clearance of the infection, the majority of effector T cells undergo apoptosis with a small subset remaining as long-lived memory T cells [17,18]. These memory T cells revert back to a relatively quiescent catabolic state. However, unlike their naïve cell counterparts, memory T cells quickly respond to antigenic challenge upon re-exposure through elevated metabolic activity, increased proliferation and production of cytokines [19,20].

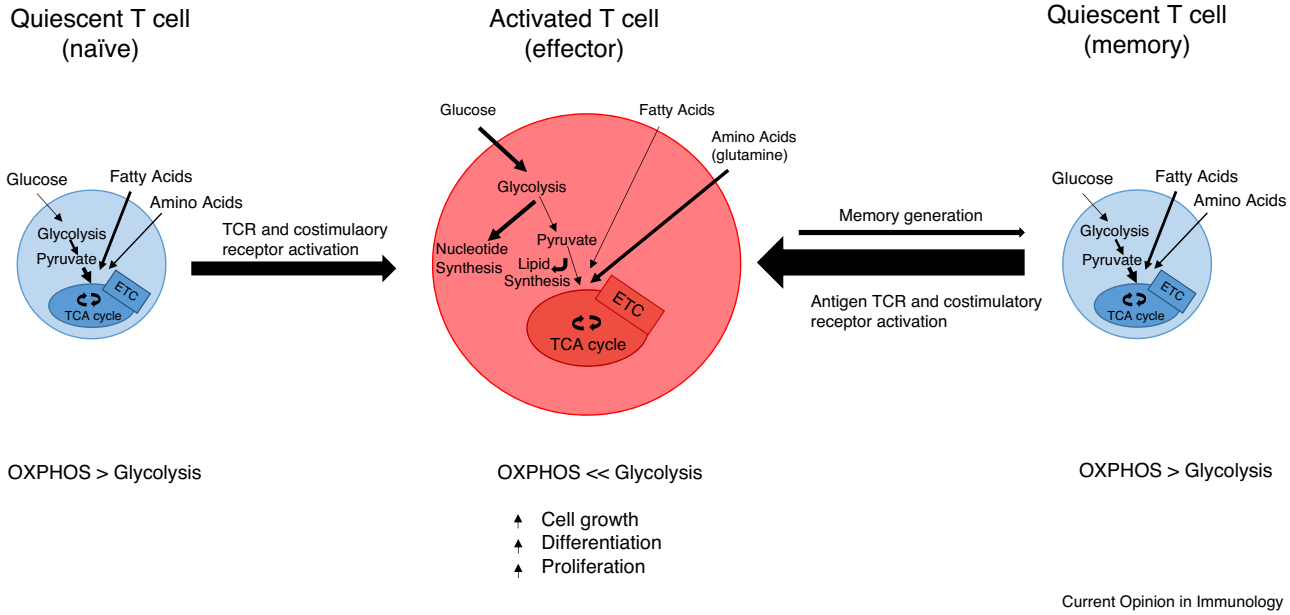
These different metabolic states of T cells require signaling molecules to support homeostasis, effector function and survival. Cytokines such as IL-7 and IL-15 support the catabolic survival functions of naïve and memory T cells, respectively [16,21,22]. Other cytokines, such as IL-2, support proliferation upon stimulation [23•], while interferon gamma (IFN-γ) promotes pro-inflammatory T cell subtypes like Th1 and cells of innate immunity [24]. T cell subsets also help to down-regulate the inflammatory response once pathogen clearance has occurred. For example, regulatory T cells ($T_{reg}$) and the cytokine IL-10 help to suppress T cell activation and proliferation [24,25].

Aside from cytokine and growth factor signals, nutrients and hormone signaling also influence T cell metabolism [8,23•,26••]. These signals have been shown to affect regulatory pathways controlled by enzymes such as the mammalian target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK) to influence cell growth/proliferation or homeostasis [27,28]. In the absence of these extrinsic signals, T cells lose their ability to maintain homeostasis and eventually succumb to apoptosis through Bcl-2 mediated cell death [7,28].

### Obesity impairs the immune response to infection

As of 2014, for the first time in recorded history, obese adults outnumber underweight adults worldwide, with the global prevalence of obesity equaling 10.8% in men and 14.9% in women [29]. In the United States, obese adults comprise 36.5% of the population [30]. Obesity has been linked with increased incidences of infectious diseases, including periodontal infections, influenza, bacterial pneumonia, nosocomial and surgical site infections, among others [13,31]. Furthermore, obesity has been

**Figure 1**




T cell metabolism and state of quiescent and activated T cells. Quiescent T cells utilize oxidative respiration of glucose-derived pyruvate as well as fatty acids and amino acids to produce ATP through the TCA cycle and electron transport chain. This energy production supports immune surveillance and homeostasis. Upon stimulation of the T cell receptor (TCR) and costimulatory receptors, T cells upregulate glycolysis and glutamine oxidation while reducing fatty acid oxidation to support cell growth, differentiation and the production of daughter cells. Following clearance of the pathogen, the majority of T cells undergo apoptosis with a subset surviving as memory T cells, which return to a quiescent state dependent on oxidative phosphorylation of fatty acids.

shown to impair immunological responses in both adults and children [32–34].

Following the first influenza pandemic of the 21st century, obesity was identified as an independent risk factor for increased morbidity and mortality from pandemic H1N1 infection [31]. Our laboratory studied the response to influenza vaccination in obese adults and found that increasing BMI was associated with greater declines in influenza-specific antibody titers one-year post vaccination [33]. In addition, influenza-stimulated T cells from obese adults were less functional and less activated compared with T cells from vaccinated healthy weight adults [35].

Obesity has been shown to reduce circulating levels of γδ T cells, as well as impair their function through reduced IL-2 receptor expression and IFN-γ production [36]. Moreover, obesity has been implicated in reduced function of $T_{reg}$ cells in obese patients with asthma [37]. Finally, growing evidence suggests obesity impairs immune responses to vaccines such as hepatitis B (HB), hepatitis A (HA), rabies and tetanus, as well as increases risk of several bacterial infections [38].

Despite this growing evidence supporting the notion that obesity impairs immunological responses to infection, it is worth noting that some studies have found a protective effect of obesity against infection. Roth *et al.*, in their review of over 20 epidemiological studies, found that obesity was associated with better outcomes from infections such as tuberculosis, community-acquired pneumonia and sepsis [39]. They argue that aspects of the metabolic syndrome often found in obesity provide an advantageous niche for immune cells to fight off infection. While there is controversy between findings on obesity's impact on the immune response to infection, it is important to note that obesity is a multifactorial condition that impacts a variety of tissue and organ systems.

### Obesity alters the metabolome during infection

Studies using murine models of obesity have shown great similarity to obesity in humans, providing a translational model to study this complex condition [40]. Recent studies have shown altered metabolic profiles in diet-induced and genetically obese mice following influenza virus challenge *in vivo*. Using $^{1}$H NMR and global liquid chromatography-mass spectrometry, Milner *et al.* reported specific alterations in the metabolic profiles of influenza-infected diet-induced obese mice when compared with infected lean mice in serum, liver, lung, mesenteric white adipose tissue, urine, feces and bronchoalveolar lavage fluid [41,42••]. Changes in metabolites included increased levels of fatty acid, cholesterol and phospholipids in lung tissues isolated from obese mice compared to lean mice, correlating with increased lung damage and mortality observed in the infected obese mice [42••].

Notably, obese mice showed significant fold increases in glutamyl-proline, tetrahydrocortisol, 3-hydroxybutyric acid and numerous acyl-carnitine metabolites in lung tissues [42••], suggesting differential metabolism in these tissues may be driving immune dysregulation in the influenza-infected lung. Additionally, diet-induced obese mice also had a 55-fold increase in *p*-cresol sulfate concentrations in lungs at 4 days post infection compared to lean mice [42••]. *P*-cresol sulfate, a metabolite produced by gut microbiota during secondary metabolism of *p*-cresol, accumulates during kidney failure and can impact cell function [42••]. This increase in secondary metabolites in obese mice suggests that obese microbiome may differ from lean, and thus contribute to differences in immune function.

In order to differentiate between the dietary vs. obesity effects, mice lacking hypothalmic leptin receptors ($LepR^{H-/-}$) were utilized in the influenza infection model. $LepR^{H-/-}$ knockout mice were established by crossing fully floxed leptin receptor mice with Cre transgene expressing C57BL/6J-Tg(Nkx2-1-cre)2S mice driven by the Nkx2.1 promoter. These transgenic mice lacked leptin receptor signaling in hypothalamic neurons, resulting in obesity from excess consumption of a low fat chow diet; therefore removing the influence of high fat diet on immune function. Compared to lean controls ($LepR^{HFlox/Flox}$ consuming an identical diet), obese mice that gained weight on the chow diet also exhibited altered metabolic profiles. Similar to high fat fed diet-induced obese mice, the $LepR^{H-/-}$ obese mice had altered fatty acid, cholesterol and nucleic acid metabolites in urine and lung tissues following influenza virus infection [42••]. Again, these variations in metabolites correlated with greater lung pathology and inflammation, as well as reduced levels of quiescent and activated $CD4^{+}$ and $T_{reg}$ cells in the lung and bronchoalveolar lavage fluid during the immune response to influenza virus infection [42••]. These studies suggest that obesity itself, not the diet, alters metabolites both in circulation and in tissue specific regions impacted by infection. This work supports our proposal that obesity alters the metabolic landscape of the host, thus impairing T cell function, leading to increased susceptibility to infectious disease.

### Adiopocytes in the obese state promote inflammatory T cell activation through altered metabolism

Another theory as to how obesity impairs the T cell response to infection involves the distorted cytokine and adipokine milieu brought about by excess adiposity. Leptin, a hormone involved in energy homeostasis, has been shown to be essential for glucose uptake in effector T cells [26••]. Upregulation of Glut1 receptors by leptin signaling under normal conditions represents a bioenergetic advantage for T cells to prevent suppressed proliferative and functional responses when glucose concentrations become limited [7,23•,26••]. However, in obesity,

when leptin secretion becomes systemic and chronic, leptin signaling may lead to altered $CD4^+$ T cell differentiation. Leptin signaling has been shown to promote pro-inflammatory T cell subtypes, $Th_1$ and $Th_{17}$ [26••,43,44], suggesting leptin plays a critical role in the development of an inflammatory adipose tissue microenvironment. Leptin's role in modulating T cell repertoires, leading to inflammatory adipose tissue microenvironments is further supported with the identification that pro-inflammatory $CD8^+$ T cells precede adipose tissue macrophage (ATM) infiltration in visceral adipose tissue, with marked declines in $CD4^+$ helper T cell and $T_{reg}$ cell populations in obese mice compared to lean [45].

Infiltration of T cells in adipose tissue has received attention for its suggested role in the development of insulin resistance [46]. Recent findings by Morris *et al.* identified a mechanism by which ATMs function as antigen presenting cells (APCs) to regulate the activation of $CD4^+$ T cells in mice [47]. This finding, reproduced by Cho *et al.*, identified a novel MHCII-dependent activation loop between $CD4^+$ T cells and ATMs which supports T cell driven metainflammation in adipose tissue in mice [48].

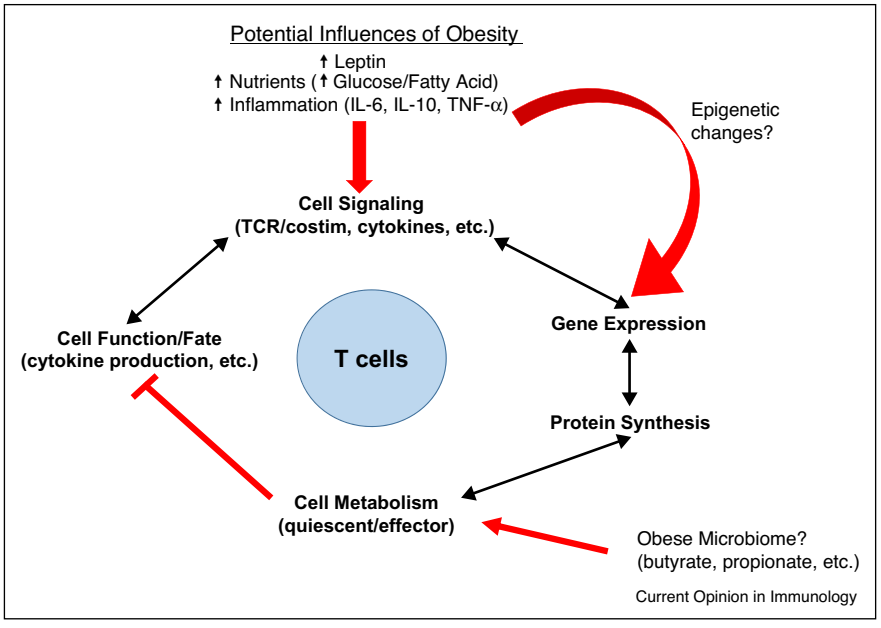
However, large human adipocytes were also shown to activate $CD4^+$ T cells through MHCII-upregulation, thereby acting as APCs to stimulate T cell inflammatory effector functions [49•]. This activation of adipose tissue associated T cells by MHCII-mediated APCs and leptin costimulation supports the notion of an inflammatory microenvironment observed in obese adipose tissue. These findings suggest the possibility that obesity leads to suppressed T cell response to infection through altered T cell populations caused by premature activation to pro-inflammatory T cell subtypes.

### Adipocytes in the obese state promote T cell senescence

Senescence, typically associated with aging, is described as a fate in which cellular proliferation becomes halted but metabolic activity and function remains [50]. This cell phenotype represents a state of cellular exhaustion, supported by chronic activation of Akt and mTOR, thereby supporting cytokine production but limiting proliferation [50,51]. Recently, obesity was proposed to increase T cell senescence in visceral adipose tissue (VAT) of high fat fed obese mice [52•]. These mice displayed increased accumulation of $CD153^+PD\text{-}1^+CD44^+CD4^+$ T cells in VAT, resembling the activity of senescent associated T cells, with increased osteopontin secretion and VAT inflammation [52•]. Previously, osteopontin has been shown to be a Th1 promoting cytokine that supports pro-inflammatory function [53].

This increased production of PD-1 (programmed cell death-1), an exhaustion/tolerance marker, [54], signals an exhausted state of visceral adipose T cells. This role

**Figure 2**




Mechanism of impairment of normal T cell signaling and response to infection in obesity. Nutrients, leptin and inflammation signals cause a disruption of normal T cell metabolism, resulting in impaired cellular functions. Long-term exposure to these extrinsic signals alters the metabolic profile of T cells, impacting their feedback of cytokine secretion and functional response to infection. Whether or not long-term exposure results in epigenetic changes, or metabolite influence from obese microbiota has yet to be determined.

of PD-1 as an immune regulator of TCR activation in effector T cells is evidenced by the establishment of PD-1 expressing $CD8^+$ effector memory T cells, and not central memory T cells [55]. Furthermore, strength of PD-1 expression is tied to signaling activation and effector function in T cells, such that high expression of PD-1 is needed for cell exhaustion but only low levels are required to disrupt some functions such as IL-2 or TNF-α secretion [56].

Finally, $CD4^+$ T cell metabolism was shown to alter PD-1 expression in mice cultured with glucose versus galactose [57]. This alteration in T cell metabolism from aerobic glycolysis to respiration resulted in differences in glyceraldehyde 3-phosphate dehydrogenase expression, correlating with PD-1 expression and subsequent impairment in IFN-γ production [57]. This connection between aerobic glycolysis of $CD4^+$ T cells and PD-1 expression demonstrates a novel mechanism through which T cell function is influenced by nutrition. How long-term exposure to obesogenic conditions impact gene expression remains unresolved. However, some recent studies suggest that obesity can lead to the hypermethylation of lymphocyte DNA in humans and animals [58,59], thereby proposing an epigenetic component that supports the conditions of obesity associated T cell senescence.

## Conclusion

Despite the lack of direct evidence linking obesity and altered T cell metabolism with impaired immune response to infection, foundations from several studies over recent years support the hypothesis that obesity disrupts T cell metabolism, resulting in impaired function. Altered metabolism of the obese host has been shown both in the steady state and during infection. Hormone resistance, inflammation and alterations in nutrient levels all influence T cell activation, function and survival. A surfeit of nutrients such as glucose and fatty acids, along with excess leptin production in the obese state, may elicit the activation of T cells in the absence of specific pathogens, thus, skewing naïve and memory cells towards inflammatory Th1 & Th17 subtypes, while reducing anti-inflammatory $T_{reg}$ repertories (Figure 2). The response to infection in an obesogenic environment most likely would result in disrupted T cell metabolism through increased glycolytic and oxidative flux and cause impaired T cell response by promoting inflammation and reducing anti-inflammatory immune surveillance. How chronic exposure to excess nutrients, hormones and inflammation influences gene regulation in lymphocytes remains unknown. Obesity as a complex multifactorial condition represents a growing and serious health problem, warranting further study.

## Conflicts of interest

The authors have declared no conflicts of interest.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- •• of outstanding interest


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