Minireview

The burden of obesity on infectious disease

Erik A Karlsson[1] and Melinda A Beck[2]

[1]Department of Infectious Diseases, St Jude Children's Research Hospital, Memphis, TN 38105-3678; [2]Department of Nutrition, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC 27599-7461, USA
Corresponding author: Melinda A Beck, Department of Nutrition, Gillings School of Global Public Health, 2303 MHRC, CB #7461, University of NC at Chapel Hill, Chapel Hill, NC 27599-7461, USA. Email: melinda_beck@unc.edu

Abstract

The world is now experiencing an epidemic of obesity. Although the effects of obesity on the development of metabolic and cardiovascular problems are well studied, much less is known about the impact of obesity on immune function and infectious disease. Studies in obese humans and with obese animal models have repeatedly demonstrated impaired immune function, including decreased cytokine production, decreased response to antigen/mitogen stimulation, reduced macrophage and dendritic cell function, and natural killer cell impairment. Recent studies have demonstrated that the impaired immune response in the obese host leads to increased susceptibility to infection with a number of different pathogens such as community-acquired tuberculosis, influenza, *Mycobacterium tuberculosis*, coxsackievirus, *Helicobacter pylori* and encephalomyocarditis virus. While no specific mechanism has been defined for the decreased immune response to infectious disease in the obese host, several obesity-associated changes such as excessive inflammation, altered adipokine signaling, metabolic changes and even epigenetic regulation could affect the immune response. This review will discuss what is currently known about the relationship between obesity and infectious disease.

Keywords: obesity, immune response, infection, vaccine, adipokine

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Introduction

Humans, as a species, are poorly adapted to overnutrition. Having evolved in times of frequent famine, the human body is not developed for constant exposure to a calorie-rich and sedentary environment.[1,2] The obese state can lead to serious health consequences and subsequently, increases in health-care requirements and economic burden. Caused by a change in energy balance of increased caloric intake versus expenditure,[3] obesity has been linked to numerous health problems and chronic diseases.[4–6] These co-morbidities associated with obesity have been attributed to hormonal and metabolic changes related to increased adipose tissue mass.[7–9] Although obesity is well established as a risk factor for increased morbidity and mortality, its effects on susceptibility to infection are just beginning to be understood.

Nutrition and the function of the immune system are intimately linked. Immunocompetence is dependent on nutritional status and can be easily dysregulated in states of imbalanced nutrition such as obesity. Lymphoid tissues have an extremely rapid turnover and appear to be particularly sensitive to nutrient imbalances, particularly those which affect metabolic pathways and functions necessary for adequate immune defense.[10] Although there is no 'smoking gun' directly implicating obesity in immune system impairment, many pathways that have an important role in the immune response are altered in the obese subject.[10,11] Any impairment in the immune response in the obesigenic state may leave the obese individual more vulnerable to infection. This review will focus on what is known about the effects of obesity on infectious disease and speculate on possible mechanisms for increased susceptibility of the obese host.

The epidemiological perspective

Epidemiological data support the hypothesis that obesity can affect immune function in humans. Findings from hospitalized, obese patients have been reviewed by several groups.[12–15] Briefly, in the hospital setting, obese patients are more likely to develop secondary infections and complications such as sepsis, pneumonia, bacteremia, and wound and catheter-related infections. Patients with increased body mass index (BMI) and adiposity also present a higher incidence of surgical site infections, which have been associated with increased risk of other wound complications, increased length of stay and increased risk of death.[16–18] Obesity negatively affects pulmonary function, and hospitalized

obese patients have been shown to be at increased risk for pulmonary aspiration and community-related respiratory tract infections.[19,20] In the Health Professionals Follow-up Study and the Nurses Health Study II, increased BMI (kg/m^2) and weight gain (versus weight maintenance) were directly associated with increased risk for community-acquired pneumonia in women.[21,22] Increased susceptibility to acute respiratory tract infection has also been shown to be associated with BMI in overweight children.[23]

Recent studies have further confirmed these findings. Obesity has been associated with increased risk of wound complications and surgical site infections both in and out of the hospital setting.[24–28] Obesity has also been confirmed to increase risk of infection apart from surgical outcomes. Increased BMI is associated with increased risk of infection in institutionalized, geriatric patients.[29] Obese individuals are at increased risk for *Helicobacter pylori* infection,[30] and children with increased BMI were found to be at three times greater risk of being asymptomatic carriers of *Neisseria meningitides*.[31] Perhaps most notably, for the first time, morbid obesity has been considered an independent risk factor for increased severity of infection and death from the novel H1N1 pandemic influenza strain.[32]

Studies of obesity and immunity in humans

Studies of the immune system in obese humans are primarily focused on *ex vivo* cellular functionality (Table 1). Obese subjects have altered the overall number of circulating T-cells and obesity has been associated with decreased thymic output of naïve T-cells in middle-aged subjects.[33,34]

Table 1 Studies of immune cell prevalence and functionality in obese humans

Immune cell type		Impact of obesity	References
T-cell	Total lymphocytes	Increased or decreased	35–38
	Naïve	Increased Decreased thymic output Preactivation	34
	CD8	Decreased Lowered proliferation in response to mitogen	35–38
	CD4	Increased or decreased Th1 polarizaton	35,37,38,182
	NK	Decreased number and functional capacity	41,183
B-cell		Lowered prolifertion in response to mitogen	35,36
Macrophage		Increased monocyte and granulocyte phagocytosis and oxidative burst activity	35

DC, dendritic cell; NK, natural killer cell

Interestingly, obese subjects appear to have altered numbers, either increased or decreased, of total lymphocytes in peripheral blood populations.[35–38] When analyzed by flow cytometry, obese subjects appear to have decreased $CD8^+$ T-cell populations and increased or decreased numbers of $CD4^+$ T-cells compared with lean controls.[37,38] The differences in these studies could come from a number of factors as discussed below. Aside from altered frequency of circulating T lymphocytes, studies do demonstrate a lowered capacity of lymphocytes from obese individuals to respond to mitogen stimulation.[39] Nieman *et al.* (1999) reported obesity was related to elevated leukocyte and lymphocyte subsets with lowered T- and B-cell proliferation in response to mitogen stimulation.[35,36] In addition, these alterations in T-cell subsets have been suggested to be linked to increases in proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), and dysregulated expression of other cytokines.[35,36,38,40] Obese individuals have been shown to have decreased circulating natural killer (NK) cell populations with diminished activity.[33,41]

Several studies have assessed immune functionality in obese individuals following weight loss or dietary restriction. The majority of these studies show increased immune responsiveness and improvement. For example, a study by Tanaka *et al.*[38] showed increased T-cell responsiveness to mitogen following a weight reduction program. It must be noted that these improvements have not been assessed in the long term after subjects have achieved and maintained 'healthy' weight. Further research in this area would greatly increase our understanding of the impact of obesity, and the potential positive effect of weight loss, on immunity. Overall, it does appear that obesity can impact the number and functionality of immune cells; however, a number of factors could influence these results. The majority of the studies conducted on obese subjects utilize relatively small subject groups with wide age ranges. In addition, subjects are excluded based on a number of obesity-associated co-morbidities, such as diabetic status, which could also impact the immune response. Future studies need to be conducted using large populations stratified by age, gender and co-morbidities. It must also be considered that tissue-specific populations of immune cells at the site of infection, such as the lungs, may be altered; however, accessing populations of lymphocytes from sites other than blood would be very difficult to test in a large number of subjects.

Studies of obesity and immunity in animal models

The use of animal models of obesity has further defined the impact of obesity on immune functionality *ex vivo* (Table 2). Numerous studies using genetically obese rodents, mainly arising from the single-gene, loss-of-function mutations in the leptin gene (*ob/ob*) or leptin receptor (*db/db*), demonstrate a global impairment in *ex vivo* immune function. Genetically obese animals exhibit marked thymic atrophy as well as diminished splenic and circulating T-cell populations. The majority of these studies demonstrate that

Table 2 Studies of immune cell prevalence and functionality in obese rodents

Immune cell type	Impact of obesity	Model of obesity	References
T-cell	Diminished circulating T-cells Reduced T-cell responses Lymphoid atrophy Decreased memory T-cell function Decreased memory T-cell maintenance	Genetic, DIO	109,110,184
NK	Impaired activation Impaired cytotoxicity	Genetic, DIO	72,185,186
B-cell	Decrease in pre-B and immature B-cells	Genetic	83
DC	Impaired antigen presentation Decreased stimulation of T-cells Decreased steady-state number	Genetic, DIO	52,73
Macrophage	Reduced phagocytic activity Defective clearance of apoptotic cells Increased inflammatory properties	Genetic, DIO	184,187–189

DC, dendritic cell; DIO, diet-induced obesity; NK, natural killer cell

T-cells isolated from the spleen of genetically obese animals have markedly reduced capacity to respond to mitogen stimulation.[42–50] In addition, T-cells isolated from these animals have shown reduced cell-mediated cytotoxicity.[47,51] In addition to alterations in adaptive immune responses, genetically obese animals also display significant alterations in innate immune defenses. Dendritic cell (DC) steady-state number and functionality is reduced in genetically obese mice[52] as well as diminished and decreased functional NK cell populations.[53]

Genetically obese animals provide an excellent model for observing the effects of extreme obesity; however, leptin and leptin receptor mutations that cause obesity in these models are an extremely rare phenotype in humans. Therefore, the use of diet-induced obesity more closely models the effects of chronic overnutrition on the immune response. In diet-induced obese animals, similar, though usually less pronounced, impairment of the immune system has been found.[39] Yang *et al.*[34] have shown that diet-induced obese mice had significantly reduced thymocyte counts and significantly increased apoptosis of developing T-cell populations, resulting in acceleration of the age-related reduction of the output of naïve T-cells from the thymus. Similar to the genetic models, diet-induced obesity in mice and rats has been found to reduce splenic T-cell proliferation in response to mitogen.[39,49,54] Sato-Mito *et al.*[54] found that feeding high-fat diets to mice resulted in significantly reduced splenocyte proliferation when stimulated by three different T-cell mitogens (PHA, ConA and anti-CD3 antibody). High-fat dietary intake and diet-induced obesity in mice and rats results in decreased NK cell numbers and function.[55,56] Impairment of DC function and altered T-cell responsiveness to antigen presentation also occurs in high-fat-fed mice.[57]

Cytokines are also altered in diet-induced obese mouse models. Obese mice had lower levels of mitogen-induced interleukin (IL)-2, although interferon (IFN)-γ and IL-4 production was increased.[56] Takahashi *et al.*[58] found that diet-induced obese mice had increased levels of adipocyte-derived mRNA for monocyte chemoattractant protein-1 (MCP-1) as well as higher protein levels of MCP-1 in the plasma. $CD11b^{+}$ macrophage/monocyte population was also increased in the obese mice.[58]

Obese host–pathogen interaction and infectious disease challenge models

An intact and functioning immune response is critical for protection against infectious disease. Impairment of the immune response of the obese host would be expected to have an impact on the response to infectious diseases. Indeed, genetically obese animals have been shown to exhibit decreased resistance to bacterial and viral infections. *Ob/ob* mice have been shown to have increased susceptibility to a number of different bacterial infections including *Mycobacterium abscessus*,[59] *Klebsiella pneumoniae*,[60] *Streptococcus pneumoniae*[61] and *Mycobacterium tuberculosis*.[62] However, a separate group (Weiland *et al.*) found no differences in bacterial growth in *ob/ob* mice challenged with the *K. pneumoniae and S. pneumoniae* strains.[63] The differences between the Weiland *et al.* and Mancuso *et al.* studies may be due to age-related susceptibility. Indeed, Weiland *et al.* suggested that susceptibility may have been decreased in the Mancuso model because they were using older mice, which are inherently less susceptible. *Db/db* mice have been shown to have increased susceptibility to *Staphylococcus aureus*[64] and *H. pylori*.[65] Both *ob/ob* and *db/db* mice have been shown to have increased susceptibility to *Listeria monocytogenes*.[66] Obese Zucker rats (*fa/fa*) have been shown to have increased susceptibility to *Candida albicans*.[67] In regards to viral infection, *ob/ob* mice have been found to have increased susceptibility to viral myocarditis induced by coxsackievirus B4[68] as well as encephalomyocarditis virus.[69] Even fewer studies have observed the effects of diet-induced obesity on infection. Similar to genetically obese models, diet-induced obese mice are more susceptible to bacterial infection, including infection with *Porphyromonas gingivalis* and *Staphylococcus aureus*-induced sepsis.[70,71] To date, very few studies have been conducted observing the influence of obesity on the immune response to viral infection. Previous studies in our lab have demonstrated that mice with diet-induced obesity have a dysregulated primary immune response to influenza infection. Influenza-infected, diet-induced obese mice had seven times greater mortality, and increased lung pathology compared with infected lean controls. In the lungs of influenza-infected, diet-induced obese mice, a significant decrease in the expression of mRNA for IFN-α/-β and an increase and delay in the expression of proinflammatory cytokines and chemokines was noted.[72]

In addition, DCs from obese mice failed to efficiently present influenza antigen to T-cells (Figure 1).[73] Overall, it appears that diet-induced obesity can increase susceptibility to bacterial and viral infections; however, our understanding of which types of infections and to what extent susceptibility is increased must be further investigated.

Obesity and response to vaccination

Traditional methods of protection against viral infection focus on the induction of virus-neutralizing antibodies using vaccination strategies. Painfully little is known about the impact of obesity on the response to vaccination. The first study to describe a relationship between vaccine response and obesity was conducted by Weber *et al.*[74]. His group found that higher BMI was the single best predictor of failure to develop detectable antibody to serum-derived hepatitis B vaccine in health-care workers.[74] A follow-up study demonstrated that non-response to vaccine was strongly associated with BMI in health-care workers. Non-responders had a weight–height index of 36.4 compared with 30.0 for responders. In those with a BMI higher than the 75th percentile of the US population (in 1986), vaccine response rate was only 36%, compared with 66% in those with lower BMI.[75] In addition to the studies by Weber *et al.*, a number of other studies have shown an association between obesity and poor antibody response to hepatitis B vaccines.[76–80] Simò Miñana *et al.*[76] reported an inverse relationship between BMI and antibody level achieved through a three-dose regimen of recombinant hepatitis vaccine in adolescents. In addition, a randomized controlled trial was conducted to compare a triple-antigen recombinant hepatitis B vaccine to a standard single antigen vaccine delivered in standard three injections over six months. The standard vaccine had a 71% protection rate in obese (BMI $>$ 30) adults compared with 91% in the healthy, young non-smoking control group. The triple-antigen vaccine also showed a difference between lean and obese subjects with 99% protection in the lean group and 95% protection in the obese group.[79]

Aside from responses to hepatitis B vaccines, vaccine efficacy has not been well studied in the obese host. Eliakim *et al.*[81] reported that antibody response to standard tetanus immunization was lower in overweight 13-year-olds (BMI $>$85th percentile) than in age-matched controls with lower BMIs. In addition, the authors point out the need for the study of vaccine response in obese individuals for diseases more common than tetanus. Currently, there are no published studies of BMI in relation to influenza vaccination. The effectiveness of the flu vaccine in protecting individuals against illness or serious complications of flu depends primarily on the immunocompetence of the person receiving the vaccine, previous exposure to influenza and flu vaccine, and the similarity between the virus strains in the vaccine and those infecting the population.[82] If obese

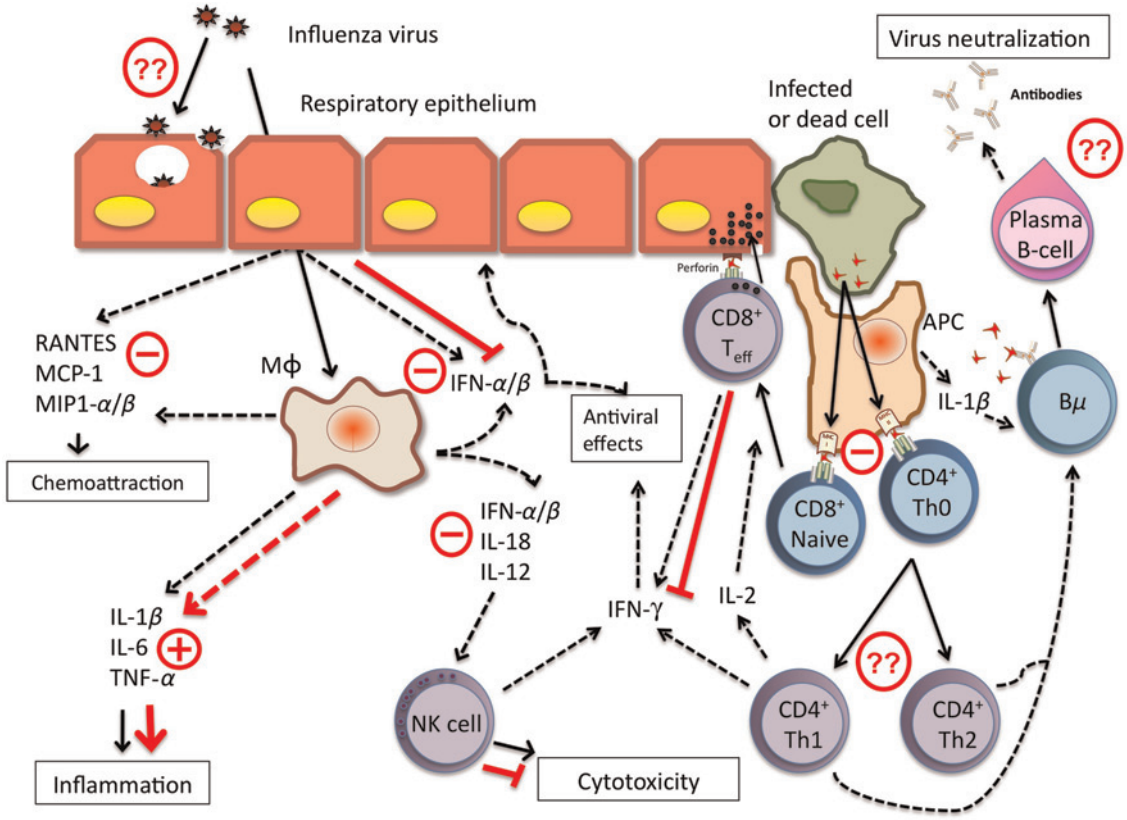

Figure 1 Immune response to influenza infection is impaired in the obese host. The response to infection with influenza virus results in influenza-specific effector T-cells killing infected cells and B-cells producing neutralizing antibody to protect against further infection. Altered responses known to be a result of the obesigenic state are shown in red. IL, interleukin; MCP, monocyte chemoattractant protein; TNF-α, tumor necrosis factor alpha; IFN-γ, interferon; NK, natural killer cell

individuals are immunocompromised and display similarly decreased antibody responses to influenza vaccination as they do with hepatitis B vaccines then they may not be as protected from influenza infection, a major cause of morbidity and mortality worldwide.

What mechanism(s) is responsible for the impact of obesity on reducing the antibody response to vaccination? Claycombe *et al.*[83] described a 21% and 12% decrease in pre-B and immature B-cells, respectively, in *ob/ob* mice compared with wild-type C57BL/6 mice. These differences were normalized with the treatment of *ob/ob* mice with leptin indicating a role for the adipokine in B-cell generation.[83] There is also the question of how weight reduction could help to improve vaccine responsiveness. An interesting case report from Dinelli and Moraes-Pinto[84] showed that an obese female remained non-responsive even following six doses of hepatitis B vaccine. Following gastric bypass and weight loss, a three-dose vaccine scheme resulted in seroconversion.[84] It appears that vaccine responses in obese individuals may be very different from vaccine responses in lean individuals. This suggests that obese adults/children may not be receiving the full benefits of our current immunization protocols.

Obesity and cellular immune memory

Apart from traditional vaccination approaches, studies of the generation of long-term immunity and efficacious vaccination against viral agents have begun to focus on the generation of large numbers of long-lived, antigen-specific $CD8^+$ memory T-cells. The generation, function and maintenance of these memory T-cells has been well reviewed.[85–103] Following an infectious challenge, antigen-specific T-cells are activated and go through a period of prolific expansion. This expansion results in a large population of effector T-cells containing both short-lived effector cells (SLEC) and memory precursor effector cells (MPEC) needed to clear the infection. Following pathogen clearance, SLEC, composing 90–95% of the effector population, go through activation-induced cell death during the subsequent contraction phase of the response, leaving the smaller MPEC subset to form a long-lived, antigen-specific memory cell pool. These memory T-cells can then act to mount larger, faster and stronger responses to subsequent encounters with the same pathogen.[90,102,104,105]

A number of studies have attempted to determine how SLEC versus memory T-cell fate is determined during a primary encounter with a pathogen. From these studies, reviewed by Jameson and Masopust[90], it has become apparent that generation and function of $CD8^+$ memory T-cells requires a balancing act between MPEC potential and terminal differentiation into SLEC. Both inherent programming during initial contact with an antigen-presenting cell and environmental factors such as inflammation can affect the balance between effector and memory potential.[90] This balance can be considered using the 'Goldilocks model' of generation.[96] Memory T-cell generation is best when things are 'just right' with the first infection. If the response becomes 'too hot' or 'too cold' then memory T-cell generation, function and maintenance will be impaired.[96]

How can obesity potentially impact memory T-cell generation, function and maintenance? Obesity could potentially impact both the inherent programming of T-cells during a primary infection as well as affect the environmental aspects of the primary immune response. As stated above, diet-induced obesity in mice has been shown to alter DC steady-state number and function and antigen presentation by DC is impaired in obese animals.[52,57,73] As exposure to antigen is so important for memory cell generation, decreased DC function or numbers could lead to altered $CD8^+$ T-cell priming. In terms of environmental effects, obesity has also been associated with a low-grade inflammatory state, which has been implicated in the development of several obesity-associated disease states such as type 2 diabetes mellitus and atherosclerosis.[106] Current research of adipose tissue as an endocrine organ has also added to this theory, demonstrating the ability of adipocyte and immune cells within the adipose tissue to secrete inflammatory mediators such as TNF-α and IL-6.[107,108] As noted previously, studies in our laboratory have shown that inflammatory signals are delayed and increased during primary influenza infection in diet-induced obese mice.[72] Taken together, altered antigen presentation as well as the chronic inflammatory state and greater expression of inflammatory mediators during infection could tip the balance of memory cell generation toward the 'too hot' end of the memory T-cell generational spectrum, resulting in a greater number of SLEC and diminished MPEC during a primary infection in the obese host (Figure 2).

Studies in our laboratory have focused on the impact of diet-induced obesity on the memory T-cell response to

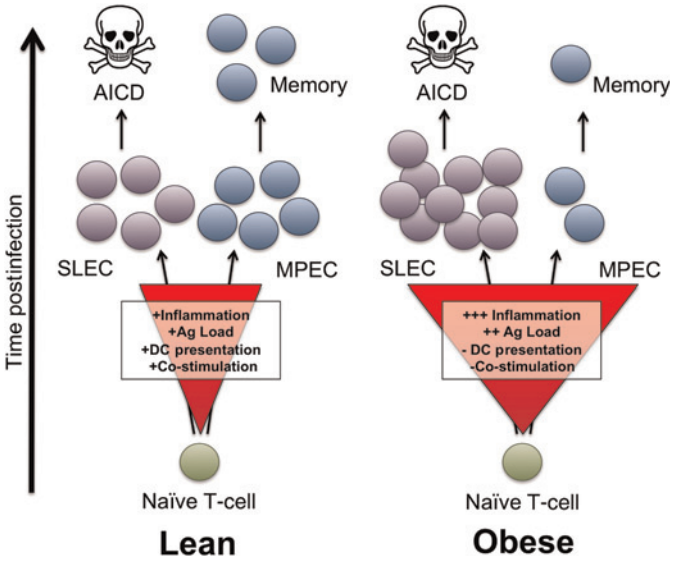

Figure 2 Impact of obesity on memory T-cell formation during a primary influenza infection. Following viral challenge, naïve T-cells are subjected to intrinsic and environmental cues that determine their effector versus memory potential. In addition, these cues can then influence susceptibility to activation-induced cell death (AICD) or the ability to be maintained for long periods of time as a antigen-specific memory T-cell. The obese state alters these intrinsic and environmental cues, resulting in increased numbers of primary short-lived effector cells (SLEC) and decreased memory precursors (MPEC). In addition, maintenance of antigen-specific memory T-cells is also decreased in the obese state

influenza infection. Obese mice primed with influenza X-31 (H3N2) and then challenged with a lethal dose of influenza A/PR/8 (H1N1) had a 25% mortality rate with no loss of lean controls. Obese mice also had increased lung pathology and significantly increased lung viral titers and failed to regain weight postsecondary influenza challenge. Furthermore, mRNA expression for IFN-γ was significantly decreased in lungs of obese mice. This decrease in IFN-γ production was attributed to a significant decrease in memory T-cell functionality as flow cytometry revealed one-third the number of influenza-specific $CD8^+$ T-cells from the lungs of obese mice producing IFN-γ postsecondary infection versus lean controls. In addition, the amount of IFN-γ produced per cell was significantly less than their lean counterparts. The defect in memory T-cell function was not due to impairment in DC functionality because influenza-specific memory $CD8^+$ T-cells from obese mice had a >50% reduction in IFN-γ production when stimulated with influenza-pulsed DCs from lean mice.[109]

In addition to defects in memory T-cell functionality, our lab has also observed deficits in memory T-cell generation and maintenance following a primary influenza challenge. Expression of Blimp-1 mRNA, an effector T-cell-associated transcription factor, was significantly increased during infection. In addition, expression of T-bet, another effector T-cell-associated transcription factor, was significantly increased in responding CD8+ T-cells as measured by flow cytometry. In contrast to the effector-related transcription factors, both mRNA and cellular expression of the memory precursor-associated transcription factor, eomesodermin, was significantly decreased (unpublished data). Taken together, these data suggest that the balance of effector versus memory T-cell generation is indeed tipped towards the generation of effector cells and reduces the memory T-cell pool. In addition to generation, memory T-cells were not maintained in the obesigenic lung environment with significantly decreased numbers of memory T-cells in the lungs of obese mice 84 days postprimary influenza challenge.[110] Thus, our lab has demonstrated that diet-induced obesity can significantly alter the memory T-cell response to a pathogen, rendering the obese host susceptible to re-infection.

How does obesity affect the immune response? The leptin connection

Conventionally, obesity can be considered an overaccumulation of white adipose tissue (WAT). Although adipocytes occupy the bulk of the volume of WAT, adipose tissue also includes many more cells types, including a diverse population of preadipocytes, macrophages, endothelial cells, fibroblasts and leukocytes.[111] In the past two decades, research has pushed the concept of WAT as an endocrine organ in its own right rather than a storage depot for fats. Indeed, WAT has been found to produce close to 100 cytokines and other molecules including leptin, adiponectin, resistin, visfatin/pre-B-cell colony-enhancing factor, nicotinamide phosphoribosyltransferase, apelin, vaspin, hepcidin, B-cell activating factor of the TNF family, TNF-like weak inducer of apoptosis, a proliferation inducing ligand, TNF-α, omentin and MCP-1. These 'adipokines' participate in a wide variety of physiological or physiopathological processes including food intake, insulin sensitivity and inflammation. As reviewed previously, many of the adipokines have been found to play an intricate role in various aspects of the innate and adaptive immune response (Table 3).[112–115] In the obese state, secretion of these adipokines is altered in correlation to the increased adipose tissue mass.[8,116–118]

Based on WAT's function as an endocrine organ and its ability to influence inflammatory processes within the body, it is not surprising that local, obesity-driven changes in adipokine secretion have a systemic impact on the immune system. To date, adipokine modulation of immune function by leptin is the best characterized link between obesity and immune function; however, the exact changes caused by an overabundance of leptin in the obesigenic state have yet to be elucidated. Leptin levels act as a general signal of energy reserves and to modulate food intake and, therefore, concentrations increase proportionately to adipose mass (and BMI) that result in high circulating leptin levels in obese individuals.[119–123] Leptin acts to control food intake by acting on an intricate neuronal circuit involving hypothalamic and brainstem nuclei where it integrates a variety of different orexigenic and anorexigenic signals.[124–127] In the obese state, leptin concentrations are already high as a consequence of increased fat mass. The persistence of obesity and no significant response to this increased fat mass with a reduction in food intake in spite of increased leptin levels suggest that chronically elevated leptin levels can induce a state of central leptin resistance.[128]

The effect of leptin on the immune response has been reviewed previously.[11,129–135] Leptin's role in regulating immunity has been fueled by early observations of thymic atrophy in *db/db* mice.[42] Indeed, genetically obese *ob/ob* mice display an increased thymocyte apoptosis and reduced thymic cellularity compared with wild-type controls and peripheral administration of leptin reverses these defects.[46,50,136,137] In malnourished infants, which have low plasma leptin, impairment of the immune response has been observed.[138] The leptin receptor is expressed by B and T lymphocytes and may directly modulate the T and B responses.[139,140] Leptin seems to exert its effects on immune cells through the JAK/STAT pathway. In peripheral blood mononuclear cells, leptin increases JAK2/3 and STAT3 phosphorylation, which promote proliferation and activation of T lymphocytes upon mitogen stimulation.[141]

In terms of infectious disease, the general consensus seems to be that leptin exerts a proinflammatory role, while at the same time serving in a protective capacity against infections.[8,142,143] Inflammation is used as a localized, protective response to infection and fluctuations in body weight and metabolic state are often associated with acute or chronic inflammatory processes resulting from infection. These changes in metabolic state have been associated with injury/infection-induced anorexia and have been found to be present in animal models of infection and inflammation and have been reviewed previously.[144,145] Interestingly, leptin may be involved in the acute

Table 3 Adipokine effects on metabolism and immunity and the impact of obesity

Factor	Metabolic effect	Immune effect	During obesity	References
Adiponectin	↓ Gluconeogenesis ↑ Glucose uptake β-oxidation Insulin sensitivity Weight loss Energy metabolism	Anti-inflammatory ↓ T-cell responses ↓ B-cell lymphopoesis	Reduced	111,115,190–192
Leptin	↑ Lipolysis ↓ Food intake	Inflammatory ↑ T-cell proliferation ↑ Lymphopoesis ↑ Thymocyte survival ↑ Th1 response	Increased (signal reduced)	130,141,193–196
Visfatin/NAMPT/PBEF	↑ Insulin sensitivity	Inflammatory	Increased	8,111,112
Resistin	Diabetogenic	Inflammatory	Increased	197
Chemerin	↑ Lipolysis Adipocyte differentiation	Chemoattractant	Increased	111,198
Apelin	↑ Insulin sensitivity ↓ Insulin secretion		Increased	199
Omentin	↑ Glucose uptake	Anti-inflammatory	Reduced	200–202
Vaspin	↑ Insulin sensitivity		Increased	203
Adipsin	↓ TAG production	Complement activation	Increased	8,204
Hepcidine	Iron homeostasis	↓ Iron release from macrophages	Increased	205
BAFF	↑ Adipogenesis	B-cell survival, metabolic fitness and readiness for antigen-induced proliferation T-cell co-stimulation	Decreased in sera, increased in adipose	206–208
TWEAK	↓ Adipogenesis	Inflammatory	Increased in severe obesity	209
APRIL	↓ Adipogenesis			208,210
Glucose (High)	↑ Insulin	Inflammatory	Increased	211,212
Insulin	↑ Glucose uptake ↓ Food intake ↓ Lipolysis	Inflammatory	Increased (signal reduced)	213
IL-6	↓ Insulin sensitivity ↑ Lipolysis	Inflammatory	Increased	214
TNF-α	↓ Insulin sensitivity ↑ Lipolysis	Inflammatory	Increased	215
MCP-1		Chemoattractant	Increased	58,111

APRIL, a proliferation-inducing ligand; BAFF, B-cell activating factor of the TNF family; IL, interleukin; MCP, monocyte chemoattractant protein; NAMPT, nicotinamide phosphoribosyl transferase; TAG, triacylglycerol; TNF-α, tumor necrosis factor alpha; TWEAK, tumor necrosis-like weak inducer of apoptosis

inflammatory response to infectious disease. In experimental animal models, inflammatory stimuli acutely induce leptin mRNA and increase serum leptin levels.[131,146] Indeed, previous studies in our lab have shown an acute spike in serum leptin one day post-primary and -secondary influenza infection in lean mice. This spike was not observed in obese mice that had significantly increased serum leptin at all time points postinfection (unpublished data and ref.[109]).

Similar to leptin deficiency, severe malnutrition has been associated with thymic atrophy, reduced T-cell function and increased susceptibility to infection. These changes are in correlation with the sharp reduction in leptin levels observed at extremely low BMIs.[147–149] While it is unclear whether leptin expression during an acute infection is a primary response to infection or secondary to other inflammatory stimuli, recent evidence has shown that leptin signaling in the central nervous system (CNS) is critical for a systemic immune response.[150] Taken together, experimental data indicate that chronic leptin deficiency differentially affects innate and adaptive immune responses. Innate responses are altered by inadequate control of the inflammatory response while adaptive responses are severely attenuated. Obesity has been associated with a state of leptin resistance in the CNS, which may be affecting the overall immune response. In addition, if peripheral leptin resistance causes a state similar to that of leptin deficiency in immune cells themselves, this resistance could account for the immunodeficiencies observed in obese individuals.

Other potential effects of obesity on the immune response

Obesity is an extremely multifactorial disease and numerous pathways and processes are altered by obesity, which could potentially alter the immune response. Aside from leptin, factors such as altered immune cell metabolism and even epigenetic alterations could influence the immune response to infectious disease in the obese host.

Metabolic effects

Another possible factor impacting immune response in the obese host is metabolism. Recent studies have found that metabolic state is extremely important for the functionality

and effectiveness of immune cells, especially T-cells. Proliferation of mammalian cells, including T-cells, is controlled by external signals which then activate and regulate internal nutrient utilization.[151] Non-proliferating, quiescent T-cells (naïve and memory T-cells) use catabolic metabolism to fuel ATP generation.[152] Stimulation and co-stimulation results in a metabolic switch to glycolysis and anabolic metabolism, which supports proliferation and effector functions.[153,154] This switch is achieved by the activation of Akt, which then promotes the mTOR pathway as well as increasing utilization of glucose and amino acids.[155–158] Therefore, this switching between differing metabolic states is required for effective generation of T-cell fates. Indeed, the fact that metabolism underlies the functional capacity of a T-cell either to respond to infection or to remain as a memory cell suggests that alteration of metabolic parameters could greatly affect memory T-cell fates.[159]

Very recently, reduced mTOR activity has also been associated with increased generation of memory $CD8^+$ T-cells. Araki *et al.*[160] and Pearce *et al.*[161] have shown that blocking mTOR function by rapamycin treatment promoted memory generation during both the expansion and contraction phases of the T-cell response. Additionally, Pearce *et al.* showed that the antidiabetic drug metformin, activated AMPK and enhanced memory T-cell generation by inhibiting the mTOR pathway.[160,161] Interestingly, dietary restriction studies that have been shown to promote lifespan in a number of organisms are thought to result in reduced mTOR activity.[162] While the exact mechanisms of T-cell metabolic switching are still under study, it may be interesting to pursue how obesity can alter T-cell metabolism and subsequent T-cell fate. Obesity has been associated with significant alterations in insulin and glucose utilization and is a significant risk factor for the development of type 2 diabetes.[106,163,164] Moreover, there have been recent implications that overnutrition directly inhibits insulin signaling in muscle at the level of IRS1 through the hyperactivation of the mTOR pathway.[165] Additionally, leptin signaling also appears to alter AMPK/mTOR activation.[166,167] If obesity hyperactivates mTOR, memory T-cell generation may be at a significant disadvantage. Future studies are needed to focus on the alteration of metabolism in T-cells from diet-induced obese mice and the effects on memory T-cell generation as well as other cells of the immune response.

Epigenetic effects

Activation and proper function of many cell types require that the cell transcribes specific sets of genes while repressing or silencing others. Much of this gene expression is not controlled by permanent alteration of primary genetic information but by changes in epigenetic differences in the genes that are expressed.[168–170] The production of biologically active proteins is under regulation at several points, such as the initiation of transcription. Accessibility to genetic information by the transcription machinery depends on the 'openness' of the chromatin structure. Modifications of DNA and DNA-binding histone molecules result in different chromatin structures. Epigenetic changes in DNA, such as DNA methylation and histone modifications, allow for structural alterations in chromatin organization resulting in permissibility of transcription machinery to initiate gene transcription.[171] Although epigenetic changes are established early during development and differentiation, adaptations occur throughout life in response to intrinsic and environmental stimuli. For example, DNA demethylation occurs in the IL-2 promoter of T-cells within 20 min of stimulation.[172] Indeed, cell fate decisions of T-cell lineages are significantly altered in mice unable to promote the gene-silencing effect of DNA methylation. These mice have profound changes in the susceptibility and resistance to parasitic infections.[173,174] Altered $CD4^+$ differentiation has also been documented by experiments using an inhibitor of methylation and through genetic abrogation of the maintenance methyltransferase, Dnmt1.[175,176]

Genetic reduction of methylation ability has been found to decrease memory T-cell precursor formation and the responsiveness of the resulting memory T-cell pool.[177] Interestingly, diet-induced obesity has been found to alter methylation status in rats, resulting in an increase in methylation of the leptin promoter in retropertioneal adipocytes;[178] however, there appear to be few studies observing the effect of dietary treatment on the epigenetic modification of immune cells. Further studies need to be conducted observing the effects of diet-induced obesity on epigenetic modification of T-cell fate decisions as well as other cells of the immune system and their potential effects on subsequent function in the context of response to infection.

Conclusions – obesity and infection: a public health perspective

Obesity has become a worldwide epidemic. Rates of obesity are increasing worldwide, not only in adult populations but also in children. The WHO predicts that by the year 2015, approximately 2.3 billion adults will be overweight with greater than 700 million of these adults being obese worldwide. In addition, globally, in 2005, there were more than 20 million overweight children under the age of five and this number continues to increase.[179] Obesity is not only increasing, the prevalence of super obese individuals is also increasing at an alarming rate.[180] Recently, a study by Flegal *et al.*[181] reported that the prevalence of obesity in the USA may be leveling off; however, according to 2007–2008 data, 68.0% of the US population still has a BMI $\geq$25, meaning that two out of every three people are overweight or obese. Therefore, even if the prevalence of obesity is leveling in the USA a significant portion of the population is still at risk for the co-morbidities associated with obesity. In addition, the worldwide explosion of obesity has shown no signs of abating.

Apart from the health problems and chronic diseases arising from low-grade, chronic inflammation, obesity results in a state of immunodeficiency including altered lymphocyte and monocyte functionality. In humans and animals, both diet-induced and genetic obesity leads to increased susceptibility to bacterial and viral infection.

While this increase in susceptibility has been documented for a small handful of infections, a significant number remain unexplored. In addition, while several, possible, individual mechanisms for increased susceptibility have been suggested, the exact systemic impact of obesity on infection susceptibility has not been fully investigated. Future studies should focus on expanding our knowledge of the weight of obesity on susceptibility to diseases.

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