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Micronutrients, immunology and inflammation
The impact of obesity on the immune response to infection

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There is strong evidence indicating that excess adiposity negatively impacts immune function and host defence in obese individuals. This is a review of research findings concerning the impact of obesity on the immune response to infection, including a discussion of possible mechanisms. Obesity is characterised by a state of low-grade, chronic inflammation in addition to disturbed levels of circulating nutrients and metabolic hormones. The impact of these metabolic abnormalities on obesity-related comorbidities has undergone intense scrutiny over the past decade. However, relatively little is known of how the immune system and host defence are influenced by the pro-inflammatory and excess energy milieu of the obese. Epidemiological data suggest obese human subjects are at greater risk for nosocomial infections, especially following surgery. Additionally, the significance of altered immunity in obese human subjects is emphasised by recent studies reporting obesity to be an independent risk factor for increased morbidity and mortality following infection with the 2009 pandemic influenza A (H1N1) virus. Rodent models offer important insight into how metabolic abnormalities associated with excess body weight can impair immunity. However, more research is necessary to understand the specific aspects of immunity that are impaired and what factors are contributing to reduced immunocompetence in the obese. Additionally, special consideration of how infection in this at-risk population is managed is required, given that this population may not respond optimally to antimicrobial drugs and vaccination. Obesity impacts millions globally, and greater understanding of its associated physiological disturbances is a key public health concern.

Obesity: Infection: Obesity and immunity: Leptin: Insulin

Globally, the number of obese individuals has reached alarming proportions. According to the WHO latest estimates, approximately 500 million adults and nearly forty-three million children under the age of 5 years are considered to be obese (BMI $\geq$ 30)[1]. Obesity is defined as a state of excess adiposity and its cause, although multifactorial, is primarily due to prolonged positive energy balance. Several comorbidities are associated with this disease, especially immune dysfunction. Alterations in inflammation and immune cell function in the obese play a significant role in nearly all pathophysiological effects of obesity[2,3]. However, few studies have directly addressed how this may affect host defence. In fact, there is striking evidence in both human subjects and mice that a state of excess adiposity greatly increases susceptibility to infections. Despite the strong epidemiological evidence in human subjects and immunological findings in rodents, much remains to be learned about obesity-related immune impairment. Furthermore, the mechanisms directly and indirectly responsible for differences in immune activity and host defence between healthy weight and obese individuals remain unclear.

In addition to an increased research focus on this topic, there may be implications for management of infections in the obese. For example, evidence is accumulating that obese individuals may respond differently to vaccination

Abbreviations: DIO, diet-induced obesity; ICU, intensive care unit; TLR, Toll-like receptor; Treg, regulatory T-cell.

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and various drugs, such as antibiotics. In combination with impaired immunity, altered responses to interventions may further affect the outcome of infection. Increased susceptibility to infection has obvious health and monetary consequences at the individual level. However, given that one out of every ten adults is obese, concerns of rising health care costs and disease transmission become a concern for all[1].

Evidence of impaired immunity in obese human subjects

Recent studies have demonstrated altered immune cell function in obese human subjects compared with those of healthy-weight. Nieman *et al.* reported considerable discrepancies in leucocyte number and subset counts and phagocytic and oxidative burst activity of monocytes between lean and obese individuals[4]. Additionally, circulating mononuclear cells in the obese exhibit a pro-inflammatory state compared with healthy-weight persons[5]. Impaired lymphocyte proliferation to polyclonal stimulation has been reported as well[4]. Type II diabetes, a common complication of obesity, is associated with impaired immune cell activity[6]. Individuals with a genetic mutation preventing proper synthesis of the hormone leptin, become morbidly obese and display weakened immune defences[7]. Interestingly, obesity has been shown to enhance thymic aging and reduce T-cell repertoire diversity, thus possibly impacting immune surveillance[8]. The reported findings of immune cell dysfunction suggest that obesity may result in impaired host defence. Indeed, studies have linked obesity with increased risk of infection[9]. Several reports have found obesity to be a significant risk factor for post-operative and surgical site[10], nosocomial[11], periodontal[12] and respiratory infections[13].

Infections in clinical settings

Obese patients have increased intensive care unit (ICU) length of stay[14] and are more likely to die[15–17] in the hospital. Further, several epidemiological investigations have reported that obesity increases infection susceptibility in clinical settings[9]. Obese patients are prone to developing post-operative complications. In fact, numerous studies have reported obesity to be an independent risk factor for post-operative infections[18–28]. In a recent secondary analysis of a large prospective observational study including critically ill and injured patients remaining in the ICU for 48 h or more, obesity was reported to be an independent risk factor for catheter and blood stream infections[11]. A study in critically injured blunt trauma patients reported that morbid obesity (BMI ≥ 40) was associated with increased risk of pneumonia and urinary tract infection but not with increased mortality[21].

The impact of obesity on clinical outcomes in hospitalised patients is clearly multifactorial and complex. In addition to decreased immunocompetence, there are other potential factors that may contribute to increased susceptibility to infection in the hospital setting. For example, underlying disease in the obese may inhibit proper mobility in the hospital, which can increase risk for skin breakdown[29]. Due to inadequate equipment or improperly trained staff, obese individuals may have prolonged visits at the hospital, thus increasing risk for acquiring nosocomial infections[9,29]. Another consideration is that pharmacokinetics of antibiotics may differ in the obese, potentially affecting susceptibility to post-operative infections[30]. Therefore, it is difficult to determine the direct impact of impaired immunity on severity of nosocomial infections in obese patients, but accumulating evidence suggests a significant role.

Obesity and respiratory infections

A striking number of recent studies have reported obesity to be a predictor for a worse outcome of infection with the 2009 influenza A (H1N1) pandemic strain[31]. In fact, several countries across the world have reported data indicating that obese individuals were disproportionately represented among influenza-related hospitalisations and deaths. Obesity or morbid obesity increased risk of ICU admission and even death among those infected with the pandemic strain[32–35]. Those admitted to ICU had a reportedly longer duration of mechanical ventilation and increased time in ICU and hospitals compared with non-obese individuals[36]. Before the advent of the 2009 pandemic season, there were no such reports investigating the relationship between obesity and influenza infection in human subjects. Recently, however, Kwong *et al.* published a study that explored the relationship between BMI and seasonal influenza infection using a series of Canada's cross-sectional population-based health surveys[37]. The surveys covered twelve influenza seasons. Analysis of the retrospective cohort demonstrated that the obese are at greater risk for respiratory hospitalisations during the seasonal flu periods.

In contrast to the recent surge of publications highlighting a connection between influenza severity and obesity, there is very little known about obesity and other respiratory tract infections[38]. A recent study by Akiyama *et al.* suggests that obesity may impact the response to respiratory syncytial virus infection in children[39]. A study from Poland reported that BMI was significantly related to susceptibility to respiratory infections in children[13]. In critically ill trauma patients, obesity or morbid obesity was associated with respiratory infections[11,15,23]. Conversely, a few studies have also reported obese individuals are not at greater risk for respiratory infections[14,40]. Therefore, our understanding of the effect of obesity on risk for pulmonary infection remains unclear. However, it is important to consider that obesity can complicate lung mechanics, such as restricting lung volume (reviewed in[41]), which could potentially increase risk for pneumonia or other infections. Although the mechanisms contributing to increased susceptibility may include impaired immunity, there may be non-immune factors to consider.

Vaccination and management of infection in the obese

Vaccination is universally recommended by public health officials to combat several types of infections. However, there is some evidence suggesting that obese individuals may not respond to vaccination to the same extent as

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healthy-weight individuals. Obesity was associated with a poor antibody response to hepatitis B vaccination[42,43]. Additionally, overweight children displayed considerably lower anti-tetanus IgG antibodies in response to vaccination compared with healthy-weight children[44]. This reduced immunogenicity in response to vaccination could be caused by several factors. One possibility is impaired generation and/or function of the antibody-secreting plasma cells. Another factor could be reduced absorption of the vaccine at the site of injection due to excess adiposity[44]. Interestingly, a recent study reported that using a larger vaccine needle length resulted in considerably higher antibody titres to hepatitis B surface antigen in obese adolescents[45]. As mentioned, poor response to vaccination has important public health implications. Reduced protection against viral infections, such as hepatitis B, increases individual susceptibility and may increase the likelihood of transmission to others. Therefore, more research on how obesity may negatively impact vaccination response is necessary to ensure proper protection in this at risk population.

In addition to the infections mentioned earlier, increased BMI is associated with greater risk for several other bacterial infections including periodontal infections[12], *Staphylococcus aureus* nasal carriage[46] and gastric infection by *Helicobacter pylori*[47]. Also, a recent study reported that obesity was significantly associated with herpes simplex virus 1 infection, which was determined by seropositivity[48]. Despite increased risk for several types of microbial infections, there is little known about how obesity may alter the pharmacokinetics of antimicrobial drugs (reviewed in[30]). Studies assessing dosing of the antibacterial drug, vancomycin, suggest that obese patients may require different dosages[49] and different dosing intervals[50] compared with non-obese individuals. An additional study of the antimicrobial drug, linezolid, reported diminished serum concentrations in the obese compared with healthy-weight volunteers receiving the same dose[51]. As pointed out previously, there is greater risk of skin breakdown in obese individuals in clinical settings due to restricted mobility, improperly sized rooms and equipment and the special challenges of caring for patients undergoing or post-bariatric surgery[9,29]. Additionally, excess adiposity may reduce tissue perfusion and affect wound healing[29]. Taken together, it is clear that obesity predisposes individuals to nosocomial infections, and that careful consideration of infection prevention and treatment is required.

Rodent models of obesity and infection

A limited number of studies have demonstrated the negative impact of excess adiposity on immune cell function in rodent models. The implications of these studies, in terms of obesity-related immunity impairments, are often complicated by the use of genetic models of obesity. The most commonly used genetically altered rodents for this purpose are the *ob/ob* and *db/db* mice and the rat *fa/fa* counterpart. These rodent models lacking leptin or the leptin receptor are very useful for the study of obesity-related comorbidities, as they display metabolic abnormalities characteristic of obesity such as hyperglycaemia, dyslipidaemia, glucocorticoid excess and hyperinsulinaemia[52,53] (all of which could potentially alter immune cell homoeostasis and function). However, given the vast amount of research highlighting the importance of leptin in immunity[54], a global deficiency in leptin signalling makes it difficult to tease apart the mechanisms contributing to impaired immunity and greater susceptibility to infections in these genetic models of obesity. Nonetheless, these models still provide insight into how excess adiposity may directly or indirectly alter immune cell function and host defence against infectious agents.

In general, a deficiency of leptin (*ob/ob*) or the leptin receptor (*db/db*) in mice increases susceptibility to bacterial infections and pneumonia[38]. Using *ob/ob* mice, Mancuso *et al*. demonstrated that a complete deficiency of leptin resulted in impaired pulmonary clearance upon *Klebsiella* challenge, likely due to defective alveolar macrophage and neutrophil phagocytosis[55]. Similarly, an investigation by Hsu *et al*. reported that *ob/ob* mice exhibited enhanced lethality and delayed clearance of *Streptococcus pneumoniae* following a pulmonary challenge[56]. Interestingly, intraperitoneal injections of leptin prior to *Streptococcus* infection improved survival after the bacterial challenge, but not to the level of wild-type mice. This discrepancy in survival percentages may, in fact, be caused by the increased adiposity of the *ob/ob* mice. Other studies have reported that *ob/ob* mice exhibit greater pulmonary *Mycobacterium tuberculosis* load[57] and delayed clearance of the *Mycobacterium abcessus*[58] upon challenge.

In addition to these pulmonary infection models, mice lacking the leptin receptor were shown to be more susceptible to hind paw staphylococcal infection and exhibited a greater inflammatory response compared with wild-type mice[59]. Furthermore, *db/db* and *ob/ob* mice displayed impaired resistance to hepatic *Listeria monocytogenes* infection[60]. Obese Zucker rats show decreased ability to clear yeast infection upon challenge with *Candida albicans*[61].

It is clear that evidence highlighting the importance of leptin for host defence is rapidly accumulating. However, these studies do not offer insight into the mechanisms by which excess body fat (and related metabolic abnormalities) may actually hinder host defence. Adding exogenous leptin to *ob/ob* mice is helpful in understanding the impact of other metabolic abnormalities on immune dysfunction, but exogenous administration of leptin in mice still differs from studying animals with intact leptin production and signalling. Some key considerations include indirect effects of leptin on immune responses and the fact that leptin has been shown to have autocrine signalling capabilities on select immune cells[62]. Although infection models in *ob/ob* or *db/db* mice provide important information on the role of leptin in host defence and immunity, these mice do not properly model non-genetically induced obesity, which constitutes the vast majority of human obesity.

Diet-induced obesity (DIO) in rodents more closely mimics human obesity. DIO mice, similar to their human

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counterparts, develop the typical comorbidities associated with obesity including elevated leptin, insulin resistance and elevated liver TAG. Although the diet models of obesity are often utilised to study metabolic problems associated with obesity, fewer studies have utilised these models in the context of an infection.

Compared with lean control mice, DIO mice have greater morbidity and mortality during either a primary or secondary influenza infection[63,64]. Several forms of immunity impairment were observed in the DIO mice, including reduced natural killer cell activity, poor dendritic cell processing and presentation and impaired $CD8^+$ T-cell function[64,65]. The mechanism(s) for the immune alterations in the DIO mice remains unclear.

An interesting study by Shamshiev *et al*. reported $apoE^{-/-}$ mice fed a high fat and cholesterol diet displayed impaired resistance to *Leishmania major* infection due to impaired dendritic cell function and T-helper type 1 cell immunity[66]. Impaired T-cell activity was also reported in DIO mice transgenic for a T-cell receptor specific to a peptide derived from ovalbumuin[67]. One complication associated with using DIO is elucidating whether the observed outcome of infection can be attributed to the abundance of adipose tissue, the influence of the high-fat diet or both. In this case, utilising both genetic obesity models with intact leptin signalling and DIO models in conjunction may be beneficial in advancing our understanding of the impact of the diet *v*. the state of excess adiposity on immunity[68,69]. Another important aspect of diet studies to consider is use of a proper control diet. A defined high-fat diet is commonly used for DIO models, but rarely do investigators include the matched control diet that only differs in fat and carbohydrate content[70]. In addition to major differences in macro- and micronutrient content, phytoestrogens are nearly absent in defined high-fat diets, whereas chow has high but variable levels[71]. Phytoestrogens can have marked effects on rodent physiology including hormone levels, metabolism and locomotor activity[72–74]. Thus, usage of a chow diet can potentially confound the effects of a high-fat diet[70]. Careful consideration of diet and experimental design is important in assessing the impact of obesity or diet on immunity.

Mechanisms of altered cellular immune function in the obese

It is well known that obesity is associated with a state of chronic, low-grade inflammation both in white adipose tissue and systemically[75–78]. Additionally, obesity is characterised by altered levels of circulating hormones and nutrients such as glucose and lipids. Circulating immune cells and those resident in peripheral tissues are thus exposed to an energy-rich environment in the context of altered concentrations of metabolic hormones. Understanding how this pro-inflammatory, excess energy milieu impacts immune cell function is key in understanding the immunodeficient state associated with obesity. Although these metabolic abnormalities can undoubtedly have indirect effects on immune cells, this review will focus on the direct impact of these abnormalities on immune cells.

Immunomodulatory adipokines and hormones in obesity

The primary adipose derived immunomodulatory adipokines include leptin, adiponectin and the pro-inflammatory cytokines: TNFα, IL-6 and IL-1β[76,77,79]. Adiponectin, levels of which are decreased during obesity, has been shown to alter natural killer cell cytotoxicity and cytokine production by human myeloid cells[80,81]. Conversely, there is excess production of TNFα, IL-6 and IL-1β in white adipose tissue of the obese[77]. These cytokines can be secreted into the blood and potentially have distal effects; however, exactly how chronic production of these cytokines impacts cellular immunity remains to be elucidated. It is possible that chronic exposure to pro-inflammatory cytokines may desensitise immune cells to inflammatory responses during an actual infection[82].

The pleiotropic effects of leptin on immune cell activity are highly diverse and complicated[54]. Nearly all cells of the innate immune system express the isoform of the leptin receptor, obRb, required for leptin signalling[83–87]. In monocytes, leptin up-regulates pro-inflammatory cytokine production of IL-6, IL-12 and TNFα, as well as phagocytic activity[55,88,89]. In polymorphonuclear neutrophils of healthy individuals, leptin signalling induced chemotaxis, reactive oxygen species generation and influenced oxidative capacity[87,90,91]. Natural killer cells are highly influenced by leptin signalling, including aspects of differentiation, proliferation, activation and activity[85,92]. Given the importance of leptin to innate immune cell function, it follows that nearly all innate immune cells are impaired in mice lacking intact leptin signalling.

The adaptive arm of the immune response is equally affected by leptin signalling[83,86]. Leptin is an important source of pro-survival signals to double-positive and single-positive thymocytes during the maturation of T-cells[93]. Leptin has been shown to play a key role in lymphopoieses and myelopoieses given that *ob*/*ob* mice had only 60% as many nucleated cells in bone marrow as compared with wild-type controls[94]. In the presence of a polyclonal stimulator, leptin can increase T-cell proliferation and can modulate expression of activation markers on both $CD4^+$ and $CD8^+$ T-cells[95]. Leptin can also have profound effects on cellular activity by functioning as a regulator of immune cell metabolism[62,96].

Although several papers have discussed how leptin may be required for or may enhance immune cell function, few have taken into consideration the fact that obese individuals are hyperleptinaemic[97]. Therefore, in obese models, we should ask what are the potential impacts of excess leptin signalling on immune cells? Indeed, studies have demonstrated that T-cells[86] and natural killer cells[98] can become resistant to leptin in rodent models of obesity. Leptin signals through a JAK/STAT (Janus kinase/signal transducer and activator of transcription) signalling pathway, resulting in translocation of the transcription factor, STAT3 (signal transducer and activator of transcription 3), into the nucleus and subsequent transcription of leptin-induced genes, including suppressor of cytokine

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signalling-3[99]. Suppressor of cytokine signalling 3 functions as a negative feedback mediator of JAK/STAT signalling, and thus may play an important role in impairing leptin signalling and contributing to central and peripheral leptin resistance[100]. Leptin resistance could very well explain obesity-related impaired immunity, as this would mimic a state of leptin deficiency. Leptin resistance, induced by hyperleptinaemia, would obviously not occur in *ob/ob* mice, which is another reason these mice are not the best model for studying obesity-related immune dysfunction. Although it is widely accepted that leptin resistance occurs centrally in the hypothalamus[100–102], peripheral leptin resistance requires further investigation.

An additional and somewhat novel consideration is how hyperleptinaemia may impact the function and distribution of regulatory T-cells (Treg). An elegant study by De Rosa *et al*. demonstrated a role for leptin signalling in Treg proliferation and function[62]. Abrogation of leptin signalling alters the anergic state of Treg, and allows for enhanced proliferation. Although highly proliferating Treg tend to lose some of their suppressive activity[62], resistance to leptin signalling might contribute to greater Treg number. Treg have the capacity to suppress nearly all aspects of the immune response[103]. Thus, this hypothesis fits with the immunosuppressive phenotype associated with infections in the obese. In fact, a recent investigation demonstrated a greater percentage of Treg in the spleen of DIO mice despite lower levels in adipose tissue[104]. It is clear that obesity can alter Treg number and function[104–106], but the extent to which this population of immune cells affects infection outcomes in the obese remains unknown.

Hyperinsulinaemia and insulin resistance are common features of obesity; however, there is little known regarding the immunomodulatory effects of excess insulin or impaired insulin signalling in the context of obesity. How the effects of insulin on cellular immunity are only partially understood. Monocytes have been shown to express insulin receptors and are insulin sensitive immune cells[107–110]. Interestingly, resting T-cells are insulin insensitive in that the insulin receptor is absent from the plasma membrane. However, once T-cells are activated by a polyclonal stimulator, such as phytohaemagglutinin or by specific antigen, effector T-cells up-regulate *de novo* emergence of insulin receptors[111,112]. Insulin signalling induces glucose uptake, amino acid transport, lipid metabolism and can modulate T-cell activation and function[111,113]. Furthermore, insulin promotes an anti-inflammatory T-helper type 2 cell phenotype[112], but MacIver *et al*. speculate that insulin resistance in obesity may actually enhance T-helper type 1 cell development[96]. It is thus clear that insulin can have potent effects on immune cell metabolism and function, but the effects of excess insulin on immunity remain relatively unresearched.

Altered immune cell metabolism in an abnormal metabolic environment

Immune cells from both innate and adaptive defences require nutrients such as glucose, amino acids and fatty acids to meet energy needs[114]. However, energetic demands and nutrient preference depend on cell type and cellular activity. For example, once T-cells are activated, they become highly proliferative and secretory, and thus require an abundant source of energy that will rapidly yield large quantities of ATP[115]. Conversely, macrophages and neutrophils are generally considered to be non-proliferative and thus have a different metabolic profile and nutrient requirements[114,116]. Although glucose and fatty acids are important sources of energy for host defence and immune function[117], elevated levels of these nutrients, as in the obese, may have consequences for immune cell activity.

Glucose uptake by immune cells is facilitated by the family of glucose transport proteins, GLUT. A variety of GLUT are expressed on immune cells. For example, increased expression of GLUT3 and GLUT5 occurs during the differentiation of monocytes to macrophages[118]. GLUT1 appears to be the primary GLUT on T-cells, and functions to maintain glucose uptake for basic metabolic requirements[96,115]. Upon stimulation, GLUT1 and GLUT3 levels were shown to increase on T-cells and monocytes[118]. Glucose is required for proper T-cell proliferation and survival[96]. However, it has also been shown that exposing T-cells to high concentrations of glucose can result in reactive oxygen species generation and lipid peroxidation[119]. Although little is known of the *in vivo* effects of hyperglycaemia on immune cell function, Jacobs *et al*. demonstrated that overexpression of GLUT1 in mouse T-cells resulted in altered T-cell metabolism and cytokine production[120]. The mechanisms by which elevated glucose influence immune cell function are not entirely clear, but glucose plays a crucial role in activity of immune cells, and thus excessive levels are likely to have a significant impact on cellular function.

Similar to glucose, fatty acids are important in fuelling an immune response, as they are a readily available source of abundant energy. However, the impact of excess circulating NEFA, a hallmark of obesity[121], on immune cells has not been well studied. Interestingly, SFA, such as palmitate, share similarities in chemical structure to lipopolysaccharide. This observation sparked studies indicating that SFA can induce an inflammatory response by initiating Toll-like receptor (TLR) signalling pathways[122–126]. TLR are critical in inducing innate immune responses as they recognise conserved molecular patterns on microbial pathogens[127]. SFA, but not unsaturated, have been shown to activate both TLR2 and TLR4 resulting in TIR (Toll/IL-1 receptor) domain-containing adaptor-inducing interferon-β-dependent and myeloid differentiation factor 88-dependent signalling pathways and a subsequent inflammatory response[122–128]. NEFA have been shown to trigger inflammatory responses in both macrophages and dendritic cells indicating that both innate and adaptive immune responses can be affected[126,129]. The effect of elevated NEFA on insulin resistance and type II diabetes has been widely examined[128]. Cells of both innate and adaptive immunity express TLR2 and TLR4, and other than a small number of studies in macrophages[3,129–131], there is very little known of the impact of NEFA on TLR signalling in other immune cells, such as T-cells. However, a study by Stentz and Kitabchi reported that increasing concentrations of palmitate but not unsaturated fatty acids resulted in

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activation of T-cells and a dose-dependent increase in cytokine production as well as reactive oxygen species generation and lipid peroxidation *in vitro*[132].

An additional consideration in which excess fatty acids, as well as glucose and metabolic hormones, may affect immunity is highlighted in several recent studies demonstrating that T-cell populations can have distinct metabolic programmes that are critical to cell fate and function[133]. Michalek *et al*. show that $CD4^+$ T-cell metabolism is fundamental in regulating differentiation to an effector or regulatory subtype. The $CD4^+$ T effector subset requires glycolytic metabolism, and Treg require lipolytic oxidation[133]. Interestingly, recent studies have shown that $CD8^+$ effector T-cells displayed a glycolytic phenotype, whereas a $CD8^+$ memory T-cell population was associated with a lipid oxidation metabolic profile[134–136]. What remains to be studied is how nutrition may alter these distinct metabolic programmes. In the context of obesity, how do elevated levels of glucose, fatty acids and metabolic hormones, such as leptin and insulin, impact the metabolic fate of immune cells during an infection?

Conclusion

The best solution to improving health of obese individuals is significant weight loss. However, the aetiology of this highly complex disease is multifactorial, and thus no solution to obesity will be an easy fix. The burden of obesity is shared by adolescents and adults alike, and of the numerous comorbidities associated with obesity, host defence and immune cell dysfunction are less studied compared with type II diabetes or cardiovascular complications. Obesity clearly interferes with protection against infectious agents, and therefore increased research for a better understanding of the interactions between excess adipose-related metabolic abnormalities and immune cell activity is needed. Strong epidemiological evidence highlighting an association between obesity and infection is accumulating, and there are rodent models offering insight into potential mechanisms. An additional, yet key, consideration is how best to prevent and manage infections in this at risk population. Antimicrobial drugs and vaccines may not function as intended in obese individuals. This is cause for major concern in the context of outbreaks of infection, as for the 2009 influenza pandemic. Further consideration and investigation on the impact of obesity on immunity could potentially save millions of lives, especially during the current obesity epidemic dilemma.

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