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Adipose Tissue, Diabetes and Chagas Disease

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Abstract

Adipose tissue is the largest endocrine organ in the body and is composed primarily of adipocytes (fat cells) but also contains fibro-blasts, endothelial cells, smooth muscle cells, macrophages and lymphocytes. Adipose tissue and the adipocyte are important in the regulation of energy metabolism and of the immune response. Adipocytes also synthesize adipokines such as adiponectin which is important in the regulation of insulin sensitivity and inflammation. Infection of mice with *Trypanosoma cruzi* results in an upregulation of inflammation in adipose tissue that begins during the acute phase of infection and persists into the chronic phase. The adipocyte is both a target of infection and a reservoir for the parasite during the chronic phase from which recrudescence of the infection may occur during periods of immunosuppression.

10.1. INTRODUCTION

Chagas disease, caused by *Trypanosoma cruzi*, remains an important cause of morbidity and mortality in endemic areas of Latin America and among immigrant populations in non-endemic areas (Tanowitz et al., 2009). There has been an increase in obesity and type 2 diabetes in the tropical world including those in which Chagas disease is endemic. For example, the clinical-nutritional profile of individuals with chronic disease in one study, evaluated at the Tropical Diseases Nutrition Out-Patient Clinic of the Botucatu School of Medicine, São Paulo State University, Brazil, revealed that 94% of patients with Chagas disease were overweight or obese (Geraix et al., 2007). The relationship between this parasite and adipose tissue and the adipocyte (fat cell) has not been fully evaluated.

Depending on the individual, adipose tissue may account for 10–50% of body composition. The adipocyte is the major component of adipose tissue, and it is well established that it contributes to the pathogenesis of diabetes, obesity and the metabolic syndrome (Asterholm et al., 2007; Attie and Scherer, 2009; Horrillo et al., 2010; Nawrocki and Scherer, 2005; Rajala and Scherer, 2003), and its secretory products have been implicated in other processes (Attie and Scherer 2009; Nawrocki and Scherer 2005). Although the adipocyte was once considered to be a static storage compartment for triglycerides, it is now appreciated that adipocytes are active endocrine cells playing a critical role in various metabolic and immune responses (Halberg et al., 2008; Kaminski and Randall, 2010; Yang et al., 2010; Zuniga et al., 2010). Adipocytes contribute to these functions by influencing systemic lipid homeostasis and also through the production and release of a host of adipocyte-specific and adipocyte-enriched hormonal factors and inflammatory mediators, including adipokines. Until recently, there has been little attention given to the role of adipose tissue and adipocytes in infectious disease (Desruisseaux et al., 2007).

Adipose tissue is a heterogeneous tissue composed not only of adipocytes but also of other cell types including fibroblasts, endothelial and smooth muscle cells and especially in the setting of infection and morbid obesity, macrophages and leukocytes (Anderson et al., 2010; Weisberg et al., 2003). It is important to note that in experimental *T. cruzi* infection, there is a similar infiltration of macrophages into adipose tissue, which raises the possibility that similar signalling pathways could be involved. The mechanisms for macrophage recruitment have included cell damage/death by apoptosis/necrosis, tissue hypoxia and, more recently, lipolysis (Kosteli et al., 2010).

Different adipose tissue depots display distinct gene expression patterns and vary widely in their size and proximity to neighbouring organs. As noted, adipose tissue stores lipid in the form of triglycerides as well as non-esterified cholesterol on the surface of lipid droplets that act as specialized organelles inside the adipocyte. Since the lipid droplet is such a large component of the adipocyte, changes in the amount of lipid stored within it affect fat cell size (which can range from 25 to 250 μ m).

A potential endocrine function of adipose tissue was first recognized over two decades ago when it was reported that the serine protease, adiponectin was secreted by cultured 3T3-L1 adipocytes (Cook et al., 1987). Subsequent investigations discovered additional adipokines, including adiponectin originally known as Acrp30 (Scherer et al., 1995), leptin (Zhang et al., 1994), resistin (Steppan et al., 2001), SAA3 (Lin et al., 2001), omentin (Yang et al., 2006), visfatin (Fukuhara et al., 2005) and RBP4 (Yang et al., 2005). These adipokines are critically important to the regulation of energy homeostasis through effects on both central and peripheral tissues. They also contribute to non-metabolic processes in the body such as the immune response. The most adipocyte-specific adipokine is adiponectin although other adipokines can also be synthesized by tissues other than adipose tissue and/or by cells other than adipocytes.

10.2. ADIPONECTIN

Systemic energy homeostasis is maintained by the competing effects of a number of different hormonal factors, some of which originate in adipose tissue. These adipocyte-derived factors (adipokines) influence processes such as food intake, energy expenditure and insulin sensitivity. Two adipokines, resistin and adiponectin, have opposing effects on whole-body glucose homeostasis (Combs et al., 2001; Rajala and Scherer, 2003). Pharmacological doses of recombinant resistin hyperactivate gluconeogenesis through decreased hepatic insulin sensitivity.

Adiponectin is a hormone-like peptide that is almost exclusively produced by the adipocytes (Scherer et al., 1995). It is a 30-kDa molecule with three defined domains. The N-terminus contains a hypervariable region, which is commonly used as the antigenic site for species-specific antibody generation. The collagenous stalk containing 22 GXY repeats is followed by a globular domain at the C-terminus. Both intracellularly and extracellularly, adiponectin exists in three different higher-order complexes: a high molecular weight form (HMW; 12–36 mer), a low molecular weight form (hexamer) and a trimeric form. The different complexes have distinct functions, and the ratio of HMW to the other forms serves as an independent predicting factor of metabolic disorders. Total levels and HMW ratio are decreased in obese patients and obese mouse models suggesting that adiponectin, especially the HMW form, may be involved in obesity-related disorders. Adiponectin modulates glucose and lipid metabolism by exerting insulin-sensitizing effects. This may be due in part to the increase in insulin sensitivity by the inhibition of hepatic glucose output. In the normal metabolic state, adiponectin is present in high concentrations in plasma, but there is also noted an inverse relationship with body-fat mass, insulin resistance and type 2 diabetes mellitus. Lower levels of circulating adiponectin are associated with increased susceptibility to a variety of diseases associated with the metabolic syndrome, including diabetes, hypertension, obesity and a increase in the expression of endothelin-1 (Yudkin, 2007).

There is an association between circulating adiponectin levels and metabolic parameters that regulate insulin sensitivity in different patient populations. For example, Arita et al. (1999) demonstrated decreased plasma adiponectin concentrations in obese humans which was confirmed with obese animal models. The pattern of decreased adiponectin secretion with increasing adiposity, though contrary to what is observed for the majority of adipose-specific secretory proteins such as leptin, has been well recognized. There is a reduction in the levels of adiponectin in diabetics with coronary artery disease compared to diabetics without coronary artery disease, and adiponectin levels in serum are negatively correlated with basal metabolic rate, plasma glucose, insulin and serum triglycerides (Hotta et al., 2000). Moreover, even a moderate weight loss may be associated with significant increases in circulating adiponectin levels (Yang et al., 2001) and an increase in insulin sensitivity. The paradox of why adiponectin levels tend to increase with decreasing adiposity has never been adequately explained. After weight loss, the remaining adipocytes may be more insulin sensitive and therefore secrete increased amounts of adiponectin. Alternatively, adiponectin expression and/or secretion may be directly or indirectly regulated by plasma insulin levels. Supporting this view are the observations that insulin treatment of 3T3-L1 adipocytes results in significantly decreased adiponectin expression (Fasshauer et al., 2002) and serum adiponectin levels are inversely proportional to fasting insulin levels. Thus, it is likely that an inhibitory feedback pathway exists to down-regulate the expression and secretion of adiponectin in the obese.

Central adipose pads are the predominant sources of systemic adiponectin in the lean state. The production of adiponectin by this tissue in the obese state is reduced. Those with the highest levels of adiponectin had a reduced risk of myocardial infarction compared with those with the lowest adiponectin levels. This relationship persisted even when controlling for several variables. Animal models have corroborated these observations, demonstrating the importance of adiponectin for preventing diet-induced progression of atherosclerosis. Life style changes leading to improvements in insulin sensitivity such as weight reduction and exercise will result in an increase in the level of plasma adiponectin. The administration of peroxisome proliferator-activated receptor- γ (PPAR- γ) agonists, such as the thiazolidinediones, increases adiponectin secretion in cultured adipocytes and increases circulating adiponectin levels in rodents and in patients with diabetes (Arita et al., 1999; Long et al., 2010).

The mechanistic basis of the anti-atherosclerotic activity of adiponectin has not been completely elucidated. It has been hypothesized that adiponectin has inflammation-modulating activities and clinical studies have demonstrated inverse associations between adiponectin levels and serum markers of inflammation (Goldstein and Scalia, 2004; Ouchi et al., 2003). Several studies have reported that the physiologically relevant, full-length form of adiponectin has anti-inflammatory effects on both endothelium and macrophages. However, it is unclear how or whether adiponectin itself exerts anti-inflammatory properties. It has been demonstrated that the synthesis of adiponectin by cultured adipocytes is inhibited by inflammatory cytokines such as TNF- α (Ruan and Lodish, 2003). This inhibition may be mediated in part by NF κ B signalling. I κ B kinase inhibition leads to increased plasma adiponectin levels and an improvement in systemic insulin sensitivity (Keller et al., 2003). The anti-inflammatory activity of adiponectin may be mediated in some instances by activation of AMP-activated protein kinase (AMPK; Ouchi et al., 2000). Recently, Holland and colleagues demonstrated that the broad spectrum of effects attributed to adiponectin, including its anti-inflammatory, antiapoptotic and insulin-sensitizing actions are due to the adiponectin-mediated stimulation of a potent ceramidase activity that leads to a lowering of cellular ceramides and an increase in its degradation product, sphingosine-1-phosphate (Holland et al., 2011). The ceramidase activity is adiponectin receptor inherent or at least closely associated with these receptors.

Chemokines positively control the secretion of leptin, suggesting a role for these molecules in the regulation of adipose tissue. Importantly, leptin is vital in immune cell differentiation and development. Targeting chemokines may provide a novel therapeutic basis for the treatment of obesity, diabetes and cachexia (Gerhardt et al., 2001). A high-fat diet increases the expression of inflammatory genes, including the early induction of MCP-1 and MCP-3 (Chen et al., 2005). Some of the proven anti-atheromatous effects of adiponectin may be mediated by anti-inflammatory actions directly on the vasculature. Okamoto et al. (2008) recently reported that adiponectin inhibits the production of CXCR-3 chemokine ligands in macrophages and causes a reduction in T-lymphocyte recruitment. Interestingly, Miller et al. (2010) have reported that IL-33 may play a protective role in the development of adipose tissue inflammation, but the relationship to infection is unclear. Recent studies have shown a direct link between inflammation and diabetes and obesity.

Adiponectin has been reported to contribute in protecting against cardiac hypertrophy and ischaemic heart disease. In mouse models, adiponectin has been shown to protect against myocardial ischaemia-reperfusion injury and overload- and adrenergically induced cardiac myocyte hypertrophy by inhibiting hypertrophic signals via AMPK (Ouchi et al., 2006; Shibata et al., 2004, 2005). Importantly, adiponectin null mice have a cardiomyopathic phenotype (Ouchi et al., 2006; Shibata et al., 2005; Shimano et al., 2010). Taken together, the current information is consistent with the notion that adiponectin is anti-inflammatory and that a reduction in adiponectin levels is proinflammatory.

10.3. ADIPOSE TISSUE AND INFECTION

The potential contribution of adipose tissue and the obese state to the infectious process in general had been recently reviewed (Desruisseaux et al., 2007). It has been appreciated that obese humans and animals have difficulties responding to many types of infections including frank sepsis. The first well-designed study to examine the possible relationship of infection and adipose tissue was published by the Scherer laboratory (Pajvani et al., 2005). In this study, it was demonstrated that injection of LPS into mice that were rendered fatless, using the regulated fat apoptosis murine model, did not result in the immediate death of mice as seen in control mice with a normal component of adipose tissue (Pajvani et al., 2005). This observation suggested that adipose tissue makes a significant contribution

during the acute phase response to infection. Interestingly, during the recent H1N1 influenza epidemic, it was reported that in individuals with increased BMI the morbidity rate was increased (Tsatsanis et al., 2010), and this has been confirmed by studies in obese mice (Karlsson et al., 2010). Responses to *Staphylococcus aureus* infection have recently been studied by injection of *S. aureus* into the footpad of the leptin receptor null mouse model of diabetes and obesity. Whereas non-diabetic lean mice resolved this infection within 10 days, in the obese mice the infection was prolonged and was associated with a significant increase in the associated inflammatory response (Park et al., 2009). One of the most intensively investigated areas in the interface between infection and adipose tissue has been in HIV/AIDS where receptors for the virus have been reported on adipocytes and HIV-associated lipodystrophy has been described (Anuurad et al., 2010; Garrabou et al., 2011; Hazan et al., 2002; Jan et al., 2004; Maurin et al., 2005; Mynarcik et al., 2002).

10.4. CHAGAS DISEASE AND ADIPOSE TISSUE

In the 1970s, Shoemaker and colleagues (Shoemaker and Hoffman, 1974; Shoemaker et al., 1970) demonstrated that *T. cruzi* parasitized adipose tissue and Andrade and Silva (1995) subsequently demonstrated that *T. cruzi* parasitized adipose tissue and the adipocyte (Andrade and Silva, 1995). Buckner et al. (1999) demonstrated the detection of *T. cruzi* in adipose tissue using special staining techniques. However, it was not until the publication by Combs et al. (2005) that the potential impact of parasitism of adipose tissue and the adipocyte was appreciated (Fig. 10.1).

Interest in the association between *T. cruzi* infection and adipose tissue and diabetes has been a recent focus for several reasons. First is the general belief, although not conclusively proven, proven that Chagas disease may be associated with obesity and diabetes. The clinical-epidemiologic evidence linking Chagas disease, obesity and diabetes is unclear because published studies have been at variance and many of the studies have not been subjected to rigorous statistical scrutiny (dos Santos et al., 1999; Geraix et al., 2007; Guariento et al., 1993; Hidron et al., 2010; Oliveira et al., 1993). Secondly, it is now well established that adipose tissue and adipocytes are both targets of infection and a storage site from which infection can arise later in life under circumstances of immunosuppression. Supporting this view, it was recently demonstrated that *Rickettsia prowazekii*, the cause of Brill-Zinsser disease (the relapsing form of epidemic typhus), lives in adipocytes and adipose tissue and are a reservoir from which the infection can recrudesce and cause disease decades later (Bechah et al., 2010). Thus, the parasitism of adipose tissue by *T. cruzi* may create in some individuals a “low-grade” chronic inflammatory state similar to what is observed in obesity (Ferrante, 2007; Weisberg et al., 2003).

When mice are infected with *T. cruzi*, the plasma levels of adiponectin are significantly reduced (Combs et al., 2005; Nagajyothi et al., 2010). There is a concomitant reduction in expression of adiponectin and of PPAR- γ ; both negatively regulate inflammation. Reduced levels of adiponectin are often associated with insulin resistance, hyperglycaemia and obesity, that is, the metabolic syndrome. At 30 days post-infection, the acute-phase reactants α -1 acid glycoprotein and SAA3, which are expressed in adipocytes, were upregulated. The levels of resistin, a fat cell-specific secretory factor with insulin-desensitizing properties, was unchanged in adipose tissue obtained from *T. cruzi* (Brazil strain) mice. Additionally, plasminogen activator inhibitor-1 levels were unaffected by infection. Conversely, proinflammatory markers such as cytokines (TNF- α , IL-1 β , IFN- γ) and chemokines and toll-like receptors (TLRs) were markedly elevated in the adipose tissue from acutely infected mice, and this elevation often persisted into the chronic phase (Combs et al., 2005).

Fifteen days after *T. cruzi* (Brazil strain) infection of CD-1 mice, there is no peripheral parasitaemia and no mortality. There is a significant parasite load in both brown and white adipose tissue as compared to other organs such as the heart and spleen. At this early stage of infection, we have demonstrated a significant influx of macrophages into adipose tissue as determined by immunostaining with antibodies to macrophage specific markers such as Iba-1 and PCR analysis employing primers to F4/80. There is also a reduction in fat mass as determined by magnetic resonance imaging (Fig. 10.2). Concomitantly, there is a reduction in fat content as determined by Oil red O staining and reduction in the size of adipocytes. Western blot analysis indicates an increase in lipolysis although apoptosis and necrosis may also be involved. This early process may lead to release of parasites into the general circulation resulting in increased peripheral parasitaemia. This ongoing process may represent a mechanism by which low levels of parasites are continuously released into the circulation (at a level below detection by routine blood smear) resulting in chronic infection. During the chronic phase of infection, examination of adipose tissue reveals persistence of both macrophages and parasites. Thus, adipose tissue is both an early sensor and target of *T. cruzi* infection and a chronic reservoir from which infection can recrudesce during periods of immunosuppression and/or lipotrophic states. Recently, Kosteli et al. (2010) have demonstrated that local lipolysis-induced increases in fatty acids in adipose tissue lead to an increased infiltration of immune cells, particularly macrophages. This offers a potential explanation for the long-term effects we observe on some fat pads after acute *T. cruzi* infection. The presence of parasites within chronically infected fat pads leads to insulin resistance, associated with increased lipolysis with chronically elevated local free fatty acid levels that in turn will be triggering the observed increased infiltration of macrophages.

Since adipose tissue is composed of many cell types, it was important to determine if infection of adipocytes in the absence of other compounding variables found in the tissue also resulted in an inflammatory phenotype. Indeed, *T. cruzi* infection of cultured adipocytes resulted in an increased expression of chemokines, such as CCL2, CCL3, CCL5 and CXCL10, as well as the cytokines TNF- α , IL-10 and interferon- γ (Nagajyothi et al., 2008). The expression of STAT3, an important down-stream mediator of cytokine signalling, was also increased. TLR expression was increased (TLR-2 and -9), and there was evidence of activation of components of the mitogen-activated protein kinase (MAPK) pathway, such as ERK. Cyclin D1 expression was increased, and it is usually upregulated by ERK and inversely regulated by caveolin-1 (Hulit et al., 2000). Indeed, we demonstrated that infection resulted in a reduction in the expression of caveolin-1 and the activation of ERK. Both of these events increase the expression of cyclin D1. A reduction in caveolin-1 expression has also been demonstrated to be associated with an increased proinflammatory cytokine response (Cohen et al., 2003, 2004). Interestingly, *T. cruzi* infection activates the Notch pathway, which also regulates, in part, the expression of cyclin D1 (Stahl et al., 2006).

T. cruzi infection of cultured adipocytes results in increased expression of PI3 kinase and the activation of AKT, strongly suggesting that *T. cruzi* infection induces the insulin/IGF-1 receptor pathway. This is an unexpected observation since the upregulation of proinflammatory pathways is usually associated with a down-regulation of the insulin signal transduction pathway (Ferrante, 2007; Hotamisligil, 2006). Whether other pathways influenced by insulin are affected is not known. Thus, *T. cruzi* infection of cultured adipocytes as well as adipose tissue results in alterations of several important pathways early in infection that persist well into the chronic phase.

10.5. CHAGAS DISEASE AND GLYCAEMIA

We and others have demonstrated that *T. cruzi* infection of mice results in severe hypoglycaemia (Combs et al., 2005; Holscher et al., 2000). Acute infection of CD-1 mice

with the Brazil strain of *T. cruzi* is usually associated with severe hypoglycaemia and generally correlated with mortality (Combs et al., 2005). It has been suggested that the hypoglycaemia was the result of “cytokine storm” and reduced food intake. Interestingly, the metabolic response to bacterial sepsis is often associated with hyperglycaemia, insulin resistance, profound negative nitrogen balance and the diversion of protein from skeletal muscle to splanchnic tissues. Thus, the response to *T. cruzi* infection differs from that generally observed in bacterial sepsis. It is possible that there is an effect on glucose metabolism due to invasion of the liver by the parasite. During acute infection, glucose levels in all of the *T. cruzi*-infected mice were below those measured in the control mice. Even though the baseline glucose levels in the infected animals were lower, the oral glucose tolerance test indicated a relatively normal ability to clear ingested glucose despite the high degree of inflammation associated with this infection (Combs et al., 2005). The decreased insulin levels observed 30 days post-infection in the mouse model of *T. cruzi* infection are consistent with a physiological response to very low glucose levels during that time (Combs et al., 2005).

Observational studies in people and case reports are suggestive that the incidence of diabetes may be increased in the chagasic population (dos Santos et al., 1999; Guariento et al., 1993; Oliveira et al., 1993). One such study demonstrated a significant reduction in insulin among chronically infected individuals (dos Santos et al., 1999). However, the data in this report could also be interpreted to reflect weight loss or illness rather than pancreatic β -cell destruction. The notion that *T. cruzi* could cause diabetes is not entirely new since it has been known that this parasite can invade any cell type including those of the pancreas. When streptozotocin-induced diabetes was produced in mice which were then infected with *T. cruzi*, they displayed higher parasitaemia levels and mortality rates (Tanowitz et al., 1988). After insulin was administered, the glucose levels returned to normal and the parasitaemia levels and mortality rates were reduced.

Mice carrying a defective leptin receptor gene (*db/db* mice) are metabolically challenged in that they are hyperglycaemic, obese and have low levels of adiponectin. They are bred on a FVB background. When these mice are infected with the Brazil strain of *T. cruzi*, they have a high peripheral parasitaemia and tissue parasitism and suffer 100% mortality. These mice also displayed an upregulation of the inflammatory pathway as well as an increase in myocardial pathology, and a large numbers of parasite pseudocysts. In genetically modified *db/db* mice, (NSE-Rb *db/db* mice), central leptin signalling is reconstituted only in the brain, which is insufficient to correct the metabolic defects (de Luca et al., 2005). They are lean and normoglycaemic. In order to determine the consequences of the lack of leptin signalling on infection in the absence of metabolic dysregulation, we infected these mice with the Brazil strain and found a minimal transient peripheral parasitaemia and tissue parasitism and no mortality. The myocardium was virtually devoid of parasites. The observation in the NSE-Rb *db/db* mice was similar to that observed in the wild-type FVB mice (Nagajyothi et al., 2010). Thus, the restoration of the metabolic dysfunction was sufficient to control the Brazil strain infection. More recently, we observed that when we infected the NSE-Rb *db/db* mice with the virulent Tulahuen strain the mortality was 100% (unpublished observations). This is an example demonstrating that both the strain of mouse and parasite are important in the final outcome of infection. These findings suggest that leptin resistance in individuals with obesity and diabetes mellitus may have adverse consequences in *T. cruzi* infection.

10.6. CONCLUSIONS

There is a close association between adipocytes and glucose metabolism. The small numbers of studies that have examined *T. cruzi* infection and adipocytes and glucose metabolism have given us increased insight into the pathogenesis of Chagas disease but have also raised

interesting questions that require more research. For example, what are the precise roles of the adipocyte and leptin signalling on *T. cruzi* infection? Since adiponectin null mice have a cardiomyopathic phenotype, could the *T. cruzi*-induced reduction in adiponectin expression contribute to the cardiomyopathy of Chagas disease?

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FIGURE 10.1.

(A) Four representative scanning electron micrographs of 3T3-L1 adipocytes infected with *T. cruzi*. (B) Representative transmission electron micrographs of 3T3-L1 adipocytes 48-h post-infection. Note the close proximity of parasites to lipid droplets indicated by arrowheads. The picture on the top left corresponds to an uninfected cell. (C) Electron microscopy analysis of brown adipocytes at different magnifications. LD, lipid droplet. Arrows indicate intracellular amastigotes (4–5 μm in diameter) (images from Combs et al., 2005).

FIGURE 10.2.

Representative transverse MRI of the abdominal region of a normal control mouse with 15% total body fat (A), an infected mouse with a normal sized heart and 7% total body fat (B) and an infected mouse with an enlarged heart and 3% total body fat (C). The solid white arrows indicate the visceral and subcutaneous fat which appears bright in these images. The spine is indicated for orientation. Total body fat was determined using images spanning the entire mouse body. Three-dimensional reconstructions of adipose tissue in an uninfected control mouse (D) and a chronically infected mouse (E). MRI was performed using 9.4T Varian animal imaging system. Transverse images of the mice were acquired from the tail to the neck. Images were imported into Amira 3D visualization software. Image segmentation was performed, and the adipose tissue is indicated in semi-transparent grey (spanning the base of the tail to the neck). An image acquired at the level of the kidneys is included, and one of the kidneys of each mouse is indicated and circled in white. The perirenal and visceral fat depots are indicated. The images clearly show a reduction in adipose tissue mass in the infected mouse.