REVIEW

Advances in understanding the role of adipose tissue and mitochondrial oxidative stress in *Trypanosoma cruzi* infection

[version 1; peer review: 2 approved]

Jyothi F. Nagajyothi¹, Louis M. Weiss²

¹Department of Microbiology, Biochemistry and Molecular Genetics, Public Health Research Institute, New Jersey Medical School, 225 Warren Street, Newark, NJ, 07103, USA

²Departments of Pathology and Medicine, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Room 504 Forchheimer Building, Bronx, NY, 10461, USA

V1 First published: 22 Jul 2019, 8(F1000 Faculty Rev):1152
<https://doi.org/10.12688/f1000research.19190.1>

Latest published: 22 Jul 2019, 8(F1000 Faculty Rev):1152
<https://doi.org/10.12688/f1000research.19190.1>

Abstract

Trypanosoma cruzi, the etiologic agent of Chagas disease, causes a latent infection that results in cardiomyopathy. Infection with this pathogen is a major socio-economic burden in areas of endemic infection throughout Latin America. The development of chagasic cardiomyopathy is dependent on the persistence of this parasite in host tissues. Pathogenesis of this cardiomyopathy is multifactorial and research indicates that it includes microvascular dysfunction, immune responses to host and parasite antigens, and various vasoactive and lipid mediators produced by both the host and parasite. It has been demonstrated that *T. cruzi* persists in adipose tissue and uses fat as a nutritional niche in infected hosts. This chronic infection of adipose tissue plays an important role in the pathogenesis and persistence of this infection and involves mitochondrial stress responses as well as the production of various anti-inflammatory adipokines and pro-inflammatory cytokines by both white and brown adipose tissue. The changes in diet in endemic regions of infection have resulted in an epidemic of obesity that has significant implications for the pathogenesis of *T. cruzi* infection and the development of chagasic cardiomyopathy in infected humans.

Keywords

Trypanosoma cruzi, Chagas Disease, Adipocytes, Metabolism, Mitochondria, Latency

Open Peer Review

Approval Status

	1	2
version 1		
22 Jul 2019		

Faculty Reviews are review articles written by the prestigious Members of **Faculty Opinions**. The articles are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

1. **Nisha Jain Garg**, Institute for Human Infections and Immunity, University of Texas Medical Branch, Galveston, USA
2. **Carlos Robello**, Institut Pasteur de Montevideo, and Departamento de Bioquímica, Facultad de Medicina., Montevideo, Uruguay

Any comments on the article can be found at the end of the article.

Corresponding author: Louis M. Weiss (louis.weiss@einstein.yu.edu)

Author roles: Nagajyothi JF: Conceptualization, Writing – Original Draft Preparation; Weiss LM: Conceptualization, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

Copyright: © 2019 Nagajyothi JF and Weiss LM. This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Nagajyothi JF and Weiss LM. **Advances in understanding the role of adipose tissue and mitochondrial oxidative stress in *Trypanosoma cruzi* infection [version 1; peer review: 2 approved]** F1000Research 2019, 8(F1000 Faculty Rev):1152 <https://doi.org/10.12688/f1000research.19190.1>

First published: 22 Jul 2019, 8(F1000 Faculty Rev):1152 <https://doi.org/10.12688/f1000research.19190.1>

Introduction

Infection with *Trypanosoma cruzi* causes Chagas disease. Cardiomyopathy, due to *T. cruzi* infection, develops in about 30% of patients with Chagas disease and is a major socio-economic burden in Latin America¹. Evidence of *T. cruzi* infection has been found in mummies over 9000 years old from northern Chile and southern Peru². Chagas disease-related cardiomyopathy develops several years or decades after the initial infection. The pathogenesis of chronic Chagas cardiomyopathy is multifactorial³. Mechanisms contributing to the progression of cardiomyopathy involve the persistence of parasites, myocardial damage, microvascular dysfunction, and neurogenic disturbances. Many of these changes are regulated by host immune-metabolic mediators. Although cardiomyopathy is the characteristic manifestation of chronic Chagas disease, this chronic infection can alter the function of other organs and tissues. One such organ is adipose or fat tissue⁴⁻⁶. Previously, we demonstrated that *T. cruzi* persists in adipose tissue and uses fat as a nutritional niche in infected murine models of *T. cruzi* infection and confirmed this finding in fat tissue from infected humans⁷.

Adipose tissue is now recognized to function as an endocrine organ involved in whole body immune-metabolic homeostasis^{8,9}. In mammals, three types of adipose depots commonly exist: white (WAT), brown (BAT), and beige/brite/brown-like (bAT) adipose tissues¹⁰. These three types of adipose tissues differ in morphology (shape, color, number, and size of lipid droplets and number of mitochondria), development, localization, and functions¹¹. WAT and BAT have been extensively studied. WAT is a storage organ for energy in the form of lipids, whereas BAT regulates body temperature by producing heat via the expenditure of stored energy. Therefore, energy expenditure is greater in BAT compared with WAT. The morphology of white and brown adipocytes differs. In WAT, lipids are organized in a unique droplet (unilocular) and in BAT lipids are present in many droplets (multilocular). The size and number of mitochondria are significantly greater in BAT compared with WAT¹¹.

Adipose tissue is composed of adipocytes (80% of the cells) and a stromal fraction containing a variety of cells, including preadipocytes, adipose tissue-specific macrophages (ATM), T cells, endothelial cells, and nerve cells¹². The physiology of adipose tissue is highly regulated by the systemic energy homeostasis and vice versa. Importantly, fat tissue is highly sensitive to the whole body immune-metabolic challenges because of various infections, drug treatments, and disease states. Human hearts have epicardial and pericardial fat tissues, which may play a role in the pathogenesis of Chagasic cardiomyopathy. In this brief review, we summarize data on the role of adipose tissue and its dysfunction in the pathogenesis of chronic Chagas disease and in the progression of Chagasic cardiomyopathy.

Adipose tissue: a reservoir for *T. cruzi* during infection

T. cruzi is an obligate intracellular protozoan that persists indefinitely following infection in mammals. For several decades, invasion mechanism(s) and persistence have been studied mainly in infected macrophages and cardiomyocytes^{13,14}. In 1970, Shoemaker *et al.* first reported that *T. cruzi* may exist in BAT

of infected mice¹⁵. Using acute and chronic murine models of Chagas disease, our laboratory subsequently demonstrated that adipose tissue can serve as a reservoir for *T. cruzi*⁷. Parasite load significantly increased in adipose tissues (both WAT and BAT) of *T. cruzi*-infected mice compared with heart tissue during early acute infection, suggesting that these parasites likely prefer lipid-rich fat cells over cardiomyocytes as a host cell environment⁷. We also demonstrated the persistence of these parasites in adipose tissue during chronic cardiomyopathy, when parasite loads in the heart were significantly reduced⁷. In humans, the persistence of this organism was demonstrated in adipose tissue in elderly seropositive patients with chronic chagasic heart disease¹⁶.

Fat cells are a unique niche; they increase in number with age and generally are stable in adults. Although adipocytes die (about 10% of cells per year in an adult die), they are replaced by new cells. Adipocytes are rich in nutrients and secrete the anti-inflammatory adipokine adiponectin^{17,18}. They therefore represent an excellent cell for persistence of an intracellular pathogen. Furthermore, in the adipose tissues of chronic *T. cruzi*-infected mice, there is a polarization of macrophages toward an M2 phenotype, probably further limiting sterilizing immunity and thereby allowing *T. cruzi* to persist in adipose tissue⁶.

Adipose tissue physiology during the acute and chronic stages of *T. cruzi* infection

T. cruzi infects both BAT and WAT⁷. Interestingly, the parasite load was greater in both WAT and BAT of *T. cruzi*-infected mice compared with that found in the corresponding heart tissue at the early stages of acute infection (15 days after infection)⁷. This time point of acute infection is characterized by a lack of blood parasitemia and overt illness. There is a significant change in adipose tissue physiology, even at this early stage of infection, and these changes differed in WAT and BAT⁴. Adipose tissue physiology depends on the levels of adipogenesis and adipolysis (lipolysis), which are tightly regulated by the levels of localized adipokines, mainly peroxisome proliferator-activated receptor gamma (PPAR γ) and adiponectin and adipose tissue-specific macrophage (ATM)-secreted tumor necrosis factor alpha (TNF α)¹⁹⁻²¹.

Adipocyte differentiation is controlled by a tightly regulated transcriptional cascade in which PPAR γ and members of the C/EBP family are key players²². *T. cruzi* infection significantly decreased the expression of PPAR γ in BAT and significantly increased PPAR γ levels in WAT at 15 days after infection and this was probably due to their different responses to infection-induced inflammation⁴. Although there were significant similarities between BAT and WAT in regard to an increased infiltration of immune cells and elevated levels of lipolysis and inflammatory markers, WAT demonstrated a unique feedback response to elevated lipolysis by inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) activation⁴. PPAR γ was not decreased in the WAT during early acute infection⁴. Levels of adiponectin were significantly reduced in both BAT and WAT, suggesting that deregulated lipid loss in adipose tissue may affect adiponectin levels independent of PPAR γ levels⁴.

By the end of the acute stage of infection (30 days after infection), mice displayed a threefold decrease in total body fat mass

because of significant loss of lipid droplets compared with uninfected mice⁷. The loss in lipid droplets was associated with significantly increased levels of infiltration of macrophages and inflammatory markers such as TNF α , interferon gamma (IFN γ), and interleukin 1 beta (IL-1 β) in adipose tissue⁷. The levels of adiponectin, an anti-inflammatory cytokine specifically secreted by adipose tissue, were significantly reduced by the end of acute infection⁷. This is consistent with reported results of increased levels in serum of several inflammatory markers²³. Although TNF α and IFN γ were increased, they weakly correlated in the acute phase²³. The levels of inflammatory markers that were contributed mainly by adipose tissue, such as IL-6, monocyte chemoattractant protein-1 (MCP-1), and resistin, were significantly increased during acute infection in the murine *T. cruzi* infection model⁷. Patients with the acute phase of Chagas disease also display increased circulating levels of IL-6²⁴. Infants with congenital exposure to *T. cruzi* (diagnosed between 6 and 12 months of age) also have increased levels of IL-6 at 1 month of age²⁴. These data suggest that an intense inflammatory response in adipose tissue probably contributes to the circulating cytokine levels during acute infection.

The levels of body fat mass increased in *T. cruzi*-infected mice when they reached the chronic stage (90 days after infection) of infection compared with the acute stage of infection (30 days after infection); however, these levels of body fat were significantly lower than those of uninfected mice of the same age, suggesting that impaired fat tissue physiology and metabolism may occur in chronic *T. cruzi* infection. Levels of TNF α , IFN γ , and IL-1 β in the adipose tissue of chronically infected CD1 mice significantly increased at 90 days after infection⁷. Serum levels of several cytokines and chemokines (TNF α , IL-1 β , IL-4, IL-5, CCL-5, CCL-11, CXCL-9, IL-2, IL-10, IL-17, and CCL-3) also increased during chronic infection in C57BL/6 mice (depending on the strain of *T. cruzi*)^{25,26}. These levels of serum pro-inflammatory markers subside during the indeterminate stage and then increase during chronic stages in *T. cruzi*-infected humans with cardiac abnormalities^{27,28}. Symptomatic chronic Chagas patients displayed greater levels of pro-inflammatory cytokines such as TNF α , IFN γ , and IL-6, and asymptomatic patients showed higher levels of IL-4, IL-10, IL-13, and transforming growth factor beta (TGF β)^{27–29}. There is a significantly increased loss of fat tissue in mice that develop cardiomyopathy compared with mice that do not develop cardiomyopathy during the chronic stage of infection⁷ and adipose tissues from these mice expressed higher levels of TNF α , IFN γ , and IL-1 β ⁷. These data suggest that adipose tissue physiology is altered during acute and chronic infections and adipose tissue-generated anti-inflammatory adipokines and pro-inflammatory cytokines contribute to the levels of serum inflammatory markers.

Mitochondrial and endoplasmic reticulum stress during acute and chronic *T. cruzi* infection

Mitochondria play a significant role in crucial metabolic processes, including the tricarboxylic acid cycle, pyruvate decarboxylation, oxidative decarboxylation of fatty acids (β -oxidation), and degradation of branched amino acids. A primary function of mitochondria is to produce more than 95% of adenosine triphosphate (ATP) for cellular energy consumption³⁰. WAT adipocytes are classically large with a single big lipid droplet, and at

the periphery of lipid droplets, a few mitochondria and tiny (but detectable) smooth endoplasmic reticulum (ER)¹¹. BAT adipocytes are small with multiple small lipid droplets surrounded by abundant mitochondria and little to no ER¹¹. Metabolic processes such as lipolysis and lipogenesis are strictly regulated in adipocytes and the mitochondria play a major role in this process¹¹. Lipolysis of triglycerides in lipid droplets results in the cytoplasmic accumulation of free fatty acids. Fatty acids can be translocated—through the carnitin acyl transferases—to the mitochondrial matrix, where they undergo β -oxidation, with the concomitant generation of acetyl coenzyme A (acetyl-CoA) and synthesis of ATP³¹. Incomplete oxidation of accumulated fatty acids results in cell death due to lipotoxicity³².

We have demonstrated that elevated levels of lipolysis of lipid droplets and loss of lipid contents (and adipocytes) are key factors in adipose tissue pathogenesis during acute *T. cruzi*-infected mouse models⁴. The increased free fatty acids undergo further catabolism as demonstrated by increased levels of PPAR α in adipose tissue⁴. This increase in β -oxidation increases the cellular levels of reactive oxygen species (ROS)³³. In WAT adipocytes, which have relatively few mitochondria and very large lipid droplets compared to BAT, dysregulated lipolysis of lipid droplets during infection creates an immense burden on mitochondrial β -oxidation function and leads to elevated cellular ROS levels and mitochondrial oxidative stress. Continued stress on mitochondria during the acute stage of infection leads to significant ER stress and dysfunctional mitochondria function, eventually resulting in cell death³³. Wen *et al.* demonstrated that both BAT and WAT display oxidative stress markers during acute and chronic *T. cruzi* infection; however, the pattern of intensity changes between BAT and WAT and acute and chronic stages of infection³⁴.

Adipose tissues from *T. cruzi*-infected mice demonstrate significantly increased mRNA levels of genes encoding components of NADPH oxidase complex, suggesting that the production of ROS might be enhanced in BAT and WAT during infection³⁴. In addition, mRNA levels of anti-oxidant markers such as glutathione peroxidase (GPX) and superoxide dismutase (SODs) are reduced in BAT and WAT, consistent with an increase in oxidative stress in acutely and chronically infected mice³⁴. Interestingly, mRNA levels of eosinophil peroxidases increase in both BAT and WAT during acute infection but decrease in BAT during chronic infection³⁴. This suggests that an eosinophil response may occur in both WAT and BAT.

WAT is under significant oxidative stress during acute *T. cruzi* infection which probably persists in chronic infection. This is supported by data showing increased levels of protein carbonylation and malonyldialdehydes in BAT and WAT during acute and chronic stages of infection, respectively, in a murine Chagas model³⁴. The levels of protein carbonylation and malonyldialdehyde are biomarkers of oxidative stress and lipid peroxidation, respectively. Increased ROS production and mitochondrial oxidative stress are associated with ER stress³³. In the adipocyte, the ER is directly involved with lipid droplet formation and the maintenance of lipid homeostasis³⁵. Adipocytes generally have scant ER and are highly susceptible to ER stress under conditions of deregulated lipolysis and oxidative stress³⁶. The

combination of elevated ROS production and ER stress can easily trigger adipocyte apoptosis and cell death, leading to the observed loss of fat cells in the murine models of *T. cruzi* infection (Figure 1).

The impact of loss of adipose tissue on the pathogenesis of human Chagas cardiomyopathy

Murine models of chronic Chagas cardiomyopathy display an inverse relation between body fat mass and susceptibility to Chagas cardiomyopathy progression⁷. The exact role of fat tissue and its immune-metabolic dysregulation in the pathogenesis of Chagas disease in patients with or without cardiomyopathy or heart failure is currently unknown; however, a few studies have evaluated body mass index (BMI) data in patients with various stages of Chagas disease. A study on beta-blocker therapy and mortality, reported that patients with Chagas heart failure displayed a significantly lower BMI compared with other non-Chagas heart failure patients (24.1 ± 4.1 versus 26.3 ± 5.1 , $P = 0.001$)³⁷. Data (from the United Network for Organ Sharing database) collected from patients who were

heart transplantation recipients between 1987 and 2015 in Brazil indicate that patients with Chagas cardiomyopathy had a significantly decreased BMI compared with idiopathic dilated cardiomyopathy patients (24^{22-26} versus 26^{23-30} , $P = 0.007$)³⁸. In a study that reported on the mode of death due to progressive heart failure in Chagas patients compared with non-Chagas patients with heart failure, the BMI was significantly lower in Chagas patients with heart failure compared with non-Chagas patients (23.5 [$21.3-26.4$] versus 25.3 [$22.5-29.0$], $P = 0.003$)³⁹. Overall, these various studies provide human data which are consistent with observations in the murine model of Chagas cardiomyopathy; however, more clinical data with cross-sectional and longitudinal studies need to be collected to elucidate the role of fat tissue in patients with different degrees of Chagas cardiomyopathy.

Limitations and Future direction

The changes in body fat mass content during *T. cruzi* infection depend on the strain of mouse, strain of *T. cruzi*, size of the inoculum used to induce infection, and stage of the disease. The findings that are described in this review may not be applicable in general to all mouse-parasite strains and to humans. Further studies are warranted to evaluate the role of adipose tissue in the pathogenesis of this infection, including assessing changes seen in Chagas patients with different degrees of cardiomyopathy.

Conclusions

The pathogenesis of Chagas cardiomyopathy is complex and multifactorial. Adipose tissue is an immune-metabolic organ that has been demonstrated to play a significant role in the pathogenesis of Chagas cardiomyopathy in murine models, to be a niche and reservoir to *T. cruzi* in both human Chagas cardiomyopathy and murine models, and is an immune-metabolic regulator to the progression of Chagas cardiomyopathy in murine models. Adipocyte function in adipose tissue physiology depends mainly on its mitochondrial β -oxidation capacity. The number of mitochondria in white adipocytes is very small and thus mitochondrial β -oxidation stress induced by *T. cruzi* infection could easily result in a loss of adipocytes. Altered adipose tissue physiology, depending on its mitochondrial stress, complicates cardiac pathology, especially in the case of chronic Chagas disease. It is important to further investigate the pathophysiological role of adipose tissue and its signaling pathways in the progression of Chagas cardiomyopathy.

Grant information

The author(s) declared that no grants were involved in supporting this work.

Acknowledgments

We dedicate this article to the late Dr. Herbert Tanowitz (Albert Einstein College of Medicine, Bronx, NY, USA), a renowned physician, for his lifetime of valuable contributions to Chagas disease research and insights into the pathophysiology of this important endemic infection of Latin America.

Figure 1. A pictorial representation of the effect of *Trypanosoma cruzi* infection on adipose tissue physiology. Infection causes adipocyte lipolysis, leading to mitochondrial oxidative stress, endoplasmic reticulum (ER) stress, inflammation, and a loss of fat cells. These pathologic changes contribute to the development of cardiomyopathy. ROS, reactive oxygen species.

References

1. Bonney KM: **Chagas disease in the 21st century: a public health success or an emerging threat?** *Parasite*. 2014; **21**: 11.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
2. Aufderheide AC, Salo W, Madden M, *et al.*: **A 9,000-year record of Chagas' disease.** *Proc Natl Acad Sci U S A*. 2004; **101**(7): 2034–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
3. Nunes MCP, Beaton A, Acquatella H, *et al.*: **Chagas Cardiomyopathy: An Update of Current Clinical Knowledge and Management: A Scientific Statement From the American Heart Association.** *Circulation*. 2018; **138**(12): e169–e209.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
4. Nagajyothi F, Desruisseaux MS, Machado FS, *et al.*: **Response of adipose tissue to early infection with *Trypanosoma cruzi* (Brazil strain).** *J Infect Dis*. 2012; **205**(5): 830–40.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
5. Nagajyothi F, Desruisseaux MS, Jelicks LA, *et al.*: **Perspectives on adipose tissue, chagas disease and implications for the metabolic syndrome.** *Interdiscip Perspect Infect Dis*. 2009; **2009**: 824324.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
6. Cabalén ME, Cabral MF, Sanmarco LM, *et al.*: **Chronic *Trypanosoma cruzi* infection potentiates adipose tissue macrophage polarization toward an anti-inflammatory M2 phenotype and contributes to diabetes progression in a diet-induced obesity model.** *Oncotarget*. 2016; **7**(12): 13400–15.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
7. Combs TP, Nagajyothi, Mukherjee S, *et al.*: **The adipocyte as an important target cell for *Trypanosoma cruzi* infection.** *J Biol Chem*. 2005; **280**(25): 24085–94.
[PubMed Abstract](#) | [Publisher Full Text](#)
8. Grant RW, Dixit VD: **Adipose tissue as an immunological organ.** *Obesity (Silver Spring)*. 2015; **23**(3): 512–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
9. Ferrante AW Jr: **The immune cells in adipose tissue.** *Diabetes Obes Metab*. 2013; **15** Suppl 3: 34–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
10. Giralt M, Villarroya F: **White, brown, beige/brite: different adipose cells for different functions?** *Endocrinology*. 2013; **154**(9): 2992–3000.
[PubMed Abstract](#) | [Publisher Full Text](#)
11. Cedikova M, Kripnerová M, Dvorakova J, *et al.*: **Mitochondria in White, Brown, and Beige Adipocytes.** *Stem Cells Int*. 2016; **2016**: 6067349.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
12. Makki K, Froguel P, Wolowczuk I: **Adipose tissue in obesity-related inflammation and insulin resistance: cells, cytokines, and chemokines.** *ISRN Inflamm*. 2013; **2013**: 139239.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
13. Vieira M, Dutra JM, Carvalho TM, *et al.*: **Cellular signaling during the macrophage invasion by *Trypanosoma cruzi*.** *Histochem Cell Biol*. 2002; **118**(6): 491–500.
[PubMed Abstract](#)
14. Epting CL, Coates BM, Engman DM: **Molecular mechanisms of host cell invasion by *Trypanosoma cruzi*.** *Exp Parasitol*. 2010; **126**(3): 283–91.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
15. Shoemaker JP, Hoffman RV Jr, Huffman DG: ***Trypanosoma cruzi*: preference for brown adipose tissue in mice by the Tulahuen strain.** *Exp Parasitol*. 1970; **27**(3): 403–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
16. Ferreira AV, Segatto M, Menezes Z, *et al.*: **Evidence for *Trypanosoma cruzi* in adipose tissue in human chronic Chagas disease.** *Microbes Infect*. 2011; **13**(12–13): 1002–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
17. Rajala MW, Scherer PE: **Minireview: The adipocyte—at the crossroads of energy homeostasis, inflammation, and atherosclerosis.** *Endocrinology*. 2003; **144**(9): 3765–73.
[PubMed Abstract](#) | [Publisher Full Text](#)
18. Chandran M, Phillips SA, Ciaraldi T, *et al.*: **Adiponectin: more than just another fat cell hormone?** *Diabetes Care*. 2003; **26**(8): 2442–50.
[PubMed Abstract](#) | [Publisher Full Text](#)
19. Duncan RE, Ahmadian M, Jaworski K, *et al.*: **Regulation of lipolysis in adipocytes.** *Annu Rev Nutr*. 2007; **27**: 79–101.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
20. Corrales P, Vidal-Puig A, Medina-Gómez G: **PPARs and Metabolic Disorders Associated with Challenged Adipose Tissue Plasticity.** *Int J Mol Sci*. 2018; **19**(7): pii: E2124.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
21. Takagi M, Uno H, Nishi R, *et al.*: **ATM Regulates Adipocyte Differentiation and Contributes to Glucose Homeostasis.** *Cell Rep*. 2015; **10**(6): 957–67.
[PubMed Abstract](#) | [Publisher Full Text](#)
22. Siersbaek R, Nielsen R, Mandrup S: **PPARGamma in adipocyte differentiation and metabolism—novel insights from genome-wide studies.** *FEBS Lett*. 2010; **584**(15): 3242–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
23. Santi-Rocca J, Fernandez-Cortes F, Chillón-Marinas C, *et al.*: **A multi-parametric analysis of *Trypanosoma cruzi* infection: common pathophysiological patterns beyond extreme heterogeneity of host responses.** *Sci Rep*. 2017; **7**(1): 8893.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
24. Volta BJ, Bustos PL, Cardoni RL, *et al.*: **Serum Cytokines as Biomarkers of Early *Trypanosoma cruzi* infection by Congenital Exposure.** *J Immunol*. 2016; **196**(11): 4596–602.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
25. Ferreira BL, Ferreira ER, deBrito MV, *et al.*: **BALB/c and C57BL/6 Mice Cytokine Responses to *Trypanosoma cruzi* Infection Are Independent of Parasite Strain Infectivity.** *Front Microbiol*. 2018; **9**: 553.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
26. Sousa GR, Gomes JA, Damasio MP, *et al.*: **The role of interleukin 17-mediated immune response in Chagas disease: High level is correlated with better left ventricular function.** *PLoS One*. 2017; **12**(3): e0172833.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
27. Gomes JA, Bahia-Oliveira LM, Rocha MO, *et al.*: **Evidence that development of severe cardiomyopathy in human Chagas' disease is due to a Th1-specific immune response.** *Infect Immun*. 2003; **71**(3): 1185–93.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
28. Poveda C, Fresno M, Gironès N, *et al.*: **Cytokine profiling in Chagas disease: towards understanding the association with infecting *Trypanosoma cruzi* discrete typing units (a BENEFIT TRIAL sub-study).** *PLoS One*. 2014; **9**(3): e91154.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
29. Sousa-Rocha D, Thomaz-Tobias M, Diniz LF, *et al.*: ***Trypanosoma cruzi* and Its Soluble Antigens Induce NET Release by Stimulating Toll-Like Receptors.** *PLoS One*. 2015; **10**(10): e0139569.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
30. Kühlbrandt W: **Structure and function of mitochondrial membrane protein complexes.** *BMC Biol*. 2015; **13**: 89.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
31. Lodish H, Berk A, Zipursky SL, *et al.*: **Oxidation of glucose and fatty acids to CO₂.** *Molecular Cell Biology*. 4th edition. WH Freeman. 2000.
[Reference Source](#)
32. Ertunc ME, Hotamisligil GS: **Lipid signaling and lipotoxicity in metaflammation: indications for metabolic disease pathogenesis and treatment.** *J Lipid Res*. 2016; **57**(12): 2099–114.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
33. Cortassa S, Sollott SJ, Aon MA, *et al.*: **Mitochondrial respiration and ROS emission during β -oxidation in the heart: An experimental-computational study.** *PLoS Comput Biol*. 2017; **13**: e1005588.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
34. Wen JJ, Nagajyothi F, Machado FS, *et al.*: **Markers of oxidative stress in adipose tissue during *Trypanosoma cruzi* infection.** *Parasitol Res*. 2014; **113**(9): 3159–65.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
35. Heid H, Rickelt S, Zimbelmann R, *et al.*: **On the formation of lipid droplets in human adipocytes: the organization of the perilipin-vimentin cortex.** *PLoS One*. 2014; **9**(2): e90386.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
36. Bogdanovic E, Kraus N, Patsouris D, *et al.*: **Endoplasmic reticulum stress in adipose tissue augments lipolysis.** *J Cell Mol Med*. 2015; **19**(1): 82–91.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
37. Issa VS, Amaral AF, Cruz FD, *et al.*: **Beta-blocker therapy and mortality of patients with Chagas cardiomyopathy: a subanalysis of the REMADHE prospective trial.** *Circ Heart Fail*. 2010; **3**(1): 82–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
38. Benatti RD, Al-Kindi SG, Bacal F, *et al.*: **Heart transplant outcomes in patients with Chagas cardiomyopathy in the United States.** *Clin Transplant*. 2018; **32**(6): e13279.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
39. Ayub-Ferreira SM, Mangini S, Issa VS, *et al.*: **Mode of death on Chagas heart disease: comparison with other etiologies, a subanalysis of the REMADHE prospective trial.** *PLoS Negl Trop Dis*. 2013; **7**(4): e2176.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Open Peer Review

Current Peer Review Status:

Editorial Note on the Review Process

Faculty Reviews are review articles written by the prestigious Members of **Faculty Opinions**. The articles are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

The reviewers who approved this article are:

Version 1

1. **Carlos Robello**

Unidad de Biología Molecular, Institut Pasteur de Montevideo, and Departamento de Bioquímica, Facultad de Medicina., Montevideo, Uruguay

Competing Interests: No competing interests were disclosed.

2. **Nisha Jain Garg**

Departments of Microbiology and Immunology and Pathology, Institute for Human Infections and Immunity, University of Texas Medical Branch, Galveston, TX, USA

Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research