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Minireview

Inflammation and mitochondria in the pathogenesis of chronic Chagas disease cardiomyopathy

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Impact Statement

This review article highlights the significant impact of mitochondrial dysfunction on Chagas disease (CD) cardiomyopathy. By examining the existing body of research, it provides a comprehensive analysis of the detrimental consequences resulting from impaired mitochondrial function in this cardiac condition. We review new intricate relationship between CD cardiomyopathy, inflammatory response, mitochondrial dysfunction and energy disbalance, elucidating some molecular mechanisms and pathways involved. This review not only enhances our understanding of the disease pathogenesis but also emphasizes the crucial role of mitochondria in cardiac function and its potential as a therapeutic target for mitigating CD cardiomyopathy.

Abstract

Chagas disease (CD), caused by the protozoan parasite *Trypanosoma cruzi*, is a neglected disease affecting around 6million people. About 30% of CD patients develop chronic Chagas disease cardiomyopathy (CCC), an inflammatory cardiomyopathy that occurs decades after the initial infection, while most infected patients (60%) remain asymptomatic in the so-called indeterminate form (IF). Death results from heart failure or arrhythmia in a subset of CCC patients. Myocardial fibrosis, inflammation, and mitochondrial dysfunction are involved in the arrhythmia substrate and triggering events. Survival in CCC is worse than in other cardiomyopathies, which may be linked to a Th1-T cell rich myocarditis with abundant interferon (IFN)- γ and tumor necrosis factor (TNF)- α , selectively lower levels of mitochondrial energy metabolism enzymes in the heart, and reduced levels of high-energy phosphate, indicating poor adenosine triphosphate (ATP) production. IFN- γ and TNF- α signaling, which are constitutively upregulated in CD patients, negatively affect mitochondrial function in cardiomyocytes, recapitulating findings in CCC heart tissue. Genetic studies such as whole-exome sequencing (WES) in nuclear families with multiple CCC/IF cases has disclosed rare heterozygous pathogenic variants in mitochondrial and inflammatory genes segregating in CCC cases. In this

minireview, we summarized studies showing how IFN- γ and TNF- α affect cell energy generation, mitochondrial health, and redox homeostasis in cardiomyocytes, in addition to human CD and mitochondria. We hypothesize that cytokine-induced mitochondrial dysfunction in genetically predisposed patients may be the underlying cause of CCC severity and we believe this mechanism may have a bearing on other inflammatory cardiomyopathies.

Keywords: Mitochondria dysfunction; inflammation, Chagas disease cardiomyopathy, IFN- γ , cell metabolism, antioxidants

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Introduction

Clinical and epidemiological features of Chagas disease

Chagas disease (CD) (*American trypanosomiasis*) caused by the protozoan parasite *Trypanosoma cruzi* is estimated to affect 6 million people in endemic areas of Latin America.^{1–3} Due to migration, *T. cruzi*-infected individuals have spread throughout the world, and it is estimated that 400,000

infected persons live in non-endemic countries, mainly in the United States and Europe.⁴ One-third of the patients advance into chronic Chagas disease cardiomyopathy (CCC), an inflammatory dilated cardiomyopathy that frequently leads to heart failure and arrhythmia, resulting in fatality. In addition, 10% of individuals develop digestive disorders such as megacolon and megaesophagus, while the remaining patients exhibit an asymptomatic condition throughout their lives referred to as the “indeterminate”

form (IF).⁵ CCC is the most prevalent etiology of myocarditis in the world, and the most important cause of non-ischemic cardiomyopathy in endemic regions of Latin America. The annual mortality rate for individuals with chronic Chagasic heart disease varies depending on their risk stratification, with a range of 1–10% in the low-risk group and up to 84% in the high-risk group.⁶ The overall mortality rate is estimated at 33%, in which approximately 35–45% are directly linked to the advancement of heart failure. The worsening of heart failure can result in a significant decline in cardiac function, impaired circulation, fluid retention, and the development of life-threatening complications, ultimately contributing to the observed mortality rate.⁷ Sudden cardiac death (SCD) accounts for about 50–60% of total mortality, where 80–90% are caused by ventricular tachycardia/ventricular fibrillation (VT/VF) and the remainder by bradyarrhythmia. In general, the rate and complexity of ventricular arrhythmias are higher in CCC, and prognosis is worse than in other cardiomyopathies.^{8,9} Non-sustained ventricular tachycardia (NSVT) is recognized as an independent predictor of SCD.⁸ In common with other cardiomyopathies, CCC shows myocardial hypertrophy and fibrosis. However, inflammation is particularly important in CCC, as clinical severity in CD is closely associated with presence of myocarditis.¹⁰ The histopathological substrate of CCC is chronic myocarditis and fibrosis, which can occur in electrical conduction tissue or in atrial or ventricular myocardium, leading to conduction system disorders and arrhythmias, or left ventricular dysfunction associated with progressive dilation leading to heart failure. Unfortunately, no vaccine or antiparasitic drug with proven efficacy is available for chronically infected adults, when most patients are diagnosed.¹¹ The development of effective drugs for CCC is hampered by the limited knowledge of its pathogenesis.

In this review, we conducted a comprehensive search in journal databases for scientific studies examining the effects of the pro-inflammatory cytokines IFN- γ and TNF- α in *in vitro* experiments. Specifically, we focused on studies that investigated the impact of these cytokines on cardiomyocyte cell metabolism and mitochondrial dysfunction, as the cytokine-mediated disruption of redox balance and energy generation has emerged as a prominent topic in CD cardiomyopathy research. Our search encompassed papers published across all time ranges available in public databases (i.e. PubMed, Web of Science, Google Scholar). The following keywords were used in our search: “TNF- α and/or IFN- γ and mitochondrial dysfunction”; “TNF- α and/or IFN- γ and Chagas disease cardiomyopathy”; and “TNF- α and/or IFN- γ in cardiomyocytes” as well as “Chagas disease and mitochondria.” We also included any additional papers that were cited in the selected studies. This review can support new studies and may shed light on novel treatment modalities that would be effective in ameliorating the morbimortality of CCC.

Pathogenesis and genetics of CCC

Immune dynamics in acute and chronic *T. cruzi* infection, central role of IFN- γ

The intracellular life cycle of *T. cruzi* is a major target of the antiparasite immune response.¹² While extracellular *T. cruzi* components engage Toll-like receptors (TLR) TLR2

and TLR4,¹³ *T. cruzi* RNA and DNA activate endosomal TLR7 and TLR9. TLR engagement promotes the Myd88-mediated activation of NF- κ B. The acidification of lysosomes facilitates the escape of *T. cruzi* into the cytoplasm, where it undergoes differentiation into replicative amastigote forms. Amastigote replication in the cytoplasm triggers the activation of inflammasomes, resulting in the release of inflammatory cytokines and activation of NF- κ B. This inflammatory stimulus induces expression of pro-inflammatory cytokines including interleukin (IL)-12 in macrophages and dendritic cells, which elicits differentiation of IFN- γ -producing Th1 cells. IFN- γ induces expression of multiple other genes involved in resistance to *T. cruzi*, such as *TNFA* and *NOS2*.^{14,15}

Although powerful, the immune response that occurs during acute infection leads to partial parasite control. *T. cruzi* evades complete eradication, leading to the establishment of a chronic persistent infection with low parasitism. *T. cruzi*-infected individuals maintain increased production of inflammatory/Th1 cytokines like IFN- γ and TNF- α as compared to healthy individuals, as a result of persistent stimulus of innate and specific immunity.^{16,17} CCC patients show an even more increased number of IFN- γ -producing Th1-T cells accompanied by elevated levels of plasma IFN- γ and TNF- α when compared to IF patients. Conversely, the numbers of IL-10-producing regulatory T cells, as well as Ebi3/IL-27p28, are lower in CCC patients as compared to IF. These observations align with a deficiency in the regulatory arm of the immune response in CCC.^{17–20}

The increased proportion of circulating Th1-T cells is reflected in CCC myocardium. IFN- γ is the most upregulated cytokine²¹ and the top upstream regulator of the gene expression profile in CCC heart tissue.^{21,22} Circulating IFN- γ -producing CCR5 + CXCR3 + Th1-T cells are more abundant in the blood of CCC than IF patients,²³ and the same cells were identified in CCC heart tissue, along with the chemokine ligands of receptors CCR5 and CXCR3, CCL5 and CXCL9, respectively.²⁴ Together, this suggests that locally produced Th1-T cell-attracting chemokines play a role in the selective accumulation of Th1-T cells in CCC hearts. Thus, we believe the unopposed IFN- γ action in CCC myocardium is linked to the fact that factors that reduce IFN- γ production and/or Th1-T cell differentiation and regulatory T cells are downregulated in CCC patients. This lack of regulation could explain the destructiveness of the inflammatory infiltrate, most likely due to excessive collateral damage by IFN- γ -producing T cells as described in acutely *T. cruzi*-infected mice. IFN- γ is thus considered the culprit of CCC.²⁵

Mitochondria in the pathogenesis of CCC

Evidence of mitochondrial dysfunction has been found in hearts of animal models of CD, as well as the myocardium of CCC patients. This is especially relevant for CCC pathogenesis, since mitochondrial dysfunction is a paramount feature of heart failure of diverse etiologies.²⁶ Nisha Garg and her group pioneered and studied in detail mitochondrial dysfunction in hearts of murine models of acute and

chronic CD and *in vitro* infection models.²⁷ In addition, two studies reported that IFN- γ transgenic mice exhibit chronic active myocarditis and cardiomyopathy, which is mediated by TNF- α .^{28,29} Regarding mitochondrial damage in human CCC, our group described altered expression of mitochondrial genes and 16S mitochondrial rRNA in CCC heart lesions.^{21,30} We also found a selective reduction of protein expression of ATP synthase and creatine kinase activity—key mitochondrial energy metabolism enzymes—in CCC heart lesions.³¹ Six enzymes belonging to fatty acid beta-oxidation present reduced expression in CCC myocardium, as compared with one or two in non-inflammatory cardiomyopathies.³² Cevey *et al.*³³ reported that treatment with fenofibrate, a PPAR α agonist, was able to induce mitochondrial fatty acid beta-oxidation, restore left ventricular function, reduce myocarditis and fibrosis in a murine model of CCC. A reduction of high-energy phosphates, indicative of reduced ATP production, has been observed *in vivo* in CCC heart tissue.³⁴ In agreement, mitochondrial DNA content was found to be reduced in CCC heart tissue as compared to healthy or DCM patients.³⁵ Comparatively, CCC exhibited heightened nitro-oxidative stress in contrast to DCM, further indicating that mitochondrial function is especially disturbed in CCC. Upon performing pathways analysis of proteomic and transcriptomic studies in CCC myocardium, our research team observed an enrichment in the pathways of mitochondrial dysfunction, mitochondrial translation, and quality control. In addition, we observed suppressed pathways associated with the tricarboxylic acid (TCA) cycle, respiratory electron transport chain, lipid oxidation, and transmembrane potential of mitochondria. Notably, these findings were more pronounced in CCC compared to non-inflammatory cardiomyopathies.^{21,32}

IFN- γ and TNF- α and energy generation

IFN- γ and TNF- α are essential pro-inflammatory cytokines in the antimicrobial response. Indeed, these cytokines allow a metabolic reprogramming essential to immune cells to activate and fight a pathogen. When innate immune cells such as dendritic cells and macrophages are activated, by a molecular pattern associated with a pathogen/danger (PAMP/DAMP) or metabolism-associated danger signal (MADS) via pattern recognition receptors (PRR), some of these cells become antigen presenting cells (APCs).³⁶

The APCs change their metabolism depending on whether they are anti-inflammatory or pro-inflammatory. In a pro-inflammatory role, APCs will release inflammatory cytokines including IL-1, TNF- α , and IL-6, among others. These cytokines contribute to the initiation and amplification of the inflammatory response, which lead to a polarization of M ϕ macrophages into M1 macrophages which is the form most adapted to a pro-inflammatory profile, this type of macrophage has a much stronger phagocytic capacity and pathogenic destruction activity.^{37–39} M1 macrophages in turn, secrete high levels of pro-inflammatory cytokines such as IL-1 β , IL-6, IL-12, and TNF- α ,^{40,41} which leads to macrophage self-activation but also to natural killer (NK) cell activation and amplification of the Th1 response.⁴²

To activate M0 macrophages in M1 with IFN- γ and LPS, cells switch metabolism. M0 macrophages showed a transition of metabolic pathways to produce adenosine triphosphate (ATP), between the oxidative phosphorylation (OXPHOS) pathway and the tricarboxylic acid cycle (TCA) versus energy production by the glycolytic and pentose phosphate pathways (PPPs).^{43,44} An alteration of OXPHOS will cause a disruption of TCA, as many positive and negative allosteric regulators control the metabolic flux of this cycle. The disturbed functioning of these two pathways leads to the formation of reactive oxygen species (ROS).³⁶ Moreover, this alteration could be due to the stimulation of the cells by TNF- α . Indeed, several studies showed that TNF- α leads to production of mitochondrial reactive oxygen species (mtROS) by altering the complex I of the mitochondrial respiratory chain.^{45,46} Superoxide, along with nitric oxide, plays a crucial role in the inflammatory and antimicrobial response, as demonstrated in the context of *T. cruzi* infection. This combination generates peroxynitrite (ONOO $^-$), which effectively eradicates intracellular *T. cruzi* amastigotes.^{47,48} In addition, it has been shown that stimulation with IFN- γ and TNF- α leads to NO production by induction of nitric oxide synthase 2 (NOS2).^{49,50} IFN- γ is also essential for the polarization of T cells into cytotoxic CD8 + T cells, upon activation the Th1-T cells will switch from OXPHOS to glycolysis.³⁶ Although IFN- γ and TNF- α are essential for the activation and polarization of the immune system toward a pro-inflammatory action, their action in other cell types of the organism—in special, cardiomyocytes—can have a deleterious effect.

Several diseases that are due to chronic inflammation, such as Chronic inflammatory bowel disease,⁵¹ chronic CD,³⁵ psoriasis,⁵² non-infectious uveitis⁵³ and many others, all have in common the deleterious effect of pro-inflammatory cytokines such as IFN- γ and TNF- α . During chronic inflammation, cells belonging to the inflammatory sites, cardiac, intestinal, epithelial cells are constantly stimulated with inflammatory cytokines. These cytokines will have the effect of switching the cellular metabolism from OXPHOS and TCA to glycolysis.⁵⁴ A decrease in ATP is then visible, concomitant with an increase in the generation of mtROS.^{31,35,46} NO production was also observed in the case of stimulation with IFN- γ and TNF- α in human cell cardiomyocytes *in vitro* and in a model for Alzheimer's disease by the STAT1/NF- κ B/NOS2 pathway.^{35,55} IFN- γ and TNF- α also mediated mitochondria depolarization, increased NO, ROS, lipid peroxidation, and decreased creatine kinase activity in other cell types, such as hepatic cells⁵⁶ and skeletal muscle cells.⁵⁷ The decrease in ATP, the increase in ROS and the switch between OXPHOS and glycolysis may be partly explained by the fact that TNF- α has the ability to reduce the expression of the four subunits of the complex I.⁴⁶ Indeed, reduced expression of complex I may cause increase in ROS, a reduction of ATP but also an accumulation of nicotinamide adenine dinucleotide (NADH). NADH inhibits all enzymes in the TCA cycle, so the TCA is possibly altered in this case. In M1 pro-inflammatory macrophages, it has already been said that stopping the TCA causes the modification of the metabolism with citrate which no longer participates in the TCA but joins the

cycle of PPP.⁵⁸ Succinate, which activates hypoxia-inducible factor- α (HIF1- α), could be one of the causes of the metabolism change, as HIF1- α promotes glycolysis and PPP.⁴⁶ IFN- γ and TNF- α also cause damage to mitochondria via the reduction of mitochondrial membrane potential ($\Delta\Psi_m$) and the decrease in mitochondrial DNA.^{35,59}

Stimulation with IFN- γ and TNF- α leads to an increase in glucose and PPP metabolism by impairing the OXPHOS metabolism and the fatty acid pathway. In one study, it was shown that these cytokines decrease the dependency of cardiac cells on the fatty acid pathway and the glutamine oxidation pathway.³⁵ In addition, a study on patients with CCC, a condition in which IFN- γ and TNF- α are locally present in large amounts, showed a decrease in enzymes of the beta-oxidation pathway in cardiac biopsies.³² These elements suggest that TNF- α and IFN- γ cause a shift in metabolism between OXPHOS/fatty acid pathway and toward glycolysis/PPP (Figure 1).

Role of IFN- γ and TNF- α in mitochondrial damage

Mitochondrial dysfunction is one of the main pathophysiological mechanisms of chronic disease, like cardiomyopathies and neurodegenerative diseases.⁶⁰ Multiple studies demonstrate that inflammatory cytokines such as IFN- γ and TNF- α cause mitochondrial damage in diverse cell types. IFN- γ and TNF- α are abundantly produced in CD in response to the persistent stimulus of *T. cruzi* infection. Multiple studies have shown that these cytokines cause a reduction in oxidative metabolism, in the expression of energy metabolism enzymes, in the activity of the lipid beta-oxidation pathway and mitochondrial ATP production, by an NF- κ B dependent pathway.⁶¹ In our research, we have discovered that IFN- γ and TNF- α stimulation of AC16 cardiomyocytes leads to the promotion of nitro-oxidative stress and reduction of mitochondrial copy number, which closely mirror the findings in IFN- γ and TNF- α -rich CCC heart tissue.³⁵

OXPHOS is the process by which ATP is generated from the energy released by the transfer of electrons from NADH and flavin adenine dinucleotide (FADH₂) to molecular oxygen in the mitochondria. This process is mediated by a series of enzyme supercomplexes, called the electron transport chain (ETC), which are located in the inner mitochondrial membrane.⁶²

The energy released by the electron transfer is used to pump protons (H⁺) across the inner mitochondrial membrane, creating an electrochemical gradient (mitochondrial membrane potential, $\Delta\Psi_m$) which drives ATP synthase for ATP synthesis. TNF- α and IFN- γ also can disrupt cardiomyocyte metabolism, decreasing basal and maximal respiration and ATP production.⁶³ Recent results showed that IFN- γ caused a dose-dependent reduction in $\Delta\Psi_m$ and that TNF- α alone or in combination with IFN- γ decreased mitochondrial, glycolytic, and total ATP in human cardiomyocyte AC16 cells.³⁵ Furthermore, these two cytokines together change cardiomyocytes energetic metabolism decreasing the dependency of glutamine and fatty acid oxidation and increasing the capacity of glucose oxidation.^{35,60}

Mechanistically, TNF- α can induce glucose oxidation by downregulation of peroxisome proliferator-activated

receptor-gamma coactivator (PGC-1 α) and pyruvate dehydrogenase kinase 4 (PDK4).⁶⁴ Through TNF- α stimulation, NF- κ B activation is triggered, facilitating its translocation to the nucleus and promoting the interaction between NF- κ B p65 subunit and the transcription factor E2F1. The DNA-binding capability of E2F1 is required for the expression of PDK4, which in turn inhibits the pyruvate dehydrogenase complex through phosphorylation.⁶⁵

A significant crosstalk occurs between NF- κ B and mitochondrion-protecting proteins. NF- κ B signaling down-regulates sirtuin-1 (SIRT1) activity through the expression of IFN- γ , ROS and NO.⁶⁶ SIRT1, an antioxidant and anti-inflammatory protein, regulates the oxidative respiration and cellular survival and is highly expressed in the heart, acting as an inhibitor of NF- κ B inflammatory signals by deacetylating the p65 subunit of the NF- κ B complex.⁶⁷ While NF- κ B stimulates glycolytic energy flux in acute inflammation, SIRT1 inhibits NF- κ B and enhances mitochondrial oxidative metabolism through 5'-AMP-activated protein kinase (AMPK), an energy sensor that regulates the metabolism in cardiomyocytes in health and disease.⁶⁶ Indeed, treatment of *T. cruzi*-infected mice with SIRT1 and/or AMPK agonists SRT1720, resveratrol and metformin reduced myocardial NF- κ B transcriptional activity, inflammation and oxidative stress, resulting in beneficial results for the amelioration of cardiac function.^{68,69} Likewise, treatment of AC16 human cardiomyocyte cell line stimulated with IFN- γ /TNF- α with the same agents, NRF2 agonists, or antagonists of NOS2 and NF- κ B led to restoration of $\Delta\Psi_m$.³⁵

Dysregulated myocardial fatty acid metabolic signals were reported in some *in vitro* research using TNF- α -stimulated cardiomyocytes.^{70,71} A study depicted that TNF- α -treated cells have decreased levels of AMPK.⁷² The authors showed that activation of AMPK can mediate the transport of fatty acids into mitochondria through phosphorylation and inhibition of acetyl-CoA carboxylase (ACC), an important enzyme that inhibits the fatty acid oxidation, AMPK therefore enhanced the oxidation of fatty acids in HL-1 cardiomyocyte cells.⁷³ The same group reported that the expression of PPAR- α and PPAR- δ , transcription factors that regulate fatty acid oxidation, is decreased when cells are exposed to TNF- α .⁷³ TNF- α decreased carnitine O-palmitoyltransferase 1 (CPT-1) expression, which is required for the translocation of long-chain fatty acids into the mitochondrial matrix (a limiting step in beta-oxidation). The unphosphorylated ACC state catalyzes the carboxylation of acetyl-CoA into malonyl-CoA, which decreases fatty acid oxidation by inhibiting CPT-1.⁷⁴ Also, the oxidation of fatty acids is deregulated in IFN- γ -treated cardiomyocytes, similar to that observed in TNF- α treatment, where ACC phosphorylation is decreased.⁷³ Impairment of these enzymes by TNF- α could have, therefore, a great implication for heart dysfunction, as fatty acid oxidation is the primary source of energy for contractile function of cardiomyocytes.

Additional pathways that can be related to energetic dysfunction could be TNF- α induction of class I histone deacetylases that can alter mitochondrial complexes I and II activity⁷⁵ and a decreased inositol 1,4,5-trisphosphate (IP3) formation, possibly by decreased activity of

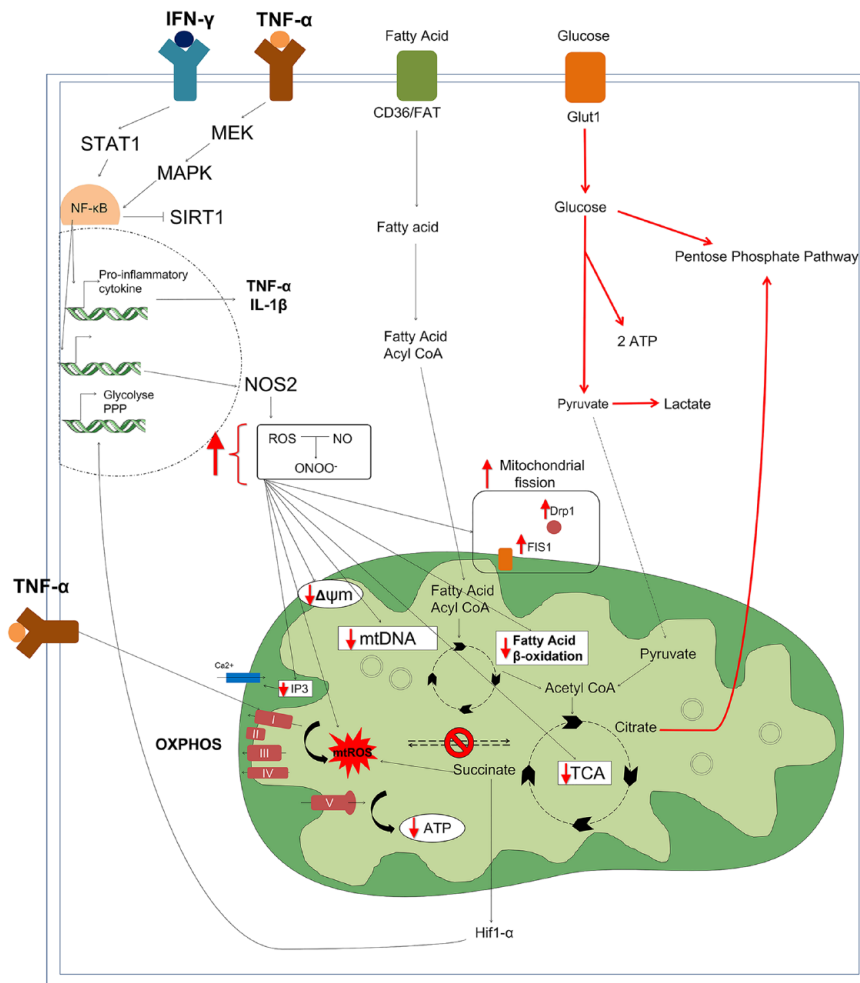


Figure 1. IFN- γ and TNF- α dysregulate energy production in mitochondria. Upon binding to their receptors, IFN- γ and TNF- α trigger the production of pro-inflammatory cytokines, including TNF- α and IL-1 β , as well as the generation of nitric oxide (NO) by NOS2. This process occurs through the activation of the STAT1/NF- κ B and MEK/MAPK/NF- κ B pathways, respectively. Consequently, an increase in NO levels within the cells leads to alterations in mitochondrial functions such as changes in membrane potential, a decrease in mitochondrial DNA (mtDNA), a reduction in ATP production, and an elevation of mitochondrial reactive oxygen species (mtROS). Furthermore, TNF- α -induced reduction in complex I of the respiratory chain enhances mtROS production, further lowering ATP levels and causing an accumulation of NADH. This accumulation disrupts the proper functioning of the tricarboxylic acid (TCA) cycle. Consequently, several compounds, such as succinate, accumulate, which, in turn, activates HIF-1 and promotes glycolysis and the pentose phosphate pathway (PPP). The cytokines can also modulate mitochondrial fusion-fission mechanism by affecting the expression of FIS1 and DRP1 phosphorylation. Stimulation of cells with IFN- γ and TNF- α induces a metabolic shift, leading to alterations in the oxidative phosphorylation (OXPHOS) and TCA pathways. In addition, it results in a decrease in the β -oxidation of fatty acids pathway and an increase in the glucose pathway of the PPP.

glycerol-3-phosphate dehydrogenase enzyme that regulates some lipid synthesis.⁷⁶ IP₃ can induce Ca²⁺ uptake in mitochondrial matrix and increases ATP production in cardiomyocytes.⁷⁷

The cytokines can have numerous effects on cardiomyocytes, deteriorating their functions and homeostasis (Table 1). TNF- α mediates changes in mitochondrial function leading to dysfunction by several mechanisms. For instance, Shen and co-workers have shown that TNF- α increases the phosphorylation of dynamin 1 like (DRP1) and its translocation to mitochondria in H9c2 cardiomyocytes, likely through increased RhoA GTPase expression.⁷⁸ In addition to increased p-Drp1, IFN- γ and TNF- α were shown to induce mitochondria fragmentation by upregulating the expression of the mitochondrial fission protein 1 (FIS1).⁷⁹ Both DRP1 and FIS1 play key role in mitochondrial fission and their modulation by IFN- γ and TNF- α is reported to change the cell metabolism, to increase the $\Delta\Psi$ m and ROS

production and also to dampen basal and maximal respiration and ATP synthesis.^{73,79}

Clinical similarities between genetic mitochondriopathies and CD: a whole-exome sequencing study

We have recently used whole-exome sequencing (WES) to identify pathogenic variants in nuclear families with multiple CCC/IF cases, disclosing rare heterozygous pathogenic variants in mitochondrial and inflammatory genes linked to CCC cases. In each family, the identified variants were shared only by family members with CCC, which were absent from IF siblings; such mutations occurred in mitochondrial genes in five out of the six studied families.⁸⁰ One of the variants identified is a complete loss of function mutation in the dihydroorotate dehydrogenase (*DHODH*) gene, which supplies electrons to complex III of the ETC. Significantly, incubation

Table 1. Summary of IFN- γ and TNF- α effect in *in vitro* cellular assays.

Stimulation	Effects	Model	Reference
IFN- γ	↓ Basal respiration ↓ Maximal respiration ↓ ATP ↓ Spare respiratory capacity ↓ pACC ↓ FAO	Primary cardiomyocytes from neonatal mouse hearts	Ni et al. ⁶³
IFN- γ	↓ ATP	Primary cardiomyocytes from neonatal rat hearts	Wang et al. ⁶¹
IFN- γ	↓ Creatine kinase activity	Human muscle cells	Kalovidouris et al. ⁵⁷
TNF- α	↓ ATP ↓ Complex I subunits	Sprague-Dawley mitochondria extracted from LV	Mariappan et al. ⁴⁶
TNF- α	↓ Basal respiration ↓ Maximal respiration ↓ ATP turnover ↓ pAMK ↓ pACC ↓ PGC-1 α ↓ CPT-1 ↓ DGAT	HL-1 cardiomyocytes	Lee et al. ⁷³
TNF- α	↓ Basal respiration ↓ Maximal respiration ↓ ATP turnover ↓ total ATP levels ↓ Complex I and II activity	HL-1 cardiomyocytes	Lkhagva et al. ⁷⁵
TNF- α	↓ Inositol phosphate synthesis ↓ PIP2 synthesis	Neonatal rat cardiomyocytes	Reithmann and Werdan ⁷⁶
TNF- α	↑ Glucose oxidation ↓ PGC-1 α ↓ PDK4	AC16 cardiomyocytes TNF1.6 transgenic mice hearts	Palomer et al. ⁶⁴
TNF- α	↑ phospho-DNM1L ↑ Mitochondrial fragmentation	H9c2 cardiomyocytes	Shen et al. ⁷⁸
IFN- γ and TNF- α	↑ Mitochondrial hyperpolarization ↑ Mitochondrial fragmentation ↓ ATP ↑ phospho-DNM1L ↑ hFIS	H9c2 cardiomyocytes	Buoncervello et al. ⁷⁹
IFN- γ and TNF- α	↑ Mitochondrial depolarization ↓ Total ATP ↓ Mitochondrial ATP ↓ Glycolytic ATP ↑ Basal respiration ↑ Maximal respiration ↑ Spare respiratory capacity ↓ Fatty acid dependency ↓ Glutamine oxidation dependency	AC16 cardiomyocytes	Nunes et al. ³⁵
IFN- γ and TNF- α	↑ Mitochondrial depolarization ↑ NO ↑ ROS ↑ lipid peroxidation ↑ Apoptosis ↑ STAT1 nitration	Hep3B and primary hepatocytes	Lee et al. ⁵⁶
IFN- γ and LPS	Metabolic Shift: ↑ Glycolysis ↓ FAO ↓ TCA	Bone marrow-derived macrophages	Liu et al. ⁴³
IFN- γ and LPS	↑ PPP	Bone marrow-derived macrophages	Haschemi et al. ⁴⁴

IFN- γ : interferon- γ ; TNF- α : tumor necrosis factor- α ; ATP: adenosine triphosphate; CPT: carnitine O-palmitoyltransferase 1; PDK4: pyruvate dehydrogenase kinase 4; NO: nitric oxide; ROS: reactive oxygen species; TCA: tricarboxylic acid; PPP: pentose phosphate pathway; pACC: phosphorylated acetyl-CoA carboxylase; FAO: fatty acid oxidation; LV: left ventricle; DGAT: diacylglycerol O-acyltransferase; STAT1: signal transducer and activator of transcription 1; LPS: lipopolysaccharide.

with IFN- γ on the human cardiomyocyte cell line treated with an inhibitor of dihydroorotate dehydrogenase brequinar markedly reduced $\Delta\Psi_m$ in synergy with IFN- γ and TNF- α , indicating increased mitochondrial dysfunction.⁸⁰ Another variant linked to CCC in another family leads to a stopgain variant at exon 8 of RPSUD3, involved in the assembly of the mitochondrial ribosome, creating a truncated version of the RPSUD3 protein, lacking 24% of its C-terminal sequence.

Mitochondriopathies, caused by homozygous pathogenic variants of genes encoded in the nuclear DNA, or in the mitochondrial DNA, are the most common group of monogenic syndromes. They severely damage the energy metabolism and cause mitochondrial dysfunction and functional impairment in tissues with high metabolic demand, such as cardiac and skeletal muscle, nervous tissue, liver, and kidneys. They can present as syndromes affecting individual organs or tissues or combinations of them and each clinical syndrome is associated with a specific gene or gene

group bearing the variant; the clinical presentation can vary between intrauterine to the adult age. Significantly, 30–40% of mitochondriopathy patients evolve with cardiomyopathy, heart conduction abnormalities and severe arrhythmia,^{81,82} and 15% to gastrointestinal motility disorders, including megaesophagus and megacolon, with denervation of myenteric nervous plexi, and autonomic nervous system disturbances. The similarity in the proportions of clinical outcomes with those of CD (30% CCC, 10% digestive form motility disorders⁸³) is impressive and made us hypothesize that heterozygous pathogenic variants, which may cause a partial reduction in mitochondrial function, may play a role in differential progression for CD in a two-hit phenomenon where cytokine-induced mitochondrial damage is the second hit. Genetic alterations with direct implications to mitochondrial function and immune response can therefore be important components for CD cardiomyopathy and megaesophagus susceptibility and progression.^{80,83}

Limitations

This review has compiled most, if not all, relevant scientific data concerning the interplay between genetics, inflammation/cytokines, and mitochondrial dysfunction in the pathogenesis of human CCC, but it did not include reports on animal models of CD. While this review may not directly influence public policies regarding CCC therapy, it significantly improves our understanding of the disease's pathogenesis. Furthermore, it underscores the vital role of mitochondria in cardiac function and highlights their potential as a therapeutic target for mitigating CD cardiomyopathy.

Future directions

This review provides a summary of the significant roles played by genetic factors and IFN- γ and TNF- α in mitochondrial dysfunction in cardiomyocytes, which could explain the worse prognoses for CD cardiomyopathy. The harmful effects of these cytokines together with gene polymorphisms in mitochondria genes could contribute to the progression of cardiac dysfunction. Therefore, targeting antioxidant and mitochondria-sparing pathways that can mitigate cytokine-induced mitochondrial dysfunction holds great potential as a therapeutic approach to alleviate the detrimental effects of IFN- γ and TNF- α . Further research is required to explore the effectiveness and safety of antioxidant- and mitochondria-sparing-based interventions on cytokine-induced mitochondrial dysfunction. Repositioning of clinically approved drugs may pave the way for novel treatments that ameliorate mitochondrial dysfunction and enhance the clinical prognosis and treatment of patients with CD cardiomyopathy, as well as other conditions associated with chronic inflammation and dysregulated inflammatory cytokines.

Conclusions

IFN- γ and TNF- α have negative impacts on mitochondrial function through various mechanisms. These cytokines induce the production of reactive oxygen species (ROS), disrupt the activity of the electron transport chain, disturb mitochondrial membrane potential ($\Delta\Psi_m$), and trigger the opening of mitochondrial permeability transition pore. They also cause mitochondrial DNA damage and alter mitochondrial biogenesis, creating a cycle of mitochondrial dysfunction and cardiac injury. The specific implications of IFN- γ and TNF- α in CD cardiomyopathy have not been fully explored, underscoring the unique nature of mitochondrial dysfunction in this context.

Considering the critical role of oxidative stress in the detrimental effects of IFN- γ and TNF- α on mitochondria, therapeutic strategies aimed at enhancing antioxidant defense systems show promise for intervention. Various approaches have been investigated to boost antioxidant pathways, such as administering external antioxidants, modulating internal antioxidant enzymes, activating antioxidant signaling pathways, and utilizing AMPK and sirtuin agonists.

AUTHORS' CONTRIBUTIONS

JPSN, VMdPR, PA, JK, CC, and ECN wrote and revised the manuscript.

DECLARATION OF CONFLICTING INTERESTS

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