TOPIC HIGHLIGHT

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Interferon-γ and other inflammatory mediators in cardiomyocyte signaling during Chagas disease cardiomyopathy

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Abstract

Chagas disease cardiomyopathy (CCC), the main consequence of *Trypanosoma cruzi* (*T.cruzi*) infection, is an inflammatory cardiomyopathy that develops in up to 30% of infected individuals. The heart inflammation in CCC patients is characterized by a Th1 T cell-rich myocarditis with increased production of interferon (IFN)-γ, produced by the CCC myocardial infiltrate and detected at high levels in the periphery. IFN-γ has a central role in the cardiomyocyte signaling during both acute and chronic phases of *T.cruzi* infection. In this review, we have chosen to focus in its pleiotropic mode of action during CCC, which may ultimately be the strongest driver towards pathological remodeling and heart failure. We describe here the antiparasitic protective and pathogenic dual role of IFN-γ in Chagas disease.

Core tip: Chagas disease cardiomyopathy (CCC) occurs in 30% of those infected with the protozoan *Trypanosoma cruzi*, endemic in Latin America. It is an inflammatory cardiomyopathy with a worse prognosis than cardiomyopathies of other etiologies. Interferon (IFN)- γ is the main cytokine produced locally and induces strong signaling in cardiomyocytes. This review focuses on the pleiotropic protective and pathogenic effects of IFN-γ on CCC.

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INTRODUCTION

Chagas disease cardiomyopathy (CCC) is a particularly

aggressive inflammatory dilated cardiomyopathy that occurs decades after the initial infection with the obligate intracellular parasite *Trypanosoma cruzi* (*T.cruzi*) in 30% of infected individuals[1]. *T. cruzi* infection affects 10 million subjects in endemic areas of South and Central America and migratory waves have taken patients to the United States, Europe and Japan[2-4]. Patients with CCC have a worse clinical progression and survival than those with cardiomyopathy of other etiologies. The development of CCC is associated with inflammation and activation of the immune system, with a local increased cardiac production of cytokines by the heart-infiltrating T cells and other mononuclear cells[5]. These mononuclear cells infiltrating CCC heart tissue express predominantly interferon (IFN)-γ and tumor necrosis factor (TNF)-α, with lower levels of interleukin (IL)-2, IL-4, IL-6 and IL-10. Cytokines like IL-7 and IL-15, which promote T cell survival, are also found to have increased expression in CCC heart tissue[6,7]. Significant IFN-γ signaling was observed in the myocardium of CCC patients, including genes that are not ordinarily expressed by inflammatory cells[8]. A similar increase in IFN-γ and TNF-α expression is observed in cardiac tissue from animals infected with *T. cruzi*[9]. CCC patients have a progressive myocardial remodeling process with hypertrophy and fibrosis causing heart fiber damage, heart conduction abnormalities, arrhythmias, apical aneurysm, heart failure and sudden death[10,11]. Several hypotheses have been raised to explain the lesions in the myocardium of CCC, which includes persistence of the parasite or its antigens at the inflammatory site and autoimmune tissue damage[5,12]. There are two drugs available to treat the acute phase of the disease, nifurtimox (nitrofurane) and benznidazole (nitroimidazole). The use of these drugs to treat the acute phase of the disease is widely accepted. However, their use in the treatment of the chronic phase is controversial. There is no specific treatment, against the parasite, that can benefit patients at the chronic stage of Chagas disease[13]. The undesirable side effects of both drugs are a major drawback in their use, frequently forcing the physician to stop treatment. The treatment of chronic patients consists of control of the symptoms and improvement in quality of life, by preventing cardiovascular complications according to the guidelines for treating heart failure and arrhythmias[14]. Regardless of the mechanisms underlying the initiation and maintenance of the myocarditis, the bulk of the evidence indicates that the inflammatory infiltrate is a significant effector of heart tissue damage. Our group has demonstrated over the past several years that, aside from direct inflammatory damage, several cytokines and chemokines produced in the myocardium of CCC patients may also have a non-immunological pathogenic effect beyond direct inflammatory tissue damage, *via* modulation of gene and protein expression in cardiomyocytes and other myocardial cell types[5,7,15,16]. While IFN-γ acts as an immunological mediator during the acute stage of the disease suppressing overt parasitism, in the chronic phase of the disease it will both curtail parasitism and cause tissue damage through immunological and non-immunological effects entertaining the gradual progression to CCC.

IFN-γ IN HEALTH AND DISEASE

IFN-γ is a protein with 146 amino acid residues, the only member of the type Ⅱ IFN family, and in humans is encoded by a chromosomal locus separate from type Ⅰ IFNs, on chromosome 12q24.1 with approximately 5.4 kb and four exons[17]. IFN-γ is mainly produced by CD4+ T helper cell type 1 (Th1) lymphocytes, CD8+ cytotoxic lymphocytes, and natural killer (NK) cells, but can also be produced by other cells, such as B cells, NKT cells, and professional antigen-presenting cells (APCs). Cytokines secreted by APCs, most notably IL-12 and IL-18, control IFN-γ production and differentiation of cells capable of producing the cytokine. Interaction of macrophages and other APCs with pathogen-associated molecular patterns (PAMPs) induces secretion of IL-12 and chemokines. These chemokines attract inflammatory cells to the site of inflammation, and IL-12 promotes IFN-γ synthesis in these cells[18]. Negative regulators of IFN-γ production include IL-4, IL-10, transforming growth factor (TGF)-β, and glucocorticoids[19]. Animal models as well the analysis of different human diseases are good examples of the paradoxical roles of IFN-γ. Mice lacking IFN-γ and its receptor (IFNGR) showed no developmental defects, and their immune system appeared to develop normally[20]. However, these mice show deficiencies in natural resistance to infection. In humans, inactivating mutations of the human IFNGR1 or IFNGR2 chains show clinical presentation similar to the mouse models. At the same time IFN-γ can be beneficial in infectious diseases where it strengthens cellular defense mechanisms and favors the generation of specific immunity, and can be disease-promoting as described in non-infectious diseases. Reifenberg *et al*[21] have shown that SAP-IFN-γ transgenic mice, which constitutively express IFN-γ in their livers, developed chronic active myocarditis. These mice exhibited IFN-γ-mediated cardiotoxicity with left ventricular dilation and impaired systolic function, a true cardiomyopathy[21]. Morino *et al*[22] have reported a case of cardiomyopathy in a renal cell carcinoma patient treated with IFN-γ. In humans, IFN-γ is also implicated in the pathology of diseases such as systemic lupus erythematous[23], insulin-dependent diabetes mellitus[24] and multiple sclerosis[25]. Like other cytokines, the IFN-γ coding region is invariant with no reported polymorphisms. However, single nucleotide polymorphisms (SNPs) in intronic regions have been described and a microsatellite polymorphism consisting of a dinucleotide (CA) repeat in the first intron is the one most extensively studied as it is correlated with high IFN-γ production[26]. An association between IFN-γ SNPs and diseases like rheumatoid arthritis has been reported[27,28]. Nevertheless, as a cytokine with ambiguous effects, IFN-γ polymorphisms are correlated with increased longevity[25]. It has been proposed that a slightly dampened inflammatory status caused by an IFN-γ polymorphism, while not enough to significantly impact on

the individual's ability to clear infection, may prevent or defer inflammation-related diseases such as cardiovascular disease, neurodegeneration, osteoarthritis, osteoporosis, and diabetes[29]. In experimental *T. cruzi* infection, it has been shown by several investigators that IFN-γ can enhance macrophage killing of the parasite *in vitro* and increase resistance to an infectious challenge *in vivo*, an effect dependent on the *de novo* synthesis of TNF-α and NO by infected macrophages[9,30,31]. It has also been demonstrated that parasite-induced IFN-γ produced during *T. cruzi* infection by T and NK cells is involved in resistance to infection and protection in mice. This protection seems to be dependent on the IFN-γ/TNF-α pathway[31].

IFN-γ INDUCED SIGNALING IN CARDIOMYOCYTES INFECTED WITH *T.CRUZI*

Although infective *T. cruzi* trypomastigotes are capable of invading a wide variety of tissues and cell types in the vertebrate host, the majority of *T.cruzi* laboratory strains and isolates have tropism for cardiac tissue and or cardiomyocytes[32]. The establishment of a long-term infection in the heart and the development of a cardiomyopathy condition are directly related to the ability of *T. cruzi* to infect and persist within cardiomyocytes during the acute phase of infection[33,34]. Cardiomyocytes are differentiated cells that respond to *T.cruzi* infection by initiating adaptive strategies. These strategies can involve immunological and non-immunological events. For example, during *T.cruzi* infection cardiomyocytes reactivate an embryonic gene expression pattern[8] (*e.g.*, an increase in expression of atrial natriuretic factor), inhibit apoptosis[34], increase cell size by producing myofibrils (cardiac myosin heavy chain, several α-actin isoforms, smooth muscle myosin, actin-binding proteins, and collagen) and initiate a hypertrophic program, that are not related to an immunological response to the parasite[7]. However, these cells are actively integrated in the inflammatory process and can secrete chemokines such as C-C chemokine monocyte chemotactic protein 1 (*JE*/MCP-1/CCL2), chemokine (C-C motif) ligand 5 (RANTES/CCL5), keratinocyte chemoattractant (KC/CXCL3), macrophage inflammatory protein (MIP-2/CXCL2), Mig/CXCL9, and *cytokine*-responsive gene-2 (Crg-2/CXCL10), and the cytokines TNF-α, IL-1β and inducible NO synthase (iNOS)[35]. These chemokines will drive the early influx of leukocytes, and influence T-helper cell recruitment and local IFN-γ production defining the inflammatory infiltrate in the hearts during experimental *T.cruzi* infection and, presumably, also in acutely infected patients. It was recently demonstrated that there is a segregation of CD8+ cell populations in the heart in *T.cruzi* infected mice into two groups: CD8+ T cells producing perforin and no IFN-γ (IFN-γ[neg] Pfn[+]) and perforin-negative and IFN-γ-producing cells (IFN-γ[+] Pfn[neg]). These data supported the idea that CD8+ Pfn+ T-cells are involved in cardiomyocyte injury during *T. cruzi* infection, whereas CD8+ IFN-γ+

cells play a beneficial role in cardiomyocyte damage[36].

IFN-γ A DUAL ROLE IN CHAGAS DISEASE

A dual role in pathogenesis and protection during Chagas disease was described for IFN-γ and other cytokines, such as TNF-α[37]. Bahia-Oliveira *et al*[38], taking into account only the inflammatory actions of the cytokine, also described the dual role of IFN-γ during chronic Chagas disease. Our observations from the standpoint of the pleiotropic biological effects, both inflammatory and non-inflammatory, in Chagas disease made us remodel the concept as will follow in these review. During *T. cruzi* infection, once the inflammatory process starts, IFN-γ will be produced by Th1 cells and act as a prime inflammatory cytokine in different pathways of the immune system, such as upregulating MHC class I and class II molecules, suppressing Th2 immune responses by antagonism of IL-4 production, inducing high levels of antigen presentation and activating macrophages[18]. Our group has demonstrated the importance of IFN-γ, TNF-α and several chemokines in CCC by showing that they play a role in the generation of the inflammatory infiltrate[8,15,39]. CCC patients have an increased peripheral production of IFN-γ and TNF-α when compared to patients with the asymptomatic/indeterminate form. On the other hand, IFN-γ has direct effects on cardiomyocytes and perhaps other cells of the myocardium[8]. In the following sections we describe in detail the dual mechanism of IFN-γ during Chagas disease (acute and chronic phases) as illustrated in Figure 1.

IFN-γ ACTS AS AN IMMUNOLOGICAL MEDIATOR INDUCING PROTECTION DURING THE ACUTE PHASE AND ALLOWING CONTROL OF CHRONIC PARASITISM

Data from animal models and from the earliest stages in a proportion of naturally infected individuals has shown that inflammatory cytokines such as IFN-γ play a central role in acute *T. cruzi* infection. During invasion, *T. cruzi* or its derived molecules like DNA and glycosylphosphatidylinositol-anchored mucin-like glycoproteins derived from trypomastigotes forms (tGPI-mucins) can stimulate the host cutaneous cells, macrophages, cardiomyocytes and dendritic cells (as seen in *in vivo* and *in vitro* infection) to produce mediators that will trigger a local inflammatory response[40]. This activation will induce these cells to promptly release pro-inflammatory cytokines such as IL-1, IL-6, IL-12, IL-18, IL-27 and TNF-α and further activate other inflammatory cells. These cytokines will participate in the control of the infection, killing the parasite with the help of NO production *via* iNOS/NOS2. *T. cruzi*-specific T cells will produce IFN-γ, which in conjunction with macrophages producing TNF-α will migrate with other blood leukocytes to the site of inflam-
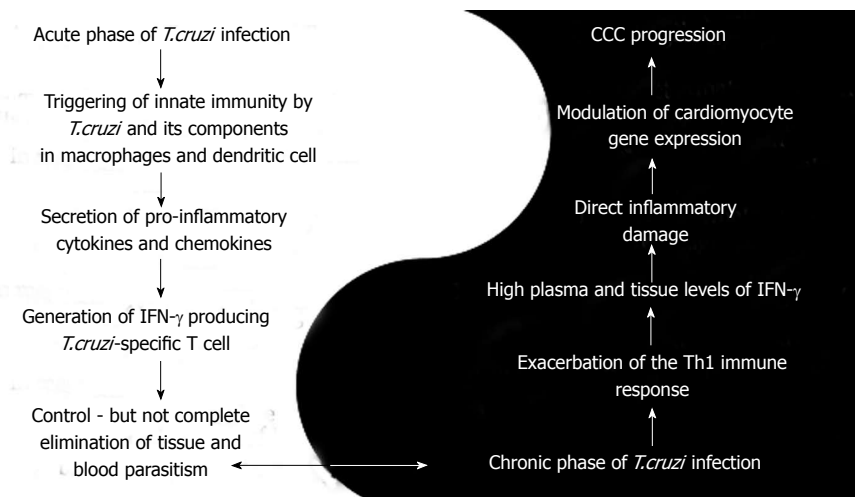
Figure 1 Interferon-γ a dual role in Chagas disease (acute and chronic phases). CCC: Cardiomyopathy; INF: Interferon.

mation in response to chemokines such as CCL2, CCL3, CCL4, CCL5, CXCL10 and CCR5[41]. The blockade of one, CCR5, by Met-RANTES significantly decreased the intensity of cardiac inflammatory infiltrate, suggesting that lymphocyte migration to the myocardium during acute infection is dependent on CCR5 ligands[42,43]. IFN-γ-inducible adhesion molecules, such as fibronectin and VCAM-1, can also be detected at high levels in cardiac tissue from *T. cruzi*-infected mice[44]. Few studies have investigated the immunology of the acute phase infection in human patients. It has been described that acutely infected children display increased expression of inflammatory cytokines, such as circulating IL-6 and TNF-α[45] and increased production of IFN-γ by mononuclear cells[46]. Serum C-reactive protein (CRP) and IL-6 concentrations have also been shown to increase in children infected with *T. cruzi* during the acute phase, but not in the chronic phase of Chagas disease[47].

IFN-γ INDUCES DISEASE PROGRESSION DURING THE CHRONIC PHASE ACTING AS A NON-IMMUNOLOGICAL MEDIATOR OF TISSUE DAMAGE

During the chronic phase of *T. cruzi* infection, CCC patients have an exacerbation of the Th1 immune response compared with those with the indeterminate form of Chagas disease. It was observed that CCC patients displayed greater cytokine production (Table 1) by mononuclear cells, higher plasma levels of TNF-α and IFN-γ and an increased number of IFN-γ-producing CCR5^{+}CXCR3^{+}CD4^{+} and CD8^{+} T cells, with reduced numbers of IL-10-producing and FoxP3^{+} regulatory T cells[15,48-50]. It has been hypothesized that this increased production of IL-10 by regulatory T cells restricts Th1 T cell differentiation and IFN-γ production in the majority of chronically *T. cruzi*-infected individuals, leading to the asymptomatic form of the disease[15,48-50]. Aside from the delayed hypersensitivity type of tissue damage classically seen in tissue lesions induced by IFN-γ, with cardiomyo-

cyte loss and fibrosis, the local production of IFN-γ in CCC heart lesions can induce profound changes in the cardiomyocyte gene expression pattern as observed by our group using cDNA microarrays. Significant IFN-γ signaling was observed in the myocardium of CCC patients, including genes that are not ordinarily expressed by inflammatory cells. We have observed that 15% of the genes selectively upregulated in CCC are IFN-γ-inducible genes, including inflammatory response genes expressed by the infiltrating inflammatory cells (*e.g.*, cytokine receptors, immunoglobulin, T cell receptor genes). Several IFN-γ modulated genes are not expressed by inflammatory cells, including angiotensin Ⅱ receptor 2, fatty acidbinding protein 5, cardiovascular 27-kd Hsp and genes encoding a number of proteins involved in oxidative phosphorylation and lipid catabolism in the CCC myocardium, compared with idiopathic dilated cardiomyopathy or donor myocardium[8]. cDNA microarray experiments in mice infected with *T. cruzi* showed changes in oxidative phosphorylation and depressed energy metabolism[51] and respiratory chain complexes with a reduced ATP-generating capacity[52]. Moreover, expression profiling in hearts of mice infected by *T. cruzi* also showed diminished myocardial energy metabolism and altered oxidative phosphorylation[51,53]. Significantly, mice infected for 100 d showed morphological alterations in the mitochondria and diminished expression of genes from the oxidative phosphorylation pathway, with a detectable reduction in OXPHOS-mediated mitochondrial ATP production[51]. Thus, both IFN-γ and *T. cruzi* infection can depress energy metabolism to reduce myocardial ATP generation, which has potential consequences for myocardial contractility, electric conduction and rhythm. Interestingly, one of the genes downregulated in CCC hearts, SERCA Ca^{2+}-ATPase is repressible by IFN-γ and is also involved in cardiac metabolism. *In vitro* experiments have shown that IFN-γ may induce profound changes in the cardiomyocyte gene expression program, including induction of atrial natriuretic factor and of the hypertrophic gene expression program, which can ultimately lead to heart dilation and heart failure[8]. Other inflammatory mediators and chemokines such as IL-18 and CCR7 ligands, up-

Table 1 Cytokine and chemokine expression in Chagas disease and animal models[80]

Cytokines/chemokines	Phase (acute/chronic/IND/severe/moderate CCC)	Host (mouse/human)	Organ/cell type	Ref.
IFN-γ	Severe CCC	Human	Mononuclear cells	[15,49]
IFN-γ	Severe CCC	Human	Myocardium	[63,64]
IFN-γ	Severe CCC	Human	Heart-infiltrating T cells	[15]
IFN-γ	IND, Severe CCC	Human	Plasma	[15,65,66]
TNF-α	Severe CCC	Human	Mononuclear cells	[15,49]
TNF-α	Severe CCC	Human	Heart-infiltrating T cells	[15]
TNF-α	Severe CCC	Human	Myocardium	[63,64]
TNF-α	IND and Severe CCC	Human	plasma	[15,65,66]
IFN-γ	Acute/chronic	Mouse	Heart	[67-69]
TNF-α	Acute/chronic	Mouse	Heart	[70]
IL-6	Severe CCC	Human	Heart-infiltrating T cells	[15,63,64]
IL-2	Severe CCC	Human	Heart-infiltrating T cells	[15,63,64]
IL-4	Severe CCC	Human	Heart-infiltrating T cells	[15,63,64]
IL-10	Severe CCC	Human	Heart-infiltrating T cells	[15, 63, 64]
IL-7	Severe CCC	Human	Myocardium	[71]
IL-15	Severe CCC	Human	Myocardium	[71]
IL-12	Acute	Mouse	Mononuclear cells	[72]
IL-18	Acute	Mouse	Mononuclear cells	[73]
IL-10	Acute	Mouse	Mononuclear cells	[74-76]
TGF-β	Acute	Mouse	Mononuclear cells	[74-76]
IL-17	Chronic	Mouse	Mononuclear cells	[77]
CCL2, CXCL10, CXCL9 (mRNA)	Severe CCC	Human	Myocardium	[8]
CCR2, CXCR3 (mRNA)	Severe CCC	Human	Myocardium	[8]
CCR5, CXCR3	Severe CCC, IND	Human	Mononuclear cells	[48]
CCL5, CXCL9, CXCL10	Chronic	Mouse	Cardiomyocytes	[35]
CCR5	Chronic	Mouse	Heart	[43,78]
CCL5, CCL4, CXCR3 (mRNA)	Chronic	Dog	Heart	[79]

CCC: Cardiomyopathy; INF: Interferon; IL: Interleukin; TNF: Tumor necrosis factor.

regulated in the CCC myocardium[39], induce cardiomyocyte hypertrophy and molecules involved in the fibrotic process[54-56]. Transgenic mice overexpressing CCL2, TNF-α or IFN-γ in the myocardium develop myocardial hypertrophy and ventricular dilation[21,57,58]. Inflammatory cytokines may also affect myocardial energy metabolism, and ventricular dysfunction is associated with reduced energy metabolism[59,60]. Treatment of cardiomyocytes with IFN-γ inhibited oxidative metabolism and ATP production[61] and reduced gene and protein expression of creatine kinase, which is responsible for translocation of mitochondrial ATP to the sarcoplasm in cultured human skeletal muscle cells[62]. We observed that the myocardium of CCC patients displays reduced expression of some key energy metabolism enzymes, including isoforms of creatine kinases, Krebs cycle enzymes, and members of the ATP synthase complex, in comparison with the myocardium of patients with non-inflammatory cardiomyopathies and heart donors (unpublished observations), which could be partly due to IFN-γ inflammatory cytokine signaling. cDNA Microarray experiments in mice experimentally infected with *T. cruzi* showed changes in oxidative phosphorylation and depressed energy metabolism[51], and respiratory chain complexes with a reduced ATP-generating capacity[52]. Thus, both IFN-γ and *T. cruzi* infection can depress energy metabolism, reducing myocardial ATP generation, with potential consequences for myocardial contractility, electrical conduction and rhythm. Taken together, data show that, apart from the direct inflammatory damage, the non-immunological effects of IFN-γ in the myocardium may play a significant pathogenic role in CCC, resulting in disease progression observed by a high degree of heart failure-inducing hypertrophy and fibrosis. The in-depth understanding of these pathways may lead to the development of new therapies for CCC.

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