

Cytokines that regulate autoimmune myocarditis

Michael O. Kurrer^a, Manfred Kopf^b, Josef M. Penninger^{c, d}, Urs Eriksson^{c, d, e}

^a Department of Pathology, University Hospital, Zurich, Switzerland

^b Molecular Biomedicine, Swiss Federal Institute of Technology, Zurich-Schlieren, Switzerland

^c Departments of Medical Biophysics and Immunology, University of Toronto, Canada

^d IMBA, Institute for Molecular Biotechnology of the Austrian Academy of Science

^e Medicine A, University Hospital, Basel, Switzerland

Summary

A growing body of evidence suggests that autoimmune responses are involved in the pathogenesis of myocarditis and postinfectious cardiomyopathy. Autoimmunity may also arise after ischaemic or traumatic damage to heart tissue. Myocarditis leading to heart failure can be mimicked in rodents by immunisation with cardiac alpha myosin and peptides derived from it. Cytokines and chemokines, produced mainly by T-cells and antigen-presenting cells, control immune responses by acting as either potentiating or inhibitory agents. Gene targeting and experiments with antibodies and/or antagonists blocking cyto-

kines and their receptors have uncovered mechanisms whereby such regulatory molecules are involved in the pathogenesis of myocarditis. Identification of regulatory key cytokines and the associated pro- or anti-inflammatory pathways involved in the pathogenesis of cardiac inflammation may have important implications for therapeutic strategies and vaccine design in the future.

Key words: myocarditis; experimental autoimmune myocarditis; autoimmunity; cytokines; TNF- α ; interferon- γ ; interleukin-4; interleukin-10; interleukin-12; chemokines

Methods

This minireview is based on articles from 1998–2002 retrieved by a MEDLINE search matching the key words *autoimmune myocarditis*, *cytokine* and *chemokine*. All articles were reviewed and cited if they referred to animal

models. Reviews on distinct cytokines, clinical studies and some outstanding articles published before 1998 were cited at the authors' discretion.

Cytokines and chemokines – regulatory molecules that control cardiac inflammation

Dilated cardiomyopathy is a prevalent cause of human heart failure. It is often associated with a history of viral myocarditis [1, 2]. The immune response normally clears the pathogen, followed by healing of the damaged heart. However, the balance between viral clearing and continued immunological surveillance may result in either inefficient elimination of the pathogen or overaggressive immunological activation. Indeed, many patients with cardiomyopathy and/or a history of myocarditis show evidence of autoimmunity against

heart muscle proteins [1, 3, 4]. The idea that autoimmune responses may be involved in the pathogenesis of myocarditis and cardiomyopathy focuses our attention on the role of cytokines and chemokines. Cytokines are mainly, but not exclusively, secreted by antigen-presenting cells and lymphocytes. Their local expression regulates inflammation by modulating migration, homing, antigen recognition and activation of distinct cell populations including lymphatic cells, endothelia and even cardiomyocytes [see 5 for review].

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The experimental autoimmune myocarditis model

As in humans, infection of rodents with cardiotropic microorganisms results in transient tissue damage and inflammation. However, after infection with coxsackie B3 viruses some mouse strains with a well-defined genetic background develop persistent myocarditis [6]. In these mice disease can also be induced by immunisation with cardiac myosin or peptides derived from it [6, 7] (fig. 1). Interestingly, the most immunogenic alpha myosin epitope for BALB/c mice shares a MAxxxST amino acid sequence with structural proteins of cardiotropic bacteria such as chlamydia and helicobacter [8]. Immunisation with cardiac myosin together with complete Freund's adjuvant also induces severe myocarditis in Lewis rats.

Autoimmune myocarditis is dependent on CD4⁺ T cells recognising heart-specific peptides together with MHC class II molecules on antigen-presenting cells [for a comprehensive review on the autoimmune myocarditis model see 6]. Disease severity usually peaks 3 weeks after immunisation and months later some of the affected mice develop heart failure (Eriksson et al., unpublished). The autoimmune myocarditis model offers the advantage of studying *in vivo* the role of immune mechanisms independent of microorganisms invading the heart. Furthermore, gene-targeted mice allow identification and functional characterisation of the cytokines and their signalling pathways involved in the pathogenesis of myocarditis (table 1).

Table 1

Myocarditis prevalence and severity in cytokine and cytokine receptor knock-out mice

Mutation	Background	Severity	Prevalence (day 21)	Reference
TNFRp55 ^{-/-}	A/J	–	no disease	[10]
IL-4 ^{-/-}	BALB/c	severe	intermediate	Eriksson & Kurrer, unpublished
IL-4Rα ^{-/-}	BALB/c	severe	low	[19]
IFN-γ ^{-/-}	BALB/c	severe	high	[19, 22]
IFN-γR ^{-/-}	BALB/c	severe	high	[21]
IL-12p40 ^{-/-}	BALB/c	–	no disease	[19]
IL-12Rβ1 ^{-/-}	BALB/c	–	no disease	[19, 22]

TNF-α and various chemokines promote activation and recruitment of inflammatory cells

In the heart, TNF-α is produced mainly by resident macrophages, but cardiac myocytes are also able to release it [9]. TNF-α binds either to the low-molecular-weight TNF-receptor p55 or to the high-molecular-weight TNF-receptor p75. TNF-α has been shown to promote apoptosis of cardiomyocytes, depression of cardiac contractility and autoimmune myocarditis through the TNFRp55 receptor [10, see 6 and 9 for review]. The crucial role of TNF-α in the pathogenesis of inflammatory heart disease is further supported by the fact that heart-specific overexpression of TNF-α in transgenic mice causes myocarditis and cardiomyopathy [11]. Binding to TNFRp55 results in activation of several signalling cascades leading to downstream transactivation of cytokine, adhesion molecule, and chemokine genes by nuclear factor kappaB (NFkappaB). Indeed, NFkappaB is a key regulator in the progression of autoimmune myocarditis, since NFkappaB blockade

by infusion of an NFkappaB decoy partly protects rats from disease [12]. These findings are in line with the observation that treatment of TNF-α transgenic mice with a soluble TNF-α receptor p55 fusion protein blocked myocardial expression of IL-1, adhesion molecules, and monocyte chemoattractant protein-1 [13]. Chemokines such as monocyte chemoattractant protein-1 [14], macrophage inflammatory protein-1 alpha [15], and others are upregulated in the inflamed heart. So far, experiments with MIP-1α knock-out mice have indicated a crucial role for macrophage inflammatory protein-1 alpha in inducing virus-induced myocarditis [16]. In sum, TNF-α appears to induce mechanisms necessary for activation, recruitment and homing of inflammatory cells to the target organ. These mechanisms involve different chemokines, which in turn are essential for disease induction.

Proinflammatory IFN- γ limits autoreactive CD4⁺ T-cell response

Two major subsets of CD4⁺ T-cells may be characterised according to their cytokine expression pattern. Th1 cells typically produce IFN- γ , whereas Th2 cells preferentially secrete IL-4 [see 17 for review]. The Th1 cytokine IFN- γ has long been considered essential for the expansion and effector function of autoreactive CD4⁺ T-cells. A proinflammatory role in cardiac inflammation is suggested by the fact that mice lacking the SOCS-1 (suppression of cytokine signalling-1) gene develop spontaneous myocarditis and myositis in the presence of IFN- γ only [18]. However, in the context of autoimmune myocarditis, recent advances have shown that IFN- γ is dispensable for disease development [19, 20]. Mice deficient for the ligand and binding chain of the IFN- γ receptor are not only highly susceptible, but also develop ongoing disease with high mortality [21]. Microscopic evaluation of the inflamed hearts shows extensive patchy infiltrates with significant numbers of eosinophils, reflecting a Th2 biased immune response (figure 1a, b). N. Rose and coworkers treated immunised wild-type mice with anti-IFN- γ antibodies and observed enhanced disease scores three weeks after immunisation [22]. Thus it appears that interferon- γ is not only dispensable but even protective in murine autoimmune myocarditis. This idea is further supported by the fact that pancreatic expression of interferon- γ in mice confers resistance to myocarditis following fatal cox-

sackievirus B3 infection [23]. Interestingly, the histological pattern of human eosinophilic myocarditis appears to be similar to the infiltrates observed in IFN- γ -receptor-deficient mice (fig. 2). Lewis rats, on the other hand, develop granulomatous infiltrates that are distinct from the inflammatory lesions observed in susceptible mice after myosin immunisation. In the classical perception, granulomatous infiltrates are associated with Th1-biased immune responses. So far the role of IFN- γ in the pathogenesis of rat autoimmune myocarditis has not been assessed.

Since IFN- γ is not required for disease development in the mouse model, the intriguing question of how CD4⁺ T-cells mediate autoimmune myocarditis has not been answered. The enhanced interferon- γ production in CD4⁺ T-cells of myosin-immunised IFN- γ -receptor-deficient mice (Eriksson and Kopf, unpublished observation) suggests that Th1 commitment occurs in the absence of interferon- γ signalling. The mechanisms by which interferon- γ protects from myocarditis have not been elucidated. Given the absence of iNOS induction in interferon- γ knock-out mice, together with the failure to suppress the expansion of activated CD4⁺ T cells [21], it is tempting to speculate that interferon- γ may confine inflammation by NO-mediated apoptosis of myosin-specific CD4⁺ T-cells. However, other mechanisms may be involved as well.

IL-4 – a puzzling role for the Th2 cytokine

Conflicting data exist regarding the role of the prototypic Th2 cytokine IL-4 in autoimmune myocarditis. Given the higher disease susceptibility of interferon- γ deficient mice, it has been suggested that autoimmune myocarditis is a Th2-mediated disease [24]. Indeed, treatment of A/J mice with an anti-IL-4 antibody markedly reduces disease severity [20]. However, IL-4-receptor-deficient mice on a BALB/c background are not protected [19] (Fig. 1c, d). These differences may be strain-specific. However, the absence of IL-4 signalling

also alters the disease course. Immunisation in IL-4R^{-/-} mice and treatment of wild-type BALB/c mice with an IL-4 receptor antagonistic protein results in severe myocarditis as early as 10–14 days after immunisation [19]. Taken together, current data do not support the view of autoimmune myocarditis as a Th2 mediated disease, but further studies addressing the role of the signalling pathways involved in Th1 and Th2 commitment of myosin-specific CD4⁺ T-cells are needed.

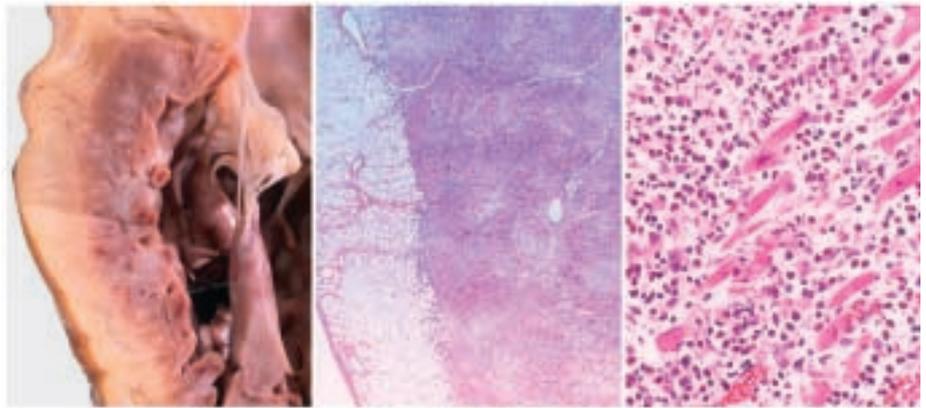
IL-12 is essential for generation of autoreactive myosin-specific T-cells

IL-12 is chiefly produced by macrophages and dendritic cells upon CD40 ligation, viral infection, and/or stimulation with pathogen components. The IL-12 receptor (IL-12R), composed of IL-12R β 1 and IL-12R β 2 chains, mediates signal transduction, which involves the recruitment of Janus family tyrosine kinase 2 and signal transducer and activator of transcription (STAT)4. The STAT4 pathway is also important for IFN- γ in-

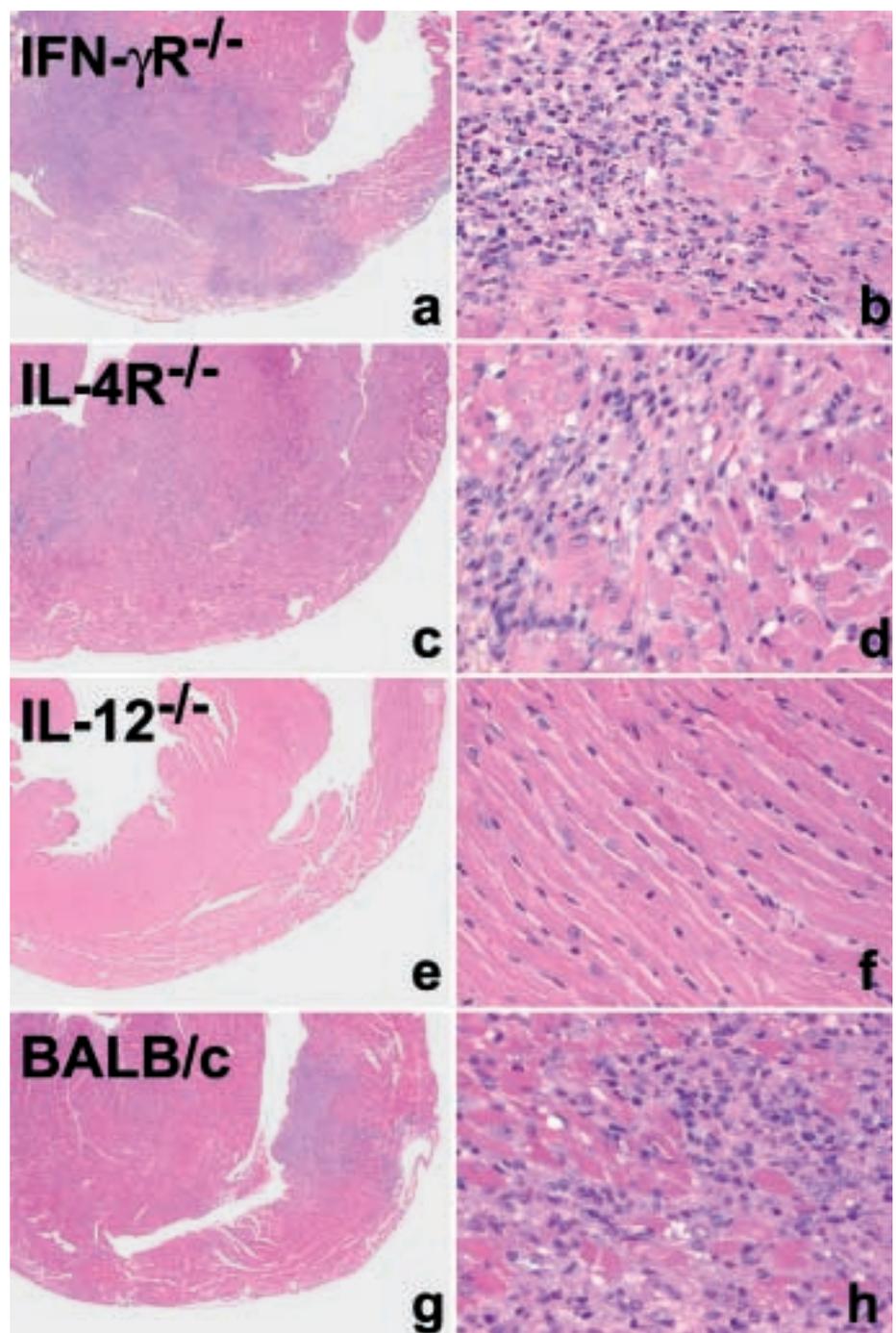
duction through direct interaction of STAT4 with the IFN- γ promoter [for a comprehensive review see 25]. IL-12 therefore plays a key role in the induction and maintenance of IFN- γ production by CD4⁺ T-cells. Hitherto it had been assumed that the proinflammatory effects of IL-12 were mediated by IFN- γ . In rats, however, autoimmune myocarditis is exacerbated by IL-12 treatment [26]. Further, mice deficient in both the IL-12 receptor

Figure 1

Fatal myocarditis 4 weeks after onset of flu-like symptoms in a 47-year-old previously healthy female. The macrophotograph of the right ventricular wall shows patches of white-looking inflammatory infiltrates. The low power microphotograph shows a dense inflammatory infiltrate essentially sparing the epicardial adipose tissue. The high power microphotograph shows inflammatory cells infiltrating between and replacing cardiomyocytes. The inflammatory infiltrate contains numerous eosinophils in this example of eosinophilic myocarditis, which is reminiscent of the myocarditis observed in interferon- γ receptor knock-out mice. Eosinophilic myocarditis is seen in about 5% of endomyocardial biopsies with myocarditis, and represents a distinct form of myocarditis additional to lymphocytic and giant cell myocarditis (haematoxyllin-eosin staining, original magnifications 30 \times and 400 \times).

**Figure 2**

Microphotographs of experimental autoimmune myocarditis in wild-type and gene-targeted mice – (a, b) IFN- γ R^{-/-} mice develop extensive patchy inflammatory infiltrates which include numerous eosinophils – (c, d) IL-4R^{-/-} mice develop patchy inflammatory lesions infiltrating between and replacing cardiomyocytes – (e, f) IL-12p40^{-/-} mice are protected from myosin peptide-induced myocarditis and cellularity between myocytes is composed of vascular endothelial cells and tissue resident immune accessory cells – (g, h) myocarditis in wild-type BALB/c mice is shown for reference (haematoxyllin-eosin staining, original magnifications 30 \times and 400 \times).



and IL-12p40/IL-12p35 ligands are completely protected from myocarditis [19, 22] (fig. 1e, f). Disease resistance correlates with minimal IFN- γ production but enhanced IL-4 and IL-10 production by myosin-specific CD4⁺ T cells. Because STAT4^{-/-} mice are also protected from myo-

carditis [22] it appears that the IL-12/IL-12-receptor/STAT4 pathway is indeed critical for disease induction, but independent of IFN- γ . A mechanism by which IL-12/STAT4 controls the onset of autoimmune myocarditis has not yet been established.

IL-10 downregulates inflammation in autoimmune myocarditis

IL-10 has been observed mainly to mediate anti-inflammatory and disease-limiting effects in various autoimmune disease models [see 27 for review]. IL-10 administration protects mice from autoimmune myocarditis [28, 29]. On the other hand, the disease is exacerbated by administration of anti-IL-10 antibodies during the late phase [30]. However, no studies on IL-10 or IL-10 receptor-deficient mice are yet available. No mechanism

explaining the apparently negative role of IL-10 in autoimmune myocarditis has so far been delineated. The fact that the suppression of autoimmune myocarditis by nasal administration of cardiac myosin depends on IL-10 production [30, 31], supports the view that an antigen-specific mechanism inhibits T-cell activation. Such a scenario could involve regulatory T-cells.

Clinical perspectives

Supportive care is the first line of therapy for patients with myocarditis and, with the exception of giant-cell myocarditis [32], immunosuppressive treatment is not beneficial [33]. Cytokine or cytokine-directed strategies may offer a more refined and more specific treatment approach. However, because myocarditis is often asymptomatic and its outcome unpredictable, it is difficult to define the decisive point in the time course of the disease at which treatment should be considered. Treatment delivered too early may result in suppression of protective antiviral effects, whereas a delay may not reverse the self-aggressive (deleterious) damage to the heart. Care must be taken to ensure that a potentially anti-inflammatory intervention does

not turn a self-exhausting severe immune response into a smouldering chronic autoimmune disease [34]. Further studies are therefore needed until our knowledge gained from animal models is translated into new treatment strategies against a devastating heart disease.

Correspondence:

Urs Eriksson, MD
University Health Network
OCI - Princess Margaret Hospital
620 University Ave
Toronto, ON M5G-2C1
Canada
E-Mail: ueriksson@uhnres.utoronto.ca

References

- 1 Caforio ALP. Role of autoimmunity in dilated cardiomyopathy. *Br Heart J* 1994;72(Suppl.):S30-4.
- 2 Martino TA, Liu P, Sole M-J. Viral infection and the pathogenesis of dilated cardiomyopathy. *Circ Res* 1994;74:182-8.
- 3 Caforio ALP, Goldmann JH, Haven A J, Baig KM, McKenna W. Evidence for autoimmunity to myosin and other heart-specific autoantigens in patients with dilated cardiomyopathy and their relatives. *Int J Cardiol* 1996;54:157-63.
- 4 Kawai C. From myocarditis to cardiomyopathy: mechanisms of inflammation and cell death: learning from the past for the future. *Circulation* 1999;99:1091-100.
- 5 Luther SA, Cyster JG. Chemokines as regulators of T-cell differentiation. *Nat Immunol* 2001;2:102-7.
- 6 Penninger JM, Pummerer C, Liu P, Neu N, Bachmaier K. Cellular and molecular mechanisms of murine autoimmune myocarditis. *APMIS* 1997;105:1-13.
- 7 Neu N, Rose NR, Beisel KW, Herskovitz A, Gurri-Glass G, Craig SW. Cardiac myosin induces myocarditis in genetically predisposed mice. *J Immunol* 1987;139:3630-36.
- 8 Bachmaier K, Neu N, de-la Maza LM, Pal S, Hessel A, Penninger JM. Chlamydia infections and heart disease linked through antigenic mimicry. *Science* 1999;283:1335-9.
- 9 Meldrum DR. Tumor necrosis factor in the heart. *Am J Physiol* 1998;274:R577-R595.
- 10 Bachmaier K, Pummerer C, Kozieradzki I, Pfeffer K, Mak TW, Neu N, et al. Low-molecular-weight tumor necrosis factor receptor p55 controls induction of autoimmune heart disease. *Circulation* 1997;95:655-61.
- 11 Bryant D, Becker L, Richardson J, Shelton J, Franco F, Peshock R, et al. Cardiac failure in transgenic mice with myocardial expression of tumor necrosis factor- α . *Circulation* 1998;97:1375-81.
- 12 Yokoseki O, Suzuki J, Kitabayashi H, Watanabe N, Wada Y, et al. Cis element decoy against nuclear factor- κ B attenuates development of experimental autoimmune myocarditis in rats. *Circ Res* 2001;89:899-906.
- 13 Kubota T, Bonoutas GS, Miyagishima M, Kadokami T, Sanders VJ, Bruton C, et al. Soluble tumor necrosis factor receptor abrogates myocardial inflammation but not hypertrophy in cytokine-induced cardiomyopathy. *Circulation* 2000;101:2518-25.
- 14 Fuse K, Kodama M, Hanawa H, Okura Y, Ito M, Shiono T, et al. Enhanced expression and production of monocyte chemoattractant protein-1 in myocarditis. *Clin Exp Immunol* 2001;124:346-52.

- 15 Toyozaki T, Saito T, Shiraishi H, Tsukamoto Y, Takano H, Nagai T, et al. Macrophage inflammatory protein-1 alpha relates to the recruitment of inflammatory cells in myosin-induced autoimmune myocarditis in rats. *Lab Invest* 2001;81(7):929-36.
- 16 Cook DN, Beck MA, Coffman TM, Kirby SL, Sheridan JF, Pragnell IB, et al. Requirement of MIP-1 alpha for an inflammatory response to viral infection. *Science* 1995;269(5230):1583-5.
- 17 Falcone M, Sarvetnick N. Cytokines that regulate autoimmune responses. *Curr Opin Immunol* 1999;11:670-76.
- 18 Metcalf D, Di Rago L, Mifsud A, Hartley L, Alexander WS. The development of fatal myocarditis and polymyositis in mice heterozygous for IFN- γ and lacking the SOCS-1 gene. *Proc Natl Acad Sci* 2000;97:9174-9.
- 19 Eriksson U, Kurrer MO, Sebald W, Brombacher F, Kopf M. Dual role of the IL-12/IFN- γ axis in the development of myocarditis: induction by IL-12 and protection by IFN- γ . *J Immunol* 2001;167:5464-9.
- 20 Afanasyeva M, Wang Y, Kaya Z, Park S, Zilliox MJ, Schofield BH, Hill SL, et al. Experimental autoimmune myocarditis in A/J mice is an Interleukin-4 dependent disease with a Th2 phenotype. *Am J Pathol* 2001;159:193-203.
- 21 Eriksson U, Kurrer MO, Bingisser R, Eugster HP, Saremaslani P, Follath F, Marsch S, Widmer U. Lethal autoimmune myocarditis in IFN- γ receptor deficient mice: enhanced disease severity by impaired iNOS induction. *Circulation* 2001;96:585-91.
- 22 Afanasyeva M, Wang Y, Kaya Z, Stafford EA, Dohmen KM, Sadighi Akha AA, et al. Interleukin-12 receptor/STAT4 signaling is required for the development of autoimmune myocarditis in mice by an interferon-gamma-independent pathway. *Circulation* 2001;104:3145-51.
- 23 Horwitz MS, La Cava A, Fine C, Rodriguez E, Ilic A, Sarvetnick N. Pancreatic expression of interferon-gamma protects mice from lethal coxsackievirus B3 infection and subsequent myocarditis. *Nat Med* 2000;6:693-7.
- 24 Cunningham MW. Cardiac myosin and the TH1/TH2 paradigm in autoimmune myocarditis. *Am J Pathol* 2001;159(1):5-12.
- 25 Gately M, Renzetti LM, Magram J, Stern AS, Adorini L, Gubler U, et al. The interleukin-12/interleukin-12-receptor system: role in normal and pathologic immune responses. *Annu Rev Immunol* 1998;16:495-521.
- 26 Okura Y, Takeda K, Honda S, Hanawa H, Watanabe H, Kodama M, et al. Recombinant murine interleukin-12 facilitates induction of cardiac myosin-specific type 1 helper cells in rats. *Circ Res* 1998;82:1035-42.
- 27 Moore KW, de Waal MR, Coffman RL, O'Garra A. Interleukin-10 and the Interleukin-10 receptor. *Annu Rev Immunol* 2001;19:683-765.
- 28 Nakano A, Matsumori A, Kawamoto S, Tahara H, Yamato E, Sasayama S, et al. Cytokine gene therapy for myocarditis by in vivo electroporation. *Hum Gene Ther* 2001;12:1289-1297.
- 29 Watanabe K, Nakazawa M, Fuse K, Hanawa H, Kodama M, et al. Protection against autoimmune myocarditis by gene transfer of Interleukin-10 by electroporation. *Circulation* 2001;104:1098-100.
- 30 Kaya Z, Dohmen KM, Wang Y, Schlichting J, Afanasyeva M, Leuschner F, et al. A critical role for IL-10 in the induction of nasal tolerance in experimental autoimmune myocarditis. *J Immunol* 2002;168:1552-6.
- 31 Wang Y, Afanasyeva M, Hill SL, Kaya Z, Rose NR. Nasal administration of cardiac myosin suppresses autoimmune myocarditis in mice. *J Am Coll Cardiol* 2000;36:1992-9.
- 32 Cooper LT Jr, Berry GJ, Shabetai R. Idiopathic giant-cell myocarditis - natural history and treatment. *N Engl J Med* 1997;336:1860-6.
- 33 Feldman AM, McNamara D. Myocarditis. *N Engl J Med* 2000;343:1388-98.
- 34 McCarthy RE III, Boehmer JP, Hruban RH, Hutchins GM, Kasper EK, Hare JM, et al. Long-term outcome of fulminant myocarditis as compared with acute (nonfulminant) myocarditis. *N Engl J Med* 2000;342:690-5.

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