HHS Public Access

Author manuscript

Curr Allergy Asthma Rep. Author manuscript; available in PMC 2016 January 01.

Published in final edited form as:

Curr Allergy Asthma Rep. 2015 January ; 15(1): 491. doi:10.1007/s11882-014-0491-z.

Autoimmune Valvular Carditis

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Abstract

Autoimmune carditis is associated with many human rheumatic conditions, including rheumatic fever, systemic lupus erythematosous, and rheumatoid arthritis. The immune mechanisms that mediate the cardiovascular pathology connected to these diseases are poorly defined. Several animal models are used to recapitulate human pathophysiology in order to better characterize the immunopathogenic mechanisms driving autoimmune endocardial inflammation. These animal models point toward common mechanisms mediating autoimmune endocarditis; in particular, CD4+ T cells and pro-inflammatory macrophages play critical roles in directing the disease process. The goals of this review are to discuss the prevailing animal models of autoimmune endocarditis and their underlying immunologic mechanisms, and to provide insight regarding potential therapeutic targets in humans.

Keywords

Valvular Carditis; Endocarditis; Autoimmune; Rheumatic; T cell; macrophage

Introduction

Endocarditis, inflammation of the inner lining and valves of the heart, can occur in both acute and chronic settings and can be caused by either infective or non-infective insults. Valvular damage, a serious complication resulting from chronic inflammation and scarring of the endothelium, can lead to congestive heart failure, which is often fatal [1, 2].

Infective endocarditis is caused by a microbial infection of the endocardium and accounts for approximately 10.8 hospitalizations per 100,000 people in the United States annually [3]. Lesions from infective endocarditis most commonly affect damaged or abnormal valves, prosthetic valves, or those of intravenous drug abusers. *Staphylococcus aureus* and *Streptococcus spp.* account for over 50% of infective endocarditis cases in the United States, but approximately 10% of cases are culture-negative [3]. Vegetations typically form on the left-sided heart valves, the mitral and aortic valves. Such vegetations can cause permanent valve damage or can embolize to the brain and cause complications [1]. Infective endocarditis has been reviewed recently elsewhere [1, 4]; this review focuses on autoimmune endocarditis.

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Endocarditis is a serious manifestation of several autoimmune rheumatic diseases, including rheumatic fever, systemic lupus erythematosous (SLE), and rheumatoid arthritis. These forms of autoimmune endocarditis are characterized by antibody-initiated damage and activation of the endothelium, followed by inflammatory cell infiltration [5]. Rheumatic heart disease is initiated by an immune response to group A Streptococcal pharyngeal infection, in which T cells specific for group A Streptococcal M protein cross-react with cardiac myosin [5–7]. In acute rheumatic fever, all three layers of the heart become inflamed, including the endocardium, myocardium, and pericardium. Characteristic pathologic findings of rheumatic carditis include Aschoff nodules, focal granulomatous lesions of the myocardium, and Anitschkow cells, activated macrophages. In patients with SLE or anti-phospholipid syndrome, verrucous lesions form on the valvular and mural endocardium, a condition known as Libman-Sacks endocarditis [8–10]. Valve disease is also prevalent in patients with rheumatoid arthritis, with mitral regurgitation identified in 80% of patients who underwent echocardiographic evaluation [11, 12]. In each of these autoantibody-associated diseases, the mitral valve is the most commonly affected, although aortic valve insufficiency may arise [2, 10, 11].

Autoimmune endocarditis constitutes a major global health challenge. An estimated 15.6 to 17.9 million people have rheumatic heart disease worldwide and approximately 1.5% of people die each year due to the disease [13]. Rheumatic heart disease is most prevalent in developing countries is a major cause of cardiovascular death in children and young adults [13, 2]. Additionally, cardiovascular disease is a primary cause of death in patients with rheumatoid arthritis and SLE, primarily due to accelerated atherosclerosis [14–17]. Animal models have been used to recapitulate the human disease processes in order to define the immune mechanisms by which these diseases provoke endocardial inflammation. This review will focus on the existing animal models of autoimmune endocarditis and their proposed immunopathogenic mechanisms, and on how these models advance our understanding of the pathogenesis of autoimmune endocarditis in humans.

Animal Models of Autoimmune Endocarditis

Autoimmune endocarditis can be induced in experimental animals via several different means. These include inducing inflammation by injecting specific antibodies or pro-inflammatory agents or by using genetically-engineered animal models in which spontaneous production of autoantibodies occurs or in which an autoinflammatory state exists. These animal models aim to recapitulate the human disease processes, pathology, and immune mechanisms of common autoimmune diseases associated with valvular inflammation and endocarditis. Here we review the key animal models of autoimmune valvular carditis, focusing on post-Streptococcal rheumatic carditis, rheumatoid arthritis, and the spondyloarthropathies (Table 1).

Animal Models of Rheumatic Carditis

Cromartie and Craddock first demonstrated that rheumatic-like disease could be induced in mice via intraperitoneal injection of sonically-disrupted group A Streptococcal cells. This caused an inflammatory process in the endocardium, the mitral and aortic valves, myocardium, and pericardium. Within three days of injection, focal granulomatous lesions

consisting of monocytes, lymphocytes, and Anitschkow cells with central necrosis similar to Aschoff bodies developed. Within eight weeks of injection, the acute inflammatory response subsided, and the aortic and mitral valve annuli demonstrated chronic inflammation and scarring. The acute and chronic pathologic findings in the mice showed striking similarity to the lesions of acute rheumatic fever and chronic rheumatic carditis in humans [18].

The theory that antibodies specific for Streptococcal epitopes are cross-reactive with cardiac antigens gained traction based on the finding that patients with acute rheumatic fever had circulating cardiac-reactive antibodies [19]. Specifically, it was suggested that following Streptococcal pharyngitis, antibodies generated against Streptococcal M cross-reacted with human cardiac tropomyosin. Extensive work from Cunningham's group has demonstrated that monoclonal antibodies directed against Streptococcal M proteins or *N*-acetyl-βD-glucosamine (GlcNAc, the primary epitope of group A carbohydrate antigen) cross-react with cardiac myosin and laminin, thus establishing evidence for molecular mimicry [5–7, 19–21].

A rat model was developed based on this theory of molecular mimicry, in which Lewis rats were immunized with Streptococcal M protein and adjuvant. The rats developed valvular carditis and focal lesions of myocarditis with extensive T cell infiltration. Additionally, this model provided the first evidence that, in addition to antibody cross-reactivity, T-cell cross-reactivity also occurs. Specifically, T cells reactive to both Streptococcal M protein and cardiac myosin were present in the valvular lesions [22••]. Additional groups used this model to demonstrate that conserved regions of Streptococcal M protein [23] and individual peptides could also induce an immune response that mimics rheumatic heart disease [24, 25]. Furthermore, injecting rats with human or rat cardiac myosin plus adjuvant induced both myocarditis and valvular disease [26]. The lymphocytes in the myocardial infiltrate proliferated in response to Streptococcal M protein, providing further evidence that myosin-reactive T cells cross-react with Streptococcal M protein [26].

Immune Mechanisms of Rheumatic Carditis—The infiltrate in human rheumatic carditis is composed primarily of lymphocyte and mononuclear cells [27, 28]. Raizada et al first suggested a CD4+ T cell-mediated disease process in their examination of lymphocytic infiltrates in valvular tissue obtained from patients with rheumatic heart disease [27]. Similarly, both CD4+ T cells and CD68+ macrophages were identified in in the valves of Lewis rats immunized with recombinant Streptococcal M protein [24]. The expression of vascular cell adhesion molecule-1 (VCAM-1) was upregulated on the valvular endothelium of human patients with rheumatic heart disease; VCAM-1 enables extravasation of CD4+ and CD8+ T cells into the valvular tissue [29]. Mononuclear cells obtained from valve lesions of patients with rheumatic heart disease secreted tumor necrosis factor (TNF) and interferon gamma (IFNγ), suggesting that the CD4+ T cells were of the Th1 phenotype. Interleukin-10 (IL-10), a negative regulator of Th1 cells, was also secreted by the valve-infiltrating lymphocytes [30, 31].

Th17 cells, a pro-inflammatory effector lineage of CD4+ T cells that secrete IL-17, IL-21, IL-22, and TNF have more recently been identified as key participants in autoimmune inflammatory states [32–34]. Guilherme and colleagues reported evidence of increased

IL-17A expression in peripheral T lymphocytes from patients with chronic rheumatic heart disease compared to healthy donors [35]. Additionally, recurrent intranasal group A Streptococcal infection in mice shifted the antigen-specific T cell population toward an IL17A+IFN-γ+ phenotype [36]. A Th17-mediated inflammatory process has also been described in a mouse model of experimental autoimmune myocarditis in which BALB/c mice are injected with a synthesized peptide based on the cardiac myosin heavy chain α sequence. These mice developed CD4+ T cell-dependent myocarditis that progressed to dilated cardiomyopathy. It has been shown that the progression from myocarditis to dilated cardiomyopathy was dependent on the presence of IL-6 and IL-17 to drive a pro-inflammatory phenotype in monocytes and macrophages in the myocardium [37–39].

It is possible that the mechanisms that drive endocarditis in the Streptococcal model of rheumatic heart disease are similar to those described in this model of experimental autoimmune myocarditis. However, one group has suggested that the inflammatory mechanisms mediating endocarditis versus myocarditis may differ; specifically, in samples obtained from patients with rheumatic heart disease, the Th2 cytokine IL-4 was produced by many of the infiltrating cells in the myocardium, but by very few of the infiltrating cells in the mitral valve [30].

In sum, CD4+ T cells and pro-inflammatory macrophages seem to dominate the inflammatory infiltrates of human rheumatic carditis and its animals models [25]. Th1 and Th17 cells have been identified in both human patients and animal models, but the relative contributions of these two Th effector cell subsets remains undefined.

K/BxN Mouse Model of Inflammatory Arthritis

The K/BxN mouse was first described as an animal model of inflammatory arthritis with some similarities to rheumatoid arthritis in humans [40]. K/BxN mice express a transgene-encoded T cell receptor (TCR) termed “KRN” that recognizes a self-peptide derived from the ubiquitously-expressed enzyme glucose-6-phosphate isomerase (GPI), presented on the mouse major histocompatibility complex (MHC) class II molecule A^{g7} derived from the NOD mouse strain. CD4+ T cells bearing the KRN TCR are activated by A^{g7}:GPI-expessing antigen presenting cells, allowing the CD4+ T cells in turn to stimulate GPI-reactive B cells to produce arthritis-inducing anti-GPI autoantibodies [40, 41]. Arthritis can be induced in naïve mice by injecting serum from K/BxN mice containing anti-GPI autoantibodies, a model system termed “serum transfer arthritis.”

In addition to developing spontaneous autoimmune arthritis, the TCR transgenic K/BxN mice also develop autoimmune valvular carditis, primarily affecting the mitral valve [42••]. Our group has used this model to study the immunopathogenic mechanisms mediating autoantibody-associated autoimmune valvular carditis.

Immune Mechanisms—Similar to murine models of rheumatic heart disease, CD4+ T cells and macrophages are the predominant cells infiltrating the inflamed mitral valves of K/BxN mice [42••]. Genetic absence of B cells or of CD40, a molecule required for immunoglobulin isotype switching, prevented valvular carditis in this model, strongly suggesting an autoantibody-dependent process. However, transfer of K/BxN serum to naïve

mice produces only arthritis – not carditis – suggesting that autoantibodies alone are not sufficient to drive valvular carditis [42••]. Indeed, depletion of CD4+ T cells after the onset of arthritis prevented the development of valvular inflammation without affecting arthritis severity, suggesting that the sustained presence of CD4+ T cells is required to mediate valvular carditis [43].

While autoantibodies appear to be required for the development of both arthritis and endocarditis in the K/BxN mice, distinct innate immune mechanisms direct the pathologic processes. Arthritis in K/BxN mice depends on complement C5 but not activating Fcg receptors [42••]. With respect to endocarditis, although complement C3 was deposited on the inflamed mitral valves (as in the human forms of autoimmune valvular carditis), genetic deficiency of C3 or C5 did not affect the severity of valve inflammation. Rather, in K/BxN mice, autoantibodies appear to be acting through activating Fcγ receptors to drive valvular carditis, specifically FcγRIII and FcγRIV on macrophages [42••, 44••]. Furthermore, depletion of macrophages reduced the severity of valve inflammation, suggesting that valvular carditis depends, at least in part, on the presence of macrophages [44••].

The nature of the CD4+ T cell cytokine profile driving valvular carditis in the K/BxN mouse model remains incompletely defined. IFNγ and IL-17 were both found in the valve infiltrate, whereas IL-4 was not [43]. However, genetic deletion of IFNγ had no effect on the severity of valvular carditis (BAB, unpublished results). A role for Foxp3+ regulatory T cells (Treg) in this model has also been demonstrated. Specifically, Treg cell development is impaired in mice lacking β2 integrin (CD18). In the K/BxN system, deficiency of CD18 resulted in fewer Treg cells and more severe cardiac inflammation without affecting arthritis severity [43]. Additionally, dual TCR T cells accelerated the development of autoimmunity in K/BxN mice by promoting positive selection, and the absence of dual TCR T cells prevented the development of valvular carditis [45]. Ongoing work by our group seeks to identify the key Th cytokines driving valvular carditis in this model and to characterize further the contribution of macrophages.

Arthritis and Carditis due to deficiency of IL-1 receptor antagonist (IL-1Ra)

IL-1 receptor antagonist (IL-1Ra) is a naturally occurring regulator of the pro-inflammatory IL-1 cytokine signaling system. BALB/c mice lacking the gene encoding IL-1Ra (*Il1rn*) developed spontaneous chronic inflammatory arthropathy similar to rheumatoid arthritis [46]. These mice produced autoantibodies directed against immunoglobulin, type II collagen, and double-stranded DNA. In addition to arthritis, these IL-1ra-deficient mice developed inflammatory thickening and stenosis of the aortic valve [47••]. Intriguingly, the development of arthritis depended on genetic background of the mice [48]; deficiency of IL-1Ra on the CL57B6/J background resulted in severe arteritis, but neither arthritis nor valvular disease [49]. Recently, genetic deficiency of IL-1Ra (DIRA) in humans has been described in a small number of patients. These patients develop inflammatory arthropathy and cutaneous inflammation; one patient had vasculitis, but no other cardiovascular phenotype has been reported [50, 51].

Immune Mechanism—As in the K/BxN model, the infiltrate in the inflamed aortic valve of IL-1Ra-deficient mice primarily consisted of monocytes/macrophages. Additionally, transfer of peripheral T cells from IL-1Ra-deficient mice into immunodeficient BALB/c hosts induced greater aortic valve inflammation than did transfer of peripheral T cells transferred from wild-type mice. Inflammation was associated with increased TNF levels in the plasma, and BALB/c mice genetically lacking both TNF and IL-1Ra (*Tnf*$^{-/-}$/*IL1rn*$^{-/-}$) were protected from valvular inflammation relative to their IL-1Ra-deficient but TNF-sufficient counterparts [47••]. Thus, this model too suggests that T cells and pro-inflammatory macrophages cooperate to drive autoimmune valvular carditis.

IL-23-Dependent Model of Spondyloarthropathy

Following injection with type II collagen-specific antibodies, B10.RIII mice develop severe enthesitis -- inflammation of tendons and ligaments, a characteristic clinical finding in human patients with spondyloarthropathy. The development of enthesitis in this mouse model was shown to depend on IL-23. In making this connection between type II collagen-specific antibodies and an IL-23 dependent mechanism, the authors investigated whether IL-23 alone could induce the same disease. Injection of IL-23 minicircle DNA induced systemic spondyloarthropathy, including aortic root and aortic valve inflammation, even in the absence of type II collagen-specific antibodies. Whether type II collagen-specific antibodies alone provoke aortic inflammation was not investigated [52••].

Immune Mechanism—In this model, IL-23 receptor-expressing CD4− CD8− T cells in the entheses responded to the overexpressed IL-23, resulting in the production of the cytokines typically associated with Th17 cells: IL-6, IL-17, and IL-22. Phenotypically similar cells were identified in the inflamed aortic root and aortic valve, along with increased expression of IL-22. The valve infiltrate included T cells, macrophages, and neutrophils [52••]. This model thus provides further evidence that T cells, particularly those making Th17-related cytokines, and macrophages can cooperate to drive autoimmune valvular carditis.

Conclusion

Autoimmune valvular carditis accompanies many human rheumatic conditions, including rheumatic fever, systemic lupus erythematosus and the related antiphospholipid syndrome, as well as rheumatoid arthritis. We have reviewed the animal models that are currently being used to understand the immunopathogenic mechanisms mediating cardiovascular pathology. Autoantibodies appear to be critical in some of the models, but not all. Common threads do emerge, however, with predominant roles for CD4+ T cells of the Th1 and Th17 effector lineages as well as pro-inflammatory macrophages (Fig. 1). Ongoing work is directed at understanding how these components of the immune response -- autoantibodies, effector T cells, and macrophages -- interact to drive cardiac valve inflammation in the setting of systemic autoimmune disease. Identification of the key pro-inflammatory pathways involved, likely including IL-17 and related molecules, TNF, IL-1, and IL-6, is expected to lead to improved therapies for patients with autoimmune valvular carditis.

Acknowledgments

Research in Dr. Binstadt's laboratory was funded by the National Institutes of Health National Heart, Lung, and Blood Institute R01 HL121093, National Institute of Arthritis and Musculoskeletal and Skin Diseases R03 AR057101, an Innovative Research Grant from the Rheumatology Research Foundation, and by the University of Minnesota Department of Pediatrics.

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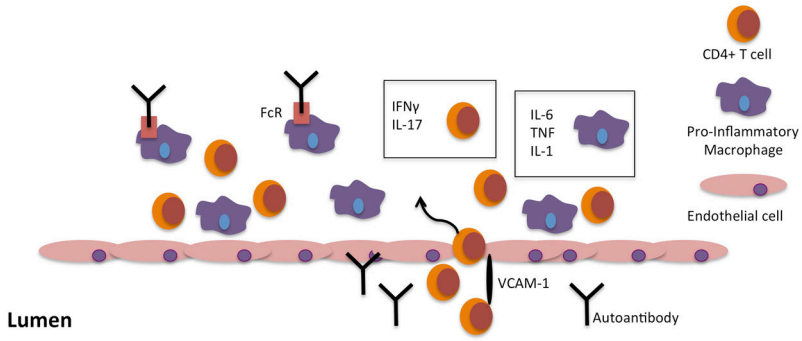

Figure 1. Model of the pathogenesis of autoimmune valvular carditis

CD4+ T cells, with the help of VCAM-1, and macrophages extravasate across the endothelium into the valve interstitium. Th1 and Th17 effector CD4+ T cell lineages are characterized by the production of IFNγ and IL-17, respectively. Macrophages, in some cases stimulated by antibodies engaging activating Fc receptors, release the pro-inflammatory cytokines IL-6, TNF, and IL-1.

Table 1

Models of autoimmune endocarditis and their associated immune mediators

Model	Human Disease	Cellular Infiltrate	Immune Mediators
Streptococcus or Streptococcal M protein-induced carditis	Rheumatic heart disease	CD4+ T cells of Th1 and Th17 effector lineage Macrophages	TNF IFNγ IL-6 IL-10 IL-17
K/BxN mouse	Rheumatoid arthritis and valvular carditis	CD4+ T cells Macrophages Tregs	Fcγ receptors IFNγ IL-17
IL-1ra-deficient mouse	Rheumatoid arthritis and aortitis Or DIRA	Macrophages T cells	TNF IL-1
IL-23 Overexpression	Spondyloarthropathy and aortic root valve inflammation	CD4+ T cells of Th17 effector lineage Macrophages	IL-6 IL-17 IL-22

Abbreviations: DIRA: deficiency of IL-1 receptor antagonist; IFNγ: interferon gamma; IL: interleukin; Th: helper T cell; TNF: tumor necrosis factor; Treg: regulatory T cell