



Rheumatic heart disease: molecules involved in valve tissue inflammation leading to the autoimmune process and anti-*S. pyogenes* vaccine

Luiza Guilherme^{1,2*} and Jorge Kalil^{1,2,3}

¹ Heart Institute (InCor), School of Medicine, University of São Paulo, São Paulo, Brazil

² Immunology Investigation Institute, National Institute for Science and Technology, University of São Paulo, São Paulo, Brazil

³ Clinical Immunology and Allergy Division, School of Medicine, University of São Paulo, São Paulo, Brazil

Edited by:

Kendall A. Smith, Cornell University, USA

Reviewed by:

Kendall A. Smith, Cornell University, USA

Antoine Toubert, Université Paris Diderot, France; Assistance Publique Hôpitaux de Paris; France

*Correspondence:

Luiza Guilherme, Heart Institute (InCor), School of Medicine, University of São Paulo, Av. Dr. Eneas de Carvalho Aguiar 44, São Paulo 05403-903, Brazil
e-mail: luizagui@usp.br

The major events leading to both rheumatic fever (RF) and rheumatic heart disease (RHD) are reviewed. Several genes are involved in the development of RF and RHD. The inflammatory process that results from *S. pyogenes* infection involves the activation of several molecules such as VCAM and ICAM, which play a role in the migration of leukocytes to the heart, particularly to the valves. Specific chemokines, such as CXCL3/MIP1 α as well as CCL1/I-309 and CXCL9/Mig, attract T cells to the myocardium and valves, respectively. The autoimmune reactions are mediated by both the B- and T-cell responses that begin at the periphery, followed by the migration of T cell clones to the heart and the infiltration of heart lesions in RHD patients. These cells recognize streptococcal antigens and human-tissue proteins. Molecular mimicry between streptococcal M protein and human proteins has been proposed as the triggering factor leading to autoimmunity in RF and RHD. The production of cytokines from peripheral and heart-infiltrating mononuclear cells suggests that T helper 1 and Th17 cytokines are the mediators of RHD heart lesions. The low numbers of IL-4 producing cells in the valvular tissue might contribute to the maintenance and progression of the valve lesions. The identification of a vaccine epitope opens a perspective of development of an effective and safe vaccine to prevent *S. pyogenes* infections, consequently RF and RHD.

Keywords: *S. pyogenes*, genes, adhesion molecules, chemokines, Th1 and Th17 cytokines, T and B cells, valve proteins, anti-*S. pyogenes* vaccine

INTRODUCTION

Rheumatic fever (RF) and its major sequelae rheumatic heart disease (RHD) are autoimmune diseases that arise following infection of the throat by *S. pyogenes* in children and young individuals (3–19 years old) who present genetic components that confer susceptibility to the disease.

The disease still remains a major cause of cardiovascular disability in school children and young individuals, and it represents a high burden for public health in the developing world. The incidence of this disease in the so-called “hotspots” ranges from 20 to 51 per 100,000 habitants, causing ~500,000 deaths each year (1). In Brazil, the number of beta hemolytic streptococcus throat infections is ~10 million cases/year, leading to 30,000 new cases of RF, of which ~15,000 cases develop RHD (2).

The aim of this review is to explore the role of several genes in the control of *S. pyogenes* infection and the associated autoimmune reactions, as well as to depict the molecular mechanisms leading to these autoimmune reactions.

GENETIC BACKGROUND

As RF and RHD are post-infectious diseases that involve an inflammatory reaction in addition to T and B cells, several genes are involved in the predisposition and manifestation of the disease.

Table 1 summarizes the genes involved in RF/RHD development and their role.

GENES RELATED TO THE INNATE IMMUNE RESPONSE

The first line of host defense against a pathogen, *S. pyogenes* in the cases of RF and RHD, involves several molecules that bind to specific pathogen-associated molecular patterns (PAMPs) through specific molecules in the host, defined as pattern recognition receptors (PRRs). These PRRs can be soluble in human serum, or they can be cell-associated, and they are described below.

Toll-like receptors (TLRs) are sensors of foreign microbial products that initiate host defense responses in multicellular organisms. The genotype 753Arg/Gln of *TLR2* gene resulting from the replacement of arginine with glutamine at codon 753 was more frequently present in a Turkish ARF cohort compared with controls (3).

Mannan-binding lectin (MBL) is a phase I inflammatory protein encoded by different variants of the promoter and exon 1 regions of the *MBL2* gene. The A and O alleles code for high and low production of MBL, respectively. Interestingly, RHD patients with mitral stenosis (MS) displayed an association with the A allele, while the majority of RHD patients with aortic regurgitation (AR) presented the O allele. The amount of MBL in the sera of RF and

Table 1 | Genes of genetic susceptibility of RF and RHD.

Genetic markers	Role
MBL; TLR2; FCN2; FCγRIIIa	Innate immunity Inadequate immune response against <i>S. pyogenes</i>
HLA class II genes (DR and DQ, several alleles)	Adaptive immune response T cell antigen presentation and immune response
TNF-α, ILRA, TGF-β, IL-10	Both innate immunity/adaptive immune response Mediators of inflammatory reactions

RHD patients presented high and low serum levels of MBL, respectively (4, 5). These results suggest that the *MBL2* gene could play a role in the development of valvular stenosis or regurgitation.

Ficolins trigger the innate immune response by either binding to collectin cellular receptors or initiating the complement lectin pathway. There have been three ficolin genes identified in humans with different functions, sequences, and specificity. Polymorphisms at -986, -602, and -4 within the promoter region of ficolin 2 (*FCN2*) are associated with the serum levels of this protein. In Brazilian chronic RHD patients, the haplotype G/G/A (-986/-602/-4) was more frequent than in controls and correlated with low levels of this protein, leading to a prolonged time of infection or to repeated streptococcal infections (6).

GENES RELATED TO THE ADAPTIVE IMMUNE RESPONSE

The susceptibility of developing RF/RHD was first associated with alleles of the HLA class II genes (*DRB1*, *DQB*, and *DQA*). Among the *DRB1* alleles, HLA-DR2, DR3, DR4, DR7 were the most frequently associated with the disease, with HLA-DR7 being the most consistently associated HLA allele found in Brazilian, Turkish, Egyptian, and Latvian RF/RHD patients [reviewed in Ref. (7)]. The role of the HLA molecules encoded by these genes is to present antigens to the T cell receptor (TCR), thus activating the adaptive immune response.

GENES RELATED TO BOTH THE INNATE AND THE ADAPTIVE IMMUNE RESPONSE

The *TNF-α* gene has an inflammatory role and is located on the same chromosome as the HLA class II genes. The polymorphism of a SNP at the promoter region of *TNFA*-308G/A was associated with the susceptibility of patients from Mexico, Turkey, Brazil, and Egypt to RHD (8–11).

IL-1α and IL-1β are cytokines that have been implicated in the inflammatory reactions and are encoded by *IL-1RA* gene. The most common alleles are 1 and 2, which encode antagonists of IL-1α and IL-1β. The absence or misrepresentation of both alleles results in a strong inflammatory response. Studies in Brazilian RHD patients with severe carditis showed low frequencies of allele 1, suggesting the absence of inflammatory control (12). Some studies showed that alleles of the *TGFβ1* gene were risk factors for the development of valvular RHD lesions (13, 14) as this gene codes for an inflammatory protein secreted by many cell types including macrophages. Thus inflammatory stimuli that activate macrophages enhance the release of active TGF-β.

HEART VALVE CHRONIC INFLAMMATION

The healing process of rheumatic carditis results in varying degrees of fibrosis and valve damage. The Aschoff body is considered the hallmark of the disease and consists of a granulomatous nodule usually located in the connective tissue around small vessels. This structure promotes the inflammatory process as the mediator of rheumatic heart lesions. Several inflammatory cells, such as neutrophils, macrophages, and T and B lymphocytes, infiltrate both the myocardium and the valves. These cells enter through the myocardium and the valves upon the upregulation of expression of the adhesion molecules. Cunningham's group showed that streptococcal heart-tissue cross-reactive antibodies increased the amount of VCAM-1 on the valvular endothelial surface, leading to myocarditis and valvulitis (15, 16). Recently, we verified that ICAM, another integrin, was also upregulated, in addition to P-selectin and several chemokines and their receptors. Among the chemokines, *CCL3/MIP1α* gene expression was up regulated in the myocardium, while *CCL1/I-309* and *CXCL9/Mig* were highly expressed in the valvular tissue of RHD patients (17). An *in vitro* assay demonstrated that valvular lesions infiltrating T cells migrated mainly toward a *CXCL9/Mig* gradient, suggesting that specific chemokines can mediate both the CD4⁺ and CD8⁺ T cell recruitment to the site of inflammation in the heart (17).

Cytokines are important secondary signals following an infection because they trigger effective immune responses in most individuals, and they most likely cause deleterious responses in patients with autoimmune disease. Cytokines generally act locally.

In RHD, in both the myocardium and valvular tissue, a large number of infiltrating mononuclear cells secreting IFNγ and TNFα inflammatory cytokines were found. Interestingly, only small numbers of IL-4 producing cells were found in the valves, while several cells producing IL-10 were observed. These data strongly indicated that the low numbers of IL-4 producing cells may contribute to the progression of valve lesions in RHD (18). Recently, we identified large numbers of IL-17 and IL-23-producing cells in the valves; IL-17 and IL-23 are a Th17 subset cytokines that are also frequently involved in the development of autoimmune diseases (19). All of the events currently known to be involved in inflammation and infiltration of the heart tissue by T cells are summarized in **Table 2**.

AUTOIMMUNE REACTIVITY

The existence of similar or identical antigens in microbes (virus, bacteria, and other pathogens) and their hosts enable the microbe to evade the host immune response. The mechanism known as "molecular mimicry," by which self antigens are recognized after an infection by cross reactivity, was introduced by Damian (20).

The presence of heart-reactive antibodies was described more than 50 years ago in sera from animals immunized with streptococcal cell wall products and in sera from acute RF and RHD patients.

Using immunofluorescence techniques, Kaplan found immunoglobulins and complement bound to the myocardium of acute RF patients (21). Studies conducted by Zabriskie et al. gave support to the hypothesis that RF has an autoimmune origin by describing the presence of antibodies that were cross reactive with streptococcal membrane antigens in acute RF sera (22).

mediated by both antibodies and T cells. However, it is interesting to note that the permanent rheumatic lesions occur in the valvular tissue, most likely due to the migration of these auto-reactive T cells from the myocardium to the valvular tissue. In the valves, we found several T cell oligoclonal populations defined by the

analysis of the TCR (32, 33) that recognized M protein peptides from the N-terminal region and human cardiac myosin beta-chain peptides, as mentioned above, as well as valve tissue-derived proteins (31), as summarized in **Figure 1**. Among the valve proteins, we identified vimentin and disulfide isomerase ER-60 precursor

Table 3 | Properties of “StreptInCor” an anti-*S. pyogenes* candidate vaccine.

Characteristics	Properties	Reference
M protein C-terminal portion	55 Amino acids residues long	Guilherme et al. (36, 38)
Structure	Alpha helical and beta-sheet conformation, encompasses both T and B epitopes	Guilherme et al. (37)
Experimental assays	Several animal models (BALB/c, C57BL6, Swiss, and HLA class II transgenic mice)	Guilherme et al. (38), Guerino et al. (39), Postol et al. (40), De Amicis Marafigo et al. (41)
Immunogenicity and safety and survival rate	Specific and high titers of opsonic IgG antibodies Absence of cross reactivity with human heart-tissue proteins Long period of survival after <i>S. pyogenes</i> challenge	Guilherme et al. (38), Guerino et al. (39), Postol et al. (40), De Amicis Marafigo et al. (41)

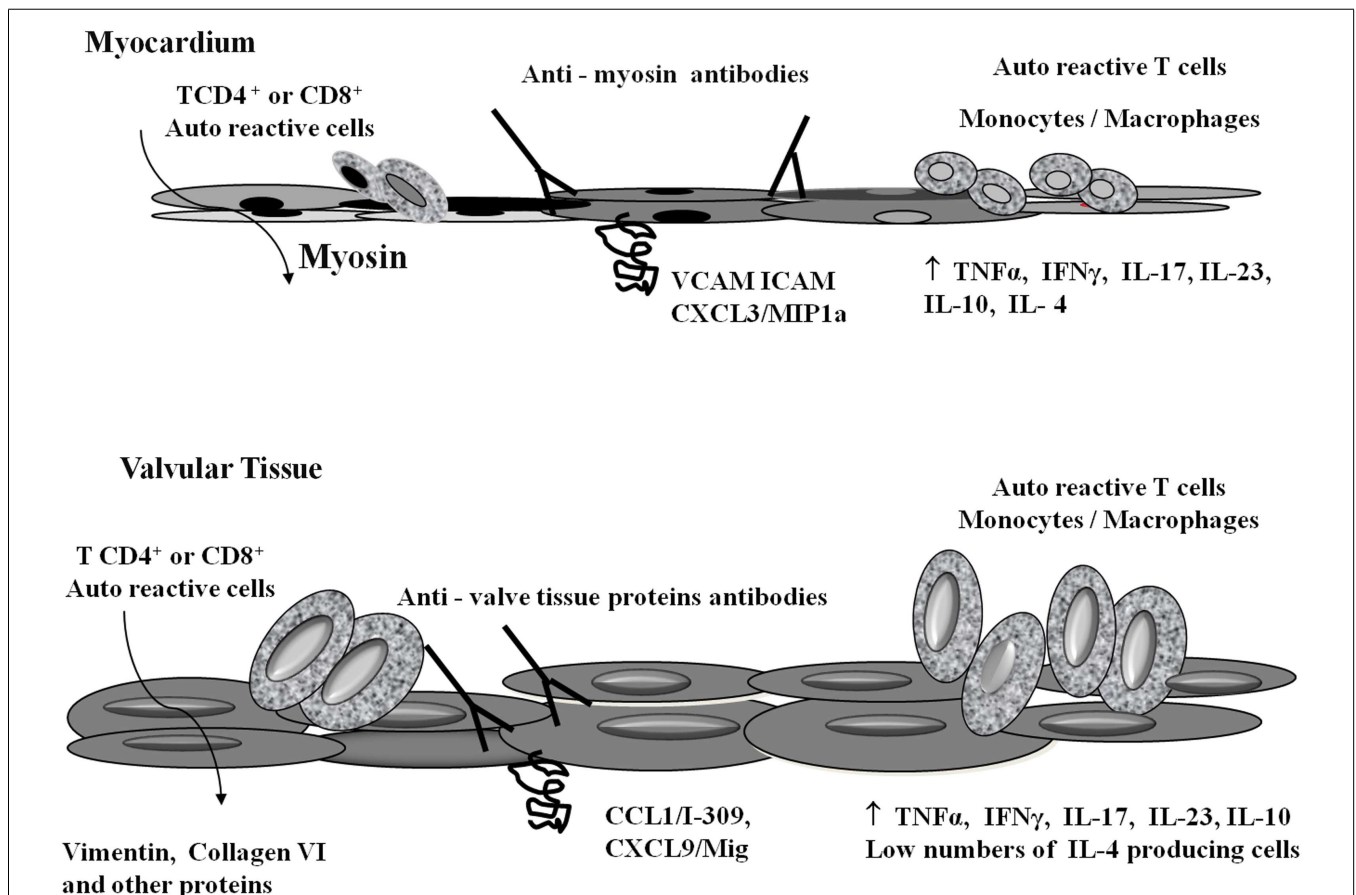


FIGURE 2 | Schematic representation of heart-tissue infiltration by T cells and autoimmune reactivity. *S. pyogenes*-reactive T cells infiltrate both the myocardium and valvular tissue through specific integrins (VCAM, ICAM) and chemokines (CCL1/I-309, CXCL3/MIP1 α , CXCL9/Mig) (16, 17). Once in the myocardium, T cells recognized cardiac myosin. In the valves, vimentin, collagen VI, and other

proteins are the targets of autoimmune reactions. Several inflammatory cytokines are involved in the inflammatory process. The presence of large numbers of regulatory cytokines (IL-4 and IL-10) in the myocardium tissue allowed the cure of myocarditis, while the low numbers of IL-4 producing cells in the valves contributes to the permanent valve damage (18).

(PDIA3) protein and a 78-kDa glucose-regulated protein precursor (HSPA5) as targets of the autoimmune reactions (34). It is interesting to note that apparently the recognition by T cells occurs in a cascade of reactivity from the myocardium to the valves.

In summary several cardiac proteins and streptococcal M peptides are recognized by both antibodies and T cells. The cross-reactivity might occur first through mimicry that results in the recognition of other human proteins, especially valve proteins, and eventually through epitope spreading and degeneracy mechanisms that amplified the number of self antigens that are targets of the autoimmune reactions.

ANTI-*S. PYOGENES* VACCINE DEVELOPMENT

The epidemiological growth of streptococcal diseases in undeveloped and developing countries has encouraged many groups to study vaccine candidates for preventing Group A Streptococcus (GAS) infections.

There are four anti-GAS vaccine candidates that target the M protein and eight other candidates targeting alternative streptococcal antigens, including group A CHO, C5a peptidase (SCPA), cysteine protease (Spe B), binding proteins similar to fibronectin, opacity factor, lipoproteins, Spes (super antigens), and streptococcal pili (35).

We developed a vaccine epitope (StreptInCor) composed of 55 amino acid residues of the C-terminal portion that is highly conserved among *S. pyogenes*. The StreptInCor epitope is recognized by individuals bearing different HLA class II molecules and could be considered a universal vaccine epitope (36, 37).

Using BALB-c, Swiss, and HLA class II transgenic mice, we evaluated the immune response over an extended period and found that StreptInCor was able to induce a robust immune response in all models (38–40). Vaccinated Swiss mice challenged with a virulent strain of *S. pyogenes* had 87% survival over 30 days. No cross-reaction was observed against cardiac proteins (40). The safety

of the vaccine epitope was evaluated by histopathology and no autoimmune or pathological reactions were observed in the heart or other organs (39). Anti-StreptInCor antibodies were able to neutralize/opsonize *S. pyogenes* strains, thus indicating that immunization with StreptInCor is effective against several *S. pyogenes* strains and can prevent infection and subsequent sequelae without causing deleterious reactions (41). These properties are summarized in **Table 3**. Taking all results into consideration, StreptInCor could be a safe and effective vaccine against streptococcus-induced disease.

CONCLUSION

The autoimmune process leading to the formation of heart lesions in RHD involves several genes that control both the innate and adaptive immune response. Consequently, several molecules play a role in the different phases of the disease. The molecular mimicry mechanism leads to the recognition of self proteins, mainly heart-tissue proteins, in the case of RHD. The autoimmune reactions are exacerbated by the inflammatory T helper 1 (Th1) and Th17 cytokines. **Figure 2** summarizes the events leading to myocarditis and rheumatic valvulitis, and later chronic rheumatic heart disease.

The knowledge acquired by us and others as mentioned through the text, allowed the search of a protective epitope giving a perspective of development of an effective and safe vaccine.

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