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

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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 \textit{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/MIP1a as well as CCL1/1-309 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 \textit{S. pyogenes} infections, consequently RF and RHD.

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

\textbf{INTRODUCTION}  
Rheumatic fever (RF) and its major sequelae rheumatic heart disease (RHD) are autoimmune diseases that arise following infection of the throat by \textit{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 \textit{S. pyogenes} infection and the associated autoimmune reactions, as well as to depict the molecular mechanisms leading to these autoimmune reactions.

\textbf{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.

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**GENES RELATED TO THE INNATE IMMUNE RESPONSE**  
The first line of host defense against a pathogen, \textit{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 \textit{MBL2} gene. The \textit{A} and \textit{O} alleles code for high and low production of MBL, respectively. Interestingly, RHD patients with mitral stenosis (MS) displayed an association with the \textit{A} allele, while the majority of RHD patients with aortic regurgitation (AR) presented the \textit{O} allele. The amount of MBL in the sera of RF and...
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 CCL17/1-309 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 mediated 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).
Many studies have focused on identifying the cross-reactive streptococcal epitope recognized by antibodies in sera from both animals and humans (23). Identification of the amino acid sequences of the N-terminal portion of the M protein in the 1980s led to the discovery of cross-reactive epitopes. The molecular mimicry between group A streptococcal proteins and several human-tissue proteins leads to the autoimmune reactions in the diverse phenotypes of the disease (24). Sydenham Chorea (SC), one of the major manifestations of the disease affects the central nervous system (CNS), in which lysoganglioside GM1 from neuronal cells are the targets of cross-reactive antibodies against N-acetyl-β-D-glucosamine, an antigen that is present in the cell wall of *S. pyogenes* (25). In RHD, the valves are severely damaged by both humoral and cellular autoimmune reactions.

The role of the cellular arm of the immune response in RF only began to be investigated 25 years after the description of heart-reactive antibodies in the sera of RF patients. The first studies focused on the reactivity of T cells from the peripheral blood of RF and RHD patients against streptococcal M protein (26, 27). These studies were followed by the description of increased numbers of CD4+ cells in the tonsils and peripheral blood of RF patients when compared with healthy subjects (28). The cytotoxic activity of CD8+ T cells from normal peripheral blood toward immortalized human heart cells was also described (29). It is now well established that heart-tissue inflammation starts by pericarditis followed by myocarditis and valvulitis, which cause serious damage to the heart valves due to the infiltration of both auto-reactive antibodies and T lymphocytes, leading to the development of valvular lesions and consequently, RHD.

Notably, CD4+ cells are predominant in the rheumatic lesions of the heart tissue. An analysis of the reactivity of both heart-tissue infiltrating T cells and peripheral cells against both the N-terminal region M protein-derived peptides and heart-tissue proteins noted three immunodominant regions of the M5 protein (residues 1–25, 81–103, and 163–177) that were cross reactive with both myocardium and valved-derived proteins (26, 27). The recognition of these regions was mainly in the context of the HLA-DR7 molecule, which is one of the most frequent HLA class II alleles associated with the susceptibility of the disease, as mentioned above (27). Among the heart-tissue proteins, cardiac myosin, the most abundant protein in the myocardium, is one of the targets of streptococcal cross-reactive antibodies and heart-tissue-infiltrating T cells. The autoimmune reaction against several synthetic peptides of the beta chain of the cardiac myosin light meromyosin (LMM) region were described by Ellis et al. (30) and Fae et al. (31) and are examples of autoreactivity against the myocardium tissue.

### Table 2 | Molecules involved with heart-tissue cellular infiltration.

| Adhesion molecules (VCAM, ICAM) | P-selectin and integrins are overexpressed in the heart-tissue and facilitates the cellular infiltration, valve scarring
| Specific chemokines such as CCL3/MIP1a gene expression up regulated in the myocardium and CCL1/1-309 and CXCL9/Mig in the valves recruited auto-reactive T cells | High numbers of TNF-α and IFN-γ, IL-17, and IL-23 secreting mononuclear cells are mediators of myocardial and valvular inflammation and drive the autoimmune response
| Low numbers of mononuclear IL-4 secreting cells in the valves probably lead to permanent and progressive valvular damage
| Infiltrating T cells are predominantly CD4+ (~80%)
| Antigen-driven oligoclonal T cells are expanded in the myocardium and valves and recognize streptococcal M peptides and heart-tissue proteins by cross reactivity
| The degeneracy of TCR and the epitope spreading mechanism allowed the recognition of several streptococcal and human proteins with some degree of homology (sequences or conformational or chemical properties) |

**Figure 1 | T cell reactivity against streptococcal M5 protein and heart-tissue proteins.** Valve-derived intralesional T cell clones from three RHD patients who underwent surgery for valve correction were established in vitro as previously described (26) and assayed for their reactivity against mitral valve-derived proteins and synthetic peptides of light meromyosin (LMM) and the M5 protein (26, 31). Black box: positive reaction in proliferation assays with a stimulation index (SI) >2.5.

![Graphical representation of T cell reactivity](image-url)
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 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).

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                         | Guilherme et al. (38), Guerino et al. (39), Postol et al. (40), De Amicis Marafigo et al. (41) |
|                                  | Absence of cross reactivity with human heart-tissue proteins               |                                                                           |
|                                  | Long period of survival after S. pyogenes challenge                        |                                                                           |

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 (CCL1/1-309, CXCL3/MIP1a, 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, reactivity might occur first through mimicry that results in the recognition of human proteins, especially valve proteins. The cross-reactivity of 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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