

The Autoimmune Side of Rheumatic Fever

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Acute rheumatic fever (ARF) is a multisystemic disease caused by an abnormal immunological response after group A *Streptococcus* (GAS) pharyngitis in predisposed people. Among the major criteria for diagnosis of ARF (Jones criteria) are carditis, polyarthritides, Sydenham chorea, erythema marginatum and subcutaneous nodules [1]. The disease usually presents with one or more acute episodes, while in 30–50% of all recurrent cases ARF may lead to chronic rheumatic heart disease (RHD) with progressive and permanent damage of the cardiac valves. Despite a notable reduction in the disease prevalence in industrialized countries, RHD remains one of the major causes of morbidity and mortality in developing countries. Over 15 million cases of RHD are estimated worldwide, with 282,000 new cases and 233,000 deaths annually.

The pathogenesis is not yet completely clarified; however, RHD may represent the most convincing model of an autoimmune disease triggered by infections, since the infectious agent is proven [Table 1]. The endocardial valve tissue is the main localization of cardiac damage. Peripheral T lymphocytes, interacting with adhesion molecules such as vascular cell adhesion molecule 1 (VCAM-1), infiltrate a non-vascularized tissue. Roberts et al. [2] demonstrated that VCAM-1 was expressed on the valvular endothelium in rheumatic valves, and that at the

valve surface CD4+ and CD8+ T lymphocytes were adherent to valve endothelium and penetrated through the subendothelial layer. Thus, T cell extravasation into the valve through the surface valvular endothelium appeared to be an important event in the development of RHD [2]. Furthermore, the evidence that the disease has an autoimmune background derives from the presence of anti-GAS antibodies as one of the major features in patients with rheumatic valvular disease. Antibodies and complement deposits have been detected in the heart of RHD patients, suggesting an autoimmune process [3]. The pathogenesis of RHD results from an immune response consisting of humoral and cellular components after exposure to *Streptococcus pyogenes*. The classic triad of the disease comprises the presence of the rheumatogenic group A streptococcal strain, a genetically susceptible host, and aberrant host immune response. There is a closer association of human leukocyte antigen (HLA) class II molecules (which participate in antigen presentation to T cell receptors) with an increased risk of acute rheumatic fever or rheumatic heart disease than class I molecules.

The autoimmune hypothesis was suggested in a 2001 study in which Lewis rats immunized with recombinant type 6 streptococcal M protein (rM6) developed valvulitis as well as focal lesions of myocarditis. Indeed, streptococcal M protein is structurally and immunologically similar to cardiac myosin working as antigenic mimicry. Interestingly, the valvular lesions initiated at the valve surface endothelium spread into the valve, and Anitschkow cells and verruca-like lesions were present. T lymphocytes from rM6-immunized rats proliferated in the presence of purified cardiac myosin, but not skeletal myosin, while a T cell line produced from rM6-treated rats proliferated in the presence of cardiac myosin and rM6 protein. It was suggested that streptococcal M protein can induce an autoimmune cell-mediated immune attack on the heart valve in such an animal model [4].

Furthermore, antibodies against group A *Streptococcus* were demonstrated to react with human heart preparations. It is suspected that after binding to the antigenic peptide, the specific HLA complexes can initiate aberrant T cell activation. Molecular mimicry is another key step since it takes place between streptococcal M protein and several self cardiac proteins (tropomyosin, keratin, cardiac myosin, laminin, vimentin). The complement cascade seems to be activated through the lectin pathway. Indeed, mannose-binding lectin (MBL), by acting as a soluble

Table 1. Summary of pathophysiological mechanisms

- Exposure to *Streptococcus pyogenes* (group A *Streptococcus* by the Lancefield system), usually after a throat infection
- HLA class II molecules which participate in antigen presentation to T cell receptors
- Antigenic mimicry (M, T, and R surface proteins associated with bacterial adherence to throat epithelial cells) and between streptococcal M protein and several cardiac proteins (cardiac myosin, tropomyosin, keratin, laminin, vimentin)
- Antibodies against group A *Streptococcus*
- Other antibodies: anti-endothelial cells/antiphospholipid antibodies
- Complement activation (via lectin pathway)
- Aberrant T cell activation

pathogen recognition receptor and binding to the carbohydrates on the surface of the pathogen, allows its opsonization, enhancing phagocytosis and activating the complement cascade. In RHD, MBL binds to N-acetylglucosamine, a molecule present on the Streptococcus cell wall and on human heart valves. It was observed that high levels of MBL- and MBL2-associated genotypes were associated with RHD, and in another study MBL2 genotypes associated with the high production of MBL seemed to be involved in the pathogenesis of rheumatic carditis and its progression to RHD [5].

One interesting observation is the linkage between antiphospholipid syndrome (APS) and ARF/RHD. Blank et al. [6] considered several common characteristics linking these conditions. Both diseases have central nervous system (CNS) and heart involvement; there is a molecular mimicry between the pathogen and the origin of the disease. Cross-reacting antibodies were found between the pathogen and self molecules, and endothelial cell activation was found to occur at the 'scene of the crime' – the valves. Finally, some patients with RHD have circulating antiphospholipid antibodies (aPL), while APS may be associated with streptococcal infection. It was recently demonstrated that cross-reactivity occurs between antibodies directed to the streptococcal M-protein and its synthetic derivative in rheumatic fever and antibodies derived from APS patients targeting the beta-2-glycoprotein-I (β 2GPI) and a β 2GPI-related synthetic peptide [6]. Antibodies to β 2GPI were found in 24.4% of ARF patients. Antibodies against various β 2GPI-related peptides were found in 1.1–36.7% of the patients. The immunoglobulin (Ig) G sera from ARF patients possessed significant anti- β 2GPI activity, while sera from APS patients contained considerable anti-streptococcal M protein activity. Affinity-purified anti- β 2GPI and anti- β 2GPI-related peptide antibodies from APS patients cross-reacted with streptococcal M protein and M5 peptide, while β 2GPI and β 2GPI-related peptides from RF patients inhibited anti-streptococcal M protein activity. These data support the hypothesis that common pathogenic mechanisms underlie the development of cardiac valve lesions and CNS abnormalities in APS and ARF [7]. Figueroa et al. [8] observed a significant association between IgM anticardiolipin antibodies (aCL) and carditis: all patients with valvulitis had IgM aCL (100%) vs. 37% of patients without valvular involvement ($P = 0.02$). This evidence suggested that antiphospholipid antibodies (aPL) may play a role in the pathogenesis of some clinical manifestations of acute rheumatic fever [8].

It was also demonstrated clinically that chorea in APS patients was associated with rheumatic fever and thrombocytopenia [9]. Indeed, the association between RF and APS, although quite rare, is of great clinical importance and APS should be included in the differential diagnosis of RF, especially when these patients suffer from stroke, or when echocardiogram does not show intracavitary thrombi.

Finally, potentially pathogenic anti-endothelial cell antibodies (AECA) were demonstrated in 40% of RHD patients [10]. As

rheumatic valve damage may begin on the surface of valvular endothelium, AECA, possibly using a mechanism of molecular mimicry, could contribute to this damage by promoting endothelial stress and exposure of the underlying basement membrane/extracellular matrix antigens. Indeed, immunoproteomic analysis was able to characterize the autoantibodies directed against endothelial antigens in RHD patients. Interestingly, vimentin was identified as an endothelial autoantigen in RHD and revealed to be cross-reactive to streptococcal antigens. These antibodies also had functional effects on human coronary microvascular endothelial cells (HMVEC-C) [3]. In a preliminary study, we induced experimental myocarditis in Lewis rats by passive transfer of synthesized cross-reactive anti-vimentin antibodies. Cross-reactive anti-streptococcal/vimentin antibodies may represent a possible pathogenic actor in RHD, suggesting that molecular mimicry is fundamental in the development of the disease.

CONCLUSIONS

Taken together, all these data strengthen the idea that ARF/RHD is an autoimmune disease, and unveiling all the mechanisms leading to the disease onset may clarify the link between infections and autoimmunity. Nonetheless, in autoimmunity, everything is infectious until proven otherwise.

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