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Molecular pathogenesis of rheumatic fever and rheumatic heart disease

Luiza Guilherme, Kellen Faé, Sandra E. Oshiro and Jorge Kalil

Molecular mimicry between streptococcal and human proteins has been proposed as the triggering factor leading to autoimmunity in rheumatic fever (RF) and rheumatic heart disease (RHD). This article summarises studies on genetic susceptibility markers involved in the development of RF/RHD. It also focuses on the molecular mimicry in RHD mediated by the responses of B and T cells of peripheral blood, and T cells infiltrating heart lesions, against streptococcal antigens and human tissue proteins. The molecular basis of T-cell recognition is assessed through the definition of heart-crossreactive antigens. The production of cytokines from peripheral and heart-infiltrating mononuclear cells suggests that T helper 1 (Th1)-type cytokines are the mediators of RHD heart lesions. An insufficiency of interleukin 4 (IL-4)-producing cells in the valvular tissue might contribute to the maintenance and progression of valve lesions.

Rheumatic fever (RF) is the most convincing example of molecular mimicry in human pathological autoimmunity. The disease is triggered by the bacterium *Streptococcus pyogenes* (group A streptococcus) and affects 3–4% of untreated children (Ref. 1). The immune response against streptococcal antigens generates cross-recognition of human tissue proteins, leading to autoimmune reactions. Rheumatic heart disease (RHD) is the most serious complication of RF and develops 4–8 weeks (or later) after group A streptococcus infection in 30–45% of individuals

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Accession information: DOI: 10.1017/S146239940501015X; Vol. 7; Issue 28; 9 December 2005

(Ref. 2). RHD patients can develop multiple valvular lesions, leading to heart failure.

Group A streptococci

Group A streptococci can cause infections that range from relatively mild throat and skin infection [e.g. pharyngitis (strep throat) and impetigo] to severe and even life-threatening invasive infection of blood, deep muscle and fat tissue of internal organs such as kidneys, liver and lungs (e.g. necrotising fasciitis, scarlet fever and streptococcal toxic shock syndrome) (Ref. 3). Patients can also develop immune-mediated post-streptococcal sequelae, such as acute RF and acute glomerulonephritis. RF manifests itself as arthritis, Sydenham's chorea (a progressive loss of neural function in the distal limbs) and carditis. In 1930, Coburn was the first physician to associate the development of RF with the presence of prior throat infection by *S. pyogenes* (cited in Ref. 4).

Studies by Lancefield in 1941 (Ref. 5) classified streptococcal bacterial groups by serology based on their cell-wall polysaccharides (groups A, B, C, F and G). The *S. pyogenes*, or group A streptococcus, cell wall (Fig. 1) consists of repeating units of *N*-acetyl β-D-glucosamine carbohydrates linked to a polymeric rhamnose backbone. In addition, group A streptococci contain M, T and R surface proteins and lipoteichoic acid (LTA), all of which are involved in bacterial adherence to throat epithelial cells. The complex structure of the cell surface accounts for many of the determinants of *S. pyogenes* virulence, especially those concerned with colonisation of host cells and evasion of phagocytosis and the host immune response. As an attachment factor that provides the bacterium with an adherence advantage, the M protein is particularly important as a virulence factor (Ref. 6).

The M protein extends from the bacterial cell wall and is composed of two polypeptide chains, of approximately 450 amino acid residues each, in a double α-helical coiled-coil configuration. The N-terminal portion contains the A repeat region that presents antigenic variations that define the different serotypes, of which 130 have been identified to date. The B repeat region also presents antigenic variations among the streptococcal serotypes. The C-terminal half is conserved, and contains multiple repeat regions (Ref. 7). The M protein is the most important antigenic structure of the bacteria and shares structural homology with α-helical coiled-coil

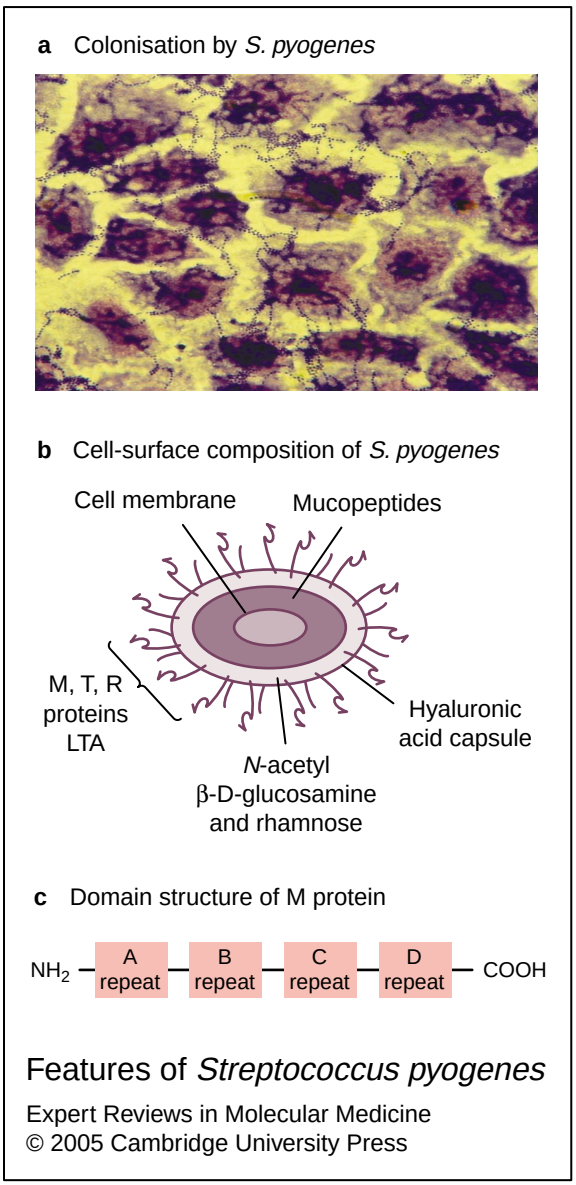

Figure 1. Features of *Streptococcus pyogenes*. (a) Image showing in vitro colonisation and adherence of *Streptococcus pyogenes* on HEp-2 cells. Magnification,1000×. (b) Schematic representation of the cell wall of *S. pyogenes* (group A streptococcus). The streptococcal cell is covered by an outer hyaluronic acid capsule and is characterised by the group A carbohydrates composed of *N*-acetyl β-D-glucosamine and rhamnose. M, T and R are surface proteins; LTA (lipoteichoic acid) is involved in bacterial adherence to the throat epithelial cells. (c) The M protein, an adhesive factor, is composed of an N-terminal portion that contains A and B repeat regions (the A region defines the serotypes of streptococci strains); the C-terminal portion contains C and D regions that are highly conserved among the streptococci strains.

Accession information: DOI: 10.1017/S146239940501015X; Vol. 7; Issue 28; 9 December 2005

human proteins such as cardiac myosin, tropomyosin, keratin, laminin, vimentin and several valvular proteins (Refs 8, 9, 10, 11, 12). As discussed below, this similarity forms the basis both of a tolerant or suppressed immune response to infection and also the molecular mimicry that results in the immune-mediated post-streptococcal sequelae of RF/RHD.

Molecular basis of RF/RHD autoimmune reactions

HLA class II alleles associated with RF/RHD

Several major histocompatibility complex (MHC) HLA class II alleles have been associated with the development of RF/RHD in different countries (Table 1). *HLA-DR7* is the allele most frequently associated with RF/RHD, with the association found in Brazilian, Turkish, Egyptian and Latvian RHD patients (Refs 13, 14, 15, 16, 17). In addition, in Egyptian and Latvian RHD patients, some *DQ* alleles in association with *HLA-DR7* seem to be related to the development of multiple valvular lesions (Refs 17, 18). *HLA-DR4* was found in American Caucasian (Refs 19, 20), Saudi-Arabian (Ref. 21) and Indian patients (Ref. 22). Both *DR7* and *DR4* alleles are in linkage disequilibrium with the *DR53* allele, which has also been associated with RF/RHD in Brazilian patients (Refs 13, 14). Other HLA class II alleles less frequently associated with the disease have also been found in other countries and are listed in Table 1 (Refs 17, 19, 23, 24, 25, 26, 27, 28). Recently, increased frequencies for some tumour necrosis factor α (TNF-α) alleles were described in Mexican RHD patients (Ref. 29). The *TNF-α* gene is located on chromosome six between *HLA-B* and *HLA-DR*. These results suggest linkage disequilibrium between HLA genes and other genes located in the same region.

One explanation for the frequent association of certain HLA class II alleles with RF/RHD, and indeed other autoimmune diseases (Ref. 30), is that such molecules might cause inappropriate T-cell activation. HLA molecules are expressed on the surface of antigen-presenting cells (APCs) such as macrophages, dendritic cells and B cells and, together with bound peptide antigen, trigger the activation of T cells. HLA-associated autoimmunity could result from the activation of peripheral T cells that have escaped immune tolerance and have the ability to crossreact with external stimuli that mimic self-antigens. In support of this notion, peripheral T cells from Brazilian RHD patients inheriting *HLA-DR7/DR53*

Table 1. HLA class II alleles associated with rheumatic fever and rheumatic heart disease

HLA class II	Country[a]	Refs
DR7	Brazil	13, 14, 15
	Turkey	16
	Egypt[b]	17
	Latvia[b]	18
DR4	USA	19, 20
	Saudi Arabia	21
	India	22
Other		
DR1	South Africa, Martinique	23, 24
DR2	USA, Mexico	19, 25
DR3	Turkey, India	16, 26
DR5 (11)[c]	Turkey	27
DR6 (13)[c]	South Africa, Egypt	17, 23
DR9	USA	19
*DQA1*0104*	Japan	28
*DQB1*05031*		

[a] Country of population in which association shown.
[b] In Egyptian and Latvian RHD patients, some *DQ* alleles in association with *DR7* seem to be related to the development of multiple valvular lesions (Refs 17, 18).
[c] Alleles of *DR5* and *DR6*.

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alleles, which include APCs that express DR7/DR53 molecules on the cell surface, preferentially recognise an immunodominant peptide [designed on the basis of published sequences (Ref. 31)] encompassing amino acid residues 81–96 of the *S. pyogenes* M5 (type 5) protein. This peptide showed crossreactivity with several heart tissue proteins and thus appears to have triggered autoimmune reactions in these patients through molecular mimicry (Ref. 32).

Molecular mimicry and autoimmune reactions following *S. pyogenes* infection

The molecular mimicry mechanism mediating RF/RHD is the process whereby T cells recognise self-antigens that have some degree of homology with streptococcal antigens, and provide help to autoreactive B cells. In RF, both the humoral and cellular arms of the immune response play a role in autoimmunity. Indeed, different manifestations of RF, such as arthritis, Sydenham's chorea and carditis, probably result from polarisation of the immune response towards either B cells or T cells.

Humoral response

Heart-reactive antibodies were described for the first time in 1945 by Calveti (Ref. 33). In 1964, Kaplan and Suchy (Ref. 34) demonstrated the presence of antibodies crossreactive for streptococcal and heart antigens both in sera from animals immunised with streptococcal cell wall products and in sera from acute RF and RHD patients. The antiheart antibodies were absorbed from human sera by group A streptococci or their cell walls or membranes. These authors coined the term 'biological mimicry' in order to explain the mechanism by which the crossreactivity observed between human and streptococcal antigens occurred. Using immunofluorescence techniques, Kaplan and Svec also found immunoglobulins and complement bound to the myocardium of acute RF patients (Ref. 35). Studies conducted by Zabriskie et al. gave support to the hypothesis that RF has an autoimmune origin by describing the presence of antibodies crossreactive with streptococcal membrane antigens in acute RF sera (Refs 36, 37).

Many studies have focused on identifying the crossreactive streptococcal epitope. Identification of the amino acid sequences of the N-terminal portion of the M protein in the 1980s (Ref. 38) led to the discovery of crossreactive epitopes recognised by antibodies in sera from both animals and humans or by monoclonal antibodies (mAbs). A summary of the crossreactive proteins found to date is presented in Table 2 (Refs 9, 10, 11, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55). Among the human proteins, cardiac myosin and vimentin seem to be the major crossreactive antigens. An early study to determine the crossreactive streptococcal epitope demonstrated the involvement of *N*-acetyl β-D-glucosamine, a polysaccharide present in both group A streptococci and heart valvular tissue (Ref. 56). More recently, Cunningham's group has also shown that human mAbs react with *N*-acetyl β-D-glucosamine, and demonstrated the in vitro cytotoxic activity of human and murine mAbs against heart cells in culture in the presence of complement. These mAbs showed crossreactivity against laminin, an extracellular matrix α-helical coiled-coil protein surrounding heart cells and also present in the valves (Refs 11, 57, 58). The potential role of these crossreactive antibodies in the development of RHD has only recently been clarified. Studies conducted by the same group describe crossreactive antibodies that are able to bind to the endothelial surface, which may lead to inflammation, cellular infiltration and valve scarring (Ref. 59). The upregulation of vascular cell adhesion molecule 1 (VCAM-1) after binding of crossreactive antibodies to the valvular endothelium facilitates cellular infiltration (Ref. 60).

It is possible that autoantibodies play a key role in clinical manifestations such as Sydenham's chorea, in which a plasma exchange therapy was curative for some patients (Ref. 61). Sydenham's chorea occurs in 10–30% of acute RF cases, either alone or in combination with other clinical manifestations such as mild carditis or polyarthritis. The pathogenic mechanism leading to the development of Sydenham's chorea was recently clarified by Kirvan et al. (Ref. 62), who showed that antibodies from sera of chorea patients were able to bind to neuronal cells. They identified gangliosides as autoantigens that crossreact with *N*-acetyl β-D-glucosamine. They also showed that the autoantibodies mediate signal transduction by calcium/calmodulin (CaM)-dependent protein kinase II, triggering dopamine release from neuronal cells (Ref. 62).

Cellular response

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

Accession information: DOI: 10.1017/S146239940501015X; Vol. 7; Issue 28; 9 December 2005

Table 2. Crossreactivity of M-protein-reactive antibodies with human proteins

M protein	Epitope position	Antibody nature	Crossreactive human proteins	Ref.
M1	13–19	Human	43 kDa kidney protein	39
	23–26		56 kDa kidney protein (vimentin)	
	1–12	Murine mAb	None	
	13–19		43 kDa protein (kidney/heart)	40
M5	–[a]	Rabbit	Sarcolemma	41
	–[a]	Rabbit	Cardiac myosin	9
	1–35	Rabbit	None	42
	84–116	Rabbit	Cardiac myosin	43
	164–197	Rabbit	40 kDa heart protein	44
	84–116, 117–134, 164–197	Human mAb	Skeletal muscle myosin, cardiac myosin, actin, keratin	45
	184–197	Murine/human mAb	Cardiac myosin	46
	–[a]	Murine mAb	Tropomyosin	10
	–[a]	Murine mAb	Valves protein	11
M6	1–20, 10–20, 12–31	Rabbit	None	47
	–[a]	Murine mAb	53 kDa glomerular protein	48
	–[a]	Human mAb	Skeletal muscle myosin; actin keratin	46
	–[a]	Murine mAb	Tropomyosin	10
	223–245,256–277, 240–260, 272–292	Rabbit	Denatured forms of myosin	49
	B repeat region	Rabbit, human	Human brain	50
M12	–[a]	Murine mAb	53 kDa glomerular protein	48
	1–25	Rabbit	Vimentin (mesangial cells)	51
M19	1–24	Rabbit	60 kDa myocardial protein	52
M24	–[a]	Human, rabbit	Brain	53
	S-CB7	Human, rabbit	None	54
	23–35, 18–35, 13–35	Rabbit	None	55

[a] Epitope not defined.
Abbreviation: mAb, monoclonal antibody.

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 cell-wall antigens (Refs 63, 64, 65). 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 (Ref. 66). The cytotoxic activity of $CD8^+$ T cells from normal peripheral blood towards immortalised human heart cells was also described (Refs 67, 68). It is now well established that the carditis that leads to the development of valvular lesions, and consequently RHD, is a T-cell-mediated autoimmune disease.

RF can cause injuries to the joints, central nervous system (Sydenham's chorea) and heart (leading to RHD). Acute rheumatic carditis, the most serious sequela of RF, is initially mediated by a humoral immune response, which facilitates cellular infiltration into the heart tissue by reacting with human valvular endothelium and the underlying basement membrane (Refs 59, 60). The pathognomonic sign of acute RHD is the Aschoff body – a granulomatous lesion containing both T and B cells, macrophages, large mononuclear cells, multinucleated cells and polymorphonuclear leukocytes (Ref. 69), described in 1903. This develops in the myocardium and/or endocardium (reviewed by Ref. 70), probably as a result of

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cellular infiltration through the endothelium. The presence of a mononuclear cell infiltrate with a predominance of $CD4^+$ T cells in rheumatic heart lesions was the first evidence of the involvement of $CD4^+$ T cells in RHD lesions (Refs 71, 72).

The significance of molecular mimicry between group A streptococci and heart tissue has been shown through an analysis of the T-cell repertoire leading to local tissue damage in RHD (Ref. 12). T-cell clones were generated in vitro from T cells infiltrating the heart lesions of severe RHD patients and were shown to recognise by crossreactivity both M protein peptides and heart-tissue-derived proteins. These results indicated three M5 regions (residues 1–25, 81–103 and 163–177) that crossreact with several heart-protein fractions, especially those derived from valvular tissue with molecular masses of 95–150 and 30–43 kDa (Ref. 12). An extension of these studies analysing the reactivity of heart-tissue-derived T-cell clones from several patients confirmed the M5(81–103) as an immunodominant region, with 62% of M-protein-reactive intralesional T-cell clones recognising this region (Ref. 32). This region comprises 22 amino acid residues, including the three overlapping peptides M5(81–96), M5(83–103) and M5(91-103) mentioned above. The same M5 epitopes were also preferentially recognised by peripheral T-cell clones (Ref. 32). These results suggest that the M5(81–103) region could be one of the streptococcal triggers of autoimmune reactions in RHD.

However, when Yoshinaga et al. (Ref. 73) assessed the reactivity of T-cell lines derived from heart valve specimens and peripheral blood lymphocytes of RF patients, they showed that, even though these cells recognised cell wall and membrane streptococcal antigens, they failed to react to the M protein, myosin or other mammalian cytoskeletal proteins. The absence of reactivity against M protein and self-antigens probably was a result of low frequencies of specific T cells.

Myosin/M5-crossreactive T-cell epitopes have also been investigated in mice immunised with intact cardiac myosin (Ref. 74). Lymph-node T cells were tested against overlapping M5 peptides, and seven regions – termed NT4/5/6, B1B2, B2, B2B3A and B3A – were predominantly recognised. Regions NT5/6 and B1B2/B2 aligned with M5(81–103) and M5(163–177) peptides, respectively (Refs 12, 32). Robinson et al. (Ref. 75) obtained lymph-node T-cell clones from mice immunised with recombinant M5 protein that were able to recognise M5 epitopes. Of the M5 epitopes recognised by mouse T cells, only the M5(1–35) region aligns with the M5(1–25) region recognised by human-infiltrating T-cell clones (Ref. 12). These findings support the argument of immunodominance of the M5(81–103), M5(163–177) and M5(1–25) regions.

Epitope spreading

Epitope spreading refers to a mechanism whereby, during an ongoing immune response, reactivity is induced to epitopes that are distinct from the original disease-inducing epitope, with the result that these epitopes now become the target of the immune response (Ref. 76). Epitope spreading is the process by which several self-antigens are recognised after an initial response against pathogens (Ref. 77). In the case of RF and RHD, the recognition of *S. pyogenes* leads to a broad collection of antibodies and T-cell epitopes that are crossreactive with human proteins, which trigger and maintain the autoimmune reactions, and consequently the development of heart rheumatic lesions. The fact that several cardiac proteins crossreact with streptococcal M peptides suggests that crossreactivity might occur first through mimicry that results in the recognition of other human proteins, especially valvular proteins, and eventually through an epitope spreading mechanism.

T-cell receptor usage in RF/RHD

The T-cell receptor (TCR) is a heterodimer composed of αβ or γδ chains; in humans, the majority of T cells express the αβ heterodimer. The TCR α chain is produced through the assembly of variable (V), joining (J) and constant (C) gene segments (Ref. 78). These segments are also present in the β chain, which has a diversity gene segment (D) as well. Combinations of these gene segments (V, D, J) generate around 10^{18} different TCRs. The 'combining site' of the TCR, which interacts with MHC peptide, comprises α- and β-chain hypervariable loops known as complementarity-determining regions (CDR1, CDR2, CDR3) together with a β-chain hypervariable loop known as HV4. The latter is within the binding site for certain antigens termed superantigens (SAgs), which are the most powerful T-cell mitogens known. SAgs bind as intact molecules to the MHC class II antigens expressed on APCs, outside the peptide-binding groove, and then sequentially bind to the TCR through the V region of the TCR β-chain (Ref. 79).

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Several SAgs have been identified in group A streptococci, including streptococcal pyrogenic exotoxins (SPEs) A, C and G-M, the streptococcal superantigen (SSA), and the streptococcal mitogenic exotoxins (SMEZ) 1 and 2 (Ref. 79). SPEs play a pivotal role in the streptococcal toxic shock syndrome and in necrotising fasciitis (Ref. 80). Interestingly, the genetic background of the infected individual might influence the magnitude of the inflammatory response triggered by streptococcal SAgs. It has been shown that patients carrying the *DRB1*1501 / DQB1*0602* haplotype show significantly reduced cytokine production and are less likely to develop severe systemic disease (Ref. 80).

SAgs might contribute to the pathogenesis of autoimmune disease by activating and expanding T-cell populations specific for self-antigens or by depleting certain T-cell populations. It has been proposed by some groups that the M protein from *S. pyogenes* could have a SAg effect. The first report to this effect was by Tomai et al. (Ref. 81), who showed that a fragment of the M protein (pepM), derived through pepsin enzymatic action, expanded restricted T-cell populations (Vβ2, 4 and 8) in patients with RF. The presence of a restricted set of T cells in the valvular tissue of patients with chronic RHD was also observed. In this work, the authors suggested that the valvular sequela in RHD patients might be related to an inflammatory process, driven by either local antigens or SAgs, that might persist for many years after the initial triggering event (Ref. 82). By analysing the expression of Vβ families in the peripheral blood of acute RF and RHD patients in comparison with healthy subjects, they showed a low frequency of $CD8^+V\beta2^+$ cells, suggesting a depletion of this population from the periphery as a result of a SAg effect (Ref. 83).

Despite these results, the SAg effect of the M protein is still controversial in the literature. Some groups showed no alterations in the T-cell repertoire in the peripheral blood mononuclear cells (PBMCs) of acute RF patients (Ref. 84). More importantly, no evidence of superantigenicity has been provided using either recombinant M5 protein (rM5) or a pepsin-derived fragment of the M5 protein (pepM5) to activate PBMCs from healthy adult volunteers (Ref. 85). Furthermore, analysis of the T-cell repertoire in PBMCs and heart-infiltrating T-cell lines obtained from RHD patients showed expansions of several Vβ families, with oligoclonal profiles especially in heart-infiltrating T-cell lines; this suggests that, at least in the chronic phase of the disease, there is no evidence of a SAg effect (Ref. 86). Vβ expansions were identified in peripheral blood that were also expanded in the heart; these results suggest that a specific T-cell population migrated from the periphery to the heart lesion, probably driven by antigen recognition. Confirming this hypothesis, it was shown that $CD4^+$ T-cell clones obtained from mitral-valve-infiltrating T cells crossreact with cardiac proteins, such as myosin peptides (LMM; light meromyosin) (Ref. 59), and with mitral valve proteins, such as the 56–53 kDa / pI6.76 and 35 kDa / pI8.4 proteins, as well as with the streptococcal M5(81–103) peptide (Refs 87, 88). These populations were characterised as Vβ13 Jβ2S7, Vα2 and Vα3. Another $CD4^+$ T-cell clone obtained from myocardium-infiltrating T cells also recognised the same 56–53 kDa / pI6.76 mitral valve protein. This population differs from those from the valvular tissue by only one α-chain (Vα7) (Refs 87, 88). Taken together, these results demonstrate that T-cell populations are expanded in the heart lesions, driven by self-antigen recognition, and probably contribute to the maintenance and progression of tissue damage. Considering that rheumatic heart lesions occur in the absence of the bacteria, a SAg effect probably does not play a role in the development of RHD lesions.

Cytokines in RF/RHD

Cytokines are likely to be important second signals following infection, triggering effective immune responses in most individuals and probably a deleterious response in autoimmune disease. Severe RHD is mediated mainly by T cells, which participate in a delayed-type hypersensitivity reaction leading to local inflammation, as mentioned above. An evaluation of the production of pro-inflammatory cytokines after streptococcal antigen and pokeweed mitogen stimulation of PBMCs and tonsillar mononuclear cells from RF / RHD patients without congestive heart failure showed different patterns between the two types of cells. TNF-α, interleukin 1 (IL-1) and IL-2 were overproduced by PBMCs and were decreased in tonsillar mononuclear cells (Ref. 89). Increased production of IL-2 has been reported in acute RF and in patients with active RHD. These patients also showed high numbers of $CD4^+$ and $CD25^+$ cells, suggesting the expansion of activated T cells in peripheral blood during the active phase

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of the disease (Ref. 90). Other authors have confirmed these findings, showing increased plasma levels of TNF-α in RF/RHD patients (Refs 91, 92). In heart lesions, during the acute phase of RHD, the production of IL-1, TNF-α and IL-2 correlated with the progression of Aschoff nodules (Ref. 93).

It has recently been shown that mononuclear cells from heart lesions predominantly secrete interferon γ (IFN-γ) and TNF-α, which are T helper 1 (Th1)-type cytokines, in both acute RF and chronic RHD patients (Ref. 94). This work showed sparse production of IL-4 by valve-infiltrating cells (under 10% IL-4-positive cells) in 82% of the valve fragments analysed, and large numbers of IL-4-positive cells (over 50%) in 78% of the myocardium fragments analysed. This suggests that low numbers of IL-4-producing cells in the valvular tissue might contribute to the progression of valvular RHD lesions (Ref. 94). In vitro analysis showed that myocardium-infiltrating T-cell lines produced IL-4 and IL-10, whereas valve-derived T-cell lines did not produce IL-4 and produced less IL-10 than myocardial-derived T-cell lines. By contrast, streptococcal M5-antigen-stimulated T-cell lines produced IFN-γ in 85% of cases, regardless of their origin. These observations reinforce the putative role of these regulatory cytokines in myocardium healing in RHD and in the induction of progressive and permanent valve damage (Ref. 94).

Animal models

Multiple animal species have been assayed in attempts to reproduce RF and RHD, although humans are the natural host and reservoir of *S. pyogenes*. No animal model reproduces the throat infection, arthritis and/or carditis after a latent period of the initial streptococcal infection as observed in humans. Recently, it was demonstrated that the intraperitoneally injection of M6 recombinant protein in Lewis rats induces myocarditis and valvulitis similar to that seen in RHD (Ref. 95). A lymph-node $CD4^+$ T-cell line obtained from an immunised rat recognised both recombinant M6 protein and cardiac myosin (Ref. 95). Following the experiments in animal models, the same group characterised different segments of cardiac myosin capable of inducing myocarditis or valvulitis (Ref. 96). These authors also described cardiac myosin S2 region epitopes that were able to induce autoimmune myocarditis associated with an upregulation of inflammatory cytokine production in Lewis rats (Ref. 97).

The development of experimental models of myocarditis and valvulitis induced by streptococcal antigens and cardiac myosin is still a challenge, but they will contribute towards a better understanding of the pathogenesis of RHD. Moreover, they could prove useful for the development of vaccines.

Clinical implications

Knowledge acquired in the past few years has contributed towards a better understanding of the global picture of the pathogenesis of RHD. The major events that trigger RHD lesions are summarised graphically in Figure 2.

The identification of streptococcal and human-protein crossreactive epitopes is fundamental for the development of new immunotherapies. For example, the stimulation of peripheral cells with major autoantigens, such as myosin, can be envisaged as a form of T-cell therapy based on the induction of anti-idiotypic responses and on the shifting of cytokine profiles: briefly, $CD4^+$ and $CD8^+$ anti-idiotypic T cells should recognise a peptide from the CDR3 region of the TCR from autoantigen-specific T cells, which will therefore be targets for T-cell regulation. Similar treatment is being used in patients with multiple sclerosis and other diseases, with encouraging results (reviewed by Ref. 98).

The definition of both humoral and cellular crossreactive epitopes is also important for the producton of a safe vaccine for preventing *S. pyogenes* infections without inducing autoimmune reactions. The isolation of T cells from heart lesions and the establishment of intralesional T-cell lines and clones are important tools in the search for safe epitopes. In addition, the recently described Lewis rat model of RHD lesions (Ref. 95) will certainly be useful for testing candidate vaccine epitopes.

Concluding remarks

Knowledge about the immune responses leading to RF and RHD gained during the past 50 years has led to significant understanding of these diseases. The association of HLA class II alleles, considered as genetic markers for these diseases, in fact pointed out HLA molecules that preferentially presented streptococcal and self-antigens to the TCR. TNF-α alleles and other genes related to immune regulation that are located in

Accession information: DOI: 10.1017/S146239940501015X; Vol. 7; Issue 28; 9 December 2005

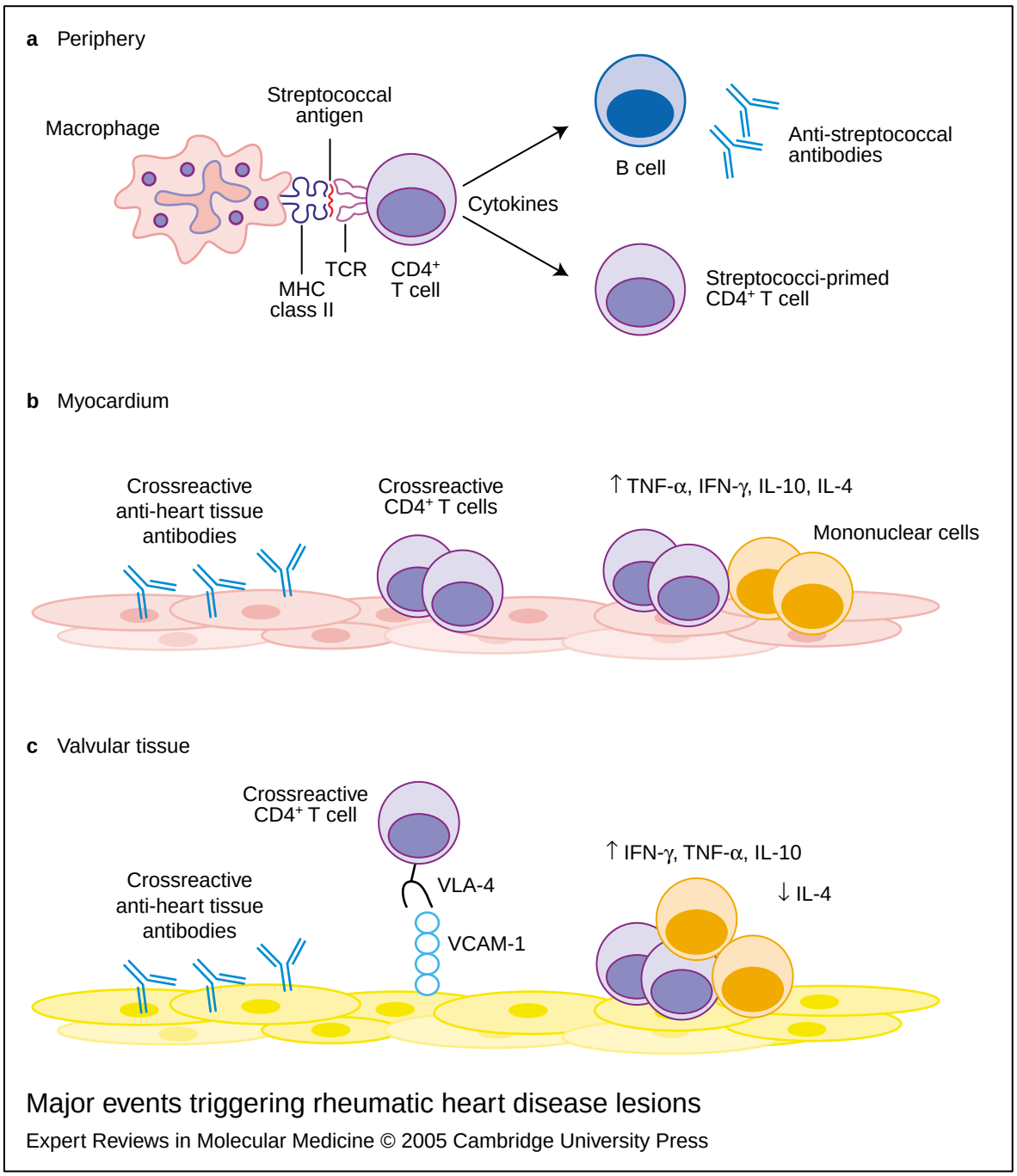

Figure 2. Major events triggering rheumatic heart disease lesions. (a) Infection of the throat with *Streptococcus pyogenes* results in presentation of streptococcal antigens by antigen-presenting cells such as macrophages, and priming of B cells and $CD4^+$ T cells to produce a humoral and cell-mediated response against streptoccal antigens. (b) Some antibodies are capable of cross-recognition of heart proteins, facilitating cellular infiltration of $CD4^+$ T cells recognising heart-tissue proteins by molecular mimicry, triggering heart lesions (Ref. 12). (c) In the valvular tissue, the deposition of crossreactive antibodies increases the expression of VCAM-1, which interacts with VLA-4 expressed on the surface of T cells and facilitates cellular infiltration (Refs 59, 60). Inflammatory cytokines such as TNF-α and IFN-γ mediate the development of the lesions, and the low numbers of IL-4-producing cells contribute to the progression and maintenance of valvular lesions (Ref. 94). Abbreviations: IFN-γ, interferon γ; IL-4, interleukin 4; MHC, major histocompatibility complex; TCR, T-cell receptor; TNF-α, tumour necrosis factor α; VCAM-1, vascular cell adhesion molecule 1; VLA-4, very late antigen 4.

Accession information: DOI: 10.1017/S146239940501015X; Vol. 7; Issue 28; 9 December 2005

the same chromosomal region as HLA genes are now being investigated, and this will contribute not only to the definition of new genetic markers but also to a better understanding of the complex network of autoimmune reactions that occurs in RF/RHD.

The recognition of several antigens by a defined TCR is in agreement with the new concept of degeneracy of the TCR – that is, recognition by a T-cell clone of more than one antigen, not necessarily presenting with sequence homology. The results discussed here reinforce the complexity of autoimmune reactions and show that the cross-recognition of self- and pathogen antigens by the TCR requires a low degree of homology. This might explain the large numbers of streptococcal crossreactive B- and T-cell epitopes that have been defined. As highlighted above, it is only recently that the interaction between B and T cells in RHD was elucidated: the deposition of crossreactive antibodies in the valvular endothelium increases adhesion molecules such as VCAM-1, which, through interaction with VLA-4 on the T-cell surface, leads to T-cell infiltration. These cells are streptococcal primed during the throat infection and able to recognise self-antigens by molecular mimicry. The evaluation of cytokines produced by infiltrating mononuclear cells in heart tissue has shed light on why the myocardium heals whereas the valves suffer severe lesions. These cells produce inflammatory cytokines such as TNF-α and IFN-γ in heart lesions, but IL-4 is produced by low numbers of cells in the valvular tissue, probably leading to progression and perpetuation of the lesions in the valves.

All this information opens new possibilities for immunotherapy such as T-cell vaccination for patients with severe RHD. Molecular knowledge of the autoimmune reactions mediated by intralesional T cells will certainly aid in the choice of streptococcal protective epitopes for the construction of an effective and safe vaccine.

Acknowledgements and funding

We acknowledge the anonymous peer reviewers for their reading and suggestions, and our collaborators: Professor Dominique Charron and Professor Antoine Toubert (Laboratoire d'Immunologie et Histocompatibilité, INSERM U396, Institut Universitaire d'Hématologie, Hopital Saint Louis, Paris, France); and Professor Madeleine Cunningham (Department of Microbiology and Immunology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA). This work was supported by grants from Fundação de Amparo a Pesquisa do Estado de São Paulo (FAPESP) (00/3402-2 and 99/035556-0); FAPESP-INSERM (00/11727-9) and USP-COFECUB (008-01) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) (301775/83-4 and 620062/01-0).

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Further reading, resources and contacts

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Luiza Guilherme, Kellen Faé, Sandra E. Oshiro and Jorge Kalil (2005) Molecular pathogenesis of rheumatic fever and rheumatic heart disease. Expert Rev. Mol. Med. Vol. 7, Issue 28, 9 December, DOI: 10.1017/S146239940501015X

Accession information: DOI: 10.1017/S146239940501015X; Vol. 7; Issue 28; 9 December 2005