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## ***S. pyogenes* Infections and Its Sequelae**

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### **1. Introduction**

Suppurative streptococcal infections of the throat and the skin generate stimuli that lead Rheumatic fever (RF) in 1 to 5% of susceptible children. The disease manifests initially as polyarthritis, carditis/valvulitis, Sydenham's chorea, erythema marginatum and/or subcutaneous nodules. Chronic renal disease can also occur.

RF occurs at an early phase of life (3 to 19 years of age); thus, heart damage (carditis) can appear in very young children. Rheumatic carditis usually presents as pancarditis, affecting the endocardium, myocardium and pericardium. Recurrent acute cardiac lesions frequently evolve into chronic rheumatic heart disease (RHD), of which valvular deformities are the most important sequelae; these deformities lead to mitral and aortic regurgitation and/or stenosis. Valve replacement surgery is usually the only treatment for chronic RHD patients and incurs high costs for both public and private health systems.

Here, we will present three cases of young RHD patients who underwent valve replacement and the autoimmune reactivity that triggered the heart-tissue rheumatic lesions.

Post-streptococcal glomerulonephritis (PSGN) is another immune sequelae that presents a latency period of one to three weeks after scarlet fever, streptococcal pharyngitis and purulent skin infections.

PSGN has become a rare disease, especially in adults in developed countries, due to an improved standard of living, earlier treatment of pharyngeal infections and widespread use of antibiotics (Rodriguez-Iturbe & Musser, 2008). Despite decades of research, the pathogenesis of PSGN remains obscure. It is still unclear whether or to what extent autoimmune reactions are involved, but several studies have shown that different streptococcal antigens are detectable by immunohistology in the diseased kidneys (Rodriguez-Iturbe & Batsford, 2007). These data are in favor of direct contributions of streptococcal nephritogenic factors to PSGN pathogenesis, although intact bacteria have never been found in affected kidneys. Two PSGN cases will also be presented.

## 2. Epidemiology

### 2.1 Acute rheumatic fever

The incidence of ARF in some developing countries exceeds 50 cases per 100,000 children (Carapetis et al., 2005). The worldwide incidence of RHD is at least 15.6 million cases and is responsible for around 233,000 deaths / year. However, these estimates are based on conservative assumptions, so the true disease burden is probably substantially higher (Carapetis et al., 2005). The incidence of ARF can vary from 0.7 to 508 per 100,000 children per year in different populations from several countries (Carapetis et al., 2005). In Brazil, according to the WHO epidemiological model and data from IBGE (Brazilian Institute of Geography and Statistics), the number of Streptococcal pharyngitis infections is around 10 million cases, which could lead to 30,000 new cases of RF, of which around 15,000 could develop cardiac lesions (Barbosa et al., 2009).

### 2.2 Post-streptococcal glomerulonephritis (PSGN)

PSGN has become a rare disease, especially in adults in developed countries, due to an improved standard of living, earlier treatment of pharyngeal infections and widespread use of antibiotics (Rodríguez-Iturbe & Musser, 2008). However, the occurrence of acute post-infection glomerulonephritis (APIGN) has emerged as a major risk in diabetic patients all over the world (Nars et al., 2008).

The global incidence of acute PSGN was estimated at 472,000 cases per year, of which 456,000 occurred in less-developed countries (Carapetis, 2005). In agreement with these data, the incidence of PSGN ranges from 9.5 to 28.5 new cases per 100,000 individuals per year in developing countries (Rodríguez-Iturbe, 2008).

## 3. Autoimmunity is the major mechanism leading to both diseases

### 3.1 Rheumatic fever and rheumatic heart disease

The autoimmune reactions in RF and RHD are controlled by several genes related to both the innate and adaptive immune responses (Guilherme et al., 2011). Briefly, in the last 50 years, several genetic markers from different populations have been studied, and the susceptibility of developing RF/RHD was first associated with some alleles of HLA (human leukocytes antigens) class II genes (DRB1, DQB and DQA), which are located on human chromosome 6. HLA alleles are involved in antigen recognition by T lymphocytes through the T cell receptor (TCR). Later, some studies showed that the TNF- $\alpha$  gene, located in the same region of this chromosome was also associated with the disease. The TNF- $\alpha$  gene encodes the inflammatory TNF alpha protein, which is involved in the inflammatory process mediating heart-tissue lesions in RHD. Several other associations have been established based on gene variability by studying single nucleotide polymorphisms (SNPs). These genes code for other proteins also involved with the immune response (innate and adaptive pathways) (see Diagram 1) (Guilherme et al., 2011).

#### 3.1.1 Molecular mimicry

Molecular mimicry mediates cross-reactivity between streptococcal antigens and human proteins. Several autoantigens have been identified, including cardiac myosin epitopes, vimentin and other intracellular proteins.

Several streptococcal and human cross-reactive antibodies have been found in the sera of RF patients and immunized rabbits and mice over the last 50 years and have been recently

reviewed. Briefly, antibodies against N-acetyl  $\beta$ -D-glucosamine, a polysaccharide present in both the streptococcal cell wall and heart valvular tissue displayed cross reactivity against laminin, an extracellular matrix alpha-helical coiled-coil protein that surrounds heart cells and is also present in the valves (Cunningham, 2000; Guilherme et al., 2005).

Among human proteins, cardiac myosin and vimentin seem to be the major target antigens. By using affinity-purified anti-myosin antibodies, Cunningham's group identified a five amino acid residue (Gln-Lys-Ser-Lys-Gln) epitope of the N-terminal M5 and M6 proteins as cross-reactive with cardiac myosin (Cunningham et al., 1989).

Cunningham's group found that streptococcal and human cross-reactive antibodies upregulate the adhesion molecule VCAM-1 after binding to the endothelial surface, leading to inflammation, cellular infiltration and valve scarring (Gavin et al., 2000, Roberts et al, 2001). These data established the role of the heart-tissue cross-reactive antibodies (anti-cardiac myosin and laminin) in the early stages of inflammation and T cell infiltration in RHD lesions.

Studies performed in the last 25 years showed that CD4+ cells are the major effectors of autoimmune reactions in the heart tissue in RHD patients (Raizada et al., 1984; Kemeny et al., 1989; Guilherme et al., 1995). However, the role of T cells in the pathogenesis of RF and RHD was demonstrated through the analysis of heart-tissue infiltrating T cell clones (Guilherme et al., 1995). Immunodominant peptides of the M5 protein (residues 81-96 and 83-103) displayed cross-reactivity with valvular proteins and cardiac myosin peptides by molecular mimicry (Faé et al., 2006; Yoshinaga et al., 1995; Guilherme et al, 1995). These M5 epitopes were also preferentially recognized by peripheral T lymphocytes from RHD patients when compared with normal individuals, mainly in the context of HLA-DR7 (Guilherme et al., 2001). Analysis of the T cell receptors (TCR) of peripheral and intralesional T cells from RHD patients showed several antigen-driven oligoclonal T cell expansions at the site of heart-tissue lesions (Guilherme et al, 2000). These autoreactive cells are CD4+ and produce inflammatory cytokines (TNF $\alpha$  and IFN $\gamma$ ). IL-4+ cells are found in the myocardium; however, these cells are very scarce in the valve lesions of RHD patients. IL-4 is a Th2-type cytokine and plays a regulatory role in the inflammatory response mediated by Th1 cytokines. These findings indicate that the Th1/Th2 cytokine balance has a role in healing myocarditis, while the low numbers of IL-4-producing cells in the valves probably induced progressive and permanent valve damage (Guilherme et al, 2004).

Three cases of RHD patients (clinical, surgical data) will be presented. Histological and immunological data obtained from peripheral blood and T-cell lines and T cell clones derived from heart-tissue infiltrating T cells of these patients are summarized in Tables 1 and 2.

Patients	Mitral Valve					Myocardium (LA)	
	Inflammation	Rheumatic Activity	Neovasc	Fibrosis	Calcification	Inflammation	Rheumatic Activity
Case 1	(++)	AB-PR(+) VER(+)	(+)	(+)	(-)	AB-PR (+)	(+)
Case 2-	(+)	(-)	(-)	(++)	(-)	(-)	(-)
Case 3-							
1 <sup>st</sup> surgery						(+)	AB(-)
2 <sup>nd</sup> surgery	(+)					(+)	(-)

LA-left atrium; AB-PR- Achoff Bodies in proliferative phase; Ver- verrucae, (-) negative;(+) mild; (++) moderate

Table 1. Histological data of Rheumatic Heart Disease patients

	HLA Class II	Heart-tissue Infiltrating Cells/field		Antigens recognized by T cell clones from myocardium and/or mitral valve		
		CD4 <sup>+</sup>	CD8 <sup>+</sup>	M5 protein peptides	Myocardium derived- proteins	Valve derived proteins
Case # 1	15,7, 52, 53	9.4	3.3	M5 (81-96) M5 (83-103) M5 (163-177)	30-44 kDa; 24-30 kDa LMM25(1607-1624)	>150 kDa, 90-150 kDa; 65-90 kDa;43-65 kDa 30-43 KDa 90-150 kDa; 30-43 KDa
Case # 2	9, 11, 52,53	6.1	1.2	M5(11-25) M5 (81-96) M5 (83-103)		43-65 kDa 90-150 kDa, 43-65 kDa 90-150 kDa; 43-65 kDa
Case # 3	17, 13, 52,	4.5	0.9	M5 (83-103)	>150 kDa LMM10(1413-1430) LMM12(1439-1456)	90-150 kDa; 43-65 kDa; 30-43 KDa

Amino acid sequences of M5 protein were based on sequence published by Philips et al, 1981 and Manjula et al, 1985. M5 (81-96)-DKLKQQRDTLSTQKET; M5 (83-103)-LKQQRDTLSTQKETLEREVQN; M5-(163-177) ETIGTLKKILDETVK; cardiac myosin beta chain sequences published by Diederich et al, 1989: LMM 10 (1413-1430) CSSLEKTKHRLQNEIEDL; LMM12 (1439-1456) AAAAALDKKRNFDKILA; LMM25 (1607-1624) RSRNEALRVKKKMEGDLN, (Guilherme et al, 1995, Faé et al, 2006).

Table 2. T cells from heart-tissue of Rheumatic Heart Disease patients recognize streptococcal peptides and cardiac proteins.

### Case # 1

Male 4 years old, presented mitral, aortic and tricuspid regurgitation, left ventricular diastolic diameter of 51 mm and systolic diameter of 34 mm, ejection fraction (LVEF) of 78%, left atrium (LA) of 40 mm, thickened pericardium.

At surgery, mitral valve prolapse was observed with very long strings and small tears of rope. Mitral annulus was dilated. A mitral valve replacement was done. Heart biopsy showed chronic valvulitis with areas of mucoid collagen degeneration and papillary muscles with Aschoff nodules in the granulomatous stage (Table 1).

### Case # 2

Male 6 years old, presented clinical features of fever, polyarthritis and carditis with mitral valve involvement. On this occasion, patient showed evidence of inflammatory activity; Gallium 67 positive scintigraphy; endomyocardial biopsy suggestive of rheumatic carditis. A left ventricular diastolic diameter of 59 mm, left ventricular systolic diameter of 39 mm, ejection fraction (LVEF) of 71% and left atrium (LA) of 52 mm were observed. Two valve correction surgeries were performed. Pathological examination of the mitral valve showed sequelae of chronic valvulitis with intense fibrosis and mucoid degeneration.

### Case #3

Male 10 years old, presented clinical features of fever, polyarthritis and carditis with progressive cardiac heart failure and mitral and aortic shortcomings as well as relapses of acute outbreak by irregular use of secondary prophylaxis with benzathine penicillin and progression to chronic atrial fibrillation, culminating in death at 18 years of life. Increased

left ventricular diastolic diameter (67/43 mm) and left atrial diameter of 62 mm, significant mitral regurgitation, aortic insufficiency and moderate impact tricuspid regurgitation with mild rebound were found. Subjected to two surgeries, first for mitral valve repair and prosthetic aortic and tricuspid valves, then for exchange of the mitral and aortic bioprostheses, and tricuspid valve repair.

### 3.2 Post Streptococcal Glomerulonephritis (PSGN)

Acute glomerulonephritis can occur sporadically or endemically as a result of infections of both the upper airways and skin by group A streptococcus strains.

Genetic susceptibility factors are likely involved with the development of the disease. HLA class II alleles (DR4 and DRB1\* 03011) have been found to be associated with PSGN compared to healthy controls. Genetic association with endothelial nitric oxide synthase intron 4 a/b (eNOSa/b) defined by variable numbers of tandem repeats (VNTR) polymorphism was also described (Ahn & Ingulli, 2008).

The disease is mediated by immune complexes and complement pathway activation. Several theories seek to explain the formation of immune complexes in glomeruli. The most accepted one is that a streptococcal antigen, with affinity for the glomerular structures, can be deposited in the glomerulus, activating the host immune response and initiating development of immune complexes *in situ* (Rodriguez-Iturbe & Bastford, 2007).

Apparently, molecular mimicry between streptococcal antigens and glomerular proteins leads to tissue damage. Two antigens have been investigated as potential causes of PSGN: the plasmin receptor linked to nephritis (NAPlr), identified as glyceraldehyde 3-phosphate dehydrogenase, and a protein known as streptococcal pyrogenic exotoxin B (SpeB). Both are present in renal biopsies of patients with PSGN and are capable of activating the alternative pathway of the complement system. In addition, they are capable of promoting enhanced expression of adhesion molecules, facilitating inflammatory reactions mediated by cytokines (IL-6, TNF  $\alpha$ , IL-8 and TGF  $\beta$ ). It seems that the nephritogenic properties of NAPlr and SpeB are related to the binding ability of plasmin, which facilitates the deposition of immune complexes (IgG and C3, properdin and C5) in the glomeruli and subsequent inflammation (Rodriguez-Iturbe & Bastford, 2007; Rodriguez-Iturbe & Musser, 2008).

Molecular mimicry, as mentioned above, leads to the recognition of streptococcal antigens and laminin, collagen and glomerular basement membrane (GBM). Sub-epithelial localization of immune complexes and complement factors in the injured glomeruli points towards a crucial role of the host immune system in tissue destruction.

As mentioned before, renal inflammation may result from a myriad of insults and is often characterized by the presence of infiltrating inflammatory leukocytes within the glomerulus or tubular interstitium. Accumulating evidence indicates that infiltrating leukocytes are the key to the induction of renal injury.

Two cases of PSGN are presented in which anti-streptolysin O (ASO) was positive, indicating a previous infection by *S. pyogenes*.

#### Case #1

Male 6 years old, presented swollen eyes followed by bilateral periorbital edema followed by progression of lower limb edema and increased abdominal size, decreased urine volume and urine darkness. Lab tests detected hematuria, increased serum levels of urea (63.0 mg/dl) and creatinine (1.2 mg/dl). Decreased levels of complement (16.1 mg/dl) and fractions C3 and C4 (both 11.7 mg/dl) were found. The patient also presented increased levels of ASO (1055 IU).

**Case # 2**

Male 15 years old, presented edema, hypertension, and gross hematuria and reported a skin abscess in the left leg 20 days before hospital admission. No previous signs of disease or significant co-morbidities were identified. Physical examination showed a 2+ lower edema, with no signs of current skin infections. Laboratory tests revealed 24 hr urine protein 2.4 g/day, serum creatinine 2.9 mg/dl, hematuria, and positive ASO (> 200 IU). Renal ultrasound showed normal kidneys. After introducing antibiotic and controlling edema and hypertension with diuretics and anti-hypertensive drugs, the patient was subjected to a renal biopsy that showed a diffuse proliferative pattern, with focal endocapillary and mesangial proliferation with no cellular crescents.

#### 4. Frequencies of *S. pyogenes* strains collected at Clinical Hospital of the School of Medicine of the University of Sao Paulo

Diverse *S. pyogenes* strains are related with the development of RF/RHD or PSGN and are considered as rheumatogenic and nephritogenic, respectively.

We analyzed 177 samples obtained from diverse biological sources. Most samples were recovered from blood, throat and wound (Table 3).

Source	n <sup>o</sup> of cases	Strains identified									
		<i>emm1</i>	<i>emm87</i>	<i>emm22</i>	<i>emm12</i>	<i>emm77</i>	<i>emm6</i>	<i>emm75</i>	<i>emm89</i>	<i>st2904</i>	others
Throat	30	6	-	5	1	-	2	1	-	2	13
Blood	58	10	6	3	7	5	3	2	1	-	21
Wound	15	3	2	-	-	-	-	-	1	2	7
Sputum	8	2	-	1	-	2	1	-	-	-	2
Surgical wound	5	-	-	1	1	1	-	-	-	-	2
Ascitis	3	-	-	-	-	-	-	1	-	-	2
Catheter	3	-	-	1	-	-	-	-	-	-	2
Lymph node	3	1	2	-	-	-	-	-	-	-	-
Ocular discharge	3	2	-	-	-	-	-	-	-	-	1
Synovial fluid	2	2	-	-	-	-	-	-	-	-	-
Liquor	2	1	-	-	-	-	-	-	1	-	-
Others	11	3	2	-	-	1	-	1	1	-	3

Table 3. Distribution of *emm* types according to biological source.

The M1 type was more frequently observed. Figure 1 shows the frequencies of all strains analyzed. Our results are similar to those previously published (Table 4). It is interesting to note that studies done by Schulman et al., 2004 and Ma et al., 2009 showed variability of frequencies for some streptococcus strains over different periods, probably due to seasonal influence.

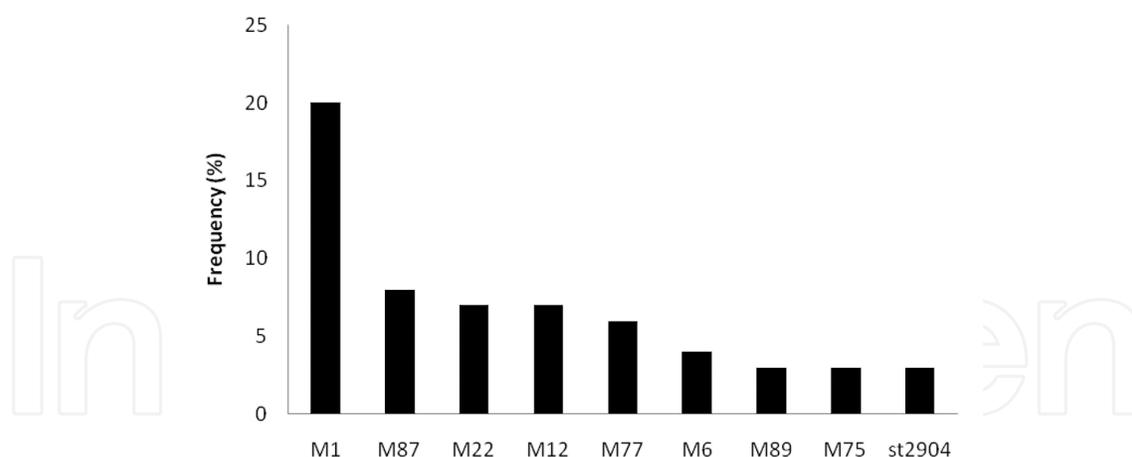


Fig. 1. Prevalence of the M types in a sample from São Paulo Beta-hemolytic samples (177) obtained from diverse biological sites at the Clinical Hospital, University of Sao Paulo during the period of 2001-2008.

Country	Year	N° isolates	N° of <i>emm</i> types identified	Source	More frequent <i>emm</i> types	References
Germany	2003-2007	586	49	invasive	1, 28, 3, 12, 89, 4, 77, 6, 75, 11, 118, 2, 83	Imöhl et al., 2010
United States	1995-1999	1586	17	invasive	1, 28, 12, 3, 11, 4, 114, 89, 17, 77, 33	O'Brien et al., 2002
North America	1 <sup>nd</sup> -2000-2001 2 <sup>nd</sup> -2001-2002	1 <sup>nd</sup> -975 2 <sup>nd</sup> - 1076	1 <sup>nd</sup> -29 2 <sup>nd</sup> - 31	Non invasive	1 <sup>nd</sup> -12, 1, 28, 4, 3, 2 2 <sup>nd</sup> - 1, 12, 4, 28, 3, 2	Schulman et al., 2004
Barcelona	1999-2003	126	29	invasive and non invasive	1, 3, 4, 12, 28, 11, 77	Rivera et al., 2006
Sweden	1986-2001	92	28	invasive and non invasive	1, 2, 4, 8, 12, 28, 66, 75	Maripuu et al., 2008
Australia	2001-2002	107	22	invasive and non invasive	1, 4, 12, 28, 75	Commons et al., 2008
Hungary	2004-2005	26	8	invasive	1, 80, 4, 28, 66, 81.1, 82, 84	Krucsó et al., 2007
China	1 <sup>nd</sup> -1993-1994 2 <sup>nd</sup> -2005-2006	1 <sup>nd</sup> -137 2 <sup>nd</sup> -222	1 <sup>nd</sup> -24 2 <sup>nd</sup> - 9	invasive and non invasive	1 <sup>nd</sup> -3, 1, 4, 12, st1815, 6 2 <sup>nd</sup> 12, 1	Ma et al., 2009
Denmark	2003-2004	278	29	invasive	28, 1, 3, 89, 12	Luca-Harari et al., 2008
Norway	2006-2007	262	29	invasive	28, 1, 82, 12, 4, 3, 87, 89, 6	Meisal et al., 2010

Two studies were reported for North America and China.

Table 4. Distribution of *emm* types around the world

*S. pyogenes* - Infections

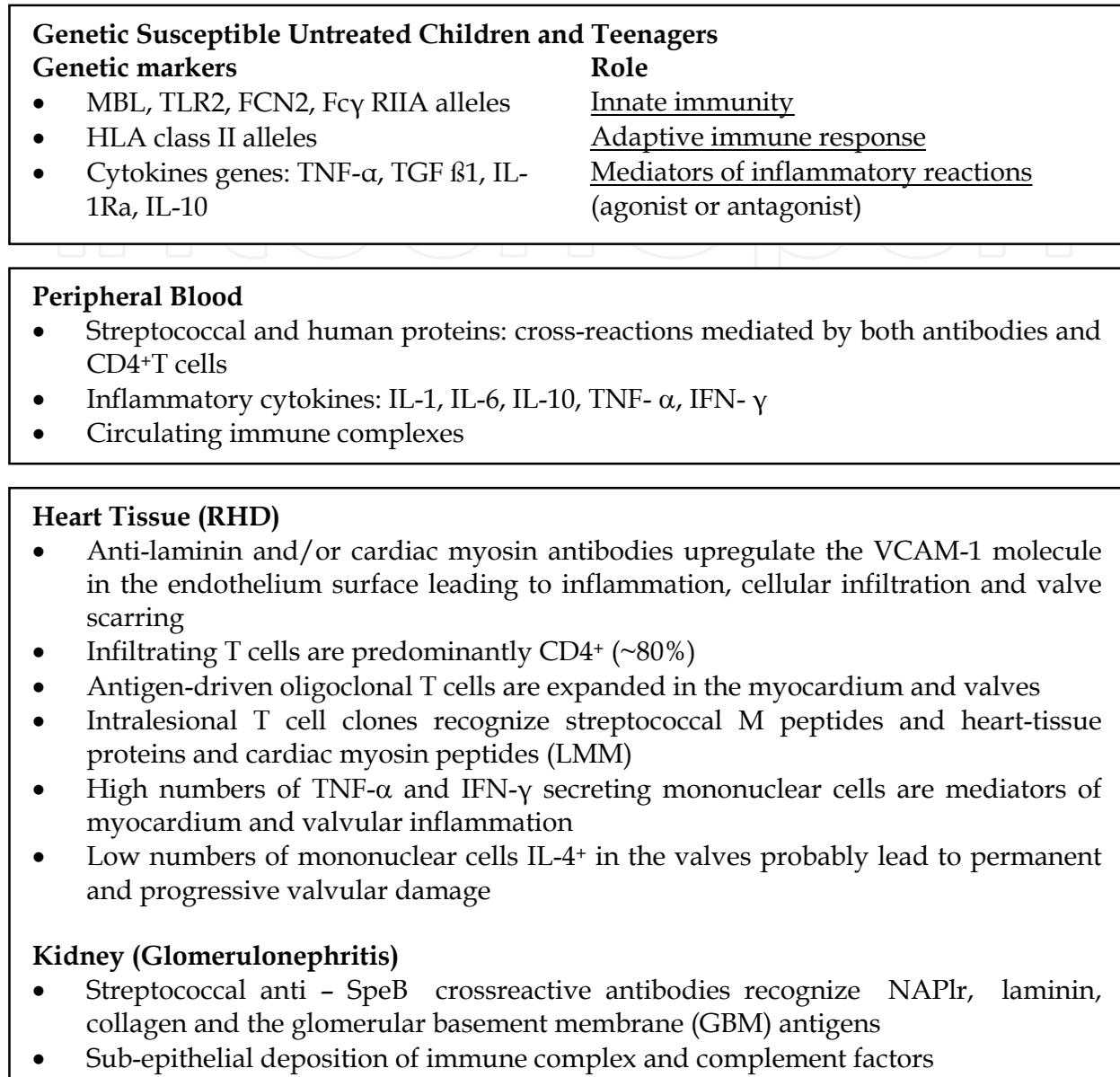


Diagram 1. Major events leading autoimmune reactions on both RHD and Glomerulonephritis

## 5. Prospective vaccines against *S. pyogenes*

Many studies have focused on developing a vaccine against *S. pyogenes* in order to prevent infection and its complications. There are four anti-group A streptococci (GAS) vaccine candidates based on the M protein and eight more candidates based on other 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 (Steer et al, 2009).

We developed a vaccine epitope (StreptInCor) composed of 55 amino acid residues of the C-terminal portion of the M protein that encompasses both T and B cell protective epitopes

(Guilherme et al, 2006). The structural, chemical and biological properties of this peptide were evaluated, and we have shown that StreptInCor is a very stable molecule, an important property for a vaccine candidate (Guilherme et al, 2011). Furthermore, experiments with mice showed that this construct is immunogenic and safe (Guilherme et al, 2011).

## 6. Conclusions

The knowledge acquired in the last 25 years pointed out the molecular mimicry mechanism as one of the most important leading autoimmune reactions in RHD and PSGN. Although both diseases are triggered by *S. pyogenes*, RHD is mediated by both antibodies and T cells while PSGN is mainly due to immune complex deposition in the glomeruli.

Several streptococcal cross reactive autoantigens were identified in both diseases.

Many proteins and cardiac myosin epitopes were identified as putative cross-reactive autoantigens in RHD and collagen, glomerular basement membrane in PSGN. Laminin, another autoantigen is also involved in the cross reactivity in both diseases.

Diagram 1 illustrates the major events leading to RHD and PSGN.

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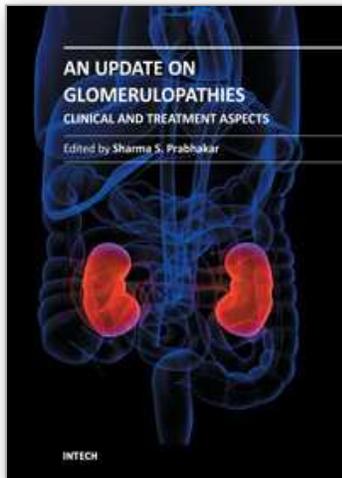
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## **An Update on Glomerulopathies - Clinical and Treatment Aspects**

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An Update on Glomerulopathies - Clinical and Treatment Aspects is a systemic overview of recent advances in clinical aspects and therapeutic options in major syndromes of glomerular pathology. The book contains twenty four chapters divided conveniently into five sections. The first section deals with primary glomerulopathies, and the second section is devoted to glomerulopathies complicating infectious conditions. The third section deals with systemic autoimmune disorders and vasculitides which constitute major causes of glomerular disease and often renal failure. The fourth section includes chapters discussing the glomerular involvement in some major metabolic and systemic conditions. The final section has chapters which relate to some general aspects of glomerular diseases. This book will form an excellent reference tool for practicing and academic nephrology community.

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