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Host-Pathogen Interactions in Streptococcal Immune Sequelae

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Abstract Otherwise uncomplicated infections with *Streptococcus pyogenes* can cause two insidious immune sequelae known as post-streptococcal glomerulonephritis (PSGN) and acute rheumatic fever (ARF). These diseases follow with a latency of a few weeks or months after primary infection and are responsible for high mortality and morbidity. PSGN has also been linked to infections with group C streptococci of the species *S. equi* ssp. *zooepidemicus* (SESZ). Moreover, there are some indications that infection with group C and G streptococci (GCGS) of the subspecies *Streptococcus dysgalactiae* ssp. *equisimilis* (SDSE) leads to ARF. Despite decades of research, the picture of the molecular pathogenesis of streptococcal immune sequelae resembles a jigsaw puzzle. Herein we try to put some of the puzzle bits together that have been collected until now.

1 Introduction

More than 15 million people worldwide suffer from consequences of the severe immune sequelae post-streptococcal glomerulonephritis (PSGN) and acute rheumatic fever (ARF). They are caused by mild but inadequately treated infections with pyogenic streptococci. ARF and PSGN claim 350,000 human lives every year (Carapetis et al., 2005). Approaches to combat these immune sequelae include the development of streptococcal vaccines for prevention of the causative infections and of diagnostic tests for early detection of these infections. For both approaches, profound information on the causative streptococci is indispensable. A wide-ranging knowledge about the factors and processes that trigger and drive the pathogenesis of PSGN and ARF is a further support and may deliver novel ideas for preventive and therapeutic approaches. The present article is a summary of the current knowledge on the etiology and pathogenesis of the aforementioned diseases.

2 *Post-Streptococcal Glomerulonephritis*

2.1 *Characteristics of PSGN*

The immune sequela PSGN follows with a delay of one to three weeks after skin infections, pharyngitis or scarlet fever caused by *S. pyogenes* (Dick and Dick, 1983; Futcher, 1940; Lyttle et al., 1938). Infections with SESZ typically occur as outbreaks. Such outbreaks can be followed by a wave of PSGN cases, which proves the nephritogenic potential of this group C streptococcal species (Balter et al., 2000; Barnham et al., 1983; Duca et al., 1969; Francis et al., 1993). The molecular pathogenesis of PSGN is still elusive. Deposition of immune complexes that contain streptococcal components, aberrant complement reactions, autoimmunity and other injurious cellular immune responses are suspected causes of this severe disease that affects the kidney (Chhatwal and Graham, 2008).

Examination of the diseased glomeruli by electron microscopy revealed characteristic electron-dense structures on the luminal site of the glomerular capillary basement membrane, called sub-epithelial “humps” (Cochrane, 1971; Fish et al., 1966). Streptococcal antigens, complement factors and immunoglobulin have been localized in these humps. This indicates formation of immune complexes, hence crucial contributions of the host immune system to PSGN pathogenesis (Andres et al., 1966; Batsford et al., 2005). Potential causes for glomerular damage comprise autoimmunity against components of the basement membrane of capillary walls, deposition of immune complexes due to anti-IgG autoantibodies and antibodies that react against streptococcal proteins. Moreover, it has been suggested that plasminogen binding and activating proteins may take part in the pathogenesis of glomerulonephritis (Rodriguez-Iturbe and Batsford, 2007).

2.2 *Role of Complement in PSGN*

Concentrations of complement factors are strongly reduced in the blood of patients with PSGN. This condition, called hypocomplementemia, indicates the activation and consumption of the complement system during disease (Dedeoglu et al., 1996). Mice that lack complement factor 1 subunit q (C1q) k.o.-mice develop glomerulonephritis that resembles PSGN, pathohistologically. Proliferation of cells in the Bowman’s space and electron-dense sub-endothelial and sub-epithelial depositions occur in the affected glomeruli (Botto et al., 1998). Observation of sub-epithelial depositions in the C1q-deficient mice suggests that deficiencies in the complement system cause the sub-epithelial humps in PSGN and contribute to the pathogenesis of this immune disease. This is contradictory to the localization of complement

factors in the humps, which indicates activity of the complement system in the affected tissue rather than diminished response (Rodriguez-Iturbe and Batsford, 2007). Similar to sub-epithelial humps in PSGN, glomerular depositions in the C1q deficient mice contained complement factor 3 (Botto et al., 1998), indicating activity of the lectin or alternative pathway of complement. The precise role of complement reactions in the pathogenesis of PSGN remains a matter of investigation.

2.3 Factors Involved in PSGN

Immunohistochemistry has localized a variety of different streptococcal antigens in the glomeruli of PSGN patients (Batsford et al., 2005; Michael et al., 1966; Ohkuni et al., 1983; Seegal et al., 1965; Treser et al., 1970; Villarreal et al., 1979). The foci of streptococcal infections that cause PSGN are distant from the kidney. Therefore, glomerular deposition of streptococcal antigens is evidence for blood borne bacteria or bacterial components. These foreign antigens are not efficiently cleared by the immune system and may be the triggers of PSGN pathogenesis. Notably, intact bacteria have never been found in renal tissue affected by PSGN.

The glyceraldehyde-3-phosphate-dehydrogenase of *S. pyogenes* has been suggested as a candidate nephritogenic protein, under the name nephritis-associated plasminogen receptor (NAPlr). As a major glycolytic enzyme, it is present in all strains and species of the genus *Streptococcus*. Although having an important intracellular metabolic function, a fraction of NAPlr is released into the extracellular space. There it binds back to the streptococcal surface and serves as a receptor for plasmin(ogen) (Pancholi and Fischetti, 1993). Although NAPlr is a trigger of the alternative complement pathway (Yoshizawa et al., 2004) it does not co-localize with complement and immunoglobulin deposits in glomeruli of PSGN patients. Therefore, activation of plasmin(ogen) by NAPlr is a more likely mode of action in PSGN pathogenesis than activation of the complement system by this bacterial protein (Oda et al., 2005). Homologues of NAPlr are also present on the surface of commensal oral streptococci, which also bind and activate plasmin(ogen) (Itzek et al., 2010; Jones and Holt, 2004). Transient bacteremia with oral streptococci is frequent in humans (Daly et al., 1997; Roberts et al., 1997; Westling et al., 2002), but not associated with PSGN. The features that distinguish NAPlr of *S. pyogenes* from other streptococcal glyceraldehyde-3-phosphate-dehydrogenases remain to be identified and may shed light on a possible role of NAPlr in PSGN.

Only a few *S. pyogenes* strains lack the streptococcal cysteine proteinase SpeB (Darenberg et al., 2007; Schmitz et al., 2003; Vlamincx et al., 2003), which is another suspected nephritogenic factor. SpeB and its zymogen zSpeB interact with plasminogen. Other than NAPlr, SpeB co-localizes with complement factor 3 and IgG in the sub-epithelial humps of glomeruli that are affected by PSGN (Batsford et al., 2005; Rodriguez-Iturbe and Batsford, 2007). The cationic character of SpeB and zSpeB is thought to allow the transmigration of these molecules from the blood through the glomerular basement membrane, which is followed by deposition of the proteins on the sub-epithelial side and development of nephritis (Vogt et al., 1983). On one hand this hypothesis is supported by examinations on kidney biopsies and anti-SpeB serum titers of PSGN patients (Cu et al., 1998; Parra et al., 1998). On the other hand a SESZ strain that caused an epidemic of PSGN in Nova Serrana, Brazil (Balter et al., 2000; Beres et al., 2008), lacks SpeB. Hence, alternative pathogenicity factors exist that cause PSGN. The chain of evidence for SpeB as a nephritogenic molecule is not yet closed.

2.4 Correlation of M Types with PSGN

The nephritogenic potential of *S. pyogenes* strains correlates with certain M-types such as M1, 2, 4, 12, 18, 25, 49, 55, 57, and 60 (Stollerman, 1969). As one of the type-specific genes the

M protein itself may be involved in the pathogenesis of PSGN. Released from the bacterial surface by the actions of bacterial and host proteases like SpeB or neutrophil elastase, M protein forms insoluble aggregates with the plasma protein fibrinogen (Berge and Björck, 1995; Herwald et al., 2004). When injected into mice, the M protein binds and precipitates in the glomeruli (Kantor, 1965; Kaplan, 1958) and causes renal lesions that could be nephritogenic (Humair et al., 1969). Notably, M-like proteins exist in SESZ, including the outbreak associated strain MGCS10565 (Beres et al., 2008) and may add to the nephritogenic potential of this species.

Serological examinations on PSGN patients suggest protein SIC (streptococcal inhibitor of complement-lysis) as a nephritogenic factor (Skattum et al., 2006; Sriprakash et al., 2002). Presence of genes that code for protein SIC or its variant DRS is limited to *S. pyogenes* strains of nephritogenic M-types like M1, 12, 55 and 57 (Hartas and Sriprakash, 1999), which supports the notion that they are nephritogenic factors. SIC binds to complement factors that form the membrane attack complex, preventing its assembly (Åkesson et al., 1996). However, it is not yet known how this property or other host-interactions of SIC or DRS may cause PSGN. SIC or similar proteins have not been found in SESZ.

Out of the variety of potential nephritogenic factors that have been under investigation, so far there is none that can be considered as the sole nephritogenic factor. Despite that many of the suspected nephritogens accumulate in the kidney of laboratory animals, leading to glomerular injury, none of the factors alone was capable to evoke a disorder that resembled PSGN, sufficiently. Moreover, some of the factors do not occur in SESZ. The repertoire of host-pathogen interactions that leads to PSGN is not yet uncovered.

3 Acute Rheumatic Fever and Rheumatic Heart Disease

3.1 Characterization of ARF

Autoimmune responses caused by an untreated or insufficiently treated *S. pyogenes* pharyngitis cause acute rheumatic fever (ARF) with a latency period of 1 to 4 weeks. The molecular and immunological processes that drive the pathogenesis of this disorder and subsequent rheumatic heart disease (RHD) have been partially discovered. (Carapetis et al., 2005; Cunningham, 2012; Dinkla et al., 2003; Guilherme et al., 2006; McCarty, 1956; Stollerman, 1969; Tontsch et al., 2000; Wannamaker, 1973). The diagnostic criteria for ARF are referred to as the major Jones criteria and include arthritis, erythema, carditis and neurological dysfunctions (chorea) (Keitzer, 2005). About a third of the patients develop RHD, leading to irreversible damage to the heart valves that requires surgical intervention. Most of the patients with ARF are children, adolescents and young adults. Globally, about 1 per 1000 people is suffering from ARF or RHD with some geographic regions and specific communities being particularly affected (Carapetis et al., 2005; Chhatwal and Graham, 2008; Cunningham, 2000). Certain humans appear particularly prone to contract ARF as indicated by associations with genetic markers such as major histocompatibility complex (MHC) antigen phenotypes (for references see (Cunningham, 2000)). In addition to host susceptibility, differences in medical care and the socioeconomic conditions are influencing the epidemiology of ARF.

3.2 Role of Humoral Immunity in ARF

Elevated titers of autoantibodies in the sera of ARF/RHD patients (Carapetis et al., 2005; Dinkla et al., 2007; Dinkla et al., 2003; Guilherme et al., 2006) and deposition of immunoglobulin and complement in the affected hearts (Kaplan et al., 1964) indicate that humoral immunity is crucially involved in ARF pathogenesis. Moreover, the early processes in rheumatic carditis involve cellular immune responses. Elevated numbers of T-lymphocytes and

macrophages occur in the cellular infiltrates that are observed in myocardial lesions of affected hearts (Cunningham, 2003; Guilherme et al., 2006; Roberts et al., 2001). The inflammation that takes place in those patients and is characterized by increased numbers of mature circulating T helper cells (CD4⁺ T-cells), elevated levels of cytokines such as IL-1 and IL-2, IFN γ , TNF- α and higher amounts of receptors for these cytokines (Guilherme et al., 2006). In summary, ARF is caused by destructive immune responses and inflammation that are not sufficiently suppressed after infection.

3.3 Streptococcal Factors in ARF

Several streptococcal factors such as superantigens, group A carbohydrate, hyaluronic acid capsule and M proteins have been suspected to trigger the autoimmunity in ARF. During acute infection superantigens act as toxins that contribute to Streptococcal toxic shock like syndrome because they are triggers of exaggerated inflammation (Eriksson et al., 1999; Kotb, 1995; Sriskandan et al., 1996; Stevens et al., 1989; Yu and Ferretti, 1989). Moreover, they exert mitogenic activity on T-lymphocytes that may crucially influence the development of destructive autoimmunity in response to streptococcal infection. By means of specific interactions, superantigens bridge the MHC class II proteins of antigen presenting cells with the variable V β -region of the T-cell receptor independent of a presented antigen. In response to that, a T-cell population that carries matching V β -regions, will be activated and release pro-inflammatory cytokines. Interaction of co-receptors CD28 or LFA-1 on T-cells with the suiting ligands B7 or ICAM-1, respectively on antigen presenting cells stimulate a polyclonal expansion of the activated T-cells. In absence of these co-stimulating interactions, the activated T-cells fall into anergy or apoptosis. As a consequence selection for a certain T-cell population takes place. Depending on further co-stimulatory interactions, activated T-cells can stimulate B-cell maturation to plasma cells and ensuing secretion of a set of polyclonal immunoglobulins. In summary, superantigens can expand certain polyclonal populations of lymphocytes while driving others into anergy or apoptosis. If this combines with a break of tolerance the patient may produce defined populations of auto-reactive cells (for references see (Kotb, 1995; Proft and Fraser, 2003)). If and how this is generating the autoimmunity against articular, neural and cardiac tissue that is seen in ARF/RHD is not yet studied in depth.

As indicated by the deposition of immunoglobulin and complement factors in the diseased heart, humoral immune reactions participate in ARF pathogenesis (Kaplan et al., 1964). Autoimmune responses against several host proteins such as cardiac myosin, heart valve glycoproteins and antigens of the sarcolemma membrane occur in ARF or RHD patients (Carapetis et al., 2005; Goldstein et al., 1968; Guilherme et al., 2006; Tontsch et al., 2000; Wannamaker, 1973). Cross-reactivity of the autoantibodies with streptococcal cell wall carbohydrates, the cell membrane or the M protein was demonstrated (Kaplan and Suchy, 1964; Zabriskie and Freimer, 1966). In 1968 Goldstein and colleagues isolated glycoproteins from the heart valve that contained N-acetylglucosamine (GlcNAc) and share epitopes with the streptococcal group A carbohydrate that contains the same monosaccharide unit (Goldstein et al., 1968). Antibodies that reacted with group A carbohydrate circulated in patients with rheumatic valvular disease implicating their role in the pathogenesis of this disorder (Dudding and Ayoub, 1968). Notably, monoclonal antibodies against GlcNAc could be isolated from ARF that cross-reacted between human and streptococcal peptide antigens (Adderson et al., 1998). As a monosaccharide subunit in N-glycosylated proteins and glycosaminoglycans, such as the hyaluronic acid, GlcNAc is ubiquitous in the host's extracellular matrix and part of the surrounding matrix (calyx) of virtually all cells. It is also located on the surface of erythrocytes. Thus, autoimmune responses against GlcNAc may be causative for the early, less specific symptoms in ARF.

3.4 Role of Collagen in ARF

S. pyogenes isolates of M type 18, which were thickly encapsulated with hyaluronic acid, caused an ARF outbreak in Utah (Veasy et al., 2004). Hyaluronic acid is not only produced by the bacteria. It is abundant in the host's extracellular matrix. Therefore, the *S. pyogenes* capsule was suspected to cause autoimmunity. Some polysaccharide antigens may activate specific B-cells, because their repetitive epitopes can crosslink B-cell receptors (Vos et al., 2000). Although it remains speculative, hyaluronic acid may be one of those polymeric antigens. In connection with a break of tolerance, which could be caused by streptococcal triggers of inflammation such as superantigens, the clonal expansion and maturation of the B-lymphocytes may lead to prolonged autoimmune responses against this carbohydrate and maybe disease. More recent work suggests that the hyaluronic acid capsule binds and aggregates collagen on the streptococcal surface, evoking the production of collagen autoantibodies (Dinkla et al., 2003). Hyaluronic acid is also produced in high quantities by SESZ (Chong et al., 2005; Woolcock, 1974), but there is no evidence for a rheumatogenic potential of this species. The isolated hyaluronic acid alone, either from animal tissues or from SESZ, seems not sufficient to trigger disease, since it is widely used as cosmetic filler with a low risk for immune complications.

Some of the vaccines that are currently under development are designed to exploit the immune responses against M protein that protect humans against reinfection with streptococci of the same or a cross-reacting M-type (Bauer et al., 2012; Dale et al., 2011; Steer et al., 2009). This is complicated by severe side effects of this streptococcal surface antigen that seem to be caused by autoimmunity. After a vaccination trial with M protein type 3 three out of 21 human vaccinees developed ARF or ARF-like symptoms (Massell et al., 1969). M3 is a collagen-binding M protein (Dinkla et al., 2003).

M proteins oligomerize via long α -helical coiled-coil regions to form extended thread-like molecules on the streptococcal surface (Fischetti et al., 1990; Phillips et al., 1981). This structural feature is also found in several host proteins such as α -keratin, human heart myosin and laminin and gives rise for immunological cross-reactivity known as molecular mimicry (Anonymous, 1979; Blank et al., 2007): This mimicry is considered as one of the triggers for the destructive immune responses in ARF (Cunningham, 2012; Guilherme and Kalil, 2010). As compared to healthy individuals, the blood of ARF/RHD patients contains higher concentrations of these cross-reactive antibodies (McCormack et al., 1993). Notably, the autoantibodies from ARF patients differ in reactivity from anti-cardiac antibodies in postcardiotomy or heart failure patients. This may reflect that the autoimmunity in ARF is the cause for the cardiologic symptoms, while in the other two patient groups autoantibodies are a sequel of cardiac damage (Zabriskie, 1967). Monoclonal antibodies derived from ARF/RHD patients were poly-reactive, binding to M-protein, aforementioned human coiled-coil proteins as well as GlcNAc (Cunningham, 2000). Antibodies with a similar reactivity against those human and bacterial antigens were raised in mice by injection of *S. pyogenes* (Cunningham et al., 1984; Cunningham and Russell, 1983). Human and murine poly-reactive antibodies with myosin cross-reactivity, as suggested by their cytotoxicity and tissue localization, appear to contribute to the pathogenesis of carditis in ARF (Cunningham, 2000). Myosin cross-reactive antibodies recognize epitopes in M proteins M5, 6 and 19 (Bronze et al., 1988; Cunningham et al., 1989; Dale and Beachey, 1985; Dale and Beachey, 1985; Dale and Beachey, 1986). Further support for a role of molecular mimicry of M protein in ARF is the isolation of reactive T-cell clones that cross-react between M5 protein and cardiac myosin from myocardial and valvular lesions of RHD patients (Fae et al., 2006). Taken together there is a considerable body of evidence for molecular mimicry as a cause for autoimmunity that leads to ARF (Cunningham, 2012; Guilherme and Kalil, 2010).

3.5 Octapeptide PARF and its Role in ARF

Alternatively, M proteins trigger autoimmune response by a mechanism that requires binding of collagen (Barroso et al., 2009; Dinkla et al., 2007; Dinkla et al., 2003). The rheumatogenic M protein of type 3 (Stollerman, 1969) that caused ARF and ARF-like symptoms in vaccinees (Massell et al., 1969), binds collagens to the streptococcal surface and causes their aggregation (Dinkla et al., 2003). This interaction, which occurs with collagen of types I to IV, has been observed in different types of M proteins including M proteins of SDSE. It depends on an (A/T/E)XYLXX(L/F)N octapeptide motif that is located in the N-terminal type-specific part of the M protein (Fig. 1) (Barroso et al., 2009; Dinkla et al., 2007; Reißmann et al., 2012) and contributes to acute infections by facilitating streptococcal colonization of the ECM (Dinkla et al., 2003; Nitsche et al., 2006). When injected into mice, M3 protein and other collagen-binding M proteins that carry the (A/T/E)XYLXX(L/F)N motif trigger production of anti-collagen IV antibodies. Collagen IV, as a major component of basement membranes, is localized underneath the endothelium that lines the heart valves. Thus, it is a potential target of the autoimmune responses that lead to or aggravate valvular damage. These collagen autoantibodies were also found in increased levels in ARF and RHD patients as compared to healthy individuals (Dinkla et al., 2007; Dinkla et al., 2003). Therefore, the collagen binding octapeptide motif was named PARF, which is the acronym for peptide associated with rheumatic fever (Dinkla et al., 2007). The increase of collagen autoimmunity occurs early during acute pharyngitis before the onset of ARF, which indicates that the collagen autoimmune response is causative for the sequelae rather than a consequence of the tissue destruction in ARF and RHD (Dinkla et al., 2003) (see Fig. 1).

Collagen autoantibodies produced in response to PARF positive collagen binding M proteins do not cross-react with the M protein. This indicates that the immune reactions against collagen in ARF/RHD, other than myosin-directed autoimmunity, are not caused by molecular mimicry. The collagen-binding M protein alters the presentation of the autoantigen in a hitherto uncharacterized way, leading to a break of tolerance (Dinkla et al., 2007; Dinkla et al., 2003). The altered presentation of collagen to the immune system could be caused by the interaction with streptococcal M protein; the underlying principle of PARF-dependent collagen autoimmunity may be a “conformeropathy” such as the Goodpasture’s syndrome, a collagen IV autoimmune disease that affects lung and kidney (Chan et al., 2011). In Goodpasture’s syndrome a conformational change in the non-collagenous domain NC1 of collagen IV leads to exposure of epitopes that evokes the production autoantibodies against the glomerular basement membrane. This causes an autoimmune glomerulonephritis with histological features that differ from PSGN (Chan et al., 2011; Rodriguez-Iturbe and Batsford, 2007).

Globally, streptococcal *emm*-types that possess collagen-binding M proteins with PARF motif had a high epidemiological relevance. Based on a world-spanning meta-analysis of *emm*-typing studies (Steer et al., 2009) type 3 is of particular relevance, amounting to 7% of the *S. pyogenes* isolates (Reißmann et al., 2012). Only M proteins with the PARF motif are shown to endow streptococci with a high binding capacity for a variety of collagens, including collagen IV. However, high affinity interaction has also been observed between M1 protein and collagens I and VI. This potential adhesin had only low affinity for the basement membrane collagen IV (Bober et al., 2011) and binds collagen VI via the non-collagenous region of this connective tissue protein. This suggests principal mechanistic differences as compared to the interaction between collagen and PARF. Thus, it remains unexamined whether M1 and other PARF-negative collagen-binding M proteins are able to trigger a collagen autoimmune response. If they do, the epidemiological relevance of collagen-binding M proteins and collagen autoimmunity in the pathogenesis of ARF and RHD may be even higher than indicated by the previous estimates (Reißmann et al., 2012).

M protein based vaccines generate serotype specific immune responses that protect the vaccinee against streptococcal infection and in spite of the ARF-like side effects that were observed in trials with M3 proteins (Massell et al., 1969), such vaccines are still under development (Bauer et al., 2012; Dale et al., 2011; Steer et al., 2009). Available data give rise to concerns. Vaccine antigens that contain a PARF motif may cause autoimmune disease (Dinkla et al., 2007; Dinkla et al., 2003). This obstacle may be overcome by well-chosen point mutations that inactivate the collagen binding motif, but do not affect the vaccine epitopes, which induce protective immune responses against streptococcal infection.

Continued research on the various processes and factors that cause the destructive immune responses will not only improve our understanding of ARF pathogenesis. It may also pave the way for a safe vaccine against the causative streptococci.

4 On the Role of *S. dysgalactiae* ssp. *equisimilis* in Acute Rheumatic Fever

In most if not all of the studies that determined the streptococcal subspecies in GCGS infections in humans, SDSE was the prevalent subspecies (Broyles et al., 2009; Reißmann et al., 2010). There are conceivable indications that infection with SDSE can cause ARF. In contrast, *S. equi* ssp. *zooepidemicus* infections are clearly associated with PSGN (Balter et al., 2000; Barnham et al., 1983; Duca et al., 1969; Francis et al., 1993), but not with ARF.

Early epidemiological data from the U.S. linked ARF to *S. pyogenes* pharyngitis only (McCarty, 1956; Wannamaker, 1973). In many regions of the world *S. pyogenes* is the predominant streptococcus in sore throat. However, in certain geographic regions with a high prevalence of ARF and RHD, β -hemolytic streptococci have an unusual epidemiology. For instance in a study from 2006 more than 60% of the throat isolates from Indigenous Australians in the Northern Territory of Australia were SDSE, exceeding the isolation rate of *S. pyogenes* (McDonald et al., 2006). In 1978 about 75% of the pharyngitis cases that occurred in Lagos, Nigeria were caused by GCGS (Ogunbi et al., 1978). Both in Lagos and in the Northern Territory *S. pyogenes* was predominant in skin infections. This is challenging the previous picture of the etiology of ARF. Speculations about a contribution of *S. pyogenes* skin infections in causing ARF have been raised (McDonald et al., 2004). However, experimental evidence is missing that suppurative skin infections can cause autoimmunity or ARF. Another possible explanation for the high prevalence of ARF and RHD in aforementioned high incidence regions could be an unrecognized or underestimated rheumatogenic potential of SDSE pharyngitis. The vast majority of SDSE strains that colonize or infect humans have M proteins like *S. pyogenes*. This explains why pharyngeal SDSE isolates from a community of Indigenous Australians, evoked anti-myosin responses in mice. Most likely, this is reflecting a rheumatogenic potential of SDSE strains that is responsible for the high prevalence of ARF in this community (Haidan et al., 2000).

Regionally and temporarily, rates of isolates with collagen binding M proteins with PARF motif that trigger collagen autoimmunity exceed 10% in different regions of the globe both, for SDSE or *S. pyogenes* (Reißmann et al., 2012). More than 10% of clinical SDSE isolates collected in Southern India bore such collagen-binding M proteins. This region is also known to suffer from a high prevalence of ARF (Reißmann et al., 2012) as well as high rates of SDSE throat carriage and pharyngitis (Bramhachari et al., 2010).

Despite that SDSE isolates carry the factors that trigger ARF-associated autoimmunity, the relevance of this in ARF requires further epidemiological and experimental examination. However, for the time being, these bacteria must not be neglected as a cause for this severe immune sequela.

5 Outlook

Pinpointing the factors that trigger the pathogenesis of streptococcal sequelae will contribute to the identification of the streptococci that cause these immune diseases. Such an ability to detect strains with a nephritogenic or rheumatogenic potential facilitates identification of patients that are at high risk of contracting these immune diseases and that benefit from an intensified preventive treatment. Moreover, our growing knowledge on the spectrum of etiological bacteria may have a substantial impact on the design of vaccines that aim at preventing ARF. For instance, the successful vaccine may have to protect against a broader range of streptococci that includes SDSE. The risk of side effects is another obstacle in the development of streptococcal vaccines. This obstacle may be overcome by excluding streptococcal factors that induce detrimental immune reactions such as molecular mimicry motifs or PARF from vaccine formulations. However, we should be aware that our current knowledge about the streptococcal inducers of immune disease is not yet complete.

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Fig. 1: Schematic representation of an M protein with PARF motif. The dimeric thread-like M protein is covalently bound to the peptidoglycan of the streptococcal surface and protrudes from the bacterium. The PARF motif (*box*) is located in the N-terminal end of all known M proteins confer to the streptococci a high binding capacity for collagen IV (Reißmann et al., 2012).