OPINION

Revisiting the pathogenesis of rheumatic fever and carditis

Rajendra Tandon, Meenakshi Sharma, Y. Chandrashekhar, Malak Kotb, Magdi H. Yacoub and Jagat Narula

Abstract | Rheumatic fever is one of the most-neglected ailments, and its pathogenesis remains poorly understood. The major thrust of research has been directed towards cross-reactivity between streptococcal M protein and myocardial α-helical coiled-coil proteins. M protein has also been the focus of vaccine development. The characteristic pathological findings suggest that the primary site of rheumatic-fever-related damage is subendothelial and perivascular connective tissue matrix and overlying endothelium. Over the past 5 years, a streptococcal M protein *N*-terminus domain has been shown to bind to the CB3 region in collagen type IV. This binding seems to initiate an antibody response to the collagen and result in ground substance inflammation. These antibodies do not cross-react with M proteins, and we believe that no failure of immune system and, possibly, no molecular mimicry occur in rheumatic fever. This alternative hypothesis shares similarity with collagen involvement in both Goodpasture syndrome and Alport syndrome.

Tandon, R. *et al. Nat. Rev. Cardiol.* **10**, 171–177; published online 15 January 2013; doi:10.1038/nrcardio.2012.197

Introduction

Rheumatic heart disease is known to affect 15 million individuals worldwide;[1,2] however, systematic echocardiographic screening in endemic areas indicates that this figure is a gross underestimation.[3,4] No effective methods for primary prevention or specific medical therapy are currently available, because the pathogenesis of rheumatic fever remains poorly understood. The pathogenesis of this condition is believed to involve cross reactivity between various moieties in the causative streptococcus strain and numerous cardiac antigenic epitopes; the most-discussed molecular mimicry has involved the streptococcal antigen M protein and some sarcomeric proteins. However, this hypothesis might not adequately explain many features of the disease, such as the common basis for the multisystem involvement in rheumatic fever, the sparing of the myocardium, and the specific effects on cardiac valvular tissue. We propose an alternative hypothesis ascribing the subendothelial extracellular matrix as a common pathology to explain the systemic nature of rheumatic fever.

Competing interests
The authors declare no competing interests.

Past theories on pathogenesis

Rheumatic fever occurs as a sequel to upper respiratory tract group A β-haemolytic streptococcal infections. The clinical manifestations of rheumatic fever are observed 2–6 weeks after streptococcal pharyngitis, when the throat cultures for bacterial infection have become negative and the elevated antibodies to streptococcal enzymes (such as streptolysin O and DNase B) provide the tell-tale evidence of antecedent streptococcal infection.[5] The long-term consequence of rheumatic fever is related to the induction of permanent cardiac damage.[6] A 1987 report on the resurgence of rheumatic fever in the intermountain area of the USA revealed that carditis, diagnosed on the basis of the echocardiographic finding of overt or subclinical mitral valve regurgitation, occurred in >90% of patients with rheumatic fever.[7] Rheumatic carditis might, therefore, be an invariable component of rheumatic fever, and the presumed low frequency of rheumatic carditis in rheumatic fever might result from insufficient sensitivity of clinical auscultatory examination.

Rheumatic carditis typically occurs as a pancarditis that involves the pericardium, myocardium, and endocardium.[6] Whereas the occurrence of fibrinous pericarditis and verrucous endocarditis or valvulitis is well characterized, the term 'myocarditis' has been used rather loosely, predominantly on the basis of the presence of interstitial granulomas. The landmark manuscripts describing the histopathology of rheumatic carditis, published in the 20th century, defined rheumatic myocarditis by the characteristic presence of focal interstitial inflammation, referred to as Aschoff bodies.[8,9]

In that latter part of the 20th century, streptococcal M proteins were widely reported to have a pivotal role in the pathogenesis of rheumatic fever,[10] and certain M serotypes of group A streptococcus—such as M types 1, 5, 6, 14, 18, and 24, which are referred to as 'rheumatogenic' strains—are particularly associated with rheumatic fever.[5] An α-helical coiled-coil structure of the M protein is similar to intramyocellular proteins (such as myosin and tropomyosin) and molecular mimicry between streptococcal and myocellular contractile proteins was proposed to be responsible for an autoimmune response.[10]

The antibodies that target the valves in humans with rheumatic fever are now thought to perhaps not target the M protein, but instead to target the group A carbohydrate from the causative streptococcus strain.[11] As early as 1968, anti-group A carbohydrate antibodies were shown to be persistently elevated in patients with valvulitis,[12] and a report published 6 years later demonstrated that surgical removal of inflamed valves resulted in a significant decrease in the level of anti-group A carbohydrate antibodies present in serum.[13] These antibodies are also thought to recognize sequences in α-helical proteins, such as myosin and tropomyosin, that behave identically to the *N*-acetyl-β-D-glucosamine dominant epitope of the group A carbohydrate.[14] Notably, a high anti-group A carbohydrate response in patients with rheumatic fever and carditis correlates with poor prognosis and valve replacement, and the responses against cardiac myosin S2 fragment peptides correlate with disease activity.[15,16]

Because coiled-coil contractile proteins are intracellular (sequestered from extracellular environs by the sarcolemma), mere production of cross-reactive antibodies to these proteins does not establish a causal relationship with the disease pathogenesis. Accordingly, some researchers have proposed that a target that resides on the surface of the cell and causes the disease to begin or ensue exists in addition to an intracellular biomarker antigen.[14,17] An example of this phenomenon occurs in Sydenham chorea, a neurological manifestation of acute rheumatic fever. The biomarker antigen for Sydenham chorea in the brain is tubulin, but the antigen target is a cell-surface antigen that, after binding the cross-reactive antibody, leads to calcium/calmodulin-dependent kinase II activation and subsequent dopamine release.[17] For rheumatic carditis, some investigators have suggested that the antibodies might recognize the intracellular biomarker antigen cardiac myosin, but that the antigen targeted on the valve surface endothelium *in situ* is laminin, or some other extracellular or basement-membrane protein.[18,19]

The current paradigm of the pathogenesis dictates that the first damage to the endocardial surface is antibody mediated, and the activated endothelium with upregulated expression of vascular cell adhesion protein 1 (VCAM-1) subsequently facilitates the infiltration of T cells into the valve.[20] The studies of human T-cell clones recovered from blood and valve tissues in rheumatic carditis[18,19] found that these clones also proliferate to M protein and cardiac myosin peptides as well as to other valvular proteins, such as the intracellular vimentin and the extracellular laminin, that share homology with cardiac myosin.[18,19] These T cells are thought to be responsible for the Th1 response in the valves[19] that leads to scarring and neovascularization.

We believe that these theories on the pathogenesis of rheumatic heart disease are circuitous. They suggest that multiple streptococcal antigens are involved in the pathogenesis of the disease through various cross-reactive antibodies, and refer to a gross immaturity of the highly evolved human immune system, which we think is very unlikely.

Insights from histopathology

The histopathological alterations in various organs during rheumatic fever seem to be essentially similar and suggest that connective tissue might be the common site for the various manifestations of the disease. The pathological changes also indicate that, unlike in the more-common lymphocytic form of myocarditis, heart muscle cells are spared in rheumatic carditis (Figure 1).

Involvement of extracellular matrix

Pathologically, rheumatic fever is characterized by inflammatory changes in subendothelial and perivascular collagen tissue.[6,21] In rheumatic carditis, the granuloma formation comprising perivascular Aschoff nodules has been described as the most-characteristic finding.[6,22] The depth of perivascular inflammation is limited, and evidence for inflammation beyond the perivascular area is infrequent; the myocardium or interstitium beyond this area appear largely normal. Microscopically, the pericardium is affected in almost all patients with active rheumatic fever; however, no residual damage in myocardium or pericardium is observed after the acute episode of rheumatic fever is resolved.[6] Unlike myocardium and pericardium, the valvular tissue often sustains permanent damage after active carditis.[6] Histopathological analysis reveals that the mitral valve is always affected,[23] and the aortic valve is frequently inflamed.[6] The tricuspid and pulmonary valves are rarely involved grossly, but these valves often show distinct microscopic lesions.[6] Adhesion molecules, such as VCAM-1, are abundantly expressed on the endothelial surface of the mitral valve, and lymphomononuclear cells adhere to the surface to traverse into the valvular tissue.[20,21]

The pathological alterations in other organs follow a similar pattern to most of those of the heart.[6,24] Effects in the central nervous system can include perivascular round cell infiltration in basal ganglia, caudate nucleus, putamen, and cerebellum, regardless of choreic manifestations; Aschoff nodules are usually not observed. Rheumatic arthritis is associated with fibrinous exudates, and thickened and edematous synovium; focal lymphocyte infiltration and histiocytic granulomas are commonly observed. Arthritis has a limited duration of presentation (2–3 weeks) and heals without residual damage. Clinically individual joints have evidence for inflammation lasting 1–7 days. Subcutaneous nodules also show a perivascular collection of fibroblasts, histiocytes, and lymphocytes, which commonly surround a zone of fibrinoid necrosis. These nodules also heal without residual damage. Numerous arterial beds demonstrate a variable degree of arteritis, including the aorta, coronary vessels, pulmonary artery, small and large muscular arteries, and even vasa vasorum.[6,24] These vessels are associated with oedema, and histiocytic and inflammatory cell infiltration of the intimal and medial layers, which can be associated with fibrinoid degeneration and, at times, thrombosis. Histological findings of the renal involvement, mostly obtained by biopsy, indicate the presence of glomerulitis. Widespread obliterating endarteritis of the medium and small renal arteries is common, but does not result in any clinical or laboratory abnormalities. Abdominal pain in rheumatic fever can occur as a result of necrotizing arteritis of visceral arteries. Although pulmonary lesions are not infrequent, the specificity of these lesions is not certain because most autopsied patients also had pulmonary oedema from left ventricular failure prior to their death. In the alveolar walls, capillary endothelial cells proliferate, and analysis of the interstitial tissue shows oedema and inflammatory cells. Vascular lesions of the capillaries and small arteries consist of intimal thickening, hyalinized thrombi, occasional scarring or necrosis of the media and adventitia, and periadventitial cellular infiltration. Pleura, pericardium, and peritoneum are lined by single layers of mesothelium, which is derived from (vimentin-positive) mesenchymal cells, but differ from (keratin-positive) epithelium. Similar serofibrinous exudates occur over the pleura, pericardium, and peritoneum, and extend to underlying tissue. Healing occurs without residual damage.

Lack of myocardial damage

Numerous clinical, imaging, and pathological studies indicate that rheumatic fever does not cause myocardial damage. The Dallas criteria define myocarditis as the presence of lymphomononuclear inflammation associated with cardiomyocellular damage in endomyocardial biopsy specimens.[25] However, myocardial necrosis is rarely observed in endomyocardial biopsy specimens obtained from patients with acute rheumatic fever.[22] Instead, a variable degree of interstitial fibrinoid degeneration, with interstitial mononuclear cell infiltration, has been reported as the most-common finding.[22] In addition, histiocytic aggregates or Aschoff nodules were detected in up to 40% of patients; the granulomatous

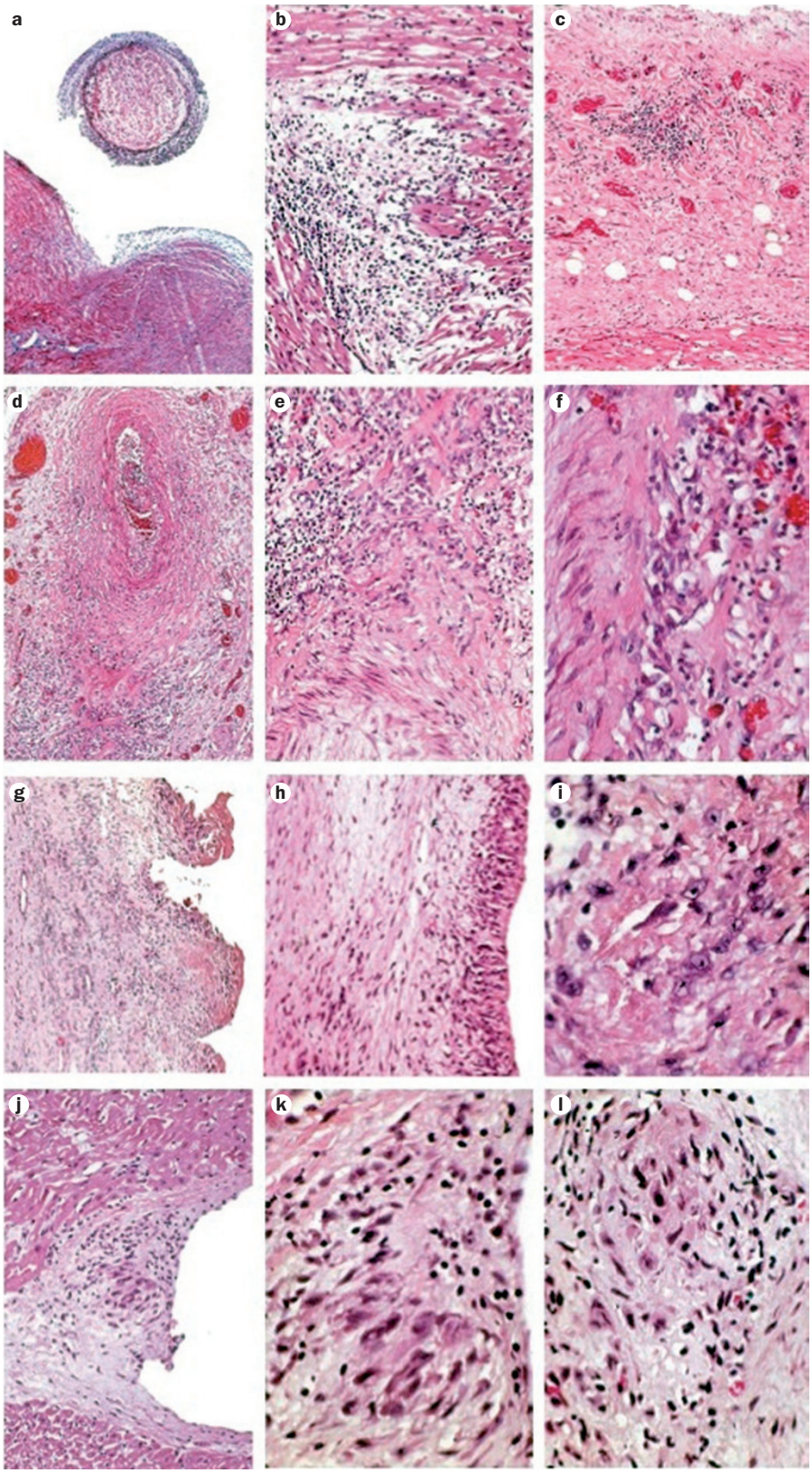

Figure 1 | Haematoxylin and eosin staining of the heart and vasculature suggests connective tissue involvement in rheumatic fever. These images highlight the interstitial alterations of the heart and that myocytes are not affected. **a**–**c** | Pancarditis in a 3-year-old girl with acute rheumatic fever. **a** | Endocardial inflammation is seen around a single chordate tendinae (magnification ×10). **b** | The myocardium reveals a focal area of nonspecific lymphomononuclear infiltrate (magnification ×125) that is more extensive than the Aschoff-nodule-rich infiltrates. **c** | The epicardium contains lymphocytic and macrophage infiltration with fibrinous exudates, but no acute inflammation (magnification ×100). **d**–**f** | Vasculitis in the same patient with rheumatic fever. **d** | In the vasculature, adventitial inflammation occurs, but the media is spared (magnification ×10). **e** | Higher magnification of the section in part d shows intense adventitial inflammation in the left upper corner (magnification ×40). **f** | The inflammatory infiltrate is predominantly lymphocytic, with interspersed macrophages (magnification ×100). **g**–**i** | In the mitral valve of a 6-year-old girl with rheumatic carditis, **g** | focal fibrinous vegetations (magnification ×25), **h** | inflammation with palisading histiocytes (magnification ×75), and **i** | rare Aschoff bodies (magnification ×150) were found. **j**–**l** | In the same 6-year-old patient, Aschoff bodies were present in the papillary muscles removed with the mitral valve, in the subendocardial location, and myocytes were unaffected. An Aschoff body from one subendocardial location in **j** | low magnification (×50) and **k** | high magnification (×150), and **l** | another from a different subendocardial location (magnification ×150) are shown. Modified from Virmani, R., Farb, A., Burke, A. P. & Narula, J. in *Rheumatic Fever* (eds Narula, J., Virmani, R., Reddy, K. S. & Tandon, R.) 217–234 (Amer. Reg. Path. AFIP, Washington DC, 1999) with permission.

lesions were more common in the presence of heart failure and recurrent rheumatic fever.[22] As such, the myocardial pathology is suggestive of the presence of interstitial carditis (and not myocarditis) and does not support the concept that myocardial damage forms the basis of myocardial dysfunction in patients with rheumatic carditis, even in the presence of clinically manifest heart failure.[26]

The lack of myocardial damage has also been inferred by various other investigative measures. Unlike for common, lymphocytic myocarditis, the levels of circulating biomarkers of myocardial damage, such as troponins and creatine kinase, have been reported to be normal, or only insignificantly increased, in patients with acute rheumatic fever.[27] The levels of these biomarkers remain normal even in the presence of cardiomegaly or heart failure. In addition, a prospectively designed, serial echocardiographic study of acute rheumatic fever demonstrated preserved myocardial systolic function, regardless of the severity of valvular involvement and heart failure, throughout the course of active

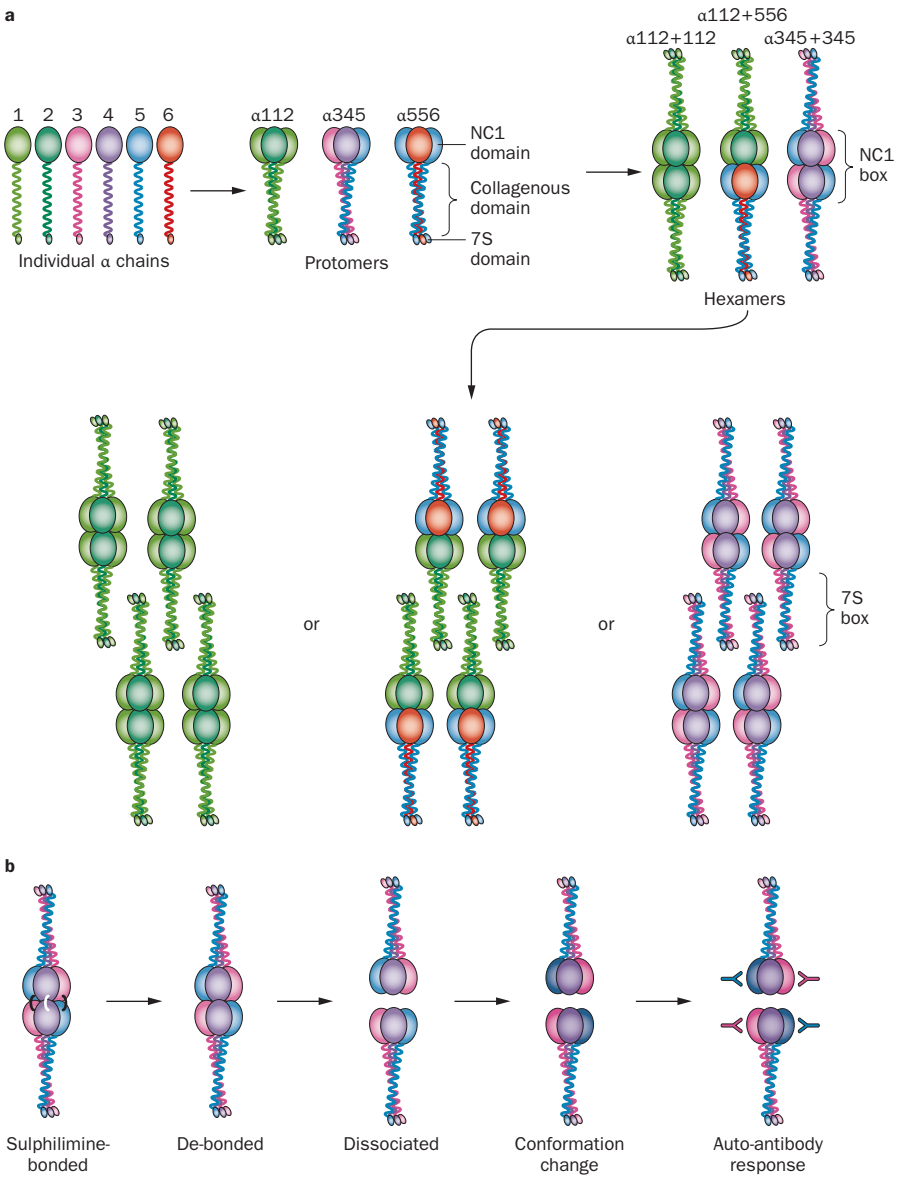

Figure 2 | Molecular architecture of type IV collagen in healthy individuals and in patients with Goodpasture syndrome. **a** | From six genetically distinct α chains, three sets of triple helical protomers are formed—α112, α345 and α556. All protomers comprise a 7S domain at the *N*-terminal and an NC1 domain at the *C*-terminal, which flank a long, collagenous domain in the middle. These protomers form a collagen network in the basement membrane by uniting two NC1 trimers to form a hexamer (NC1 box) at the *C*-terminal, and then four 7S domains (7S box) at the *N*-terminal. Three hexamer networks are composed of pairs of α345 + α345, or α112 + α112, or α112 + α556. **b** | The α345 + α345 NC1 box is strengthened by sulphilimine bonds. Environmental changes such as oxidative stress might inhibit the formation of sulphilimine bonds, or lead to the dissociation of hexamers back into trimers. In Goodpasture syndrome, the NC1 domain within the dissociated trimers undergoes a conformational change, resulting in the formation of neoepitopes (known as EA and EB regions) and eliciting autoantibody production. Inspired from Hudson *et al*.[30] and Padchenko *et al*.[31]

disease.[28] Heart failure occurred in patients with rheumatic fever only in association with haemodynamically significant mitral regurgitation. In patients with acute rheumatic fever who are deteriorating despite aggressive anticongestive measures, complete resolution of heart failure has been demonstrated after surgical mitral valve replacement.[29] The clinicians involved concluded that the heart failure was the result of an acute volume overload secondary to valvular incompetence, but not of myocarditis, and that the surgical management was life saving.

Revisiting the pathogenesis

Collagen is a recognized target for autoantibodies in various autoimmune diseases[30,31] and, on the basis of histopathological characteristics, we believe that collagen is the most-likely site of inflammation in rheumatic fever as well. This hypothesis explains the systemic manifestations in rheumatic fever and the feasibility of complete healing in most tissues (valves heal with scarring).

The seat of autoimmunity

Studies by Chhatwal and colleagues suggest that surface components of rheumatogenic streptococcal strains (such as M types 3 and 18) form a complex with human collagen type IV in subendothelial basement membranes,[32–34] and might initiate an autoantibody response to the collagen in the pathogenesis of rheumatic fever. We agree that poststreptococcal anticollagen antibodies might induce autoimmunity in patients with rheumatic fever, and believe that the pathogenesis of rheumatic heart disease might not involve molecular mimicry with streptococcal antigens nor a failure of the human immune system. If this hypothesis is proven, rheumatic fever could be added to the group of diseases characterized by collagen autoimmunity.

The pathogenesis of both Goodpasture syndrome and Alport syndrome, and the development of autoantibodies directed at the basement-membrane collagen (type IV) therein, offers insight into how this ubiquitous protein can turn into an autoantigen. In Alport syndrome, the autoantibodies are directed against mutated collagen (COL4 A3/A4/A5/A6).[30] By contrast, in Goodpasture syndrome, the antibodies are directed against perturbation of the quaternary structure of the α3NC1 and α5NC1 subunits of the α3 and α5 chains of collagen type IV of the lung and kidney.[30,31] These antibodies bind to distinct epitopes in the NC1 monomers, but they do not bind to the native cross-linked α345NC1 hexamer, and the autoantibody response follows enzymatic or nonenzymatic post-translational conformational modification in the NC1 region. Local environmental factors, such as exposure to endogenous oxidants, tobacco smoke, or hydrocarbons, are presumed to inhibit the association of hexamer NC1 regions and formation of sulphilimine bonds, or disruption of the NC1 hexamer bonds. Conformational changes are also observed in the defined epitopes in the NC1 region and the autoantibody response is induced (Figure 2).

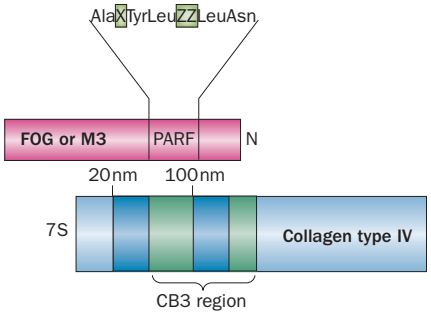

Figure 3 | Molecular basis of an interaction between collagen type IV and M protein in rheumatic fever. Two prominent sites on the collagen type IV molecule are found 20 nm and 100 nm from the 7S region; the latter site is the CB3 region and is necessary for integrin binding. All collagen-binding streptococcal M proteins contain a consensus octapeptide sequence—AlaXTyrLeuZZLeuAsn—called PARF,[33] which binds to the CB3 region of collagen type IV with high affinity.[34] This binding interferes with the collagen–integrin interaction, modulates collagen itself, and results in an antibody response directed at the CB3 region of collagen type IV. Owing to similarity between various forms of collagen, the immune response might extend beyond collagen type IV. Abbreviations: CB3, cyanogen bromide cleavage product region; FOG, fibrinogen-binding protein of group G streptococci; PARF, peptide associated with rheumatic fever.

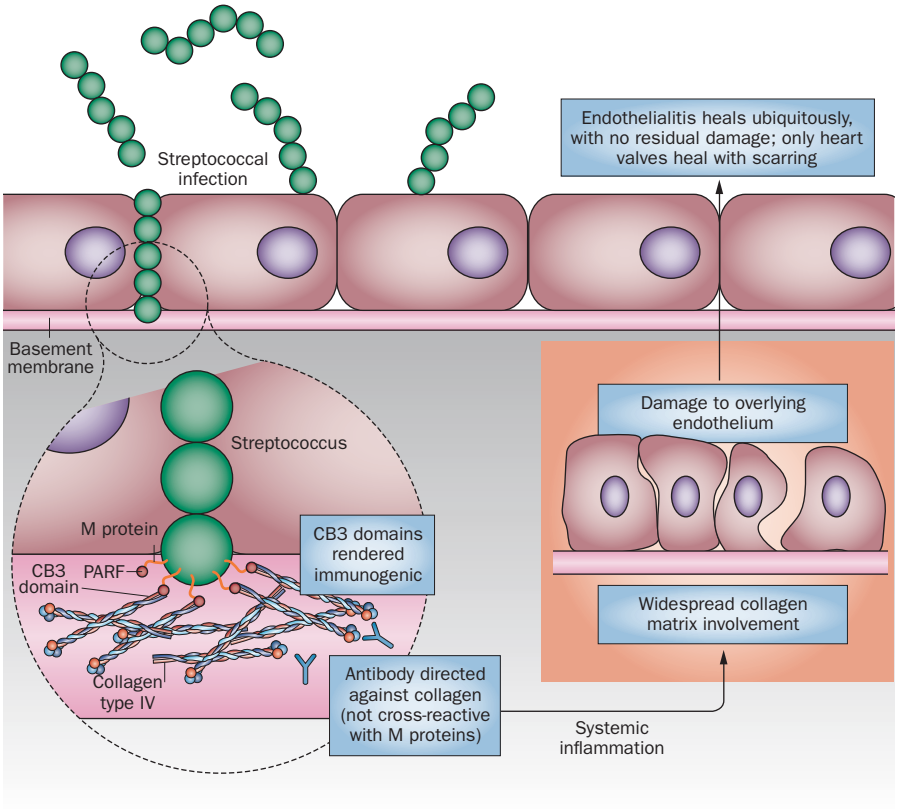

Figure 4 | Proposed pathogenesis of rheumatic fever. The collagen matrix and the overlying endothelial-cell layer are affected throughout the body during acute rheumatic fever. Owing to the two-sided endothelial coverage of the heart valves with minimal intervening tissue, healing with scar formation leads to permanent damage; other organs heal with no residual damage.

In rheumatic fever, M protein binding (Figure 3) to basement-membrane collagen might induce autoimmunity to collagen type IV epitopes. M protein from rheumatogenic M serotypes binds to the collagen via an octapeptide motif that has been identified by peptide arrays and targeted amino-acid substitutions.[32–34] Mice immunized with streptococcal proteins containing the collagen-binding octapeptide develop anticollagen antibodies.[32–34] Although immunization of mice with M protein produced a collagen autoantibody response, the antibodies did not cross-react with inducing M proteins, excluding the likelihood of molecular mimicry. Notably, sera obtained from patients with rheumatic fever (in Chandigarh, India) has been shown to have an increased level of collagen antibodies as well as increased titres for M proteins and fibrinogen-binding protein of group G streptococci (FOG).[27,28]

In some areas in which rheumatic fever is endemic, such as the Northern Territory in Australia, pharyngeal isolation of group A streptococcus is rare, whereas the prevalence of streptococcal group C and G infections is high. Therefore, group C and group G streptococci are thought likely to be involved in the pathogenesis of rheumatic fever in these regions. Similarly to M protein, the M-like protein FOG, which is described as an adhesin and is found on group G streptococcus, has been demonstrated to interact with various members of the collagen family.[32,35,36] Therefore, the proposed mechanism of onset of rheumatic heart disease might not necessarily be limited to group A streptococcal pharyngeal infection.

Endothelial heterogeneity

The immunologically challenged collagen network in basement membrane is likely to induce phenotypic changes that include apoptosis of the overlying endothelial cells.[21,37] Given that endothelial cells vary in both structure and function according to their site in various organ systems, the manifestations of the endothelial involvement might vary from tissue to tissue. Endothelial-cell heterogeneity has been attributed on the one hand to a predetermined organ-specific phenotype before the migration of endothelial cells from the mesoderm to the diverse vascular beds and the capacity for differentiation at site along a genetically determined programme[38] and, on the other hand, to local environmental factors, including cytokines, intercellular communication, and the properties of the underlying extracellular matrix. Endothelial-cell heterogeneity is probably best exemplified in the valvular endothelial cells that differ in their behaviour from the endothelium in other parts of the circulatory system and are specific to the particular part of each valve[39]—even endothelial cells on the aortic side of the aortic valve have different expression profiles on microarrays from those on the ventricular side.[38,40] Notably, a prominent phenotypic drift has been described when endothelial cells from a given organ are co-cultured with extracellular matrix from a divergent organ.[41] Several studies have shown the involvement of the genome transcriptome and glycome in regulating the response to injury.[38,42] Therefore, a variable response within different vascular beds during an acute episode of rheumatic fever should not be surprising.

Despite widespread endothelial activation and the diffuse collagen involvement

in the vasculature, one of the mysteries of the pathology of rheumatic fever is its tendency to scar only the cardiac valves and no other affected tissues. In most tissues, the endothelium has an immense capacity to heal; the damaged endothelium is replaced by new endothelium after any kind of injury, and the healed endothelium does not show scars. Moreover, in addition to the endothelium repairing itself very quickly, the subendothelial damage is limited to a shallow depth, and scarring does not usually occur. As such, except for the cardiac valves, the manifestations of rheumatic fever (including arthritis, chorea, and subcutaneous nodules) heal with no evidence of residual sequelae. The valves probably suffer as a result of their distinct anatomical structure in having a small core of connective tissue covered by two layers of endothelium; no muscle tissue and, normally, no blood vessels exist in the valves. With the involvement of connective tissue and abundant expression of adhesion molecules on the overlying endothelium, a vicious cycle of inflammation occurs,[21] causing neoangiogenesis in the substance of the valve tissue, which introduces more vascular endothelium, and valvular healing with progressive scarring.

Conclusions

Pathological findings and immunological studies suggest that the primary site of rheumatic-fever-related damage is the subendothelial collagen matrix. Upon streptococcal infection, an M protein *N*-terminus domain binds to the CB3 region in collagen type IV. This interaction initiates an antibody response to the collagen that might lead to systemic targeting of collagen, which might be associated with variable effects on overlying endothelium. The immune response to collagen is not cross-reactive with group A streptococci. Endothelial and collagen inflammation might heal completely, except in the valves, where scarring occurs. Notably, even this alternative hypothesis (Figure 4) might not explain all nuances of the pathogenesis of rheumatic fever, and studies must continue to unravel this disease, which continues to afflict millions of people in low-to-middle-income countries.

*Sitaram Bhartia Institute of Science and Research, B-16, Mehrauli Institutional Area, New Delhi 110016, India (**R. Tandon**). Indian Council of Medical Research, Ansari Nagar, New Delhi 110029, India (**M. Sharma**). University of Minnesota, VA Medical Center, Division of Cardiology, IIIc, 1 Veterans Drive, Minneapolis, MN 55417, USA (**Y. Chandrashekhar**). Department of Molecular Genetics, Biochemistry, and Microbiology, College of Medicine, University of Cincinnati, 231 Albert Sabin Way, Cincinnati, OH 45267, USA (**M. Kotb**). Imperial College London, Heart Science Centre, Harefield Hospital, Harefield, Middlesex UB9 6JH, UK (**M. H. Yacoub**). Mount Sinai School of Medicine, Zena and Michael A. Wiener Cardiovascular Institute and Marie-Josée and Henry R. Kravis Center for Cardiovascular Health, One Gustave L. Levy Place, New York, NY 10029, USA (**J. Narula**). Correspondence to: J. Narula*
jagat.narula@mountsinai.org

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Author contributions

R. Tandon, Y. Chandrashekhar, M. H. Yacoub and J. Narula researched data for the article, substantially contributed to discussion of content, wrote the manuscript, and reviewed/edited the manuscript. M. Sharma researched data for the article, substantially contributed to discussion of content, and wrote the manuscript. M. Kotb researched data for the article, substantially contributed to discussion of content, and reviewed/edited the manuscript.