The pathophysiology of RHD and outstanding gaps

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ABSTRACT

Rheumatic heart disease (RHD) is the major cause of cardiovascular morbidity and mortality in children and young adults in low- and middle-income countries. Acute rheumatic fever (ARF) is characterised by multi-organ inflammatory symptoms initiated through cross reaction of immune responses (IRs) to group A streptococcus (GAS) proteins to host proteins. Recurrence of these IRs targeting the heart valves may lead to permanent damage, a sequela which is termed RHD. Preliminary studies suggested genetic associations in RF reactions, but that other host factors are also involved, leaving the determinants of RHD progression incompletely understood. Previous clinical and recent epidemiological studies support differential clinical phenotypes, with varying history from different settings. This review summarises the protein-centric biomolecular changes in RHD and highlights outstanding molecular gaps where urgent focus is required to improve our understanding RHD pathophysiology. Numerous studies have confirmed alterations in the expression of structural and immune response proteins, but the modifications giving rise to neo-epitopes and their involvement in RHD have not been established. As RHD is associated with poor living conditions, identification of other factors driving inflammation to enhance RHD progression is necessary to advance our knowledge and improve patient management. Furthermore, biomarkers for early identification, disease stratification, and alternative therapeutic strategies are necessary to improve treatment and prevention strategies in order to reduce the burden of RHD.

Relevance: Despite the explosion of scientific innovation over the last few decades, fundamental scientific studies to understand the pathophysiological mechanisms of RHD remain in their infancy and the determinants of RHD progression thus remain uncertain. Moreover, inconsistency in natural history and phenotypic presentations are seen between Africans and other cohorts in which preliminary studies were conducted, implying that differences in genetic complexity and environmental factors may be responsible for the differential disease progression rates. SAHeart 2022;19:38-48

INTRODUCTION

Rheumatic heart disease (RHD) is an acquired, chronic autoimmune inflammatory heart valve disease that causes heart failure and premature death.[1] RHD is a consequence of a series of manifestations following pharyngeal or skin infection

by a group A streptococcus pyrogens (GAS).[2] Aggressive self-directed immune responses due to the inability of anti-GAS M antibodies to differentiate host proteins initiate generalised multi-organ inflammatory reactions, termed acute rheumatic fever (ARF).[2] RF episodes may reoccur due to GAS reinfection or repeated immune reactions to host, targeting mainly the heart valves, endothelial, and basement membrane protein epitopes, and can progress to RHD.[3] RHD is a serious public health challenge, affecting mainly children and young adults, especially in resource-limited countries where living conditions permit spread of the GAS.[4] As a result, increased rates of heart failure are seen in under-privileged young people (<40) in low- and middle-income (LMIC) settings.[5,6] Moreover, due to the limited access to health resources, patients tend to present for management at very advanced disease stages, further complicating management.[2,3,7] As 233 thousand people are dying annually from RHD complications, early diagnosis and secondary prevention are key to delaying disease progression and imperative to improve outcomes.[8,9]

RHD thus remains a major public health concern in LMICs and in a few vulnerable communities in high income countries.[4,10]

Despite a prevalence as high as TB and HIV in sub-Saharan Africa, and its resultant incapacitation of the active work force, RHD has received limited research funding and interest to date.[11,12] Meanwhile, its burden on individuals, families, and LMIC health care systems is enormous.[10,13] This review therefore seeks to highlight gaps in knowledge of underlying pathophysiology, the goal being to help the scientific community to identify key challenges and innovate solutions to an important but under-studied disease.[14]

DISEASE PRESENTATION AND DIAGNOSIS

Generalised inflammatory reactions involving the joints, skin, brain, and the heart, that present as polyarthritis, erythema marginatum (at times with sub-cutaneous nodules), chorea, or endocarditis respectively,[15] presenting 4 - 6 weeks post a pharyngitis are suggestive of an acute RF[3,9,16,17]. The endocarditis doesn't heal completely leaving a sequela which may progress to heart valve malfunction if repeated inflammatory reactions occur.[18] This functional impairment of the valves is complicated by atrial enlargement and arrhythmias in mitral regurgitation, diastolic complications leading to left ventricular (LV) dilation, and hypertrophy and dysfunction from the excess mitral and aortic loads. Other complications in the heart such as pulmonary hypertension or stroke[19] worsen prognosis, causing subsequent heart failure and premature death if not managed early.[14]

Early confirmatory diagnosis and differentiation from congenital, or other acquired non-ischemic heart conditions is necessary for referral for various management strategies, including primary, secondary and tertiary prophylaxis that are recommended to delay progression and enhance prognosis.[20,21] At late stages, oedema, pericardial effusion, cardiac enlargement with murmurs, third heart sound, rales, and pericardial friction rub can be found on clinical examination suggestive of RHD.[22,23]

A clinical assessment together with ECG may guide the diagnosis, but cardiac imaging is recommended for confirmation of valve structural changes such as restricted leaflet movement and fused commissures, with conserved or LV dysfunction.[24] Echocardiographic (ECHO) is the WHO recommended tool for confirmation and early diagnosis, of RHD.[22,25,26] Both ECHO and cardiovascular magnetic resonance (CMR) imaging allow for real-time 3D early accurate assessment of structural features such as biventricular size and function, inflammation, tissue characteristics such fibrosis, strain and cardiac haemodynamic features. ECHO is also a particularly great tool for diagnosis of associated tricuspid valve malfunction,[29] but both imaging tools require expert interpretation and are very costly for LMIC settings.[27,28] There is thus a need to complement imaging with other simpler, user-friendly biochemical diagnostic tests that may be more affordable in resource limited settings.

MECHANISMS AND OUTCOME OF VALVE INVOLVEMENT

While socio-economic conditions have a significant role in unchecked spread of GAS from person to person,[30] host genetics and immune mechanisms play critical roles in the initiation of generalised complex immune events in ARF and RHD development.[6,31]

Evidence has shown changes in the HLA type II /DR alleles sequenced from people who developed RHD. Different HLA-DR loci are identified in Caucasian, African, and Brazilian populations with RHD patients.[32-34] In addition to the HLA alleles, cytokine and innate immune genes including ficolins, toll-like receptor (TLR)-2, mannan binding lectins (MBL) and cytokine genes such as the tumour necrosis factor (TNF)-α, transforming growth factor (TGF)-β, interleukin (IL)-1 and IL-10 have also been associated with RHD development.[31] For example, the A allele of the MBL gene was found more frequently in patients with mitral stenosis,[3,31] the B allele was found in controls or ARF patients that never developed RHD.[35] MBL and ficolins promote complement activation via the lectin pathway by binding to N-acetyl glucosamine carbo-

hydrate components of the bacterial cell wall, activating undesirable complement reactions.[36-38] Coincidentally, differences in disease history have been shown in patients from different populations.[2,9,39,40] While African RHD patients progressed to heart failure within the 3 years following clinical presentation, RHD patients in Australians and Caucasians progressed to LV hypertrophy at a much slower rate.[30,41] As the burden of other endemic infections is high in Africa, it is not known whether epigenetic modifiers from other endemic infections contribute to differential disease progression rates.[42] Moreover, with inconsistency of presentation, late diagnosis due to late on set or absence of early symptoms,[40] may have contributed to poor management outcomes.

POST RF SEQUENT OF EVENTS LEADING TO RHD

For susceptible hosts, B and T cell responses are activated to initiate and amplify the self-reactive events, leading to the inflamed valve endothelium, leukocyte infiltration into the heart, neovascularisation, extravasation, and valve endothelial injury (Figure 1).[43]

These infiltrated leucocytes, specifically macrophages, and valve endothelial (VEC), as well as interstitial cells (VIC), secrete growth factors and other soluble mediators that initiate a fibrotic healing process, inducing cardiomyocyte growth and changes in synthesis and deposition or degradation of collagen and other extracellular matrix (ECM) components.[44] Changes in distribution, structure and function of ECM brought about by the fibrotic process and cellular interaction with the ECM changes the organisation and orientation of cardiac ECM components. These alterations together with inflammatory mediators and regulators of the fibrotic process, drive differentiation myofibroblasts to fibroblasts that take over and extend the process to myocardial fibrosis.[45]

The inflammatory and fibrotic processes cause valve leaflet thickening, commissural fusion, and chordae shortening. At

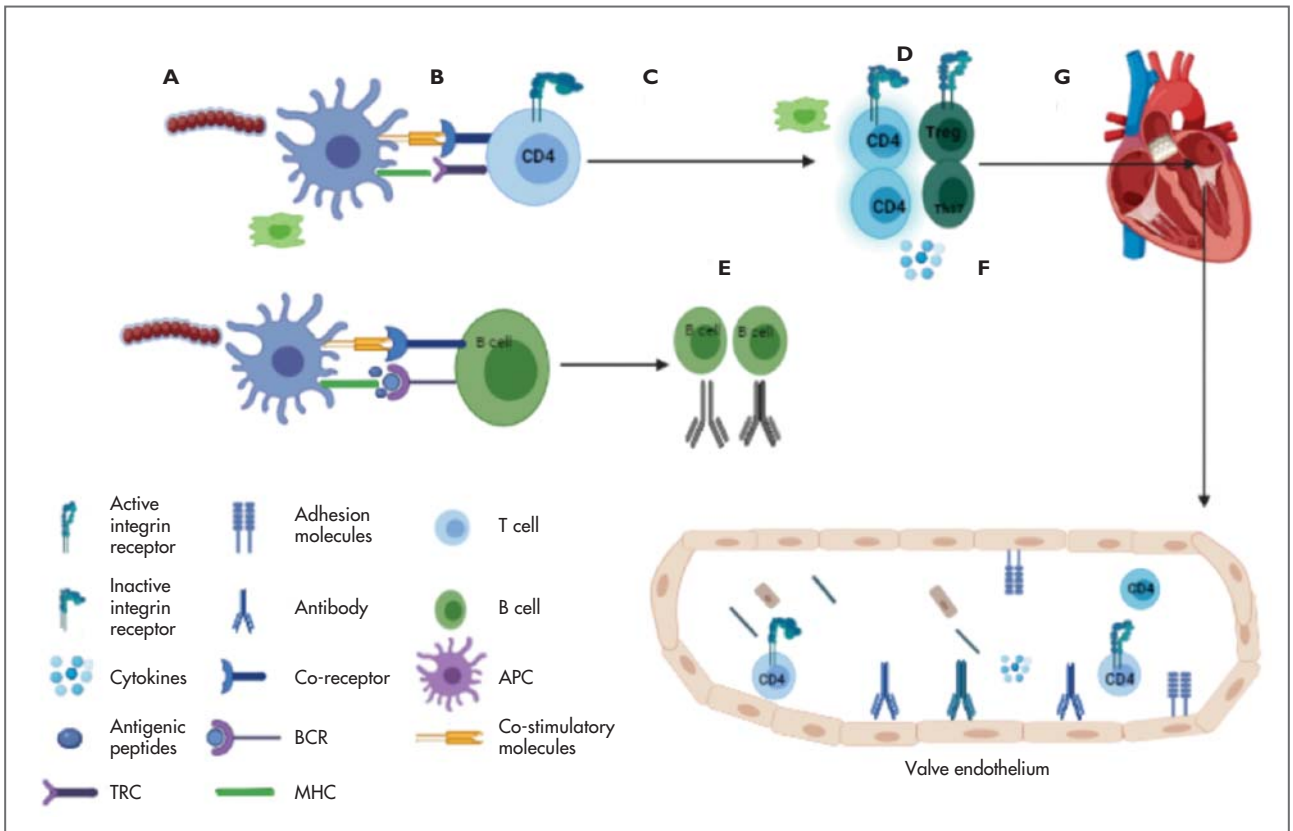

FIGURE 1: Mechanism of development of valvulitis: Exposure of a genetically susceptible host to GAS leads to antigen uptake (A) Antigen is processed and peptide presented to B and T cells by antigen presenting cells (B) GAS primed B and T cells activated, upregulate surface receptors and differentiate (C) into various leukocyte subsets (D) that secrete required cytokines (F) antibody producing B cells (G). GAS specific antibodies bind to GlcNAc of valve endothelium, induce inflammation that upregulates adhesion molecules that facilitates T cell infiltration and extravasation and binding to the heart valve endothelium aided by the cytokine gradient (G) cross-reactive of GAS Abs and T cells infiltration cause aggressive responses resulting in injury and valvular damage. (Figure 1 was created in Biolegend.)

times, these are accompanied by annular calcification in valvular stenosis,[21] or regurgitation whereby the valve annulus is dilated, with elongated chordae tendineae and a prolapsed anterior leaflet or apical displacement of the papillary muscles.[46-48] Both stenosis and regurgitation may present at late stages on the same valve in mixed valvular disease and at times, multiple valvular involvement.[46,49] These may be further complicated by tricuspid valve functional regurgitation[49] which can enhance disease progression.[46,50]

Haemodynamic changes associated with these valvular, structural, and functional deformation especially in mitral regurgitation (MR) impose more pressure or volume overloads to the myocardium.[51,52] Myocardial cells and extracellular matrix components respond to this changing load by sarcomere unit rearrangement leading to dilation or excessive contractions. LV diastolic and systolic malfunction, hypertrophy are the consequences and may eventually lead to heart failure if not managed timely.[53]

T CELL DYNAMICS AND SOLUBLE INFLAMMATORY MEDIATORS IN RHD

Both humoral and cellular IRs dominate 4 - 6 weeks post-exposure of upper respiratory mucosa to GAS.[7,54] Antibodies to GAS M proteins cross react, through antigen mimicry, with specific host endocardial proteins, activating valve endothelial inflammation.[55-57] Subsequently, epitope spreading activates self-reactive leukocytes which infiltrate the heart endothelium, extravasate and undergo T cell oligoclonal expansion, representing critical steps in RF and RHD progression.[58] Investigation of self-reactive T cell clones in RHD found that they react with cytoskeletal proteins; myosin and vimentin and other human proteins.[59-61] One early study also found that half of the population of leukocytes isolated from human valve tissues were macrophages, the other half was represented in a 4:1 ratio of CD4+ T and CD8+ T cell subsets respectively.[62] More recent studies also found increased Th17 cells[63] and decreased CD25 high- CD127 low-regulatory T cells (Treg) cells in peripheral blood of RHD patients.[63,64] Regulatory T cells play a key role in maintaining immune homeostasis and tolerance, preventing excessive immune responses. In autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and diabetics, lower ratios of Treg subsets have been described as contributing to the lack of tolerance.[65,66] Lower numbers of Treg cells have also been reported in RHD, but the mechanisms of loss of tolerance in RHD development have not been properly explored. Whether natural adaptive or somatic mutation induced loss of tolerance in RHD occurs at the level of the thymus or peripherally is not known. Restoration of Treg function through IL-2 and retinoic acid has been shown to restore immune homeostasis and control tissue damage in other autoimmune models, but has not been investigated in RHD.[65,66] Further exploration of the functionality and potency of the valve infiltrated leukocytes, including the interaction with other valvular resident cells, may enhance understanding of the mechanisms of loss or control of valvular damage in RHD.

Decreased levels of IL-4 and IL-10 and enhanced expression of TNF- and IFN-γ were shown in RHD patients valves.[3,54] Increased IL-4 was contrarily observed in myocardial tissues, suggesting the modulatory role of IL-4 may contribute to the myocardial healing both human[3,54,69] and animal models of rheumatic endocarditis.[70] Increased levels of secreted IL-1, IL-17, IL-23 and IL-6 were also found in the plasma of patients with rheumatic mitral stenosis compared to controls.[3,54,63,64,67,68] More recent studies further correlated the increased plasma IL-17 and IL-23 with an enlarged left atrium and moreover and high serum hsCRP.[63,67]

In other rheumatic diseases such as lupus nephritis and RA, innate lymphoid cells found in inflamed tissues were involved in initiation as well as aggravation of autoimmune reactions. These innate cells were suggested to act by driving amplification of the cytokine axis rather than providing immune homeostasis, through their interaction with other cells involved in this autoimmune disease model.[71] The role of these innate lymphoid cells in interaction with other leukocytes involved in RF and RHD is however not known.[62]

HEART VALVE PROTEOME CHANGES IN RHD

Cross reactivity of GAS antibodies and leukocytes to host proteins due to epitope mimicry and epitope spreading respectively. Host protein mimicry of microbial epitopes may result from increased or decreased expression, improper folding or mutation of host protein epitopes or even aberrant localisation of specific host proteins. Incorporation of differing amino acids leading to formation of isoforms with modified surface epitopes, or post translational modifications such as phosphorylation, oxidation, acetylation, citrullination, or aberrant proteolysis may also modify host protein epitopes to mimic microbial epitopes.[72] Exploratory discovery proteomic studies reported alterations in valve tissue proteins involved extracellular matrix (ECM) structural organisation and IR roles in RHD (Table I).[73-75]

Vimentin is a structural protein that binds and stabilises collagen mRNA.[76] Previous studies found that vimentin is a cross reactive target for GAS antibodies, peripheral and heart valve infiltrating T lymphocytes[75] and a neo-angiogenesis initiation factor.[73,75] Other ECM proteins such as ASAP-2 structural protein,[73] and members of the small leucine-rich proteoglycans (SLRP) family proteins such as lumican and vitronectin, and collagen VI are known to play regulatory roles; orienting collagen fibrils, tissue hydration, repair and regeneration and maintaining ECM integrity. These functions may affect their binding to integrins and soluble ligands and probably affect signalling mechanisms involved in heart valve pathology.[74,77]

Collagen IV, prolargin, biglycan and COMP are major components of the ECM of the spongiosa of heart valves.[73,74] They function in ECM integrity; receptor activity and cell adhesion, cellular migration and proliferation.[77] It is not known if their down regulation is associated with the reduced tissue integrity, repair and growth observed in RHD. However, other studies found tissue embedded and soluble prolargin, biglycan and decorin to interact with TLR4, causing receptor crosstalk and influencing innate immune responses leading to tissue damage in tumour microenvironments.[78-81] It is not known if the altered quantitative expression of SLRPs in RHD tissues also induced their further modifications, in addition to collagen cross-linking shown in ECM remodelling. Moreover, IL-1β and IL-1R1 expression were also upregulated in tissues from RHD patients relative to congenital heart disease (CHD) tissues.[82] Increased expression of molecular chaperons HSPA5 and PDIA3, proteins known to function in calcium sequestration, may serve in refolding stressed or misfolded proteins, due to ongoing inflammatory reactions enhanced RHD progression.[75]

In theory, identification of underlying early molecular events in RHD may reveal new targets for RHD treatment before severe valve damage occurs. As human tissues are only sampled at late disease stages, animal models of acute stages of RHD are studied to provide useful information. Acute stages of valvulitis were studied in Lewis rats models of valvulitis (Table 2).[70] The main role of proteins altered in acute stage of rheumatic valvulitis in the mitral valve leaflets of Lewis rats were in induction of immune reactions, focal adhesion and stress accommodating HSPs (Table 2).[75,83,84]

Increases expression of GAPDH and CD9 and evidence of lymphocyte infiltration and adhesion to the valve endothelium, initial steps to aggravation of valvulitis and tissue injury in RHD progression, were also further confirmed by histology in the tissues of these rats.[43,70]

TABLE I: Human heart valve tissues proteins altered in RHD.

Upregulated	Downregulated	Function
Vimentin	Biglycan	Collagen components of fibrosa of valve ECM, maintaining VIC integrity
Vitonectin	Collagen IV	ECM proteins for valve integrity, cytoskeletal and valve integrity
Development and differentiation-enhancing factor 2 (ASAP-2)	Haptoglobin related protein	SLRP proteins can interaction with TLR4, induce IRs
Disulfide isomerase ER-60	Prolargin	
HSPA5	Cartilage oligomeric matrix protein (COMP)	

TABLE II: Protein changes in Lewis Rat models of acute valvulitis.

Protein group	Proteins	Valve	Alterations
Focal adhesion	Myl9, Mylk, chondroadherin, Ras-related protein 1 (RAP1), Ras-related botulinum toxin substrate 1 (RAC1)	Mitral valve	Up
Possibly autoantigenic	Myosin11, collagen I & V	Mitral valve	Up
Molecular chaperones/IR regulators/ antigenic	Heat shock proteins 70 protein 12A (HSP12A)	Mitral	Up
Immune responses	CD9#	Mitral	Up
Apoptosis	GAPDH*	Mitral	Up

**GAPDH Glyceraldehyde 3-phosphate dehydrogenase. #CD9 tetraspasnin (cluster of differentiation 9).*

TABLE III: Altered myocardial proteins in RHD.

Upregulated	Downregulated	Functions
Desmin	Tropomyosin alpha-1	Immune response
PDZ LIM domain protein 1	MDH	Extracellular matrix integrity
Proteasome sub-unit alpha type 1	CABC1	Molecular chaperones (protein folding and function)
HSP60 &BCL complex homolog 1		

MYOCARDIAL CHANGES AND PATHOGENIC IMPACT IN RHD

Although initial autoreactive inflammatory reactions target both the heart valves and the myocardium, but evidence of myocardial injury during these Initial RF episodes is very limited. No secreted troponin was in plasma during acute RF, indicating lack of cardiac injury.[85] Myocardial impairment in RHD is thus mostly a consequence of haemodynamic changes associated with valve morphologic and functional changes. Sarcomere contractile unit rearrangements have been shown in response to remodelling of cardiomyocyte to accommodate these load changes, sometimes leading into myocardial hypertrophy.[86] Additionally, cardiac ECM proteins also undergo remodelling changes to accommodate the changes in contractile and functional units of the cardiomyocytes. Furthermore, infiltrated leucocytes also secrete growth factors and matrix remodelling proteins that contribute to cardiac ECM remodelling responses.[20,44,45] Various cellular and ECM proteins are thus altered in myocardial tissues from RHD patients (Table 3).

Altered HSPs putatively helped in refolding or labelled misfolded proteins for degradation by the proteasomes to accommodate protein changes involved in the remodelling process in RHD.[83,87] HSPs may contribute to regulate folding of cytoskeletal intermediate filament proteins whose expression was upregulated in response to myocardial stress in RHD. Desmin is suggested to contribute to protein aggregation in animal models of heart failure.[88,89] PDZ and LIM domain containing proteins may regulate actin and Z-line structure in cardiac muscles contraction to maintain muscle cells and ECM integrity.[90] Tropomyosin and myosin carry epitopes known to mimic GAS M proteins while MDH and CABC1 may be involved in metabolic changes that may in turn be associated with decreased cardiac muscle contraction.[83,91]

TABLE IV: Altered plasma proteins in RHD.

Upregulated	Downregulated	Functions
Brain naturetic peptide	Vitronectin	Complement proteins
Zinc-α glycoprotein	Fibronectin (αβγ)	Blood homeostatic/ antiproteases
Brain naturetic peptide	Clusterin	ECM proteolysis/ remodeling
Pentaxin	Elongation factor 2 & serotransferin	Leuckocyte recruitment
Histone 2B	C3, C4A, C4B, C9 Factor H	Immune response
Vilin-like proteins	Apo (AI & CIII), Fetuin A	
SERPIND1 and C9	Immunoglobulin chains: α, γ, κλ,	
Motile sperm	SERPIN A3	

PLASMA PROTEOMICS AND PATHOPHYSIOLOGY OF RHD

ARF is multi-systematic, but RHD progression involves mainly the heart valves, with left and right ventricles being affected secondary to the heart valves malfunction. As not all RF cases progress to RHD, differentiating changes in proteins and other molecules in progressor and non-progressors may help improve understanding of RHD pathogenesis. These may also serve as leads to early diagnostic biomarkers or new therapeutic targets to delay disease progression before severe valve damage is attained. Given its non-invasive sampling method, blood may serve as an important sample to study early pathological changes in diseases. Besides soluble immune mediators, secreted proteins reported to be unique to RHD may thus be used for diagnosis, disease stratification or outcome evaluation (Table 4).

Apart from regulation of the innate immune response, vitronectin and clusterin have been reported to help in pericellular proteolysis, complement activation, leukocyte recruitment and homeostasis of the fibrinolytic systems in other autoimmune diseases.[73,74,92,93] Vitronectin also has an RDG motive, enabling it to bind to integrins and transmit mechanical stress signals to the cell.[94] It is not known though whether down regulation of vitronectin is associated with loss of valve integrity in RHD.

Vitronectin has additionally been found to act as co-factor for plasminogen activator inhibitor-1 in regulating ECM degrada-

tion.[73,74] Furthermore, vitronectin also binds to complement proteins and the complement system is known for its important role in the development of inflammatory processes associated with diseases such as RHD.[92] Indeed, altered expression of complement factors was confirmed in the serum of RHD patients.[68]

POTENTIAL ROLE OF EPIGENETIC MODIFIERS IN RHD PROGRESSION

In addition to genetic predisposition, epigenetic events have been demonstrated to play central pathophysiological roles in determining the clinical trend and outcomes of a number of inflammatory and autoimmune disease.[95-97] Since they can regulate disease genes through control of chromatin accessibility to transcriptional regulatory factors, this allows such events to tune genes and thus protein expressions without modifying the underlying disease associated DNA sequence, thus influencing disease phenotypic or clinical spectrum.[95] Epigenetic events take place through DNA methylation as well as post-translational modification of histone proteins and can also be mediated through various non-coding transcripts.[97] Since these factors are influenced by environmental factors,[95-99] it is not surprising that RHD disease spectrum differs between population groups exposed to different environmental infections.[30,100] Understanding epigenetic modifiers may help in development of effective target directed and tolerable therapies to reduce the activation of disease specific genes and control clinical spectrum and outcomes.

Previous RHD studies found upregulation of plasma microRNA (miR)-1183 in pulmonary hypertension secondary to RHD.[101] Furthermore, Dong (2015) and Lu (2018) found down-regulation of plasma miR-101, -205-3p and -3909, which respectively regulated TLR2 and IL-1 genes in another RHD cohort.[102,103] Exosomes can protect their cargo from degradation by plasma factors and may thus also serve as rich source of biomarkers for diagnostic and outcome monitoring in RHD. Luo et al. (2019) found downregulation of exosomal lncRNA involved in Ras signalling and inflammatory responses in Chinese mitral stenosis (MS) patients.[104] As non-coding transcripts target multiple genes linked to different conditions in the host, the role of non-coding transcripts may highlight the rule of other tropical African infections on RHD progression in the African cohorts. Interestingly, the role of histone modifications in RHD has not yet been explored; given recent progress in histone proteomics, global profiling of histone PTMs in RHD may reveal mechanism of indirect modification of disease spectrum in the African tropical infections.

SIGNIFICANT GAPS IN CURRENT KNOWLEDGE

The alpha-helical coiled-coil proteins of myocardial myosin, tropomyosin and valvular laminin, vimentin and keratin mimic homologous epitopes of the M protein and cell wall (GlcNAc), resulting in cross reaction with anti-GAS antibodies.[55,56,105,106] Furthermore, an N-terminal motive of the M protein of some GAS strains termed, peptide associated with rheumatic fever (PARF), also bound to the modified cyanogen bromide fragment (CB3) region of collagen type IV, resulting in a complex that is auto-antigenic inducing antibodies that cross react to collagen, aggravating inflammatory reactions, implicating involvement of modified collagen epitopes in the pathological mechanisms of RHD progressive.[107-109] The specific post-translational modifications on the collagen peptide are not known, but they enhanced antigenicity.

Laminin, vimentin, known autoimmune proteins in RHD, are SLRP ECM proteins that may also potentially carry post-translational modifications. For example, proteoglycans, are glycosaminoglycans linked to the protein core and carry GlcNAc and GalNAc site chain PTMs, which together with collagen cross-liking and maturation, offer mechanical support during fibrotic scarring of the valvular and myocardial ECM in disease progression. These may form neo-epitopes allowing for epitope spreading and for cross reactivity as they carry GlcNAcs.[110]

Post-translational modifications such as phosphorylation, glycosylation, ubiquitinoylation, acetylation/methylation, oxidation, are known in normal physiological proteins changes.[72] Enzymatic mediated and spontaneous protein modifications have also been shown to determine their localisation and are key mechanisms in autoimmune diseases.[111] Citrullination, an enzyme mediated conversion of arginine to citrulline, is known to drive neo-epitope formation in RA.[112] RA, SLE and other autoimmune inflammatory conditions are also characterised by chronic inflammation and vimentin citrullination is a key modification in self proteins in SLE and RA. Additionally, oxidation, and glycosylation can result in formation of neoepitopes in these diseases.[112-114] Furthermore, studies of possible post-translational modifications of these altered SLRP- ECM proteins (Table 1) may plausibly identify new druggable targets in valvular heart diseases.

Citrullination and homo-citrullination during oxidative stress conditions are imposed by chronic inflammation in SLE and RA autoimmune conditions, leading to formation neo-epitopes on vimentin, filaggrin, fibronectin, fibrinogen, enolase and collagen

type II.[114] Some of these proteins have also been found to be altered in RHD (Tables 2 and 3). Vimentin and fibronectin, are known to preferentially express autoreactive epitopes in RHD to which anti-GAS M antibodies and heart infiltrating T cells cross react.[75,106] The modifications on vimentin, laminin and collagen that render these proteins cross reactive in RHD have however not been fully explored.[75,115] Monocytes and neutrophils that are sources of the citrullinating peptidyl arginine deiminase enzymes, PAD2 and PAD4, and are abundant in heart tissues. Indeed, Gilles, et al. and Fert-Bober, et al. found citrullination of heart tissues in RA and in heart failure respectively.[116,117] The role of citrullination and other PTM in RHD are however not currently known.

The crystallisable fragment (Fc) portion of immunoglobulins G (IgG) is known to bind to Fc receptors on immune cells to activate the classical complement pathways. Differential IgG and IgA sub-classes and N-glycosylation profiles have been shown to influence inflammatory mechanisms in RA.[118] The Fc component and N-glycosylation are known to affect complement activation by Fc and the subsequent inflammatory processes to influence disease progression in SLE and RA.[119,120] Downregulation of complement factors C4 and IgG and IgA heavy chains was found in severe RHD patient plasma (Table 4). It is not known though if these IgG and IgA changes were accompanied by differential N-glycosylation or if these influence their Fc interaction with host proteins in RHD, as previously reported RA and SLE patients.

CONCLUSION

While pioneering research showed that autoimmune reactions lead to sustained chronic inflammatory processes in RF, as well as recurrence and RHD development, the pathogenic autoantibodies themselves have not been well characterised. Altered protein expression in the disease has been reported, but neither the protein modifications nor the host reactive protein epitopes have been characterised in detail. Recent preliminary studies on differential quantitative protein changes in the heart tissues of RHD patients found alterations in proteins involved in blood homeostasis, molecular chaperones, immune responses and extracellular matrix integrity and regulation. Remarkably, alterations in proteins from four main biological categories - complement system, innate IRs, blood homeostasis and ECM homeostasis and integrity - were identified in discovery studies.

Following exposure to GAS, T cell infiltration into the heart, cross activation of aggressive inflammatory responses, and lack of self-tolerance play a critical role in RHD progression. Investigation of host, pathogen specific and environmental molecular drivers of GAS primed T cells homing to the heart and drivers of protein modifications to mimic GAS proteins may shed new light on ways to delay heart valve damage in RHD. Understanding PTMs in ECM remodelling and other modifications that induce lack of tolerance and the neo-epitopes involved in RHD thus remain important gaps in knowledge and represent promising avenues for future research.

Acknowledgment

ENL is funded by the National Research Foundation (NRF) of South Africa (DST-NRF) free standing innovation postdoctoral fellowship. This publication was made possible (in part) by a grant from Carnegie Corporation of New York through the Developing Emerging Academic Leaders (DEAL-1) in Africa. The statements made and views expressed are solely the responsibility of the authors. JMB thanks the NRF for a South African Research Chair.

Author's contributions

ENL conceived, ENL wrote the first draft, IP edited and proofread the manuscript, DM helped with the figure, JMB supervised the work and all the authors contributed to review and editing and approved the final manuscript.

Conflict of interest: none declared.

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