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A novel aspect may explain the mechanisms of pathogenicity of rheumatic fever, a multifactorial, autoimmune, infectious and inflammatory disorder which "licks the joints and bites the heart": A working hypothesis

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ABSTRACT

A novel hypothesis is presented to explain the pathogenesis of the multifactorial autoimmune disorder rheumatic fever (RF). It involves a synergistic interaction among streptococcal toxins, their cell wall components, M protein, immune complexes, complement components, cationic histones. These agents can act with cationic histones released by neutrophils during NETosis and bacteriolysis and can function as opsonic agents possessing properties similar to antibodies. Cationic histones can interact by strong electrostatic forces with negatively- charged domains on immune complexes and complement components. This allows their deposition and endocytosis in the myocardium, the heart valves, and in the joints. However, the main cause of cell and tissue damage observed in RF is due to a synergism among the plethora of pro-inflammatory substances released by activated neutrophils and macrophages. Cell damage may be mitigated to some extent by anionic heparins, heparinoids, and by anti-inflammatory drugs such as corticosteroids which counteract neutrophils and macrophage chemotaxis induced by cytokines.

Introduction

Rheumatic fever (RF) is considered an autoimmune disorder which develops after tonsillar infections by group A hemolytic Streptococci. RF is a disorder that "beats the joints and bites the heart". This disorder occurs mainly in non-treated throat infections mostly in susceptible children. The disease is characterized by the development of carditis, Aschoff bodies, polyarthritis, chorea, erythema marginatum, erysipelas and subcutaneous nodules. Carditis is the most serious complication which occurs in 30–45% of RF patients. This may lead to chronic rheumatic heart disease (RHD). RF is genetically determined having an association with certain human leukocyte antigen class II alleles. T cells play an important role in RHD lesions and several autoantigens have been identified including cardiac myosin epitopes, vimentin, and other intracellular valvular proteins. In the heart tissue, antigen-driven oligoclonal T cell expansions are probably the effectors of the rheumatic heart lesions. Molecular mimicry is the mechanism that mediates the cross-reactions between streptococcal antigens and human proteins and the presence of Aschoff bodies in the myocardium is a unique marker of RF [1–13].

Role of molecular mimicry in RF pathogenesis

The group A *Streptococcus pyogenes* and its link to autoimmune pathogenicity have raised the hypothesis that molecular mimicry between the group A streptococcal M protein and heart proteins is crucial for eliciting autoimmune responses in rheumatic fever. In rheumatic myocarditis, T cell responses towards group A streptococcal M protein cross-reacts with heart proteins, thereby eliciting the pathogenesis of rheumatic fever. Also the appearance of cross-reactive autoantibodies leads to heart valves damage [14,15].

Mechanisms of cell damage in RF

In streptococcal tonsillitis, the protein-rich pus is highly infiltrated by a huge number of neutrophils (PMNs), macrophages (MACs) and T cells. A pioneer publication of Kaplan [16] suggested a pivotal role of PMNs in the pathogenesis of autoimmune disorders. However, we proposed that the severe tissue damage in inflammatory and in post-inflammatory sequelae such as RF, is caused by a synergism between the plethora of toxic pro-inflammatory compounds released by PMNs, macrophages and T cells [17–22] and the deposition of immune complexes and complement components in the myocardium, heart valves

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and the joints.

Hypothesis

Here, we propose a novel hypothesis that may shed new light on the pathogenesis of autoimmunity in RF. In RF, highly cationic compounds such as nuclear histones, LL37, defensins and elastase are released from activated PMNs in the form of neutrophil extracellular traps (NETs) [23,24]. Besides being bactericidal and cytocidal, these NETs may function as potent opsonins (opsonic agents) with properties similar to antibodies [25]. These polycationic opsonins, can bind through strong electrostatic forces to negatively charged domains in immune complexes and in complement components, facilitating their deposition and internalization (endocytosis) in various parts of the heart and joints.

This hypothesis originates from our previous observations that group A hemolytic streptococci, *Candida albicans* and even whole cell nuclei pre-coated with cationic polypeptides such as histones could effectively bind to and undergo endocytosis not only by professional phagocytes such as PMNs and macrophages, but also by endothelial cells, fibroblast, epithelial cells and myocytes [26,27]. The severe damage to mammalian cells seen in various inflammatory, infectious and in post-infectious sequelae and probably also in autoimmune disorders, is proposed to be initiated by a tight synergy among the plethora of pro-inflammatory agonists released from activated PMNs and macrophages (summarized in [17–21]).

Activated PMNs and macrophages can secret into the surrounding tissues cationic histones, LL37, defensins, lysozyme, proteinases, reactive oxygen and nitrogen species, PLA2, lysophosphatides, fatty acids and many hydrolases [17–19]. Immune complexes and complement components from the circulation may by captured by these immune cell products resulting in their deposition in the heart muscle, heart valves and joints. Th17-related cytokines that attract PMNs can further stimulate their recruitment, migration and localization in the heart and joints, thereby generating new waves of vicious toxic pro-inflammatory cycles [28].

The possible role of bacteriolysis in RF pathogenesis

In inflammatory sites, Streptococci may undergo bacteriolysis, a phenomenon where nascent autolytic enzymes (muramidases) [29] are activated by cationic lysozyme [30], cationic histones or certain antibiotics [29]. It is a miracle that group A hemolytic streptococci never develop resistance to penicillin, the most effective antibiotics capable of preventing the development of RF. Bacteriolysis may release from autolyzing streptococci, toxic lipoteichoic acid and peptidoglycans [31].

Also, non-biodegradable cell wall components released from autolyzing streptococci can be internalized by and persist for long periods within macrophages [32,33]. Remnants of these non-biodegradable cell wall components may also elicit the formation of Aschoff bodies (a granuloma) [13]. The cell wall component muramic acid has been detected in tissues from streptococcal cell wall-induced polyarthritis using gas–liquid chromatography-mass spectrometry [34].

The possible effects of heparin on RF pathogenesis

We propose that the RF pathogenesis can be mitigated by neutralizing the toxic actions of cationic opsonins [25]. Highly anionic heparin [35] may suppress tissue damage in virtue of its ability to strongly neutralize the synergistic toxic actions between polycations and PMNs pro-inflammatory components. Also, heparin and heparinoids [36] were shown to prevent the binding of immune complexes containing nucleosomal antigens to the glomerular basement membrane in autoimmune nephritis and thus is likely also to delay the onset of carditis and arthritis in RF patients.

An attention has also been focused on the role of electrostatic charges in the pathogenesis of immune complex-mediated tissue injury [37]. These authors examined the ability of cationic histones and the histone mimic poly L-arginine in modulating acute immune complex-mediated tissue injury. Histones may inhibit complement activation through interacting with complement components. Polyanethole sulfonate which is used to grow bacteria from blood samples, also strongly inhibits complement activation. Since the pathogenesis of RF involves both polycations and PMNs pro-inflammatory components, we suggest that in addition to anionic heparins [35], combinations of corticosteroids and other drugs that suppress PMNs functions should be used. Also, neutralizing antibodies to TNFalpha may be effective in suppressing PMN migration [38].

Role of reactive oxygen and nitrogen species in RF pathogenesis

The NADPH-dependent generation of oxygen free radicals by peripheral blood neutrophils and macrophages from RF patients has been studied in detail [39,40]. PMNs which undergo activation, can secrete proteinases which can act in synergy with oxidants to injure cells and tissues [21]. Therefore, use of the anti-protease aprotinin and known low molecular weight anti-oxidants such as glutathione, ascorbate, N-acetyl cysteine and polyphenols found in tea and coffee, might be effective in treatment of RF. The release of oxygen radicals was found to be significantly higher in patients with recurrent rheumatic activity than in those with acute pharyngitis or chronic RHD [40].

Drugs that may be effective in RF treatment

Today, there are no specific effective drugs for RF and the antibiotic penicillin is successfully used only for RF prevention. Group A hemolytic streptococci never develop resistance to beta lactam antibiotics. If RF has already been confirmed clinically, aspirin is the drug of choice for RF therapy, but alternative drugs including the NSAID ibuprofen and the steroid prednisone are often used [41]. If the heart is severely involved in RF, treatment for heart failure may be necessary. Also anti-TNF-alpha molecular biologics [38] may be effective.

Conclusions

The present communication offers a novel hypothesis which suggests the possible mechanisms of damage to heart muscle, heart valves and joints in RF patients. RF is a synergistic multifactorial inflammatory autoimmune disease involving the interplay between a multitude of pro-inflammatory compounds produced by activated neutrophils and macrophages together with cationic substances produced during NETosis. The non-specific cationic histones in the NETs might be neutralized by polyanionic substances which thereby block the deleterious toxic effects responsible for RF.

Several overlapping and successional steps in the development and progression of RF pathogenicity, have be identified as following:

1. Hemolytic Streptococci-induced tonsillitis results in cytokine-mediated recruitment of neutrophils to the exudates [2,6–8,10].
2. Autoimmune complexes are generated and the complement cascade activated [1,7,12].
3. The PMNs release NETs in a process termed NETosis which are enriched with highly toxic cationic histones and citrullinated histones [23,24].
4. The histones may function as potent opsonic agents with properties similar to antibodies [25].
5. The histone opsonins can interact and bind by strong electrostatic forces to negatively-charged domains on immune complexes and complement components, facilitating their binding, deposition and possibly also their internalization by myocardial cells in the heart and by synovial cells in the joints [26,27].
6. The recruited PMNs and macrophages adhering to heart muscle can form myocardial Aschoff bodies (granuloma) [13] which may

contain non-biodegradable streptococcal cell wall components released following bacteriolysis induced either by polycations or by certain antibiotics [33,34].

7. PMNs and macrophages migrated to the heart and joints become activated and release into the surrounding media a plethora of toxic pro-inflammatory agonists. These include cationic peptides, oxidants, proteinases, and membrane-perforators phospholipases, which can all act synergistically to destroy heart valves cells, cartilage and bone structures [17–21].
8. Protection against tissue damage in RF might be provided by highly anionic heparin and heparinoids which neutralize polycations [36,37], if combined with drugs such as steroids, methotrexate and colchicine, all potent anti-inflammatory agents against the PMNs and macrophages functions. Also, Th17-related cytokines can be targeted by drugs which affect leukocyte recruitment [28].
9. Infections which may accompany RF, can be treated with non-bacteriolytic antibiotics since bacteriolysis may release the potent toxic cell wall components lipoteichoic acid and peptidoglycans [29].
10. Non-biodegradable microbial cell wall components may persist for long periods in macrophages in the joints capable of perpetuating chronic destructive arthritis [32,33].
11. Toxic oxidants [39,40] may be controlled clinically by the low molecular weight anti-oxidants glutathione, ascorbate, N- acetyl cysteine, by certain plant polyphenols, and by multidrug strategies [41].
12. No specific drugs to treat RF are available. Analgesics such as aspirin and corticosteroids may inhibit immune complexes formation and chemotaxis of PMNs [41]. If the heart is severely involved in RF, treatment for heart failure may be necessary.

Where do we go from here?

We would recommend to use cocktails of drugs in the treatment of RF comprising of anti-oxidants, proteinases inhibitors, PLA2 inhibitors, and highly anionic heparin to inhibit histones and other polycations [41]. Clinically, this may be a complicated task which necessitating use of appropriate animal models and in humans a permission to use such cocktails clinically. Also, this is a complicated task, which further involves highly expensive clinical trials in laboratory animals. Finally, one might also consider to compare group A hemolytic streptococci to activated human neutrophils.

Years ago, we questioned: 1) Can hemolytic streptococci be considered “forefathers” of modern phagocytes? Both cell types freely migrate in tissues and destroy host cells by a “synergistic cross-talk” among their secreted agonists [42], and:

Can we learn from the pathogenetic strategies of group A hemolytic streptococci how tissues are injured and organs fail in post-infectious and inflammatory sequelae [10]?

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Authors' contributions

MF and IG participating, writing, editing, reviewing the literature.

Conflict of interest

The authors declare that they have no competing interests.

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