HEART VALVE DAMAGE IN ACUTE RHEUMATIC FEVER.

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Relevance. Despite the successes in studying the problem of ARF, it remains relevant to this day. In economically developed countries, the clinical picture of rheumatic fever has changed; the disease has lost its classic features: acute onset, high fever, acute “flying” polyarthritis, pancarditis (Ermolova L.M. 2006).

Increasingly, a latent course of rheumatic fever with developing heart valve defects is observed - the main cause of disability in young and middle-aged people.

The relationship between the BGS and the patient's body in rheumatic fever is a complex scientific problem that integrates microbiological, epidemiological (for streptococcus), genetic, socio-economic, ecological, emotional and psychological aspects [Labinskaya A.S., Kosmatova E.N., 1978; Bobylev V.Ya. et al., 1995; Belyakov V.D.; 1996,; Burova L.A. et al., 1996; Amanzholova Sh.A., 2005; Gibofski A., Kerwar S., Zabriskie JB 1998.]

Rheumatic fever (RF) is an autoimmune disease that develops in genetically predisposed children (5 to 15 years old) after suffering streptococcal tonsillopharyngitis associated with β-hemolytic streptococcal infection of group A, during which the patient develops carditis, arthritis, chorea, subcutaneous nodules and erythema annulare.

The diagnosis of rheumatic fever is based on the Jones criteria, developed in 1944, then revised twice by the American Heart Association in 1992 and 2015.

Streptococcal complications such as rheumatic fever occur primarily in childhood and adolescence. Rheumatic fever is a global disease caused by group A streptococci occurring in many regions of the world, and a resurgence of rheumatic fever has been reported in the United States over the past 3 decades [1]. It has been shown that <3% of patients with GABHS tonsillopharyngitis develop ARF [7 , 13

]. Timely recognition and treatment of GABHS pharyngitis reduces the risk of this condition. The pathogenesis of ARF is not fully understood.

Cardiac involvement can lead to irreversible valve damage, resulting in rheumatic heart disease (RHD) and is the leading cause of acquired heart disease.

The mitral valves are composed of two main cell types: valvular endothelial cells, which line the cusps of both the atria and ventricles; and valvular interstitial cells, resting fibroblast-like cells that are important for homeostatic remodeling of matrix components [1 4]. Chronic inflammatory processes predominate in RHD, leading to accelerated loss of valve function. The anatomical features of the mitral valve may be related to its preferential involvement in this defect. However, the underlying mechanisms of preferential mitral valve involvement in RHD are unknown. The pathogenesis of acute rheumatic fever is associated with autoantibodies, which are characteristic of autoimmune diseases and are the result of host immune responses against group A streptococcal infection.

Streptococcal complications may result from autoimmune mechanisms associated with molecular mimicry [8, 10] , which is part of the normal immune response, since the sharing of host and streptococcal epitopes results in molecular mimicry between streptococcal and host antigens. Molecular mimicry is a term used to describe immunologic cross-reactivity between host and bacterial antigens. Immunologic cross-reactions between streptococcal and host molecules have been identified using antibodies or T cells that react with streptococcal components and tissue antigens [6,7].

The endothelium surrounding the valve must become inflamed to allow T cells to enter the valve and cause scarring. Human monoclonal autoantibodies in acute rheumatic fever are produced by the disease against cardiac myosin and streptococcus. The target on the valve surface is laminin and specific peptide epitopes of laminin [8]. Laminin is present in the basement membrane surrounding the myocardium and as an endothelium on the valve surface [17]. Cross-reactive

antibodies may be trapped in the extracellular matrix, which may act as a sieve to trap antibodies and lead to inflammation in host tissues. Cross-reactive antibodies in rheumatic heart disease, even if they react with cardiac myosin, affect the valve surface endothelium and laminin [8] initiate inflammation in the endocardium, T cells target the activated valve endothelium and infiltrate the valve [12,13,14] and lead to scarring and neovascularization of the normally avascular valve.

Cross-reactive T cell clones that react to epitopes of group A streptococcal M protein and cardiac myosin have been isolated from both peripheral blood [4] and heart valves [3,4] in rheumatic carditis. Studies of human T cell clones in rheumatic heart disease have identified potential sites of T cell mimicry between the streptococcal M protein and human cardiac myosin and represent some of the best-defined T cell mimicry in human autoimmune diseases. Cross-reactive human T cell clones proliferated to peptides B2 and B3A, the dominant peptide epitopes in the B-repeat region of group A streptococcal M protein 5.

The explanation for the cross-reactivity of antistreptococcal antibodies with the valve endothelium and its role as a site of infiltration of lymphocytic extravasation into the valve [4,5] is the recognition by antibodies of laminin and glycosylated proteins on the valve surface and within the basement membrane [8]. T cells recognize laminin within the basement membrane and the valve surface [16,17]. Laminin is a large alpha-helical molecule of 900 kDa consisting of three chains, A, B1, or B2, which contain domains highly homologous to streptococcal M proteins and cardiac myosins. The common amino acid sequences in the laminin protein were highly homologous to human cardiac myosin and form the basis for the cross-reactivity between the myocardium and the valve. Rheumatic heart disease mAbs have been found to be cytotoxic to human endothelial cells in the presence of complement [8]. Proposed mechanisms of antibody deposition on the valve suggest that laminin or some other similar cross-reactive protein or glycosylation of laminin or other extracellular matrix proteins exposed on the valve surface and within the

basement membrane may trap antibodies on the valve surface. Laminin or other cross-reactive proteins on the valve surface or in the basement membrane would promote antibody deposition on the valve and also enhance proinflammatory signals from the endothelium. Targeted cross-reactive antibodies may bind directly to the valve endothelium or the valve basement membrane and be further damaged by endothelial shear stress.

However, cross-reaction may also result from glycosylated proteins or other extracellular proteins on the valve surface. Glycosylated proteins and carbohydrate epitopes on the valve have been shown to cross-react with group A carbohydrates [9,15].

The study of M proteins has provided important information about the sequence and primary structure of the molecule. The hypothesis that M proteins and myosin are immunologically related was confirmed by Fischetti and colleagues, who demonstrated a periodicity of seven amino acid residues characteristic of M proteins of group A streptococci and common to such proteins as tropomyosin, myosin, desmin, vimentin, and keratin.

The role of the M protein or other superantigens in ARF may be to activate large numbers of T cells, including some that are cross-reactive, which may lead to ARF.

Studies of T-cell epitopes in rheumatic fever and in animal models have focused on the M5 protein molecule, since the M5 serotype is frequently associated with ARF outbreaks [2].

Antistreptococcal cross-reactive anticardiac myosin antibodies may initially cause valve inflammation on the endothelium, leading to edema, cellular infiltration, and fibrinous vegetations of the anterior leaflet. Scarring of the leaflets occurs after chordal elongation, causing mitral regurgitation. The valve endocardium and laminar

basement membrane will be targets for the first wave of autoantibodies in rheumatic carditis.

Repeated streptococcal infections may result in lymphocyte infiltration through neovascularized areas in the valve scar tissue, leading to disease persistence. As rheumatic heart disease progresses, immune responses in the valve will progress to epitope spreading and recognition of other valve components such as vimentin and collagen.

Thus, molecular mimicry between group A streptococci and host antigens plays an important role in the development of poststreptococcal complications. In rheumatic heart disease, laminin, an extracellular matrix molecule present in the valve basement membrane, can trap cross-reactive anti-carbohydrate autoantibodies on the surface of endocardial cells and lead to endothelial injury or inflammation. The activated endothelium will lead to subsequent extravasation of streptococcal M protein/myosin-cross-reactive T cells into the valve .

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