IMMUNOLOGICAL ASPECTS OF THE PATHOGENESIS OF RHEUMATIC HEART DISEASE IN RHEUMATIC FEVER

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ANNOTATION

Despite the progress in the study of the problem of acute rheumatic fever (ARI), it still remains relevant. In economically developed countries, the clinical presentation of rheumatic fever has changed, the disease has lost its classic features: acute onset, high fever, acute "flying" polyarthritis, pancarditis. Hidden rheumatic fever **remains one of the main reasons** for the development of heart defects, which is the main cause of disability in young and middle-aged people .

Key words: Laminin, heart valves, molecular mimicry.

The relationship between Betta hemolytic streptococcus (BGS) and the patient's body in rheumatic fever is a complex scientific problem that combines microbiological, epidemiological (for streptococci), genetic, socio-economic, environmental, emotional and psychological aspects. Rheumatic fever (RI) is an autoimmune disease that develops after tonsillopharyngitis associated with group A β -hemolytic streptococcal infection in genetically predisposed children (aged 5 to 15 years), and the patient develops carditis, arthritis, chorea, subcutaneous nodule. and is accompanied by annular erythema.

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 mainly in childhood and adolescence. Rheumatic fever is a global group A streptococcal disease 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]. BGS – tonsillopharyngitis it has been proven that <3% of patients with Timely detection and treatment of BGS-pharyngitis reduces the risk of this condition. The pathogenesis of ORI has not been fully studied. When the heart is damaged, it can cause irreversible damage to the valves, which leads to rheumatic heart disease and is the leading cause of acquired heart defects.

Mitral valves consist of two main types of cells: valvular endothelial cells that line the leaflets of the ventricles and ventricles; and caps are interstitial cells, resting fibroblast-like cells important for homeostatic remodeling of matrix components [14]. In RI, chronic inflammatory processes prevail, which leads to a rapid loss of valve function. The anatomical features of the mitral valve may be related to its main involvement in this defect.

However, the mechanisms underlying mitral valve damage in rheumatic heart disease (RHD) are largely unknown. The pathogenesis of acute rheumatic fever is associated with an antibody-antigen, which is characteristic of autoimmune diseases and is the result of immune responses against group A β -streptococcal infection.

Streptococcal complications may be caused by autoimmune mechanisms associated with molecular mimicry [8,10], which is part of the normal immune response, as the exchange of streptococcal epitopes between the patient and streptococci leads to molecular mimicry between the streptococcus and its antigens. Molecular mimicry is a term used to describe the immunological cross-reactivity between a patient's antibody and bacterial antigens. Immunological interactions between streptococcal and "host" molecules have been determined using antibodies or T cells that react with streptococcal components and tissue antigens [6,7]. The endothelium surrounding the valve must become inflamed, allowing T cells to enter the valve and cause scarring. Human monoclonal autoantibodies to cardiac myosin and streptococcal disease in acute rheumatic fever. Laminin and laminin-specific peptide on the lid surface epitopes are targets [8]. Laminin is present in the basement membrane surrounding the myocardium and in the endothelium of the valve surface [18,19,20]. Cross-reactive antibodies can remain in the extracellular matrix, where they can trap antibodies and act as an inflammatory factor in host tissues. In rheumatic heart disease, cross-reactive antibodies attack the valve surface endothelium, even when it reacts with cardiac myosin, and laminin initiates inflammation in the endocardium [8], T cells target the activated valve endothelium and enter the valve] and typically avascular valve scarring and leads to neovascularization [12,13,14]. Cross-reactive clones of T cells responding to M protein epitopes of group A streptococcus and cardiac myosin have been obtained from peripheral blood [4] and heart valves [3] in rheumatic heart disease. Studies of human T-cell clones in rheumatic heart disease have identified potential sites of T cell mimicry between Streptococcus M protein and human cardiac myosin and represent some of the most well-defined T cell mimicry in human autoimmune disease. Cross-reactive clones of human T cells expanded to B2 and B3A peptides, dominant peptide epitopes in the B-repeat region of streptococcal protein M serotype 5A.

An explanation for the cross-reactivity of antistreptococcal antibodies with valve endothelium and its role as a site of infiltration of lymphocytic extravasation into the valve [4,5] is the recognition of laminin and glycosylated proteins on the surface and inside the valve [8]. T cells recognize laminin on the basement membrane and valve surface [16,17]. Laminin is a large 900 kDa alpha-helical molecule composed of three chains, A, B1, or B2, that contain domains highly homologous to streptococcal M proteins and cardiac myosins. The overall amino acid sequence in the laminin protein was highly homologous to human cardiac myosin and provided the basis for cross-

reactivity between the myocardium and the valve. mAbs derived from rheumatic heart disease were found to be cytotoxic to human endothelial cells in the presence of complement [8]. Antibody attachment to the mitral valve proposed mechanisms suggest that laminin or other similar cross-reactive proteins or glycosylation of laminin or other extracellular matrix proteins may trap antibodies on the valve surface and basement membrane. helps to sink, also enhances endothelial pro-inflammatory signals. Target cross-reactive antibodies can bind directly to the valve endothelium or valve basement membrane and further damage the endothelium due to shear stress. However, cross-reactivity can also arise from glycosylated proteins or other extracellular proteins on the surface of the flap. Glycosylated proteins and carbohydrate epitopes in the valve have been shown to interact 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 are immunologically similar to myosin was confirmed by Fischetti and his colleagues, who identified seven amino acid residues that are characteristic of M-proteins of group A streptococci and are characteristic of proteins such as tropomyosin, myosin, desmin, vimentin, and keratin.

showed periodicity.

A role for M protein or other superantigens in ORI may be to activate multiple T cells, including some that are cross-reactive, leading to RYK. The study focused on the M5 protein molecule, because the M5 serotype

often associated with epidemics of acute rheumatic fever [2]. Anticardial myosin antibodies cross-reactive against antistreptococci may initially cause valvular inflammation in the endothelium, leading to edema, cellular infiltration, and fibrinous vegetations of the anterior leaflet. Scarring of the valves occurs after atrial fibrillation, which is the cause of mitral regurgitation. The valvular endocardium and laminar basement membrane are the targets for the first wave of autoantibodies in RYK.

Recurrent streptococcal infections can lead to infiltration of lymphocytes through neovascularized areas of the flap scar tissue, leading to disease progression. As RYK develops, immune responses in the valve attempt to spread the epitope and recognize other components of the valve such as vimentin and collagen.

Thus, molecular mimicry between group A streptococci and "host" antigens plays an important role in the development of post-streptococcal complications. In RYK, laminin, an extracellular matrix molecule present in the valve basement membrane, captures cross-reactive anti-carbohydrate antibodies on the surface of endocardial cells and endothelial damage. or can cause inflammation. Streptococcal M protein/myosin cross-reactive T cells in activated endothelial valves

leads to further extravasation.

Spisok literatury / Quotations / References

1. Vesi L.G., Tani L. L, Daly DJ, Korgenski K, Miner L, Bale DJ. i dr. Vremennaya association appearance of mucoidnyx Streptococcus pyogenes strain
2. Bisno AL. 1995. Non-Suppurative Poststreptococcal Sequelae: Rheumatic Fever and Glomerulonephritis, p 1799–1810. In Mandell GL, Bennett JE, Dolin R (ed), Principles and Practice of Infectious Diseases, vol, vol 2 Churchill Livingstone, New York
3. Cunningham MW. Molecular Mimicry, Autoimmunity, and Infection: The Cross-Reactive Antigens of Group A Streptococci and Their Sequelae. Microbiol Spectr. 2019 Jul;7(4):10.1128/microbiolspec. GPP3-0045-2018. doi: 10.1128/microbiolspec.GPP3-0045-2018.
4. Cunningham MW. Rheumatic fever, autoimmunity, and molecular mimicry: the therapeutics. 2012;2:113. http://dx.doi.org/10.4172/2161-JOURNAL OF HEPATO-GASTROENTEROLOGY RESEARCH | JOURNAL HEPATO - GASTROENTEROLOGIST ISSLEDOVANI NO 2023 35 0665.100.0113.
5. Cunningham MW. Streptococcus and rheumatic fever. Curr Opin Rheumatol. 2012 Jul;24(4):408-16. doi: 10.1097/BOR.0b013e32835461d3. PMID: 22617826; PMCID: PMC3645882.
6. Ellis NMJ, Kurahara DK, Vohra H, Mascaro-Blanco A, Erdem G, Adderson EE, Veasy LG, Stoner JA, Tam E, Hill HR, Yamaga K, Cunningham MW. 2010. Priming the immune system for heart disease: a perspective on group A streptococci. J Infect Dis 202:1059–1067 10.1086/656214. PubMed
7. Jamshedovna A. M., Garifulina L. M. CHILDREN AND IN ADOLESCENTS OBESITY AND D VITAMIN DEFICIENCY , PROBLEM MODERN VIEWS // JOURNAL HEPATO-GASTROENTEROLOGIChESKIH ISLEDOVANI. - 2022. - T. 3. – no. 2.
8. Garifulina L. M., Turaeva D. X. Faktory riska razvitiya yazvennoy oblezi u detey, klinicheskoe techenie i therapy //Journal hepato-gastroenterologicheskih issledovaniy. - 2020. - T. 1. – no. 1.
9. Garifulina L. M., Ashurova M. D., Goyibova N. S. Sovershenstvovanie therapy of metabolic syndrome and podrostkov pri adjuvant α-lipoic acid //Science, technology and education. – 2018. – no. 10 (51). - S. 69-72.
10. Umarova S. i dr. Osobennosti techenia ostroy rheumaticheskoy lixoradki u detey Samarkandskoy oblasti //Journal hepato- Gastroenterology. -2021. -T. 2. – no. 3.2. - S. 15-17.
11. Marino A, Cimaz R, Pelagatti MA, Tattesi G, Biondi A, Menni L, Sala M, Calzi P, Morandi F, Cortinovis F, Cogliardi A, Addis C, Bellù R, Andreotti M and Varisco T (2021) Acute Rheumatic Fever: Where Do We Stand? An Epidemiological Study in Northern Italy. Front.
Med. 8:621668. doi: 10.3389/fmed.2021.621668

12. Roberts S, Kosanke S, Terrence Dunn S, Jankelow D, Duran CM, Cunningham MW. Pathogenic mechanisms in rheumatic carditis: focus on valvular endothelium. J Infect Dis. 2001 Feb 1;183(3):507-11. doi: 10.1086/318076. Epub 2000 Dec 20. PMID: 11133385.
13. Siegel AC, Johnston E, Stollerman GH. Controlled studies of streptococcal pharyngitis in a pediatric population, I: factors related to attack rates of rheumatic fever. N Engl J Med. (1961) 265:559–66. doi: 10.1056/NEJM196.109.212651201
14. Shapero K, Wylie-Sears J, Levine RA, Mayer JE Jr, Bischoff J. Reciprocal interactions between mitral valve endothelial and interstitial cells reduce endothelial-to-mesenchymal transition and myofibroblastic activation. J Mol Cell Cardiol. (2015) 80:175–85. doi: 10.1016/j. yjmcc.2015.01.006
15. Swedo SE, Leckman JF, Rose NR. From research subgroup to clinical syndrome: modifying the pandas criteria to describe PANS (pediatric acute-onset neuropsychiatric syndrome)
16. Singer HS, Gilbert DL, Wolf DS, Mink JW, Kurlan R. Moving from PANDAS to CANS. J Pediatr. 2011 doi: 10.1016/j.jpeds.2011.11.040.
17. Zabriskie JB. Rheumatic fever: the interplay between host, genetics, and microbe. Lewis A. Conner Memorial Lecture. Circulation. 1985 Wool;71(6):1077-86. doi: 10.1161/01.cir.71.6.1077. PMID: 3995703
18. Lim M. V. i dr. Arrhythmia of the role and detey rannego vozrasta //Dostizheniya nauki i obrazovaniya. - 2020. - No. 10 (64). - S. 77-79
19. Garifulina L. M. Characteristics of the cardiovascular system and arterial blood flow