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REVIEWS

Neonatal molecular pathologies induced by maternal anti-Ro and anti-La antibodies

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Abstract

Maternal antinuclear antibodies with anti-Ro or anti-La specificity might be pathogenic to the fetus and could induce molecular neonatal pathologies, such as neonatal lupus (NL) with or without congenital heart block (CHB). The cutaneous manifestations of neonatal lupus appear at birth or a few weeks later, and skin lesions may persist for weeks. While CHB is characterized by intrauterine bradycardia or low heart rates at birth and may persist for months, depending on the degree of blockage. Clinical and experimental data demonstrated that anti-Ro and anti-La autoantibodies functionally inhibit L-type calcium channels and induce abnormalities in electrical conduction of the cardiac myocytes. It has been 38 years since the first clinical description of CHB. Presently, the pathophysiology of CHB has been clarified through clinical and basic research studies.

Keywords: Congenital heart block, Anti-Ro antibodies, Anti-La antibodies, Calcium channels

Discovery of LE phenomenon

The first autoantibody described in lupus was 'Lupus factor' by Hargraves at the Mayo Clinic in 1948. He reported the 'LE phenomenon' in bone marrow aspirates of patients with systemic lupus erythematosus (SLE). This finding is considered as hallmark in the field of SLE research. In 1950, Haserik from Cleveland Clinic induced the LE phenomenon in normal bone marrow cells incubated with serum from lupus patients. The study also demonstrated that the LE phenomenon was induced by the 'anti-deoxyribonucleoprotein antibody' present in the serum of lupus patients. In 1957, Holman and Kunkel found anti-nucleoprotein antibodies, which preceded full descriptions of antinuclear antibodies. In 1961, Anderson and co-workers reported a precipitation reaction against salivary gland extracts, induced by antibodies named SjD and SjT. In 1966, Eng Tan described the serum reaction against tissues extracts that contained ribonucleoproteins, particularly against Sm (Smith protein). Clark and Reichlin in 1969 characterized the Ro antigen. Alspaugh and Tan reported the existence of the SSA antigen, and the research group later demonstrated that Ro is antigenically identical to SSA. The ribonucleoprotein La or SSB was also detected at the same time. Ro52 was characterized in 1988. These ribonucleoproteins serve as important biomarkers for autoimmune connective tissue diseases, especially for lupus and Sjögren's syndrome. These autoantibodies are also of particular importance during pregnancy because they can induce neonatal pathologies.[1]

Physiological roles of Ro and La ribonucleoproteins

The Ro60 is a donut-shaped protein with binding sites for RNA. This ribonucleoprotein is localized in the nucleus and cytoplasm and its function depends on its location. Ro60 is associated with Y RNAs, and these small non-coding RNAs may form complexes with Ro60, thereby preventing Ro60 from binding to misfolded ncRNAs. Study using *Deinococcus radiodurans* model has shown that an exonuclease polynucleotide phosphorylase (PNPase) is recruited to the Ro60-related Rsr/RNP complex. This recruitment induces conformational modification of the central cavity gateway of Ro60, which enables entry of a misfolded ncRNA for degradation.[2, 3] In addition, Ro60 is likely involved in editing misfolded 5S rRNAs and in micro RNA (miRNA) regulation.[4-6]

Ro52, another member of the Ro family, is not related to

Ro60 because it is encoded by a different gene. It has a molecular weight of 54 kDa and belongs to the tripartite motif protein (TRIM) family (TRIM21).This molecule has a RING finger domain located at the N-terminal. Since the Ro52 domain displays E3-ligase activity, Ro52 can ubiquitinate different interferon (IFN) regulatory factors. Thus Ro52 participates in the regulation of cytokine production and the innate immune response. Moreover, literature evidence substantiates the role of anti-Ro52 autoantibodies in inducing neonatal pathologies.[7, 8]

La or SSB autoantigen, a 48 kDa protein, functions as a transcription termination factor of RNA polymerase III. The ribonucleoprotein participates in the folding and maturation of RNA polymerase III transcripts and it also confers protection against exonuclease degradation. Additionally, the protein interacts with viral RNAs and plays a housekeeping role in the promotion of the global miRNA expression. Thus La binding to pre-miRNA is critical for stabilizing nascent pri-miRNA, and RNA binding occurs through the conserved La motif (LAM) and N-terminal RNA recognition motif (RRM1 and RRM2) domains.[9] This ribonucleoprotein is important for cellular physiology and recent research has shown its relevance in human cancer transcriptomes and cancer prognosis.[10]

Anti-Ro and anti-La autoantibody pathological markers

Anti-Ro and anti-La autoantibodies are more prevalent in autoimmune connective tissue disease (CTD), and the range of associated diseases varies depending on the serotype ethnic group and/or the technology used for autoantibody detection.[11] For example, anti-Ro is detected in 70-100% of patients with Sjögren's syndrome, whereas La/SSB is detected in 40-90% of Sjögren's patients.[12] In SLE patients, the prevalence of anti-Ro is approximately 68%,whereas anti-La prevalence is 23%. Notably, these autoantibodies are frequently detected as 'antibody clusters' in SLE and both anti-Ro/La autoantibodies are often associated with anti-DNA antibodies. Therefore, SLE patients displaying this autoantibody cluster, exhibit a clinical phenotype associated with increased kidney involvement, which is manifested by proteinuria and nephrotic syndrome. These patients may also have secondary Sjögren's syndrome.[13] In scleroderma and inflammatory myositis, anti-Ro prevalence is lower and ranges from 3-15%.[12]

Autoimmune diseases have been associated with detailed serotypes. For example, subacute cutaneous lupus erythematosus (SCLE) has been historically associated with anti-Ro60 or anti-La antibodies. The use of recombinant proteins, such as anti-Ro60 and anti-Ro52 autoantibodies, has expanded the antigenic specificity of SCLE. Anti-Ro52 is an additional component of the SCLE autoantibody cluster.[14-16] Therefore, the most objective methods for assessing certain autoantibodies as markers of disease should consider these autoantibody groups.

Apart from anti-Ro60, anti-Ro52, and anti-La antibodies, there is a wide range of other autoantibodies associated with systemic lupus erythematosus and Sjögren's syndrome. The association of this autoantibody cluster with neonatal pathologies, induced by maternal autoantibodies, is discussed in the following sections.

Neonatal pathologies induced by anti-Ro and anti-La antibodies

Neonatal lupus (NL), with or without congenital heart block (CHB), is induced by maternal antinuclear antibodies (ANAs). Skin manifestations of neonatal lupus appear at birth or a few weeks later, and cutaneous lesions may persist for 16 weeks. CHB, another neonatal pathology associated with maternal ANAs, is characterized by intrauterine bradycardia or low heart rates at birth. It may persist for months, depending on the degree of the blockage. Both of these neonatal pathologies are associated with anti-Ro and/or anti-La antibodies.[17-24]

Molecular determinants of neonatal pathologies

The descriptions of neonatal clinical syndromes, induced by maternal antibodies, raise several questions: Why do anti-Ro and anti-La antibodies induce skin lesions in neonatal lupus? What determines the characteristic atrioventricular (AV) block in CHB? Which factors influence fibrosis of the AV node and determine permanent AV blocks?

Lee and co-workers have concluded that anti-Ro (SS-A) antibodies may be directly involved in cutaneous disease. The study was conducted by transplanting the foreskin of newborn babies into nude mice and subsequently injecting with human anti-Ro antibodies. The mice developed erythematous lesions similar to those observed in neonatal lupus, and immune deposits of anti-Ro antibodies occurred at dermoepidermal junctions and other skin structures. Additionally, the mice demonstrated that these antibodies produced antibody-dependent

cytotoxicity.[25] Subsequent studies have shown that the autoantibodies were found to produce apoptosis of basal keratinocytes, creating a major source of intracellular antigens, which induces the formation of local immune complexes, cytotoxicity, and production of inflammatory cytokines. These mechanisms appear to cause the skin lesions in neonatal lupus, but they generally disappear after the elimination of maternal antibodies.[26]

An autopsy study of infants, died due to congenital heart block (CHB), born to mothers with SLE, has shown fibrotic changes in the atrioventricular node. The study also reported that these changes affected early atrioventricular node development. Thus, nodal fibrosis presumably contributed to CHB.[17] Buyon and co-workers have established the association of the CHB with maternal autoantibodies. They have also defined the autoimmune association of this neonatal pathology.

The research by Buyon and team has reported several clinical and experimental factors associated with the pathophysiology of congenital heart block.[27-32] The current review highlights some of the important factors. Clinical observations have shown that the fetus may develop CHB between 22 and 26 weeks of pregnancy in mothers with anti-Ro and anti-La antibodies. This risk has been confirmed in several clinical studies and in experimental mouse models in which pregnant females are injected with anti-Ro60, anti-Ro52, and anti-La antibodies. The degree of AV block varies in 2-7% of animals and it is comparable to the incidence in humans.[33-37]

Chronic effects of maternal antibodies on fetal hearts have been observed during the prenatal care of women with lupus or Sjögren's syndrome. Experimental studies conducted in animal models have demonstrated that induction of acute effects in animal models via anti-Ro/La perfusion on denervated hearts (Langendorff-perfused hearts) caused bradycardia.[35, 38-41] However, none of the clinical and experimental findings clarifies the underlying cause of bradycardia. The AV node is crucial for the genesis and propagation of the electric impulse into ventricles. Therefore, electropropagation is dependent on L-type calcium channels, and experimental evidence indicates that the CHB-IgG functionally inhibits L-type calcium channels and induces abnormalities in electrical conduction of the cardiac myocytes. These abnormalities include sinus bradycardia, prolonged PR, and complete AV block.[42-46]

L-type calcium channels and congenital heart block

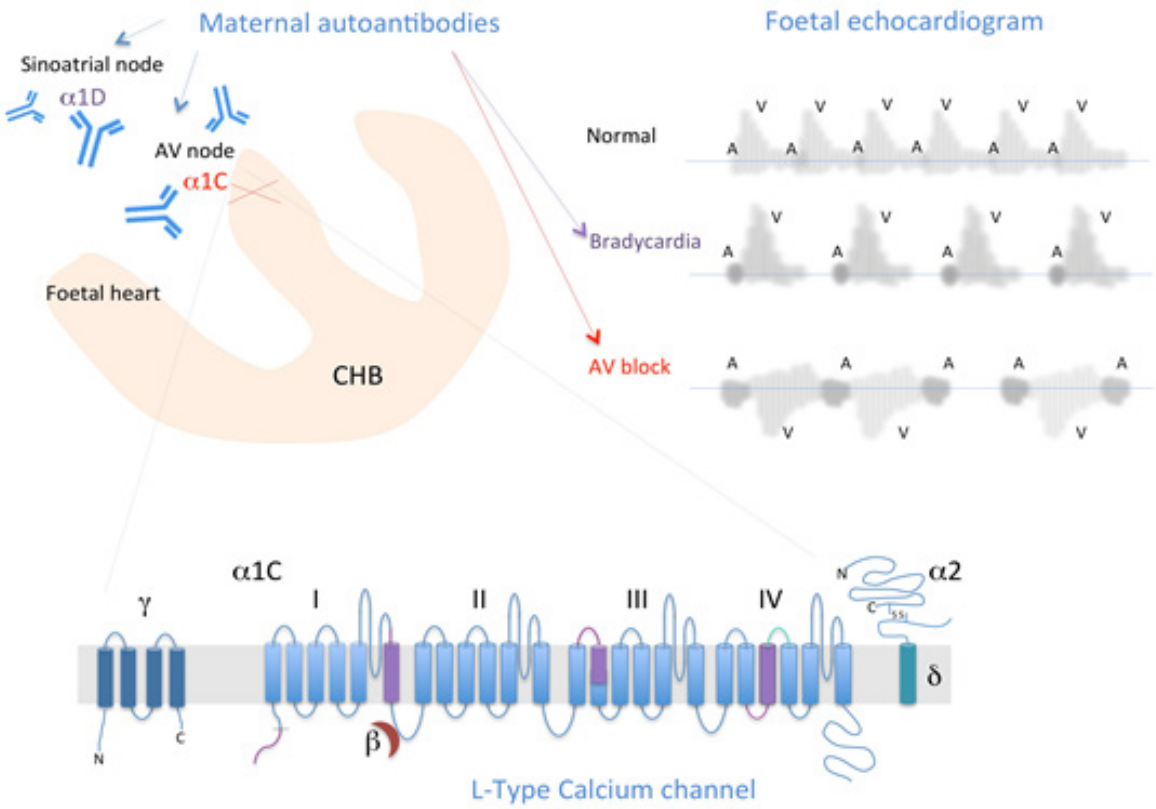
The calcium influx through calcium channels (Ca_V) in cardiac muscles generates multifunctional signals in excitable cells that trigger cardiac contraction. Ca_V also controls the duration of action potential and regulates gene expression. These voltage-gated calcium channels consist of at least four subunits; the α1 subunit forms the pore structure and contains four homologous domains, and each domain encompasses six membrane spanning segments that are connected by several intracellular loops. Each domain has a voltage sensor. Additionally, accessory subunits such as α2δ and β and γ are implicated in anchorage, trafficking, and regulatory functions.

Different *CACNA1* genes encode ten α subunits of the Ca_V1 channel. The $Ca_V1.2$ α1 gene contains 50 exons that display at least 13 alternative splicing loci, resulting in protein diversity. Therefore, during development, $Ca_V1.2$ α1 expression changes due to splice variants. These variants are associated with a depolarizing shift activation, suggesting a possible maturation role in fetal and mature isoforms of juvenile cardiomyocytes.[47, 48] Adult ventricular myocytes only express the $Ca_V1.2$ α1C subunit.[49]

CHB-IgG selectively inhibits the currents generated by L-type and T-type calcium channels in freshly isolated myocytes from the AV node. However, because α1C in the L-channel plays a minimal role in diastolic depolarization, the α1D isoform has emerged as an important component of the pacemaker node. This isoform is also expressed in neuroendocrine tissue. In contrast, the expression of α1D is distinct in the sinoatrial node. Therefore, these channels play an important role in inducing AV block and causing sinusal bradycardia in CHB. Brucato *et al.* have reported a few cases of infants with sinus bradycardia associated with anti-Ro maternal antibodies.[50] The *in vitro* studies conducted using the sera from babies with CHB had demonstrated that anti-Ro inhibited α1D and α1C channel activity, suggesting that the effect of anti-Ro may functionally affect the AV node and/or sinoatrial node (Fig. 1).[41, 51]

Although clinical and experimental evidence suggests that anti-Ro and anti-La antibodies induce congenital heart block, it is unclear how these maternal antibodies interact with their intracellular molecular targets in the fetal heart. Miranda-Carus and colleagues demonstrated that Ro and La ribonucleoproteins translocate to the

Fig. 1: Pathogenic effects of maternal anti-Ro and anti-La autoantibodies that cross-react with fetal heart antigens from the pore-forming subunit of α1C and α1D, and produce CHB



cell membrane of apoptotic cardiomyocytes.[52] Further, exposure to these proteins on the cell surface, in the presence of maternal antibodies, induces the formation of immune complexes, which are subsequently cleared by scavengers. The immune complexes stimulate signaling pathways in infiltrating macrophages, causing excess cytokine production including TGFβ. This in turn induces the transdifferentiation of cardiomyocytes into fibroblasts, ultimately producing fibrosis in the AV node.[53]

The α1D and α1C channels are functionally inhibited by maternal autoantibodies in CHB. However, the underlying mechanism remains unknown. The experiments conducted by Boutjdir *et. al* and other researchers have demonstrated that anti-Ro and anti-La autoantibodies cross-react with antigens from the pore-forming subunit of α1C and α1D channels. Additionally, a fraction of these maternal antibodies recognizes GST fusion proteins that express the extracellular S5-S6 loop of the first domain of the α1D subunit of L-type calcium and the α1G subunit of T-type calcium channels.[54, 55]

Conclusion

It has been 38 years and 25 years respectively, after reporting the first clinical description of CHB and its association with maternal anti-Ro and anti-La antibodies. The pathophysiology of CHB has been clarified by a large group of clinical and basic scientists at the cellular and molecular levels. Further research elucidating the role of autoantigen-autoantibody system may assist in developing newer strategies for treating autoimmune diseases.

Competing interests
The authors declare that they have no competing interests.

Disclosure
None

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