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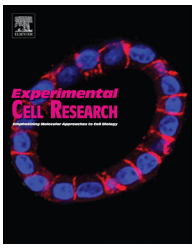

Review Article

Molecular mechanisms of congenital heart block

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ABSTRACT

Autoantibody-associated congenital heart block (CHB) is a passively acquired autoimmune condition associated with maternal anti-Ro/SSA antibodies and primarily affecting electric signal conduction at the atrioventricular node in the fetal heart. CHB occurs in 1–2% of anti-Ro/SSA antibody-positive pregancies and has a recurrence rate of 12–20% in a subsequent pregnancy. Despite the long-recognized association between maternal anti-Ro/SSA autoantibodies and CHB, the molecular mechanisms underlying CHB pathogenesis are not fully understood, but several targets for the maternal autoantibodies in the fetal heart have been suggested. Recent studies also indicate that fetal susceptibility genes determine whether an autoantibody-exposed fetus will develop CHB or not, and begin to identify such genes. In this article, we review the different lines of investigation undertaken to elucidate the molecular pathways involved in CHB development and reflect on the hypotheses put forward to explain CHB pathogenesis as well as on the questions left unanswered and that should guide future studies.

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Introduction

Autoantibody-associated congenital heart block (CHB) typically develops in absence of any cardiac structural abnormality in fetuses of women with antibodies to the Ro/SSA autoantigen. It is one of the manifestations of a passively acquired autoimmune condition denoted neonatal lupus syndrome (NLE), in which autoantibodies from the mother may also cause skin rash, elevated liver enzymes, and cytopenia in the infant. However, in contrast to other NLE manifestations that resolve once the maternal autoantibodies are cleared from the child′s circulation, CHB in the form of third-degree atrioventricular (AV) block appears irreversible and, if not fatal in utero or perinatally, often requires pacemaker implantation [1,2].

CHB is usually diagnosed between weeks 18 and 24 of pregnancy by fetal echocardiography techniques. Although it may initially appear as a first- or second-degree AV block (prolongation of the AV conduction time or blockage of some, but not all, atrial depolarizations), most cases present with fetal bradycardia and third-degree AV block. The electric signal conduction between cardiac atria and ventricles is then completely blocked and ventricular rates are typically between 50 and 70 beats per minute. Other arrhythmias, including sinus bradycardia, diverse atrial rhythms, and junctional ectopic and ventricular tachycardia, have also been reported in the context of CHB [3]. A more diffuse reaction within the endomyocardium, with an echocardiographic presentation of ventricular dilation and myocardial hypertrophy (cardiomyopathy) and/or increased endocardial echogenicity (endocardial fibroelastosis), is seen in approximately 20% of cases, and both conditions are markers of a poor prognosis [4].

The association of CHB with maternal autoantibodies to the Ro/SSA autoantigen, which comprises the two unrelated proteins Ro52 and Ro60, is well established [5–7]. Women carrying these antibodies may have rheumatic autoimmune diseases such as systemic lupus erythematosus (SLE) or Sjögren′s syndrome (SS), but may also be asymptomatic. Despite the vast prevalence of antibodies to Ro52 and to a lesser extent Ro60 in mothers of children with CHB, the risk of the fetus developing CHB in a single anti-Ro/SSA antibody-positive pregnancy is only 1–2% [8]. The fine specificity of anti-Ro52 antibodies or antibody titers have been suggested to further define the risk of CHB occurrence [7,9–12], however a recurrence rate of 12–20% in subsequent pregnancies [1,13–16], despite persisting maternal autoantibodies [17], suggest that other factors, whether fetal or maternal, are critical in the establishment of CHB.

At the cellular and molecular levels, CHB is characterized by the presence of immune complex deposits, inflammation, calcification, and fibrosis at the atrioventricular node in the fetal heart [18]. The presence of maternal autoantibodies at the site of injury, demonstrated more than 20 years ago [18], together with the recognized association of CHB with maternal anti-Ro antibodies, seem to point to these antibodies as the main drivers of CHB pathogenesis in the fetus. However, to date, the molecular mechanisms linking the placental transfer of autoantibodies to disturbances in the fetal cardiac conduction system are not fully elucidated. One of the major questions that remains to be answered is whether maternal antibodies exert their pathogenic effect by binding their cognate antigen in the heart and promoting inflammation – Ro52 and Ro60 happen to be intracellular proteins – or whether they cross-react with another molecule on the surface of fetal cardiac cells and directly affect the electrophysiology of the developing heart.

In this review, we will focus on the possible molecular mechanisms involved in the establishment of CHB in fetuses of anti-Ro antibody-positive mothers and further look at what other factors could contribute to the development of CHB in pregnancies at risk.

Anti-Ro60 antibodies, apoptosis and inflammation

Early demonstration of the presence of immunoglobulin deposition in the heart of human fetuses dying of CHB provided the first link between maternal anti-Ro autoantibodies and CHB pathogenesis at the cellular and molecular level [18,19]. Antibodies, complement, as well as signs of fibrosis and calcification were not only found at the primary site of cardiac injury, namely the AV node, but also throughout the myocardium, suggesting that the same molecular mechanisms may be involved in both the development of AV block and other cardiac manifestations associated with CHB such as other arrhythmias, dilated cardiomyopathy, and endocardial fibroelastosis.

A major stumbling block in understanding how anti-Ro antibodies could induce damage in the developing fetal heart proved to be the nature of the antibodies′ cognate antigens. Ro52 and Ro60 are two intracellular proteins; the former is a ubiquitin E3 ligase mainly expressed in immune cells and involved in the regulation of interferon regulatory factor-mediated immune responses ([20–22] and http://biogps.org [23]), while the latter is thought to play a role in RNA quality control [24]. However, the initial observation that Ro60 was relocated to surface blebs during apoptosis in keratinocytes [25] led to the demonstration by other researchers that Ro60 was also present on the surface of early apoptotic cardiomyocytes [26,27], and thereby exposed to binding by its cognate antibodies. By contrast, Ro52 was found to remain intracellular and was only bound by anti-Ro52 antibodies after plasma membrane breakdown in necrotic cells [27].

These findings and the observation of exaggerated apoptosis and infiltrating macrophages in the heart of fetuses dying of CHB [28] supported the hypothesis that maternal anti-Ro60 antibodies may bind to apoptotic cardiac cells during apoptosis normally occuring in the developing fetal heart and thus divert the removal of apoptotic debris from a non-inflammatory pathway to engulfment by macrophages through opsonization, leading to inflammation and more cell death. Subsequent in vitro studies have shown that opsonized apoptotic cardiocytes can indeed activate phagocytic cells to produce pro-inflammatory and pro-fibrotic cytokines, which in turn can promote the acquisition of a scarring phenotype by cardiac myofibroblasts [29–31]. A novel clearance mechanism, termed efferocytosis, in which resident cardiomyocytes participate in the physiological removal of apoptotic cardiomyocytes through binding of Ro60 on apoptotic cells, a process that would then be blocked by the binding of anti-Ro60 antibodies, has also been proposed [32]. However, a putative receptor for Ro60 on live cardiomyocytes has not been found yet.

While these in vitro studies support a mechanism by which anti-Ro antibodies (anti-Ro60 antibodies first binding to apoptotic cells and anti-Ro52 antibodies later binding to necrotic cells) may drive the establishment of inflammation and fibrosis in the developing fetal heart, eventually leading to complete calcification of the AV

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