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Lethal autoantibodies: Do they exist?*

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Heart rhythm disturbances belong to the most complex and pressing problems of cardiology. Sudden cardiac death (SCD) is an unexpected death due to cardiac causes that occurs in a short time period (generally within 1 hour of acute manifestations' onset). Tanatogenesis in this case is linked to ventricular arrhythmias. Patients with cardiomyopathies, myocarditis, ischemic heart disease and inherited cardiac channelopathies are at risk of SCD. However, a certain percentage of autopsy-negative cases of SCD in children and young adults remain unexplained even after a post-mortem genetic testing. Autoantibodies against cardiac proteins may be potentially involved in the pathogenesis of different heart diseases and in the occurrence of cardiac arrhythmias, including those, which can lead to SCD. In this review the prevalence of some antimyocardial autoantibodies in patients with different heart diseases and their mechanistical relevance are addressed. A classification of these autoantibodies is proposed, and their molecular and cellular effects are discussed.

Keywords: autoantibodies, autoimmunity, arrhythmia, sudden cardiac death, channelopathies, G-protein coupled receptors.

Introduction

Sudden cardiac death (SCD) is an unexpected death due to cardiac causes that occurs in a short time period (generally within 1 hour of symptoms onset) in a person with known or unknown cardiac disease. SCD constitutes major public health problem, accounting for approximately 25–50 % of all cardiovascular deaths. In overall population

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coronary heart disease, cardiomyopathies and valvular heart disease are the most common underlying pathology of SCD, while in children and young adults primary arrhythmia is more important. Ventricular tachyarrhythmias, which is the mechanism of more than two-thirds of cardiac arrests, typically result from the combination of a trigger (i.e. acute ischemia, hemodynamic alterations, autonomic nervous system fluctuations, drugs, electrolyte abnormalities, physical exertion, stress) upon an established substrate (i.e. ventricular hypertrophy, myocardial scar, conduction disorders, genetic channelopathies).

We analyze the probable contribution of different autoantibodies (AAb) to the development of SCD. The result of our work is the review article "Lethal immunoglobulins: autoantibodies and SCD" published in the Autoimmunity Reviews [1]. The present paper provides basic information about some AAb which can contribute to the cardiac diseases predisposing to SCD. However, there are some inconsistency regarding the prevalence of these AAb both in health and in cardiac diseases. This is probable because of the different methods of AAb detection, which have been used by different research groups (ELISA, Western blot, functional bioassays).

Cytotoxic and functional autoantibodies

We propose a classification of AAb in SCD and its underlying pathologies based on their targets and hence depending on their possible effects. Cytotoxic AAb can cause complement-mediated cell death or antibody-dependent cell-mediated death, which manifests on tissue level as a cardiomyocyte's loss, accompanied in some cases by severe inflammation. Considering myocardial basic properties, cell death followed by myocardialfibrosis can lead to decreased contractility and conduction disorders, which play a role of an established substrate in ventricular tachyarrhythmias.

Functional AAb can target receptors of neurotransmitters or hormones, enzymes (those involved in energy metabolism and membrane transport) and membrane channels, which are known to be affected in genetic cardiac channelopathies. These AAb modify activity of proteins, which they target and hence mimic common triggers of SCD.

Examples of AAb which contribute to the cardiac diseases predisposing to SCD

The titer of anti-cardiac troponin I Ab elevates in the sera of patients with several diseases underlying SCD. It was shown that immunization of mice with cardiac troponin I induced severe inflammation in the myocardium followed by fibrosis and heart failure with an increased mortality. Furthermore, mice which were preimmunized with murine cTnI before coronary artery ligation showed greater infarct size, more fibrosis, higher inflammation score, and reduced systolic function. In patients with acute coronary syndrome these AAb can serve as an independent predictor for left ventricular remodeling, thereby providing the background for cardiac rhythm disturbances in the future.

Anti-β1-adrenergic receptor Ab is one of the most studied AAb in cardiovascular diseases. The contribution of these AAb was demonstrated for different pathologies underlying SCD. Multivariate analysis further showed that the presence of anti-β1-AR Ab is an independent predictor of SCD in idiopathic dilated cardiomyopathy and chronic heart failure [2]. The suggested mechanism by which anti-β1-AR Ab might trigger SCD is the

electrical instability created by the increased beating frequency of the cardiac myocytes, which was verified in cell-based functional assays. Substrate establishment for arrhythmia can be also provided by anti-β1-AR Ab. These AAb transactivate receptor tyrosine kinases, which mediate hypertrophy, angiogenesis and fibrosis. Maturation and degranulation of cardiac mast cell, which play a major role in cardiac remodeling are also intensified by anti- β1-AR Ab.

Another group of functional AAb target enzymes, which are related to energy metabolism of cardiomyocyte. Anti-Na/K-ATPase Ab have an ability to inhibit Na/K-ATPase. The prevalence of these AAb is higher in patients with dilated cardiomyopathy. Ventricular tachycardia and SCD were independently predicted by the presence of these Ab, as well as poor systolic function [3]. Further, it has been shown that immunization of rabbits with sarcolemmal Na/K–ATPase results in myocardial hypertrophy due to left ventricular pressure overload and myocardial fibrosis. Interestingly, that coexistence of gastropathies and cardiac arrhythmias has been noticed by clinicians long ago. Na/K–ATPase and gastric H/K–ATPase have common epitopes. Therefore, infection with Helicobacter pylori, which induces AAb against H/K–ATPase, might lead to disturbances in cardiac rhythm and myocardial function. In line with this assumption, seropositivity for Helicobacter pylori was significantly associated with risk of short-term adverse outcomes (including SCD) in patients with acute coronary syndrome.

AAb against ion channels are also associated with SCD. Interaction of Ca2+, K+ and Na+ channels with AAb which demonstrate agonist-like and antagonist-like activities, simulates dysfunction of these ion channels caused by mutations in the encoding genes. Anti-Ro/SSA Ab, which are classical AAb with prevalence up to 0.5 % in general population, cross react with several ion channels. Congenital heart block in fetuses exposed to maternal Anti-Ro/SSAis a common knowledge. However, these AAb can also induce alterations of QT interval in adults, thus predisposing them to life-threatening ventricular tachyarrhythmia. In a prospective cohort of 25 patients who experienced torsades de pointes independently of ongoing therapies and concomitant diseases, circulating anti-Ro/SSA 52kD Ab were frequently detected (60 % of cases), mostly in patients with no history of autoimmune diseases [4].

Conclusion

An increasing number of studies provides insight into the pathogenetic role of AAb not only in classical autoimmune diseases e.g. rheumatoid arthritis or systemic lupus erythematosus, but also in those illnesses which are generally not yet accepted as autoimmune ones. Moreover, according to a novel concept, AAb are not exclusively linked with the triggering of autoimmunity. At least autoantibodies targeting G protein-coupled receptors in healthy donors were shown to provide homeostatic functions and form network signatures. Therefore, fluctuations in these AAb network signatures could contribute to progression of non-autoimmune diseases. Indeed, pathophysiological relevance of several AAB, which are not uncommon in patient with cardiac diseases predisposing to SCD, has been proved both on cell level and in the laboratory animals (including passive transfer of AAb and active immunization of the animals with corresponding antigens) [1]. At the same time, up to 70 % of SCD in subjects with structurally normal hearts remains unexplained even after molecular autopsy, which can identify genetic cardiac channelopa-

thies [5]. AAb against cardiac ion channels could be responsible for at least some of these cases, providing examples of autoimmune phenocopies of the genetic disorders.

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