Autoimmunity and the Pathogenesis of Myocarditis

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The ability to distinguish between self versus nonself is the most salient feature of the immune system. It is of vital importance for the immune system to mount vigorous humoral and cellular responses to foreign antigens. On the other hand, it is equally important for the immune system to be tolerant against self-antigens. Tolerance can be maintained either by physical elimination (clonal deletion) or functional inactivation (clonal anergy) of the autoreactive T or B cells. Several excellent reviews have explored in depth the mechanisms by which clonal deletion or anergy might occur.1-3 The failure to delete or inactivate autoreactive T or B cells would lead to generalized or organ-specific autoimmunity. In this issue of Circulation, Sharaf and colleagues show that the cardiac sarcoplasmic reticulum calcium ATPase may be a candidate autoantigen in experimental cardiomyopathy. I will briefly review key concepts in immunology before discussing the validity of this claim.

T and B lymphocytes are the two cognate arms of the immune system.6 Each lymphocyte generates its own receptor by recombinating small segments of genes that encode these receptors. Like a random number generator, the repertoire of the lymphocyte receptors is almost limitless. The immune system, however, has evolved mechanisms to select out lymphocytes with useful receptors and to select against lymphocytes with harmful receptors. T cells express on their surface T-cell receptors that recognize antigens presented by the major histocompatibility complex (MHC) on the surface of the antigen-presenting cells, which could be dendritic cells, B cells, or macrophages. There are two different classes of MHC molecules: class I, which is formed by a heavy chain and β2-microglobulin, and class II, which is formed by an α-chain and a β-chain. The class I MHC molecules present antigenic peptides to CD8-positive T cells, whereas the class II MHC molecules present peptides to the CD4-positive T cells. The MHC molecules have small grooves on their surface that allow binding of antigenic peptides. T-cell receptors only recognize antigenic peptides binding to the MHC groove but cannot recognize antigenic peptides by themselves. This process is called MHC restriction and is due to a positive selection process that occurs during T-cell maturation in the thymus. Equally important during T-cell development is a negative selection process that weans out T cells bearing receptors directed against self-peptides in the context of self–MHC molecules. Failure of the negative selection process could lead to leakage of autoreactive T cells from the thymus to the periphery, which would result in autoimmunity.

Activation of mature T cells in the periphery requires two signals: One signal is delivered by binding of the T-cell receptor to the peptide/MHC molecule; the other signal involves the interaction of accessory molecules (most importantly, the CD28/CTLA4 and the B7 antigens).3-7 If both signals are successfully delivered, T cells will enter the cell cycle and proliferate. On the other hand, if the T-cell receptor binds to the peptide/MHC molecule in the absence of a costimulatory signal, it will be inactivated. Clonal anergy thus may play an important role in controlling autoreactive cells in the periphery. Another potential mechanism in harnessing autoreactive lymphocytes in the periphery is through an antigen-specific suppression system. This process is much less well understood, however.

B cells use surface immunoglobulin as their receptors, which recognize antigens directly without the participation of MHC molecules. B-cell tolerance differs from that of the T cell in several ways. Immature B cells that encounter self-antigens are functionally inactivated.4 They express on their surface a smaller number of IgM but a normal number of IgD. Under pathogenic conditions, the functionally inactivated, autoreactive B cells may be reactivated and give rise to vigorous antibody response. Reversible B-cell anergy was elegantly demonstrated by a double transgenic system by Goodnow and colleagues4 and may account partly for the pathogenesis of autoimmune diseases. Other regulatory mechanisms such as clonal deletion, active suppression, or idiotypic regulation also could play a role in B-cell tolerance. Sometimes autoreactive B cells may be present but functionally inert because of the lack of T-cell help. In fact, T-cell help is essential for antibody production by most B cells. Thus, an autoantigen must have epitopes that can be recognized by autoreactive T and B cells. Because of the difference in the design of T-cell and B-cell receptors, small antigenic peptides derived from the autoantigen are recognized by T cells, whereas native autoantigen is recognized by B cells.

Autoimmunity is a result of the breakdown of self-tolerance. The triggers for autoimmunity are usually environmental in nature: either viral or bacterial infec-
tions or drugs. However, the host must have the right genetic environment for autoimmunity to develop. For example, the host MHC molecules must be capable of binding antigenic peptides. Non-MHC loci such as the T-cell receptor and immunoglobulin genes also determine whether an autoimmune response is feasible. Many microbial proteins have significant short-sequence homology to self-proteins. For example, the group A streptococci cell wall M protein shares homologous peptide sequences with cardiac myosin. Thus, microbial infection can trigger an immune response against self-proteins through a process called molecular mimicry. Some bacterial toxins such as staphylococcal enterotoxin B are capable of activating a large number of T cells with specific T-cell receptor β-chain. These bacterial toxins are called superantigens and may play a critical role in unleashing the autoreactive T cells in the periphery. For example, the superantigens may be chance activators of few autoreactive T cells that have escaped the negative selection process in the thymus. These autoreactive T cells could be expanded above a threshold to cause tissue damage by themselves or to induce the production of pathogenic autoantibodies.

A large number of autoantibodies have been associated with the development of cardiomyositis. They include cardiac α-myosin, adenine nucleotide translocator, β1-adrenergic receptor, calcium channel complex, laminin, heat shock protein, and now cardiac sarcoplasmic reticulum (SR) ATPase. Sharaf and colleagues generated a monoclonal IgM antibody (4C11-20.21) against canine SR-ATPase. 4C11-20.21 cross-reacted with cardiac SR-ATPase from mouse, rat, human, and rabbit. 4C11-20.21 inhibited the enzymatic activity of affinity-purified cardiac SR-ATPase by 75% but had no effect on skeletal muscle SR-ATPase. Eleven CAF1/J mice were immunized with purified canine SR-ATPase, and myocarditis was detected as early as 3 weeks after immunization. Myocarditis can also be induced by growing the hybridoma 4C11-20.21 in the peritoneal space of immunodeficient SCID/CB17 mice. Immunoperoxidase transmission electron microscopy detected localization of 4C11-20.21 to the SR-like structures in cardiac myocytes. Taken together, cardiac SR-ATPase may play a role in the pathogenesis of autoimmune cardiomyositis.

It is not possible to choose the true culprit from the large number of cardiac autoantigens in clinical cardiomyositis. Autoimmunity may play a significant role only in a subset of patients with cardiomyositis (such as idiopathic dilated cardiomyopathy). Depending on the triggering event, different autoantigens could be preferentially used in the amplification of T-cell and B-cell autoreactivity. It is important to stress that not every autoantibody is pathogenic. Certain autoantibodies have been shown to play a direct role in the pathogenesis of clinical autoimmunity, such as anti-acetylcolline receptor antibody in myasthenia gravis and antiphospholipid antibodies in hypercoagulable states. Most autoantibodies are probably just markers of immune responses, activated during the course of particular antigenic stimulation, and do not play a role in pathogenesis.

Autoantibodies directed against cell surface proteins have a reasonable chance of causing damage to the cell. Autoantibody directed against intracellular autoantigens is unlikely to be pathogenic unless the cell membrane is already leaky. There is no known mechanism for these antibodies to enter intact cells in sufficient amounts and to escape lysosomal degradation. Obviously, autoantibodies could react against two different proteins, one on the cell surface (for entry) and the other inside the cell (for causing injury). The difficulty in accepting SR-ATPase as an authentic autoantigen is its intracellular location. Although SR-ATPase is adjacent to the T-tubule, it is still topologically segregated from the extracellular milieu.

To identify the cause of autoimmunity is akin to solving a murder mystery. Unless a smoking gun is produced, most of the so-called autoantigens must be presumed innocent. One must carefully assess not only B-cell but also T-cell reactivity against these autoantigens before reaching a guilty verdict. However, with increasing understanding of the mechanism of self-tolerance induction, these mysteries will eventually be solved.

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References


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