Current and Newly Emerging Autoimmune Diseases

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KEYWORDS

• Autoimmunity • Self-tolerance • Autoantibodies • Self-reactive T cells

KEY POINTS

- There are many autoimmune diseases that are recognized in domestic animals.
- The descriptions of diseases provide examples of the magnitude of immune targets and the variable nature of autoimmune diseases.
- Autoimmune diseases recognized in dogs, cats, and horses can affect single or multiple body systems including skin, blood (anemia), endocrine, ocular, and neuromuscular.

INTRODUCTION

Autoimmunity: Horror Autotoxicus

The immune system is designed to permit discrimination between cells and tissues defined as self and infectious agents, so that the strong and effective mechanisms for causing destruction of potential pathogens or other elements foreign to the host are properly targeted. When these defense mechanisms are instead directed against the host, autoimmune disease results. This concept of horror autotoxicus was coined by Dr Paul Ehrlich in the early 1900s. Shortly thereafter the first autoimmune diseases were described.[1] Thus, autoimmune diseases are caused by the stimulation of an immune response that reacts with self. There are a variety of ways that this can occur, some well recognized and others not yet determined.[2,3] It is known that inheritance of certain genes can influence susceptibility to autoimmune diseases and that environmental factors can interact with the immune system of the host to precipitate autoimmunity. The increased incidence of some autoimmune diseases in certain dog or cat breeds shows that inbreeding can increase the frequency of genotypes that are associated with those autoimmune conditions. Many well-defined human autoimmune diseases, such as immune-mediated anemia and autoimmune thyroiditis (Hashimoto's thyroiditis), have been recognized in dogs for many years, whereas other diseases are currently under investigation as potentially having an autoimmune cause.

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Development of Self-Tolerance

Development of self-tolerance involves both central and peripheral mechanisms; these may eliminate or suppress self-reactive lymphocytes, thereby preventing immune recognition of self. Central tolerance occurs during fetal life. The thymus is an important organ of the immune system, and during fetal life it is responsible for removing T lymphocytes that are capable of binding with high affinity to self-peptides. After entering the thymus from the bone marrow, T lymphocytes acquire T-cell receptors in the thymic cortex. Once these cells enter the thymic medulla their receptors are tested for reactivity with self-peptides and are negatively selected if they show a high affinity for self-antigens. In this process T cells whose receptors bind tightly to the self are stimulated to undergo apoptosis and they die. The remaining T cells with a moderate affinity for self are preserved.[2] Moderate affinity is required because self-recognition in the context of a normal immune response is required.[2]

Besides the major histocompatibility determinants that are definitive for cells from an individual (and therefore determine what is self), there are organ-specific molecules that the immune system must not recognize as foreign. To tolerize the T cells to these organ-specific determinants/antigens the thymic epithelium expresses these multiple determinants that are present on organs of the body. A gene called the Aire gene is referred to as an autoimmune regulator. It is a transcription factor responsible for the expression of these self-proteins on the medullary epithelial cells. This ability to express multiple antigens in the thymus during fetal development allows the remaining T-cell population to be screened for nonreactivity with self-determinants on various tissues and cells in the body. In some human patients a genetic defect in the Aire gene has been described and linked with the disease called autoimmune polyendocrine syndrome type 1.[2]

Despite the expression of self-determinants in the thymus and the selection of T lymphocytes that occurs there, the depletion of self-reactive T lymphocytes is not complete. There are, however, other mechanisms that maintain tolerance, such as T-regulatory cells. The T-regulatory cells have the cell surface markers CD4+, CD25+, and the transcription factor fox P3. These cells operate by production of cytokines that can suppress the immune response.[2]

B lymphocytes develop in the bone marrow of mammals and there they acquire receptors that bind to foreign antigens. Self-tolerance in the B-cell population occurs through several mechanisms, including clonal deletion, anergy, and receptor editing.[2] But B cells require T-cell help for initiation of antibody production (with the exception of T-independent antigens, which can stimulate immunoglobulin [Ig] M only). Thus, in the absence of self-reactive T cells, a potentially self-reactive B cell is held in check and does not proliferate and produce self-reactive antibodies. On occasion, B cells can produce autoantibodies after activation of T cells that recognize an epitope cross-reactive with the host's tissues and are thereby able to act as helpers for B cells with receptors for epitopes on that antigen.[2]

Autoimmune Diseases

Autoimmune diseases can be classified by body systems that are affected. Some conditions influence multiple body systems, whereas others affect only one organ. There are several lupuslike syndromes described in human patients as well as the well-defined disease systemic lupus erythematosus (SLE), a multisystemic autoimmune disease. There are examples of both multisystem and organ-specific autoimmune diseases in dogs, cats, and horses. The more specific autoimmune diseases that affect a single type of cell, such as immune-mediated anemia and immune-mediated