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Autoimmune Diseases

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Autoimmune Diseases

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INTRODUCTION

Autoimmune diseases are a poorly understood group of diseases, affecting approximately 5% of the population in the United States. A growing number of disorders are being designated as autoimmune diseases. Autoimmunity is caused by a breakdown in self-tolerance (ie, tolerance to one's own antigens [autoantigens]). Some forms of autoimmunity occur naturally and are physiologic; however, autoimmunity is largely a morbid process. An autoimmune disease can be defined as an illness that is associated with the activation of T lymphocytes, B lymphocytes, or both when the patient has no ongoing infection and when there is no other discernible cause of the patient's condition. This manual briefly discusses mechanisms involved in the development and the loss of self-tolerance and then uses case-based discussions to highlight 4 gastrointestinal disorders with a probable autoimmune basis: chronic active autoimmune hepatitis (AIH), celiac sprue, pernicious anemia, and Crohn's disease.

SELF-TOLERANCE

Early in fetal development, T and B lymphocytes in the thymus, bone marrow, and central lymphoid tissues develop the capacity to react to all potential environmental antigens as well as to autoantigens. This establishes a complete immune repertoire, such that an immune response can potentially be implemented against any antigen. To prevent an immune response from being directed toward autoantigens, a process of lymphocyte deletion ensues, in which those lymphocytes directed at autoantigens are deleted. The process of lymphocyte deletion requires exposure of all autologous molecules to the thymic and bone marrow central lymphoid tissue. The process hinges on the fact that autoantigens are generally lethal to developing, central lymphocytes—a phenomenon termed *central tolerance*.

Additionally, self-tolerance can occur peripherally, rather than by an interaction between autoantigens and developing, central lymphocytes. One mechanism asso-

ciated with the peripheral development of self-tolerance relates to the fact that complete lymphocyte reactivity depends on costimulatory processes, which are brought about by some cytokines and some ligands on other cells. In some cases, reactive lymphocytes, including self-reactive lymphocytes, are not provided with these costimulatory chemicals, and the lymphocytes subsequently undergo apoptosis.

The immune response to autoantigens can also be regulated by other lymphocytes, other cytokines, or by processes that change the responsiveness of a self-reactive lymphocyte from a destructive mode (a classic T helper cell 1 [Th1] response) to the nondestructive Th2 response. All of these regulatory measures make the immune response to autoantigens less pronounced, conferring upon lymphocytes relative anergy.

The precise molecular mechanisms involved in the loss of self-tolerance are still poorly understood. It is commonly thought that the loss of such tolerance is caused by the introduction of antigens that mimic host antigens, allowing immune cross-reactivity; microorganisms and drugs are obvious implicated examples. Although data have accumulated supporting this mechanism, it is far from being well established scientifically. Another process that may interfere with self-tolerance is a disruption in the process of programmed cell death, or apoptosis, relating to self-reactive lymphocytes. A disruption of apoptosis has been observed experimentally in models of autoimmune diseases.¹

Regardless of the molecular events that confer self-tolerance or its converse autoimmunity, there appear to be both susceptibility factors (presumably genetic) and environmental or internal trigger mechanisms involved. One model for understanding pathologic autoimmunity is that of a chromosomal or genetic defect (with the potential for causing an autoimmune process) that is dormant until an appropriate environmental trigger is introduced, perhaps an environmental antigen that molecularly mimics an autoantigen. Although the autoimmune diseases of the gastrointestinal tract are imperfectly understood according to this model, much progress has been made in understanding them. Some major gastrointestinal diseases with a probable autoimmune basis are as follows: autoimmune hepatitis (types 1, 2, and 3),