Immunodeficiency Diseases with Rheumatic Manifestations

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• Immunodeficiency • Autoimmunity • Immune dysregulation
• Lupus • Arthritis • Vasculitis

Primary immunodeficiencies have traditionally been described in patients with recurrent, severe, or unusual infections. Before the broad availability of effective antibiotics and ready access to safe, plentiful immunoglobulin preparations, patients often succumbed to infections at an early age. As patients began to survive longer, the conundrum of autoimmunity associated with immunodeficiency became apparent; that is, why would an immune system that is incapable of effective responses to foreign antigens seemingly be capable of responding to host antigens and causing autoimmunity? Over time, more of the molecular and cellular mechanisms that underlie this autoimmunity have come to be understood, but many questions remain. As new genetic defects have been identified in association with immunodeficiency, it has become clear that autoimmunity or autoinflammation is the primary clinical manifestation of some disorders.

PREVALENCE OF PRIMARY IMMUNODEFICIENCY DISORDERS

In the absence of uniform, population-based programs that screen for all types of immunodeficiency, the actual incidence and prevalence of primary immunodeficiency disorders (PIDDs) is not clear. A recent randomized survey of 10,000 US households, however, estimated the prevalence of diagnosed PIDDs at approximately 1:1200 individuals.[1] Blood bank studies evaluating donors for the most common immunodeficiency, selective IgA deficiency, have estimated an even higher prevalence (1:333

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individuals among US donors).[2] Many of these are asymptomatic from the standpoint of recurrent or severe infections, but there is significant evidence that patients with selective IgA deficiency are at increased risk for autoimmunity.[3–5]

THE 4 MAJOR COMPARTMENTS OF THE IMMUNE SYSTEM

The body's natural defenses against pathogens include a network of physical barriers (eg, skin and mucosal surfaces), immune cells (eg, lymphocytes and phagocytes), and soluble mediators (eg, complement, antibodies, and cytokines). Trying to remember and consider all these pieces can be daunting to busy clinicians so there is value in using a framework of 4 major compartments when thinking about and evaluating patients. The 4 major compartments are complement, phagocytes, B cells, and T cells (**Fig. 1**). The Complement and phagocyte compartments together make up the majority of the immune system that is referred to as *innate*. The innate immune system mounts rapid responses to infectious organisms by recognizing patterns of molecules or groups of molecules that are present on pathogens but typically not on human cells. Each time a particular pathogen is encountered, the components of the innate immune system respond but do so in the same way each time because they are unable to adapt or improve their response. In contrast, the B-cell and T-cell compartments make up the *adaptive* portion of the immune system. The adaptive immune system has the ability to adapt and change each time it encounters a pathogen. This adaptability makes it possible to generate memory responses. Because of the time required to modify the response to each individual pathogen, the adaptive system typically takes on a major role in fighting pathogens after the innate system has already begun its response.

Together, the innate and adaptive systems work to maintain normal host function and resistance to infection. Disruption of any part of this intricate network can result in increased numbers of infections, susceptibility to specific pathogens, or autoimmunity. The pattern of infections, clinical symptoms, and laboratory abnormalities differs depending on which part of the immune system is affected and can provide important clues to the diagnosis in each individual case. Because some deficiencies can be rapidly fatal whereas others are mild, making a timely and accurate diagnosis is critical

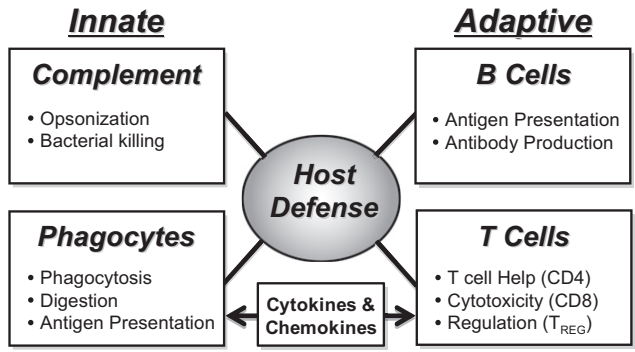

Fig. 1. The 4 major compartments of the immune system and their most important functions. The complement and phagocytes compartments constitute much of the innate portion of the immune response whereas the B-cell and T-cell compartments constitute most of the adaptive parts of the immune response. All of the compartments function together to create the host defense. In addition to direct cell-cell interactions, cytokines and chemokines play a critical role in communication of one compartment with another.