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Review Series

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Putting together the autoimmunity puzzle

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Introduction

The term "autoimmune disease" refers to a heterogeneous group of more than 80 chronic illnesses that develop when the immune system attacks its host cells, tissues, and organs, often with disabling or even fatal consequences to the host. Although the incidence of each autoimmune disease as an individual entity can be considered relatively infrequent, as a group autoimmune diseases account for the third most common category of diseases in the United States — after cancer and cardiovascular disease — affecting about 5% to 8% of the general population (1).

Phenotypes in autoimmune diseases vary greatly because the target cell(s) and affected organ(s) are different. The diverse clinical manifestations among autoimmune patients often result in problematic identification of optimal treatments and uncertainty in anticipating disease progression and/or outcomes. However, common sub-phenotypes shared by multiple autoimmune diseases can at times be observed, for example, the presence of non-specific autoantibodies such as antinuclear antibodies and rheumatoid factor or high levels of pro-inflammatory cytokines including TNF-α, IL-1, and IL-6. This aspect may reflect possible commonalities of some pathogenetic events — even when triggered or sustained by distinct factors — that facilitate the progression from reversible loss of self-tolerance to chronic autoimmunity.

Tight control of immunoregulatory mechanisms is required to avoid autoimmunity

A recurrent, apparently ingenuous query is why autoimmune diseases develop. The immune system has evolved to provide protection from a myriad of pathogens and transformed cells, discriminating between non-self and self, to avoid responses that could harm the host. The fragile balance between self-recognition and protection from non-self requires a tight control of the activity of multiple immune cell populations, i.e., those cells that produce potentially damaging inflammatory, cytolytic, or neutralizing molecules that should protect the host from injury.

Tolerance to self relies upon central and peripheral mechanisms that finely tune immune cells toward promotion or inhibition of selected activities. Yet the environment can impose a drastic pressure that often dramatically affects the homeostatic regulation and the adaptation of the host to changing situations. This can lead to changes in the network of interactions among cells, including modulation of the expression of soluble factors, changes in cell-cell interactions, migration and localization of immunocompetent cells at sites that can be distant from those of initial cell activation, and diversity of the lymphocyte repertoire (i.e., clonotypic expansion). If unbalanced or inadequately controlled, effector and regulatory responses can disrupt immune tolerance and allow autoimmunity.

The general concepts of autoimmune pathogenesis are elaborated by Abul Abbas and colleagues, who describe the predisposing, concomitant, and ongoing events that lead to development, progression, resolution, and exacerbation of dysfunctional immune responses in autoimmunity (2).

The autoimmunity puzzle

The pathogenesis of autoimmune diseases typically involves interactions among genetic, epigenetic, hormonal, environmental, and immune factors. On a predisposed genetic background, environmental factors (such as biologic, physical, or chemical agents) can facilitate the development and/or progression of autoimmune reactivity, which is then sustained by dysregulated immune responses. The key contribution of genetics to autoimmunity can be seen in the familial aggregation (tendency to cluster in families) as well as in the reduced disease concordance rate among siblings when compared with the rate for monozygotic twins. However, the lack of complete concordance between monozygotic twins implies additional factors such as environmental insults and immune differences (e.g., repertoires) that are specific to an individual. David Hafler and colleagues discuss how certain genetic backgrounds can predispose some individuals to develop abnormal immune responses when encountering environmental triggers (3). With the notable exception of monogenic autoimmune conditions, it is the combination of predisposing genetic variants that most frequently leads to an autoimmune phenotype under appropriate conditions. Indeed, when considered individually, most of the common vari-

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ants generally confer relatively modest increments in risk and only explain a small proportion of heritability. Hafler and colleagues discuss how genome-wide association studies have identified genetic risk variants affecting key biological pathways disrupted by autoimmunity, and how selected variations in non-coding DNA regions are beginning to be linked to mechanisms of autoimmunity (via enhancers, epigenomic annotation, etc.). In this regard, the importance of epigenetic changes has recently been the focus of intense investigations to explain the missing genetic heritability in autoimmunity.

Epigenetic modifications are stable, reversible changes in gene expression or cell phenotypes secondary to DNA or chromatin modification or post-transcriptional mechanisms that do not affect the DNA per se but that are transferable to progeny for generations (or indefinitely) (4). These modifications include DNA methylation, histone post-translational modifications, and microRNA (miRNA) activity. Mark Ansel and Laura Simpson discuss how epigenetic modifications that regulate miRNA expression can critically affect immune cell programming, development, and function as well as pathogenicity (5). These authors review the importance of miRNAs in regulating key events in the mechanisms of central and peripheral immune tolerance, the potential utility of miRNAs as autoimmune biomarkers, and how the failure to maintain epigenetic homeostasis can result in an altered transcriptome and subsequent aberrant gene expression and autoimmunity.

Interestingly, miRNAs are disproportionately represented on the X chromosome (113 miRNAs) as compared with the Y chromosome (2 miRNAs), and some of those X-linked miRNAs have been associated with autoimmune phenotypes, as discussed by Philippa Marrack and colleagues (6). These authors focus on the fact that the expression and activity of certain genes and/or their products in immune cells can be modulated by sex hormones, and they discuss the mechanisms by which femaleness increases risk (7), including through age-related changes in the immune system that differ between females and males. In addition to explaining the molecular basis of sex bias in autoimmunity due to hormonal differences, Marrack and colleagues discuss X chromosome-linked genes and skewed X chromosome inactivation (non-random X chromosome silencing in females) as key contributors to the sexual dimorphism in autoimmunity. They also review the recent work showing that sex hormones can influence autoimmunity by modulating gut microbiota.

Intestinal flora can also mold the cytokine repertoire. Vijay Kuchroo and colleagues point to the fact that changes in intestinal flora and diet have recently been shown to alter cytokine regulation and promote the development of pro-inflammatory, pro-autoimmune Th17 responses (8). These alterations could favor an increase in the production of cytokines with pro-inflammatory activities, which is central in the pathogenesis of autoimmunity, together with the compromised frequency and/or function of specific immune cell populations, particularly in patients with active disease. For example, a decrease in the frequency of functional Tregs has been reported for several autoimmune diseases (9).

Tregs serve as a brake on the immune system, and their dysfunction is associated with multiple autoimmune disorders. Jeffrey Bluestone and colleagues discuss how $CD4^+$ Tregs control the outgrowth of potentially pathogenic self-reactive cells (10). In highlighting the evidence for a key role of these suppressor cells in the prevention and suppression of autoimmunity, these authors review the experimental support for the existence of functionally and phenotypically distinct suppressor cell subsets and their complementary role in regulating immune responses. By including considerations of Treg stability under changing environments and the recent immunotherapeutic approaches for the restoration of peripheral immune tolerance, these authors ponder the current challenges in achieving remission of autoimmunity without continuous immune suppression (i.e., by maintaining uncompromised overall immune responses).

The restoration of immune homeostasis might be accomplished by enhancing suppressive immune responses, to limit the damage caused by T cells or B cells (or by the cytokines that they produce). George Tsokos and colleagues analyze the central role of T cells in orchestrating autoimmune responses and the characteristics of these cells in a prototypical systemic autoimmune disease (11), while Betty Diamond and Jolien Suurmond address the importance of the mechanisms that drive autoantibody pathogenicity and the mechanisms by which autoantibody production is initiated (12). Autoantibodies appear long before clinical symptoms of autoimmunity, thus representing a marker for potential disease development (13). Their predictive value is also reflected by the finding that there is an approximately six- to eight-fold increase in the risk of developing an autoimmune disease when only one autoantibody is present compared with three autoantibodies present (14).

Autoantibodies develop because of inefficient removal of autoreactive B cells, which in healthy individuals are eliminated both at central and peripheral levels. In untreated patients with active autoimmune disease, both central and peripheral B cell tolerance checkpoints can be defective (15). Fritz Melchers describes three checkpoints of central tolerance for B cells in the bone marrow and discusses the importance of the microenvironment in the effective removal of the vast majority of B cell clones that express polyreactive antibodies (16). He then discusses the mechanisms of peripheral B cell tolerance, namely checkpoint 4, which removes peripheral autoreactive new emigrant B cells before they enter the mature naive B cell pool (17), and checkpoint 5, which eliminates accidental products of hypermutation that are created during antibody affinity maturation (18).

Conclusions

In summary, this Review series surveys the complex mechanisms of autoimmunity and the potential new therapies that might target critical disease pathways, cells, and molecules. Much has been learned about the pathogenesis of autoimmune disease since the original formulation of the concept of *horror autotoxicus* that was forged by Paul Ehrlich during his study of the development of hemolytic antibodies in animals injected with blood of unrelated species (19–24). The failure to develop autoantibodies upon immunization of animals with their own blood or the blood of their own species led Ehrlich to hypothesize that an organism would not endanger itself by forming toxic autoantibodies (19–24). However, this is exactly what happens in autoimmunity, when an immune attack on self-components leads to illness and loss of organ function.

Although dysregulated immune responses in autoimmunity stem from alterations in intertwined biological processes at the innate and adaptive immune system levels, the fact that multiple autoimmune diseases share some mechanisms suggest the existence of common therapeutic targets. This provides encouragement to a field that has been revolutionized by the clinical success of biologics as effective therapeutic agents (e.g., against proinflammatory cytokines). Much remains to be done, and if we are to move forward in the field and improve the treatment of autoimmune diseases, we must continually advance our understanding of basic mechanisms.

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