CHAPTER

3

General Features of Autoimmune Disease

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OUTLINE

A host of diseases are characterized by the activation of the immune system in the absence of an external threat to the organism. In these diseases, inflammation and tissue damage occur in the absence of trauma, infection, toxin exposure, or tumor growth (Rose and Bona, 1993). These diseases can be characterized as those that display the activation of the innate immune system and an excess of inflammatory mediators, but no evidence of an antigen-specific immune response; familial Mediterranean fever and other inflammasome diseases, Behçet disease, even atherosclerosis, can be considered to fall within this category. Alternatively, there are diseases characterized by an activation of the adaptive immune response with T and B lymphocytes responding to self-antigens in the absence of any detectable microbial assault or tumor invasion. These diseases constitute the vast majority of diseases considered to be autoimmune in origin. There are over 80 defined autoimmune diseases in composite affecting 5%–7% of the population. Moreover, their incidence is increasing (Lerner et al., 2015; Patterson et al., 2009).

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INNATE IMMUNE ACTIVATION

The activation of the innate immune response is a feature of many, perhaps all, autoimmune diseases (Mills, 2011). This activation may be the primary event involved in triggering the disease process. One example is the activation of the innate immune system in systemic lupus due to complement deficiencies that permit an excess accumulation of proinflammatory apoptotic debris (Elkon and Santer, 2012; Macedo and Isaac, 2016; Manderson et al., 2004). Increased production of type 1 interferon is present in first degree relatives of some lupus patients suggesting that this enhanced innate immune activation may be a triggering immune abnormality in these patients (Niewold, 2011). Likewise, inflammatory bowel disease (IBD) is associated with genetic alterations in multiple innate pathways including bacterial sensing, autophagy, and endoplasmic reticulum (ER) stress, leading to an increased inflammatory response to intestinal flora (de Souza and Fiocchi, 2016; Stange and Wehkamp, 2016). The innate immune system also provides critical defense at epithelial barriers; loss of the mucin layer and the antimicrobial peptides that it contains allows access of bacteria to epithelial cells and the activation of myeloid cells that help to initiate disease (Exley et al., 2016; Shikhagaie et al., 2017; Stange and Wehkamp, 2016; Wenink et al., 2017). It is also apparent that the innate immune system can be activated secondarily in autoimmune disease. Immune complexes containing endogenous Toll-like receptor (TLR) ligands, such as DNA, RNA, or citrullinated proteins, can activate dendritic cells (DCs) and other myeloid cells to amplify inflammatory pathways (Green and Marshak-Rothstein, 2011; Sokolove et al., 2011). Tissue injury also leads to the activation of innate immune cell networks (Kawai and Akira, 2010; Miyake and Yamasaki, 2012); thus once autoimmune-triggered tissue injury is ongoing, the innate, as well as the adaptive, immune system is always engaged.

A low threshold for the activation of myeloid cells and differentiation of monocytes to DCs predisposes to autoimmune disease in animal models, and blockade of pathways of the innate immune system can ameliorate many autoimmune diseases. In particular, TLR signaling, both in myeloid cells and lymphocytes, seems to be a critical feature of many autoimmune diseases as deletion of MyD88, a common component of the signaling cascade for several TLRs, and neutralization of HMGB1, a cytokine which synergizes with many TLR agonists, can prevent or treat murine models of diabetes, rheumatoid arthritis, systemic lupus, IBD, and more (Andersson and Tracey, 2011; Herlands et al., 2008; Pagni et al., 2010; Rivas et al., 2012). Cytosolic innate receptors also play a role in the initiation of autoimmune responses; for example, cyclic GMP-AMP synthase (cGAS) deficiency protects completely against Systemic Lupus Erythematosus (SLE) induced by an overabundance of intracellular DNA (Gray et al., 2015a). The success of TNF and IL-6 inhibition in rheumatoid arthritis and of TNF and IL-12 inhibition in IBD also attests to the involvement of the innate immune response in autoimmune diseases. However, even when the innate immune system is involved, some diseases respond better to certain cytokine inhibitors than others. IL-6 inhibition for example is effective for the treatment of rheumatoid arthritis and giant cell arteritis but not for ankylosing spondylitis (Koster et al., 2016; Loricera et al., 2015; Schoels et al., 2013), whereas TNF inhibition is effective for both rheumatoid arthritis and ankylosing spondylitis and for Takayasu's arteritis but not for giant cell arteritis; these differences reflect the different functions of these cytokines but their exact relationship to pathogenesis of each of these diseases is still a subject of investigation (Muratore et al., 2017; Schoels et al., 2013).

Other innate immune cells may also contribute to disease pathogenesis. The role of neutrophils has recently been highlighted in lupus which is characterized by the presence of an atypical neutrophil population that is subject to cell death by NETosis and that may release pathogenic oxidized DNA after exposure to TLR containing immune complexes (Caielli et al., 2016; Grayson et al., 2015; Jorch and Kubes, 2017; Kienhofer et al., 2017; Villanueva et al., 2011). Innate immune cells derived from the lymphoid lineage but without T or B-cell receptors (TCR or BCR) have important homeostatic functions, particularly at epithelial barriers, but may become dysregulated in autoimmunity and secrete pathogenic cytokines. An expansion or imbalance of several subsets of these cells has been observed both in the blood and tissues of patients with a variety of autoimmune diseases and in some instances these changes correlate with disease activity, although a causative link remains to be shown (Exley et al., 2016; Shikhagaie et al., 2017; Wenink et al., 2017).

Interestingly, the innate immune response, and, more specifically, monocyte activation, is under the control of the cholinergic antiinflammatory pathway. This pathway is initiated in the central nervous system, is mediated through the vagus nerve (cholinergic) and the splenic nerve (adrenergic), and culminates in the induction of acetylcholine production by splenic T cells that then inhibits the production of inflammatory cytokines by monocytes that express an $\alpha 7$ cholinergic receptor (Chavan et al., 2017; Rosas-Ballina and Tracey, 2009). The identification of this pathway has provided a potential therapeutic target that regulates multiple cytokines simultaneously, and there are current trials to exploit this pathway in IBD, rheumatoid arthritis (RA), and SLE (Chavan et al., 2017; Koopman et al., 2016).

CELLS OF THE ADAPTIVE IMMUNE SYSTEM

There is a coordinated interplay among the cells of the adaptive immune system with DCs, T cells, and B cells collaborating to activate this branch of the immune system. DCs activate T and B cells, T cells activate DCs and B cells, and B cells activate only T cells. This cascade leads to an immune response that recognizes a broad spectrum of epitopes of microbial pathogens and enlists multiple effector mechanisms (Blanco et al., 2008; Goodnow et al., 2010; O'Shea and Paul, 2010; Shlomchik, 2008; Steinman, 2007).

DCs are antigen-presenting cells (APCs) that are the intermediary between the innate and the adaptive immune systems. DCs can be tolerogenic in their resting state, but when activated, they are critical in initiating an immune response (Devi and Anandasabapathy, 2017; Kalantari et al., 2011; Morel and Turner, 2011). Similarly, monocytes clear the apoptotic debris generated from the billions of cells that die daily in a tolerogenic fashion but, when exposed to inflammatory mediators, they differentiate into macrophages or DCs (Dominguez and Ardavin, 2010; Horton et al., 2017; Poon et al., 2014; Takenaka and Quintana, 2017). The activation of the innate immune system, therefore, can establish a population of immunogenic DCs for the activation of the adaptive immune system. Like essentially, all cells, monocytes, and DCs display surface expression of class I major histocompatibility complex (MHC) molecules, which permit the presentation of intracellular antigens to T cells. DCs and some macrophage subsets also express class II MHC molecules, which are present on a much more restricted set of cells and permit the presentation of extracellular antigens (Banchereau and Steinman, 1998). Multiple alleles of class I and II molecules exist, and, thus, each individual has a unique set of MHC molecules (Beck and Trowsdale, 2000). DCs also express an array of nonpolymorphic receptors, such as TLRs, and pattern-recognition receptors that bind microbial antigens, products of tissue injury, and nucleic acids (Kawai and Akira, 2010, 2011). Engagement of these receptors causes the DCs to upregulate expression of costimulatory molecules and to deliver an obligatory second signal for activation (Dzopalic et al., 2012; Engels and Wienands, 2011; Vincenti and Luggen, 2007). It is important to note that each DC can recognize and respond to a broad spectrum of microbial antigens.

MHC molecules have innate properties in that they also interact with Killer cell immunoglobulin receptor (KIR) that have inhibitory functions on innate lymphoid cells; these interactions prevent the killing of MHCI expressing cells. Some KIR receptors have an activating function, and these can enhance immune responses to pathogens and may predispose to autoimmunity (Espeli et al., 2010; Rajalingam, 2011).

Each T and B cells express a single receptor for antigen. These antigen receptors are acquired by gene rearrangements that occur in somatic cells (Gellert, 2002); thus there is no inheritance of the T- or B-cell repertoire. T cells mature in the thymus (Stritesky et al., 2012). Each T cell expresses a unique receptor (TCR) that recognizes a molecular complex on the surface of an APC consisting of a class I or class II MHC molecule associated with a small peptide derived from an intra- or extracellular protein antigen, respectively. Signaling through both the TCR and costimulatory molecules is needed to effect activation of mature T cells (Engels and Wienands, 2011; Esensten et al., 2016; Vincenti and Luggen, 2007; Weinstein et al., 2012). B cells also express a single receptor for antigen, but the BCR recognizes native antigen rather than processed antigen. B-cell activation also requires signaling through both the BCR and costimulatory molecules (Crow, 2004). Activated B cells not only secrete antibody but can also function as APCs to engage a greater number of T cells in the immune response. B cells also secrete molecules that are essential for lymphoid organization and for the formation of the germinal center (Qin et al., 2007; Wang et al., 2001) and can secrete a variety of cytokines (Leon et al., 2012; Lipsky, 2001; Marino and Grey, 2012).

A critical feature of both T and B cells is that they proliferate in response to antigenic stimulation to create clonal expansions of cells with a unique antigenic specificity and to develop cells with a memory phenotype (Bishop et al., 2003; Chen et al., 2017; Grossman et al., 2004; McKinstry et al., 2010; Watkin et al., 2017). Memory cells have an accelerated and enhanced response following reexposure to antigen. B cells have the added feature of undergoing class switching of the immunoglobulin heavy chain gene and random somatic mutation of the BCR followed by the selection of those B cells with improved affinity for the eliciting antigen (Lee et al., 2016; Li et al., 2004; Victora and Nussenzweig, 2012). Thus there is a progression from low-affinity IgM antibodies to high-affinity IgG antibodies during the course of an immune response. The memory response is characterized by the activation of high-affinity IgG-producing B cells.

Plasma cells also constitute part of the memory B-cell response as they can be extremely long-lived and may, therefore, secrete pathogenic antibodies for long periods. While some autoimmune diseases appear to involve the generation of short-lived plasma cells and are, therefore, self-limiting, others are characterized by the continued presence of autoantibodies for years, in some cases, regardless of disease activity (Liu et al., 2011).

For the immune system to function effectively there must be a sufficient number of T and B cells that can respond to an enormous diversity of microbial antigens, and a means of regulating those cells that respond to self-antigen.

DEFINING AUTOIMMUNE DISEASE

An autoimmune disease is a condition in which tissue injury is caused by T-cell or antibody reactivity to self. The immune activation may be initiated by infection but then persists in the absence of any detectable microbial antigen (Davidson and Diamond, 2001; Rose and Bona, 1993). It is important to state that although many diseases considered autoimmune display reactivity to self, evidence may still be lacking that the self-reactivity is, in fact, responsible for tissue damage. It is sometimes possible to determine whether autoantibodies are pathogenic by transferring them to a rodent host; however, T-cell reactivity is not transferable from humans to rodents because T-cell activation and T-cell effector function occur only in the context of self-MHC molecules. Thus demonstrating the pathogenicity of the autoimmune response has not been accomplished in all autoimmune diseases. In some instances, a disease is presumed to be of autoimmune origin only because B- and T cells are present in affected tissue.

Animal models of autoimmune disease have been enormously useful in aiding our understanding of both disease inception and disease pathogenesis (Bar-Or et al., 2011; Billiau and Matthys, 2011; Howell, 2002; King, 2012; Lam-Tse et al., 2002; Mandik-Nayak and Allen, 2005; Peutz-Kootstra et al., 2001; Wooley, 2004). Some autoimmune diseases can be triggered in animals by immunization with self-antigen or adjuvants and some develop spontaneously. While animal models have been very important in informing our understanding of autoimmunity, it is important to recognize that we do not know how closely they reflect human disease (Bodaghi and Rao, 2008; Kollias et al., 2011). Some may be more similar to human disease in the effector mechanisms of tissue injury than in the mechanisms of induction of autoreactivity. Indeed, autoantibody-mediated tissue damage is probably most alike in human disease and animal models (Monach et al., 2004). It is also important to consider that there may be extensive heterogeneity in human disease and that the animal models we study intensively may reflect only a subset of individuals with a given disease. A challenge that confronts us is to understand which animal models are most similar to human disease and can teach us most about the genetic predisposition to disease, external triggers of disease, disease pathogenesis, and effective therapy. The opportunity to generate new models based on the functionality of autoimmune risk haplotypes arises from an increasing understanding of genetic risk and may provide better insights into patient stratification and precision therapeutics. As more data are generated from human subjects, mouse models will also be needed to explore the functions of genes relevant to the progression of autoimmune disease.

PREVALENCE OF AUTOIMMUNITY

It is striking that while each autoimmune disease individually affects only a small number of people, the prevalence of all autoimmune diseases is approximately 5%–7% (Cooper et al., 2009; Hayter and Cook, 2012; Jacobson et al., 1997; Wang et al., 2015). Patients with one autoimmune disease also have an increased risk of a second autoimmune disease (Cooper et al., 2009; Jacobson et al., 1997; Marrie et al., 2015). Two critical facts about autoimmune disease are important in understanding the high frequency of these diseases. First, autoreactivity is an aspect of every normal immune system. In fact, the repertoire of immunocompetent lymphocytes that provides protective immunity is selected based on autoreactivity (Gu et al., 1991; Nobrega et al., 2002; Vallejo et al., 2004). T cells need to recognize self-antigen within the antigen binding cleft of MHC in order to survive the initial steps of T cell selection, whereas circulating B cells receive survival signals as a result of weak interactions with autoantigens (Gu et al., 1991; Nobrega et al., 2002; Vallejo et al., 2004). Second, autoreactivity is a crucial component of immune homeostasis. The regulation of physiologic autoreactivity helps to shape the immune system so that it does not become the pathogenic autoreactivity associated with tissue damage; this is an active process that requires constant vigilance. The immune system maintains a precarious balance between the two: too little response leads to potential neglect of danger, while an overexuberant response can potentially lead to autoreactivity. How this balance is maintained is discussed next. Second, there is a genetic predisposition to autoimmunity, and aspects of this predisposition may be similar for many different autoimmune diseases (Cho and Gregersen, 2011; Gutierrez-Arcelus et al., 2016), perhaps because these genetic traits have been selected for their

capacity to protect against infectious diseases (Liao et al., 1995; Liu et al., 2009). Furthermore, some of the studies of the genetic basis of autoimmunity show that the genetic factors governing autoreactivity are distinct from those governing specific organ vulnerability (Liao et al., 1995; Liu et al., 2009) or severity of tissue damage (Martini et al., 2014). Thus individuals may share pathways promoting autoreactivity, yet present with different autoimmune diseases (Cho and Gregersen, 2011; Cotsapas et al., 2011).

GENETICS AND EPIGENETICS OF AUTOIMMUNITY

Monogenic Disease

It is clear from epidemiologic studies and studies of animal models of autoimmune disease that there is a genetic component to essentially every autoimmune disease. A few autoimmune diseases appear to be monogenic diseases (Melki and Crow, 2015). The human disease autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, an autoimmune disease of multiple endocrine organs, is a consequence of a deletion in the autoimmune regulator (AIRE) gene that encodes a protein that causes tissue-specific genes to be expressed in medullary epithelial cells in the thymus (Akirav et al., 2011; Anderson and Su, 2011). These cells mediate negative selection of T cells reactive with peptides that derive from tissue-specific proteins. In the absence of AIRE expression, a spectrum of autoreactive T cells fails to be deleted; these cells mature to immunocompetence and mediate an immune attack on various organs. The absence of the AIRE gene appears sufficient for autoimmunity, although the phenotype of the disease that emerges, even within a single family, can be quite variable. Similarly, a defect in the Fas gene can also lead to autoimmunity. The Fas protein is expressed on activated lymphocytes. Engagement of Fas by Fas ligand leads to the death of the Fas-expressing cell, a process critical for downregulating the immune response. Individuals deficient in Fas expression have a disease called autoimmune lymphoproliferative syndrome (ALPS) characterized by an excess of T and B cells and by autoantibody production (Fleisher et al., 2001; Grodzicky and Elkon, 2002; Madkaikar et al., 2011). Of note, not all individuals with deficient Fas expression display ALPS; thus even in this disease, other genes must modulate disease phenotype. Deficiency in certain complement components also results in a high incidence of the autoimmune disease SLE. In this case, the mechanism is thought to be a failure of clearance of immune complexes and apoptotic material resulting in an overload of immunogenic material that can activate the immune system through engagement of TLRs and other innate receptors (Lewis and Botto, 2006; Pettigrew et al., 2009). Deficiency of enzymes that remove DNA to prevent TLR activation can result in SLE (Bodano et al., 2016; Rice et al., 2008; Sisirak et al., 2015; Stetson et al., 2017; Yan, 2006). Deficiency of Foxp3 or of IL2Rα that are required for the development of regulatory T cells (Tregs) is both associated with severe autoimmunity affecting the bowel and endocrine organs (Lewis and Botto, 2006; Ochs et al., 2007; Pettigrew et al., 2009; Sakaguchi, 2007).

Polygenic Disease

For most autoimmune diseases, multiple susceptibility loci contribute to the disease phenotype. Studies from mouse models of autoimmune disease have also revealed the presence of loci that suppress the autoimmune phenotype (Wakeland et al., 2001). Thus an individual's risk of developing an autoimmune disease depends on a summation of susceptibility and resistance loci. A major advance in the last 15 years has been the application of genome-wide association studies (GWAS) that evaluate large numbers of common single nucleotide polymorphisms (SNPs) as genomic markers in well-defined patients and control populations. Studies in multiple autoimmune diseases have definitively linked a number of genetic variants to disease susceptibility (Deng and Tsao, 2010; Flesher et al., 2010; Harley et al., 2008). Most of these variants are in noncoding regions of a gene and control basal expression [expression quantitative trait loci (eQTL)] or expression following stimulation (response eQTLs) (Gutierrez-Arcelus et al., 2016; Wang et al., 2015).

Despite the identification of a large number of autoimmunity associated genes using the GWAS approach, the polymorphic locus most closely linked to autoimmunity in studies of virtually every autoimmune disease is the MHC locus, an association that has long been known (Gutierrez-Arcelus et al., 2016). For example, anti-CCP seropositive rheumatoid arthritis in the Caucasian population is highly associated with the expression of a set of DR4 alleles that have a particular structural motif, called the "shared epitope" (Winchester, 2004). Reactive arthritis occurs in individuals expressing B27 or, less commonly, B7 class I MHC molecules. In type I diabetes both pathogenic and protective DR and DQ alleles have been identified and the heterodimer encoded by DQA1*0501 and

DQB1*0302 confers very high risk. In celiac disease, 98%–99% of the affected individuals bear a susceptibility DQ allele; thus DQ testing can be used clinically to exclude disease with a high degree of certainty (Wolters and Wijmenga, 2008). Multiple sclerosis and systemic lupus display particular human leukocyte antigen (HLA) associations, as do many other autoimmune diseases (Fernando et al., 2008; Tomlinson and Bodmer, 1995; Winchester, 2004; Wong and Wen, 2003). The basis for the association of MHC polymorphisms with autoimmune disease is still for the most part unknown but might be due to T-cell recognition of particular pathogenic peptides that can bind within the peptide binding cleft of certain MHC molecules, cross-reactivity of peptides derived from infectious organisms with self-peptides, or alterations in the T-cell repertoire that result in a decrease in Tregs (Cho and Feldman, 2015; Raychaudhuri et al., 2012; Sollid, 2017).

With the exception of the MHC, the other genetic risk loci for autoimmunity that have been identified by GWAS involve a conglomeration of approximately 300 relatively common alleles, each of which confers only a modest risk, with odds ratios $<1.5–2$ (Gutierrez-Arcelus et al., 2016; Wang et al., 2015). Some, but not all, of these polymorphisms cross major racial groups. In mouse models, there is evidence that genetic susceptibility can be a consequence of combinations of genes within each gene locus and not the consequence of a single gene in each locus. For example, a region on chromosome 1 that is implicated in autoimmunity in systemic lupus erythematosus has several subloci which contribute to various aspects of the disease (Morel, 2010; Morel et al., 2001).

Shared Risk Alleles

Clinically, it has long been appreciated that autoimmune diseases cluster in families. The biologic basis for this observation is now clear; the same susceptibility genes can influence many different autoimmune diseases. For example, a polymorphism of cytotoxic T-lymphocyte–associated antigen (CTLA4), an inhibitory costimulatory molecule present on activated T cells, conveys risk for insulin-dependent diabetes, autoimmune hemolytic anemia, and Graves' disease (Ueda et al., 2003), while the CARD15 (NOD-2) gene is associated with both IBD and psoriasis (Bene et al., 2011; Rahman et al., 2003; Russell et al., 2004; Zaki et al., 2011). Similarly, polymorphisms in PTPN22, a molecule that regulates lymphocyte receptor signaling, is associated with type 1 diabetes, SLE, RA, and Crohn's disease but not with multiple sclerosis (Burn et al., 2011). The differences in disease phenotype may lie in associated genes, those governing target-organ susceptibility or those that modulate disease severity (Russell et al., 2004) or in different environmental exposures. Indeed, the genetic association of HLA and PTPN22 with cyclic citrullinated peptide (CCP)-positive rheumatoid arthritis is considerably magnified in smokers, leading to a postulated pathogenic mechanism whereby damage to the lung by cigarette smoke induces autoimmunity to citrullinated proteins in genetically susceptible individuals (Mahdi et al., 2009).

One of the most striking advances made as a result of GWAS has been the identification of immune pathways associated with autoimmune tendencies, some of which are shared across diseases. A metaanalysis of the autoimmunity associated genes identified thus far suggests that individual diseases can be clustered in groups that share pathogenic mechanisms. For example, using this type of methodology, disease associations with polymorphisms in IL-2 can be distinguished from those associated with IL-21 that is within the same genetic locus (Cotsapas et al., 2011). The genetic studies in sum suggest that autoimmunity can result from a defect in almost any pathway of immune homeostasis as they affect thresholds for innate immune cell activation and for negative and positive selection of lymphocytes prior to immunocompetence and the activation of autoreactive lymphocytes (Gutierrez-Arcelus et al., 2016; Marson et al., 2015).

Applying this new information to individual patients represents a major challenge since attribution of a SNP identified by GWAS to a single gene often requires extensive resequencing of large regions of DNA from many patients. Furthermore, since the GWAS approach identifies only common polymorphisms with frequencies within the population of $>1\%–5\%$, the risk variants identified by this method account for only a small proportion of the overall heritability of the disease (Deng and Tsao, 2010; Gutierrez-Arcelus et al., 2016). New methodologies to identify rare variants or copy number variations are being developed, but these variations will only be seen in a small fraction of those who are affected. Finally, establishing a link between genetic variations, gene function, and disease pathogenesis has not been easy. Many of the risk alleles identified by GWAS are common variants with subtle effects that are compatible with normal immunological function; in most cases, the variation is not within the gene coding region but governs gene expression (Rieck et al., 2007; Zhang et al., 2011). Combinations of genes are starting to be identified in longitudinal cohorts that predict the risk of disease (Achenbach et al., 2013; Langefeld et al., 2017; Laufer et al., 2017; Lempainen et al., 2015). More studies will be

required to understand how the disease-associated variants affect immune responses and interact with each other to contribute to the risk of a particular disease. One approach is to knock-in the disease-associated variants into mouse models of autoimmunity. For example, mice with a knock-in of a variant of the RNA sensor IFIH1 that confers a high risk for type 1 diabetes have a higher basal level of type I interferons and an increased propensity to develop diabetes compared with their wild-type littermates that is dependent on the RNA sensing function of IFIH1 and is further increased by the introduction of the diabetes associated PTPN22 variant (Gorman et al., 2017). As the function of all the autoimmune-associated variants is similarly clarified and potentially pathogenic pathways are identified, personalized interventions may become possible.

Contribution of Epigenetic Modifications and Transcriptional Regulation

Despite the advances in understanding the genetics of autoimmunity, concordance in monozygotic twins remains below 50% for most diseases, indicating a contribution from random and/or environmental factors. Epigenetic alterations that change the access of DNA regions to the transcriptional machinery through DNA methylation or histone acetylation, or alterations that silence transcription through inhibitor miRNAs, or alter protein longevity or processing within the cell through ubiquitination or citrullination, may all influence the immune system function (Long et al., 2016; Tost et al., 2017). T-cell differentiation, for example, is influenced by epigenetic mechanisms that reinforce the T-cell cytokine producing phenotype (Nakayamada et al., 2012; Pereira et al., 2017; Qiu et al., 2017). While it is clear that epigenetic alterations may profoundly influence cell phenotype, the application of this concept to autoimmunity remains in its early phases. Abnormalities of methylation or acetylation or expression of particular miRNAs has been demonstrated among peripheral blood cells of patients with several autoimmune diseases (Ceribelli et al., 2011a, 2011b; Ghosh et al., 2012) and there are several examples of deficiencies of particular enzymes or miRNA species causing spontaneous autoimmune disease in mice (Glasmacher et al., 2010; Namjou et al., 2011). The inactivation of the X chromosome that contains several genes involved in immune responses is not always complete, perhaps contributing to the increased risk of autoimmunity in women (Wang et al., 2016). A study of discordance in monozygotic twins for disease demonstrates a similar epigenome despite lack of disease concordance, suggesting that epigenetic profiling might be useful in assessing risk for disease (Generali et al., 2017). Another study of patients with rheumatoid arthritis suggests that epigenetic profile correlates with response to therapy (Tost et al., 2017). Since epigenetic modifications are not immutable, they must be analyzed in all relevant tissues and cell types in order to find those that associate with disease risk, severity or response to therapy. As these are identified, the impact of drugs that modify the relevant epigenetic profiles will be of great interest.

HORMONES AND AUTOIMMUNITY

Since many autoimmune diseases occur more commonly in women than in men, there have been several investigations of the role of sex hormones in autoimmune disease. Animal studies have shown multiple effects of sex steroids on the immune system (Rubtsova et al., 2015); studies of mice lacking an estrogen receptor have clearly attributed estrogen effects to signaling through the estrogen receptor α. However, it has been difficult to extrapolate the conclusions from these studies to autoimmunity. Not all autoimmune diseases are more common in women. Some, such as ankylosing spondylitis, have a higher incidence in men. Furthermore, the predisposition to autoimmunity can be sex determined or hormonally modulated; thus the higher incidence of disease in women may not always reflect the influence of female hormones on the immune system. The X chromosome, in fact, harbors many genes of immunologic interest. In gonad matched mice the presence of XX confers a greater susceptibility to pristane-induced lupus than does XY (Smith-Bouvier et al., 2008). Similarly, in humans, the XXY phenotype is associated with an increased prevalence of SLE. Nevertheless, the genetic components of the XX chromosome that are associated with lupus risk are not yet clear. The evidence also shows that the effects of sex hormones differ in different diseases. While there is significant evidence that estrogen can exacerbate systemic lupus, estrogen seems to protect against rheumatoid arthritis. In addition, estrogen or other sex hormones might affect target-organ antigen display, target-organ susceptibility to immune-mediated damage or even the composition of the gut microbiota. Thus there is no simple paradigm to explain the relationship between sex and autoimmunity (Grimaldi et al., 2005).

AUTOIMMUNITY AND CENTRAL TOLERANCE

The hallmark of the autoimmune disease is the activation of self-reactive T and B lymphocytes. A major mechanism of self-tolerance is the elimination of self-reactive immature lymphocytes by antigen ligation of the TCR or BCR at critical stages of development. For autoimmunity to develop there must be a lack of stringency in the elimination of autoreactive cells. Because TCRs and BCRs are generated by random gene rearrangements that occur within the nucleus of the cell and are not determined by knowledge of the world of self or foreign antigen, autoreactive T and B cells arise routinely. To eliminate autoreactive cells and maintain self-tolerance, T and B cells routinely undergo a selection process during their maturation in primary lymphoid organs, the thymus and bone marrow, respectively (Alexandropoulos and Danzl, 2012; Goodnow et al., 2010; Rajewsky, 1996; Vallejo et al., 2004; von Boehmer and Melchers, 2010). B cells again undergo a second process of selection after somatic mutation of immunoglobulin genes, as somatic mutation routinely generates autoreactivity (Brink, 2014; DeFranco, 2016; Goodnow et al., 2010; Liu and Davidson, 2011; Shlomchik, 2008).

T cells that mature in the thymus and enter peripheral lymphoid organs must display TCRs with some affinity for self-peptide−self-MHC complexes in order to receive the necessary signals for survival, which is termed positive selection. T cells arising in the thymus that express TCRs lacking any affinity for the self-peptide−self-MHC complexes fail to undergo positive selection and die. T cells that are strongly reactive to self-peptide−self-MHC complexes are eliminated in a process termed negative selection (Kondo et al., 2017). The threshold for both positive and negative selection represents a continuum. As the peptide−MHC complexes present in the thymus differ in each individual and the threshold for negative selection varies from individual to individual, each individual releases a different repertoire of antimicrobial and self-reactive T cells to the periphery, each reflecting a different spectrum of foreign and self-peptide specificities (Bommhardt et al., 2004; Vallejo et al., 2004; Werlen et al., 2003). It is also probable that certain stimuli can rescue T cells.

B cells similarly undergo a process of negative selection prior to achieving immunocompetence. This process occurs in the bone marrow and continues in the spleen where B cells migrate as transitional cells after exiting the bone marrow. Whether B cells require positive selection on self-antigen for survival and need to display some degree of autoreactivity remains an area of active investigation. It is clear, however, that highly autoreactive B cells are negatively selected on self-antigens encountered during early maturation, and again, the threshold for deletion is different for each individual (Monroe et al., 2003; Nemazee, 2017). The deletion occurs with the highest extent of BCR cross-linking; anergy occurs with less cross-linking. Thus the degree of autoreactivity in the B-cell repertoire is also variable. The selection of B cell is influenced not only by the strength of the signal received through the BCR but also by the availability of the TNF-like cytokine BAFF. In late transitional B cells, the interaction of BAFF with BAFF-R cooperates with signals received through the BCR to promote B cell survival and metabolic fitness. Since the availability of BAFF depends to a large extent on the number of B cells, B-cell depletion can result in high levels of BAFF leading to relaxation in the stringency of selection and the escape of autoreactive B cells to the periphery (Liu and Davidson, 2011; Mackay and Schneider, 2009). Anergic autoreactive B cells may also be rescued in a proinflammatory setting by engagement of costimulatory molecules on the B-cell membrane or by signaling through TLRs (Monroe and Keir, 2008). Thus the repertoire of naïve B cells will vary over time within an individual, with higher affinity autoreactive B cells present during times of infection, inflammation or lymphopenia, and fewer, lower-affinity autoreactive cells present during times of immunologic quiescence (Goodnow et al., 2010; Shlomchik, 2008).

This paradigm must be understood in the context of our knowledge that autoimmunity is often accompanied by some degree of immunodeficiency. A failure of proper selection may lead to a repertoire that includes too many self-reactive T or B cells. The presence of autoreactivity in individuals who are immunosuppressed is more straightforward. For example, the increased levels of BAFF that result from B-cell lymphopenia will lead to a failure to appropriately select the B-cell repertoire. Some defects that affect T-cell activation also impair expansion of regulatory cells or T-cell apoptosis and may, therefore, impair both responses to pathogens and self-tolerance. In the presence of T-cell lymphopenia, homeostatic expansion of self-reactive cells can occur.

AUTOIMMUNITY AND PERIPHERAL TOLERANCE

Negative selection of T and B cells occurs in the periphery as well as in primary lymphoid organs, permitting the removal of autoreactive cells that do not encounter autoantigen in the thymus or bone marrow. This process

of negative selection is termed peripheral tolerance. Like central tolerance, it is mediated by engagement of the TCR or BCR in a noninflammatory setting (Devi and Anandasabapathy, 2017; Goodnow et al., 2010; Nemazee, 2017; Tsubata, 2017). Although it has been traditional to debate whether autoimmunity results from a defect in central tolerance in the thymus or bone marrow, or in peripheral tolerance in secondary lymphoid organs, current knowledge of tolerance induction suggests that this may be an artificial distinction. Engagement of the antigen receptor is critical to both central and peripheral tolerance, although there are some differences in antigen receptor signaling pathways, expression of coreceptors, and costimulatory molecules that exist between immature T or B cells and their mature counterparts. Mouse models of autoimmunity suggest that defects in negative selection can be limited to central or peripheral tolerance (Anderson and Su, 2011; Linterman et al., 2009; Vinuesa et al., 2005), whereas others may paradoxically impair central tolerance and enhance peripheral activation (Seo et al., 2003). Thus some autoimmune-prone individuals might exhibit a general lack of stringency in B or T-cell tolerance, while others might have a defect that is stage specific. This distinction has important therapeutic implications; learning to subset patients based on their tolerance impairment mechanism might permit a better pairing of a patient with the therapy, in short, more personalized medicine.

In summary, the thresholds for survival and deletion need to be set within appropriate limits at multiple times in the maturation and the activation of a lymphoid cell (Goodnow et al., 2010; Liu and Davidson, 2011; von Boehmer and Melchers, 2010). Too little deletion at any stage and autoreactivity ensues; too much deletion and the protective repertoire may be compromised. Any genetic or nongenetic change that reduces deletion or enhances activation may be a risk factor for autoimmunity.

TRIGGERS OF AUTOIMMUNITY

Environmental factors are important triggers for expression of autoimmunity. Autoimmunity may develop following sterile tissue damage. Smoking, drug exposure, diet, chemical exposure, and sunlight have all been implicated as risk factors for particular diseases (D'Cruz, 2000; Debandt et al., 2003; Knip and Akerblom, 1999; Moriyama and Eisenbarth, 2002; Price and Venables, 1995; Steen, 1999; Vaarala, 2012). Molecular pathways for some of these have been established. Smoking and periodontal disease lead to the generation of citrullinated proteins; these are a target of autoantibodies in rheumatoid arthritis (Klareskog et al., 2011; Routsias et al., 2011). Notably, PADI4, the gene encoding peptidyl arginine deiminase involved in the citrullination of proteins, contains a susceptibility allele for rheumatoid arthritis (Bang et al., 2010; Kochi et al., 2011); inhibitors of PAD4 are effective in mouse models of rheumatoid arthritis (Willis et al., 2017). UV light causes apoptosis of keratinocytes, liberating cellular debris which is then bound by SLE-associated autoantibodies initiating an inflammatory response in the skin (Bijl and Kallenberg, 2006; Kuhn and Beissert, 2005); this can be mimicked by overexpression of inflammatory cytokines in the skin (Seery et al., 1997). It is now appreciated that pattern-recognition receptors for microbial pathogen-associated molecular patterns also bind to endogenous ligands, DAMPs or damage-associated molecular patterns. The release of DAMPs in damaged tissue can establish a proinflammatory milieu leading to the immunogenic presentation of self-antigens, including intracellular antigens that are normally sequestered from the immune system (Zhang et al., 2010). Once these become targets of an immune response, ongoing inflammation may be sustained. For example, the ongoing inflammation in some diseases, such as autoimmune myositis, targets regenerating tissue in which the disease-specific autoantigens are most abundantly expressed; this prevents tissue repair and resolution of inflammation (Mammen et al., 2011; Suber et al., 2008).

Clearly, infection can also precipitate autoimmune disease. It has even been suggested that most autoimmune diseases represent the late sequelae of an infectious process (Christen et al., 2012; James and Robertson, 2012). Proving this hypothesis has, however, been difficult. For some diseases, such as rheumatic fever or Guillain–Barré disease, the causal connection between microbial infection, the antimicrobial response, and autoimmune disease is clearly established (Cunningham, 2003; Guilherme and Kalil, 2004). Persistent reactive arthritis may follow a variety of bacterial and viral infections (Schmitt, 2017). For other diseases, there is suggestive epidemiologic evidence in humans or evidence from animal models that autoimmunity can follow microbial infection, or T cell or antibody cross-reactivity with both microbial and self-antigen has been identified (James and Robertson, 2012; Kuon and Sieper, 2003; Strassburg et al., 2003). In general, researchers have sought to implicate particular infections in the pathogenesis of particular autoimmune diseases, but it is possible that for some autoimmune diseases there is more than one possible microbial trigger. Importantly, the interaction of the TCR with a peptide–MHC complex must be of higher affinity to activate a naïve T cell than a memory T cell. Thus a microbial peptide may initiate a response that can then be sustained by self-peptide. Moreover, once a response to

self-antigen is initiated, epitope spreading to other epitopes on the same protein or on associated proteins occurs, often through B cell–mediated antigen presentation (Shlomchik et al., 2001). Autoantibodies may also amplify disease, especially those that form immune complexes containing endosomal TLR ligands.

Recent studies have provided remarkable information on the progression of autoimmunity, demonstrating that the autoantibodies characteristics of a given autoimmune disease are present as early as 10 years before the onset of clinical disease (Arbuckle et al., 2003). Moreover, cytokine abnormalities can also be observed before the onset of clinical symptomatology (Arbuckle et al., 2003; Deane et al., 2010) and early transcriptional signatures of preclinical disease are now starting to be identified (Chang et al., 2016; Kallionpaa et al., 2014). These observations suggest that there may be an opportunity to abort or retard the progression to disease in predisposed individuals.

Finally, the adipocyte has joined the ranks of immunomodulatory cells. It can secrete a variety of cytokines that are either protective (Kamata et al., 2015) or that promote a proinflammatory, proimmunogenic milieu (de Heredia et al., 2012). Thus increasing obesity may be one contributor to the increasing incidence of autoimmune disease.

ACTIVATION OF THE IMMUNE SYSTEM

The activation of both T and B cells in the periphery requires that the cells receive two signals: the first one is generated by ligation of the antigen receptor and the second by engagement of a costimulatory receptor. In general, when an antigen enters the system, there is an activation of DCs, the critical APC in a primary immune response. This occurs because microbes express molecules that bind to pattern-recognition receptors or TLRs on the DC. The consequence of this binding is upregulation of the costimulatory molecules CD80 (B7.1) and CD86 (B7.2) on DCs, and transformation of the DC from resting, or tolerogenic to activated, or immunogenic. T cells recognizing a microbial peptide in either class I or class II MHC molecules on the immunogenic DC will be activated. It is a feature of memory T cells that they can be activated by a lower-affinity interaction with the TCR than is required to activate primary T cells; this is due to epigenetic changes and alterations in the structure of lipid rafts in the membrane that facilitate rapid receptor cross-linking and less requirement for costimulatory signals (Weng et al., 2012). Thus a T cell that is not activated by a self-peptide–self-MHC complex while still a naïve cell, may be activated by self-antigen once it becomes a memory T cell. There are many examples in the literature of a T cell that is derived from an individual with autoimmune disease, which recognizes both a microbial peptide and a self-peptide. This cross-reactivity is termed molecular mimicry and represents a mechanism by which autoimmunity can be triggered by infection (Cusick et al., 2012). The hypothesis that molecular mimicry predisposes to autoimmunity clearly has validity in rodent models of autoimmune disease and suggests that laxity in the selection of the naïve T-cell repertoire can be a major contributor to autoimmunity. Those individuals with less stringent negative selection will have multiple T cells that can be activated by foreign antigen and will also display pathogenic autoreactivity. In addition, the signaling cascades within activated lymphocytes may differ in autoimmune versus healthy individuals. For example, T cells from SLE patients have altered signaling and a faster T cell calcium flux than those of healthy individuals due to the replacement of the principal signaling molecule of the TCR complex, CD3ζ, by the FcRγ chain (Moulton and Tsokos, 2011). This results in use of the adaptor molecule Syk rather than ZAP70 and the activation of the downstream kinase calcium/calmodulin-dependent protein kinase type IV (CaMK4) that enhances the production of IL-17 and blocks the production of IL-2 (Koga et al., 2014, 2016).

The activated T cell provides T-cell help or costimulatory signals to B cells that are encountering microbial antigen. B cells that bind both microbial antigen and self-antigen will ingest, process, and present epitopes of self-antigen, which can then be recognized by T cells. Because B cells often process antigen to different peptides than do DCs, the B cells can present novel epitopes of self-antigen and activate T cells with novel autospecificities (Bockenstedt et al., 1995; Sercarz et al., 1993; Sinmaz et al., 2016; Yan et al., 2006). These cross-reactive B cells will, therefore, contribute to a cascade of autoreactivity, as they activate an expanded repertoire of T cells. Memory B cells are also potent APCs that can activate naïve T cells. The B-cell repertoire, therefore, critically influences the T-cell repertoire (Whitmire et al., 2009). The fewer autoreactive B cells present, the less presentation of self-antigen to T cells.

There is much complexity in the cytokine expression patterns of activated T cells with at least four subsets of well-described helper T cells (Th1, Th2, Th17, and T_{FH}) as well as regulatory cells that help to restrain immune responses. The balance of transcriptional regulators expressed in each T cell will help to determine its phenotype,

whereas epigenetic changes will help to reinforce that phenotype through subsequent rounds of proliferation. Nevertheless, there is emerging evidence that helper T cells have a substantial amount of flexibility with respect to their phenotype. Signals from the innate immune system can be drivers of T-cell reprogramming, suggesting that inflammation or infection may have a profound effect on T-cell function, converting T cells with a protective phenotype to those that amplify inflammation (Nakayamada et al., 2012). More recently, a CD8 T-cell phenotype relevant to infectious disease, cancer, and autoimmunity has been identified characterized by programmed death (PD1) expression and termed "exhausted." Exhausted T cells recognize antigen but can no longer carry out effector functions. They arise as the immune response progresses from the acute phase characterized by abundant antigen and costimulation from CD4 T cells to the chronic phase in which costimulation wanes and antigen concentration decreases (McKinney and Smith, 2016). Another feature of exhausted T cells is an altered metabolic profile characterized by high persistent mTOR, glucose dependence, and increased mitochondrial depolarization (Bengsch et al., 2016). The presence of these cells in the peripheral blood is clinically relevant as a molecular profile of exhaustion is associated with the inability to clear chronic infections or to mount vaccine responses and with cancer progression but with a better prognosis in a variety of autoimmune diseases (McKinney et al., 2015).

The appearance of a broad spectrum of autoimmune diseases in a substantial number of patients receiving antagonists of key coinhibitory molecules such as CTLA4 and PD1, drugs that activate exhausted cells as part of cancer chemotherapy, illustrates the trade-off between immunocompetence and autoimmunity (Cappelli et al., 2016; Day and Hansen, 2016). These "checkpoint inhibitor" drugs induce a broad spectrum of autoimmune adverse events in 7%–18% of the treated patients, most commonly affecting the skin, the gastrointestinal tract, the endocrine organs, and the respiratory tract. Immune side effects are less frequent and milder in patients in which PD1 has been targeted, compared with patients taking anti-CTLA4 therapy, perhaps related to the antibody-dependent cellular cytotoxicity-mediated depletion of Tregs by anti-CTLA4. Adverse effects are much more frequent and severe in patients taking a combination of CTLA4 and PD1 directed therapies, reflecting the complementary activities of each of these pathways in suppressing T cell–mediated immune responses (Naidoo et al., 2015). Furthermore, approximately 40% of the patients with an underlying autoimmune disease will flare while taking a checkpoint inhibitor. The frequency of adverse autoimmune events associated with checkpoint inhibitor drugs makes it imperative to understand how to reinvigorate the effector function of exhausted tumor-infiltrating T cells that have upregulated their coinhibitory receptors without breaking self-tolerance in distant organs. This might involve the targeting of more tissue-specific coinhibitory molecules, approaches to reverse the abnormal metabolic profile of these cells, and/or the use of synergistic regimens that enhance inflammatory responses only in the tumor (Bengsch et al., 2016; Lucca and Hafler, 2017).

Much is now known about the signaling pathways that are downstream of receptor and costimulatory molecule–mediated stimulation and that are required for B and T-cell activation and cytokine production. Since activated lymphocytes are major mediators of the effector inflammatory response, some of these pathways are targets for immune interventions with small molecules. Both inhibitors of Syk and of Jak3 have been used clinically in autoimmune diseases and other kinase inhibitors are in development (Baker and Isaacs, 2017; Hirahara et al., 2016; Kontzias et al., 2012). There is increasing recognition that immune responses and cellular differentiation pathways are linked to metabolism and that different types of effector and Tregs have different metabolic requirements (Buck et al., 2017; Gerriets and Rathmell, 2012; Morel, 2017; O'Neill et al., 2016). Recent studies have illustrated how genetic risk may be associated with metabolic irregularities in immune cells. A genetic polymorphism associated with lupus involves a gene that regulates T-cell oxidative metabolism and mitochondrial metabolism leading to an increase in T-cell inflammatory cytokines. Based on this finding, it has been shown that either an inhibitor of glucose oxidation or an inhibitor of mitochondrial oxidation can decrease autoimmune activation in mouse lupus models (Yin et al., 2015). How the fuel requirement and metabolic phenotype of each immune cell in either quiescent or activated state regulates autoimmunity requires future study. More work will also be needed to determine how metabolic irregularities in immune cells can be addressed therapeutically without disrupting homeostasis in other tissues.

ROLE OF ANTIGEN AS A DRIVER OF AUTOIMMUNITY

A major question in autoimmune disease is whether the process is autonomous or driven by antigen, and, if the latter, whether the antigen is a self-antigen or foreign antigen. Animal models of disease definitively show that molecular mimicry following activation by microbial antigen can initiate autoreactivity (Cunningham, 2003; Cusick et al., 2012; Kuwabara, 2004). There are also data suggesting that self-antigen drives the autoimmune

response. First, in animal models of systemic lupus, it appears that an excess of apoptotic cells, a problem in their clearance, or modifications in the antigens they release can result in a lupus-like serology with antichromatin reactivity (Martinez Valle et al., 2008; Mistry and Kaplan, 2016; Peng and Elkon, 2011). Current understanding would suggest that an excess of apoptotic debris and/or altered forms of nucleic acids (such as oxidized forms or biofilms) can activate endosomal TLRs and transform tolerogenic into immunogenic DCs, as well as activate B cells (Caielli et al., 2016; Colonna et al., 2013; Filardy et al., 2010). The role of each endosomal TLR is different. TLR9 is required for the production of autoantibodies to DNA in lupus models but also has a protective role in autoimmunity (Christensen et al., 2005; Nickerson et al., 2008). TLR7 and 8 recognize the same RNA antigens but have different functions because they are expressed on different cell types. Overexpression of TLR7 in B cells is sufficient to cause a lupus-like autoimmune disease (Jackson et al., 2014). The overexpression of TLR8 that is expressed mainly in myeloid cells causes generalized systemic autoimmunity due to its activation of myeloid cells (Guiducci et al., 2013).

Other DNA and RNA sensors together with their associated adaptors and downstream signaling molecules also contribute to the regulation of autoimmune responses to nucleic acids during the course of a protective immune response to viral pathogens. TREX1, DNAse1, DNAl3, and cGAS are all enzymes involved in DNA degradation either intra- or extracellularly (Koyama et al., 2016; Martinez Valle et al., 2008; Sisirak et al., 2015). Deficiency of TREX1 results in excess intracellular DNA that activates cGAS to produce the dinucleotide cGAMP which acts through its downstream adapter STING, to induce proinflammatory cytokines (Gao et al., 2015; Gray et al., 2015b). Nevertheless, the multiple functions of some of the adapters and signaling molecules involved in innate immunity can make them difficult to target therapeutically (Pawaria et al., 2017; Sharma et al., 2015).

Extensive tissue damage can lead to the presentation of normally sequestered self-antigen in a proinflammatory setting (Bratton and Henson, 2011; Horwitz et al., 2002; Vezys and Lefrancois, 2002) or posttranslational alteration of self-antigen such that it is now immunogenic (Doyle and Mamula, 2012). The proinflammatory setting may be enhanced by apoptosis of cells following tissue injury. This can clearly lead to an autoimmune response. Whether in some individuals this response is perpetuated because of a lack of appropriate restoration to homeostasis is an important question.

Finally, polymorphisms in autoantigens may also constitute risk factors for autoimmune disease (Pauza et al., 2004; Suzuki et al., 2003). As the genetic susceptibility to autoimmune disease is further explored, the degree to which molecular mimicry, aberrant expression of autoantigens, or exposure to previously sequestered antigen in an immunogenic setting contributes to disease will become more apparent.

A variety of environmental exposures might also nonspecifically accelerate disease by activating the innate immune system resulting in the release of proinflammatory cytokines that initiate autoimmunity. In mice, for example, type I interferons can initiate SLE in susceptible strains (Koutouzov et al., 2006) and may be responsible for the Koebner phenomenon observed in psoriasis (Koutouzov et al., 2006). Tissue damage also results in the release of soluble mediators (DAMPs) such as HMGB1, cathelicidins, defensins, and heat shock proteins that can activate TLRs and other proinflammatory receptors to further amplify immune activation pathways (Gallo and Gallucci, 2013).

DEFECTIVE DOWNREGULATION OF AN IMMUNE RESPONSE

The induction of an immune response needs to be followed by a downregulation or elimination of most of the cells that have undergone clonal expansion. A major observation of recent studies of autoimmune disease is that a defect in the restoration of immune homeostasis, or in a downregulation of an immune response, can be a risk factor for autoimmunity. Since all reactivity with foreign antigen includes reactivity to self-antigen, responses to self are routinely generated in the process of mounting an immune response to foreign antigen. The potential pathogenicity of the autoimmune response will vary from individual to individual. In general, however, the mechanisms that exist to dampen the immune response also diminish autoreactivity. B and T cells are routinely downregulated as soon as they are activated. For the B cell, this occurs, in part, by cross-linking of the BCR and FcRIIB by antigen–antibody complexes. When FcRIIB is absent or deficient on B cells, as it occurs in many individuals with SLE, autoantibody production is poorly controlled (Bolland and Ravetch, 2000; Fukuyama et al., 2005), whereas FcRIIB on DCs helps to maintain T-cell tolerance (Li et al., 2014). Multiple coinhibitory molecules are expressed on activated T cells. Interaction with their receptors either within lymphoid organs or in the peripheral site of inflammation transduces an inhibitory signal to the T cells, signaling them to downmodulate their response (Schildberg et al., 2016). Mutations in two coinhibitory molecules, PD1 and CTLA4, are associated

with several autoimmune diseases (Chen, 2004; Khoury and Sayegh, 2004) and pharmacologic antagonism of either of these two molecules induces autoimmunity with high frequency (Kostine et al., 2017). Both B and T cells are also susceptible to activation-induced cell death mediated through Fas−Fas ligand interactions (Brunner et al., 2003; Li-Weber and Krammer, 2003). Defects in this process can lead to autoimmunity.

Thus controlling the immune response is critical to normal homeostasis of the immune system and is mediated by multiple inhibitory pathways. A major component of autoimmune disease in some individuals may be a defect in the suppression of immune activation.

REGULATORY LYMPHOCYTES

Another area of intensive study is the phenotypic characterization and mechanisms of action of regulatory T and B cell subsets. CD4+ Tregs arise either during thymic development and others are induced after antigen exposure in the periphery (Kasper et al., 2016; Panduro et al., 2016; Wing and Sakaguchi, 2010). These cells regulate immune responses in a variety of ways that include secretion of inhibitory cytokines, promotion of apoptosis of effector lymphocytes, depriving effector T cells of cytokines or essential amino acids leading to apoptosis, or inhibition of DC function. The absence of Tregs in mice results in lymphoproliferation and fatal multiorgan autoimmunity demonstrating the need for the ongoing regulation of pathogenic self-reactive cells that escape into the periphery. A population of CD4+/CD25hi (γ chain of the IL-2 receptor) naturally occurring Tregs arises in the thymus in response to TCR encounter with self-antigens with an avidity lower than that required for negative selection; their development depends on both CD28 and IL-2. Tregs can also be generated after antigen exposure in the periphery from naïve T cells in a manner that is dependent on IL-2 and transforming growth factor (TGF)-β and may be enhanced by the vitamin A metabolite retinoic acid. Both types of Tregs express the master transcriptional regulator Foxp3 (Pesenacker et al., 2016); its expression is stabilized by epigenetic modifications of DNA that reinforce transcriptional availability of suppressive cytokines while preventing access of transcription factors to DNA-encoding inflammatory cytokines (Hsieh et al., 2012; Josefowicz et al., 2012a).

Cells expressing immunosuppressive cytokines such as TGF-β or IL-10 (Tr1 cells) (Pot et al., 2011) arise under particular conditions of antigen exposure and, once activated, mediate suppression through both limiting cytokine secretion and through contact-mediated lysis of effector cells. Tr1 cells are present in large numbers in the gut where they help to protect from colitis and they can also protect against multiple sclerosis in mice. Tr1 cells are Foxp3 negative and can be induced by IL-27 (Meka et al., 2015; Nadya et al., 2017; Wojno and Hunter, 2012) but have been difficult to study due to lack of a clear phenotype. Nevertheless, the transcriptional program of these cells is being unraveled, and recent studies have suggested that both IFNγ and galectin 1 induce DCs to produce IL-27, suggesting a way in which Tr1 cells might be induced therapeutically (Ilarregui et al., 2009).

Other studies have identified a population of CD8 suppressor cells that may directly lyse autoreactive cells or may secrete immunosuppressive cytokines (Cortesini et al., 2001; Jiang et al., 2010; Vuddamalay and van Meerwijk, 2017). In lupus models, these cells can be induced by autoantigen or by idiotype peptides (Sawla et al., 2012). CD8+ Tregs have recently been described during adaptive immune responses where they serve to regulate humoral responses in the germinal center by lysing B cells (Kim and Cantor, 2011).

The balance between effector and regulatory cells may determine whether an autoreactive response that arises in the course of microbial exposure or an inflammatory response is terminated or perpetuated (Visperas and Vignali, 2016). However, application of this new knowledge to the treatment of autoimmunity is still in its early stages. One approach has been to use inhibitors of the mTOR pathway, important in autophagy and cell metabolism, to induce or stabilize Foxp3 expression in Tregs (Chinen and Rudensky, 2012; Josefowicz et al., 2012b). Another is to use low-dose IL-2 or IL-2 anti-IL-2 complexes to enhance Treg development and function. This strategy has recently been successfully applied to the treatment of graft versus host disease (GVHD) and cryoglobulinemic vasculitis in humans in which an increase in Tregs was associated with a therapeutic response (Oo et al., 2012). In vitro expansion and delivery of a stable population of Tregs or in vivo activation of antigen-specific Tregs by tolerogenic self-peptides are in the development and trial stage. Clinical trials directed at tolerance induction in new onset type I diabetes by manipulation of Tregs have so far failed to cure disease despite an increase in Treg numbers, although several approaches have had partial effects (Gallagher et al., 2011; Skyler, 2013). Clinical trials with low-dose IL-2 to induce Tregs are ongoing, and other approaches that stabilize Treg function are being considered (Visperas and Vignali, 2016).

B cells may also have regulatory functions (Klinker and Lundy, 2012). IgM antibodies that have low-affinity autoreactivity suppress immune responses by promoting opsonization of apoptotic material and promoting

noninflammatory clearance (Chen et al., 2009). A subset of B cells with regulatory functions (Bregs) has been described by multiple investigators, but their importance in autoimmune diseases is not clear. These cells are defined by their ability, upon in vitro activation, to produce IL-10 as well as other regulatory cytokines such as TGF-β and IL-35 (Lykken et al., 2015; Mauri and Menon, 2017). Some disagreement has arisen in the literature as to their origins and phenotype since they constitute a small proportion of many different activated B cell subsets including plasmablasts. Bregs function to dampen Th1 and Th17 responses and their absence have been associated with an exacerbated disease phenotype in mouse models of autoimmunity. Decreased numbers of Bregs have been reported in human autoimmune diseases but an understanding of how and where these cells regulate autoimmunity remains to be elucidated, and the findings are currently limited and only associative.

Another way in which B cells can regulate immune responses is by posttranscriptional modification of antibodies. Alterations in galactosylation and sialylation of the Fc region of Ig molecules may have a profound effect on immune responses. Fc receptor binding is affected by changes in glycosylation (Bournazos et al., 2016). A decrease in Ig galactosylation and sialylation is found in multiple autoimmune diseases and may increase the pathogenicity of autoantibodies (Biermann et al., 2016; Le et al., 2016). Sialylated immunoglobulin found in preparations of IVIg suppresses immune responses by binding to DC-SIGN on macrophages and DCs and initiating a program that induces the suppressive Fc receptor FcRIIB on macrophages (Anthony et al., 2011; Chen et al., 2009). Moreover, IgG must be sialylated to bind FcRIIB, the inhibitory receptor. On the other hand, fully deglycosylated Ig is protective since it binds poorly to Fc receptors.

THE ROLE OF THE GUT MICROBIOTA IN AUTOIMMUNITY

An emerging theme in autoimmunity is the heretofore unrecognized role of the gut microbiota in regulating immune responses (Atarashi and Honda, 2011; Fung et al., 2017; Paun et al., 2017; Rosser and Mauri, 2016). A vast array of bacteria of multiple species is found at epithelial barriers including the skin and the gut and can vary with age, gender, genetic background, and environmental exposures such as antibiotics and diet. Gut bacteria play a crucial role in digestion and also produce essential vitamins and metabolites that can influence distant organs. One of the most important observations in this field is that the induction of Th17 cells in mice requires gut colonization with segmented filamentous bacteria; the absence of these bacteria prevents the induction of experimental forms of arthritis and multiple sclerosis in normal mice and the spontaneous onset of type 1 diabetes in a susceptible mouse strain (Romano-Keeler et al., 2012). The bacteria provide TLR ligands and induce other inflammatory genes that trigger DCs and are also a source of ATP that helps to activate Th17 cells. The precise function of these Th17 cells, either as pathogenic cells or as regulatory cells that also produce IL-10, will depend on other factors in the gut environment.

Disease-inducing bacteria may be found in some types of autoimmunity. For example, transfer of commensal bacteria from diseased to normal mice can transmit IBD, suggesting that the initiating trigger for this disease may be communicable (Garrett et al., 2007). Importantly, susceptibility to colitis may be altered by dietary changes that prevent the emergence of the pathogenic bacteria, suggesting that fecal transplants or probiotics are therapeutic strategies that should be tested. Gut microbiota also appears to be required for the generation of gut Tr1 cells, and this may be mediated by different bacterial species than those that induce Th17 cells. The capsular polysaccharide of *Bacteroides fragilis* has been identified as an inducer of Tregs (Round and Mazmanian, 2010). Conversely, the absence of Tregs can affect the composition of the gut microbiota (Chinen and Rudensky, 2012; Josefowicz et al., 2012b). How the balance of pro and antiinflammatory gut microbiota is maintained and how this might be manipulated for the prevention or treatment of autoimmunity has become an important question (Bogdanos and Sakkas, 2017; de Oliveira et al., 2017). It seems apparent, however, that gut microbiota helps to establish immune cell metabolism and, therefore, sets thresholds for activation and effector function. Metabolites released from gut bacteria may also have nonimmune distant effects; for example, intestinal microbiota control the permeability of the blood−brain barrier and may, therefore, modulate entry of immune cells into the brain (Braniste et al., 2014).

Most studies of gut microbiota in human autoimmune disease have so far been limited to comparisons of fecal colonies between diseased and healthy individuals without the establishment of causality. Several interesting new studies, however, have identified changes in the gut microbiota that correspond to seroconversion and diagnosis of type 1 diabetes (Kostic et al., 2015; Mejia-Leon and Barca, 2015). Similar studies in rheumatoid arthritis have identified gut dysbiosis in active patients that is corrected after effective treatment (Zhang et al., 2015); furthermore, transfer of disease-associated bacteria exacerbates disease in animal models (Maeda et al., 2016).

FLARES AND REMISSIONS DURING DISEASE

The vast majority of animal models of autoimmune disease develop chronic progressive disease activity. Once the autoimmune disease becomes manifest, it progresses to organ failure or death. Much human autoimmune disease, in contrast, is characterized by periods of disease remission and flare. Little is known in human disease about the cellular events that lead to disease remission. It is also true that little is known regarding the cause of disease flares. In mouse models of multiple sclerosis disease flares can result from epitope spreading with sequential recruitment of T-cell populations that recognize different epitopes of myelin (Mallone et al., 2011; Vanderlugt et al., 1998). Similarly in humans, epitope spreading has been observed among cohorts of lupus patients from whom prediseased serum was available (Arbuckle et al., 2003; Deshmukh et al., 2003). Nevertheless, a major area of ignorance concerns the cell type responsible for disease flares. It is not known for most autoimmune diseases whether flares represent de novo activation of naïve autoreactive cells or a reactivation of quiescent memory cells and whether these flares are due to a new environmental exposure or to a failure of regulation, or both. Our ignorance in this regard is largely derived from the difficulty of sampling a large enough repertoire of autoreactive T or B cells. Often, these cells are poorly represented in peripheral blood (Bischof et al., 2004; Newman et al., 2003; Reddy et al., 2003). The development of MHC class I and class II tetramers containing peptides of known autoantigens is beginning to facilitate the analysis of pathogenic T cells in human autoimmune diseases and animal models in which the autoantigens are known (Mallone et al., 2011; Massilamany et al., 2011). Similarly, the development of single-cell PCR technology and, more recently, high-throughput methods for sampling thousands of cells is allowing the analysis of the frequency and binding specificity of both pathogen-induced and autoreactive B cells from peripheral blood (Jardine et al., 2016; Thornburg et al., 2016; Tipton et al., 2015). These studies have shed light on how autoreactivity is regulated in human B cells during B cell development, with loss of autoreactivity as the cells progress from the bone marrow to the periphery (Meffre and Wardemann, 2008). Abnormalities in this regulation have been demonstrated in individuals with a variety of immune deficiencies and autoimmunity-related genetic polymorphisms (Isnardi et al., 2010; Meffre and Wardemann, 2008; Menard et al., 2011; Schickel et al., 2016; Weller et al., 2012). These studies have also demonstrated clonal expansions of both B and T cells in autoimmune patients with some shared V region use between patients (Tipton et al., 2015; Tong et al., 2016). In patients with lupus, the repertoire of clonally expanded B cells is more diverse than in healthy individuals immunized with tetanus or influenza antigens with some clones arising from naïve cells and some from memory cells (Tipton et al., 2015). As the technology for studying single cells advances (Robinson, 2015; Zheng et al., 2017), more information about the diversity of autoimmune lymphocytes in a variety of autoimmune diseases is expected to gather.

MECHANISMS OF TISSUE DAMAGE

Studies over the past decade have clearly demonstrated that the mechanisms that incite autoimmune disease may differ substantially from the mechanisms that propagate tissue damage. Autoreactive T and B cells that are activated in secondary lymphoid organs and initiate disease are activated in a different microenvironment and may have a different cytokine profile from the effector cells that migrate into target organs and cause tissue fibrosis (Campbell et al., 2001; Gerriets and Rathmell, 2012; Katzman et al., 2011). Therefore it is more clear that at each stage of autoimmune disease, inductions of autoreactivity and tissue destruction need to be separately explored, and that the previous characterization of certain cytokines, as proinflammatory, and others, as antiinflammatory, may be misleading. While TGF-β may dampen the induction of autoreactivity, it may hasten tissue fibrosis (Valluru et al., 2011). Similarly, IL-10 is antiinflammatory during disease initiation through its inhibitory effects on APCs but may lose its antiinflammatory properties (Herrero et al., 2003) and even drive T-cell proliferation, immunoglobulin class switching, and antibody production later in the disease (Mocellin et al., 2004). Even the proinflammatory cytokine interferon-γ can have antiinflammatory properties in the early stages of some autoimmune diseases (Billiau, 1996; Grohmann and Puccetti, 2002; Rosloniec et al., 2002), perhaps by antagonizing the differentiation of T cells secreting IL-17. It is, therefore, important, as we move forward in studies of autoimmune disease, to consider the mechanism of both immune activation and tissue destruction and to be aware that cytokines, hormones, or other mediators may exhibit differential effects in each process. Studies of animal models have now clearly shown that it is possible to intervene in disease progression to protect organs from immune-mediated destruction, even while autoreactivity continues unabated (Clynes et al., 1998; Schiffer et al., 2003).

Recent studies emphasize the role of innate immune cells in tissue injury, particularly neutrophils and macrophages that are recruited to lesional sites. Macrophages have a complex program in which they first release proinflammatory mediators to fight pathogens but then initiate programs to help in clearance of dead tissue and tissue repair (Huen and Cantley, 2017). While the latter response is beneficial if short-lived, the continued activation of the repair program may be detrimental (Bethunaickan et al., 2011). A role for organ-intrinsic macrophages is also increasingly being recognized; these may be activated in situ and contribute to tissue damage (Stamatiades et al., 2016).

The development of fibrosis is of major concern in autoimmune diseases since it is difficult to reverse and may lead to organ failure. Fibrosis is characterized by the deposition of extracellular matrix and collagen due to the sustained activation of myofibroblasts and failure of the normal resolution of wound healing. Multiple triggers for the wound healing response have been identified including excessive cell death, cytokines and other immune mediators, activation of coagulation pathways, and ER stress (Eming, 2017; Wynn and Ramalingam, 2012). Another major driver of fibroblast differentiation is the conversion of TGF-β by either chemical danger signals or mechanical stress from a latent form that is tethered to the cell surface to an activated profibrotic form (Friedman et al., 2013; Hinz, 2009). Several types of stromal cells can transdifferentiate into myofibroblasts and this may vary in different organs. TLR signaling in pericytes has recently been shown to be essential for their TGF-β-mediated transformation into fibroblasts (Leaf et al., 2016). Resolution of fibrosis is mediated through the induction of proteases that break down collagen and matrix and deactivation of myofibroblasts. Failed resolution and repair may occur because of local tissue hypoxia, infection, or ongoing tissue damage with an accumulation of toxic metabolites (Wynn and Ramalingam, 2012).

Macrophages are key players both in the early inflammatory process and in tissue regeneration and scar tissue formation, and their depletion has different effects depending on the stage of the inflammatory process. The transformation of inflammatory to proresolving macrophages is associated with changes in their metabolism with a switch from dependence on glycolysis to oxidative phosphorylation. Eosinophils and mast cells can also promulgate fibrosis. Profibrotic cytokines include IL-1, IL-6, IL-13, IL-33, thymic stromal lymphopoietin (TSLP), and TGF-β; fibrosis can follow either Th1/Th17 or Th2 inflammatory responses (Eming, 2017).

THERAPEUTIC ADVANCES

A major advance in the last decade has been the application of new knowledge about immune system function to the treatment of autoimmune diseases. New therapies target innate immunity, adaptive immunity, and even tissue injury. As these new drugs have entered clinical practice, it has become clear that the pleiomorphic and stage-specific functions of particular molecules can result in both beneficial and adverse therapeutic effects of the drugs that target them. TNF inhibitors, for example, while highly therapeutic in RA and IBD, can induce SLE, multiple sclerosis (MS), and vasculitis (Kollias, 2005). While some therapies are highly effective for some diseases but not for others, it has been difficult to predict efficacy or lack of efficacy based on our current understanding of disease pathogenesis. For example, global B-cell depletion using an antibody to CD20 is therapeutic in RA and MS (Barun and Bar-Or, 2012; Buch et al., 2011), diseases that were initially thought to be T-cell dependent, but has much less, if any, effect in SLE, a prototypic B-cell disease (Merrill et al., 2010). Similarly, IL-17 inhibition has been highly effective for seronegative arthritides such as psoriatic arthritis and spondyloarthropathy but is less effective for rheumatoid arthritis (Fragoulis et al., 2016; Kunwar et al., 2016). These differences point to heterogeneity in cytokine involvement in inflammatory responses that are difficult to parse out even at the molecular level. Variability among patients results in response rates that rarely reach more than 70% even for the best of the new therapies. Finding ways to identify responders and nonresponders before initiating an expensive and potentially toxic new therapy is a task that is being actively pursued using large patient databases and genetic and "omics" studies.

New drugs to treat autoimmune disease are constantly in development. A major advance has been the development of small molecule inhibitors directed at key signaling molecules within the immune system, particularly a variety of protein kinases. Because there are more than 500 protein kinases, achieving precise specificity of these drugs for their targets can be difficult, but inhibitors of Jak kinases are already in clinical use and other drugs targeting Syk, Btk, PI3 kinase, and MAP kinases are in development (Crofford et al., 2016; Shao and Cohen, 2014; Stark et al., 2015). These drugs have the advantage that they can be administered orally and have been used both for autoimmunity and for oncology indications.

Many of the current approaches are based on a perceived need to institute immunosuppression and antiinflammatory therapy at the time of autoimmune tissue destruction. Multiple pathways of immune activation,

including innate TLR and pattern-recognition receptor signaling pathways, costimulatory pathways and T- and B-cell activation and cytokine signaling pathways are being targeted to reduce the activation of the immune system (Rosenblum et al., 2012). Our most updated understanding of autoimmunity would suggest that it might also be appropriate to consider treating disease during times of disease quiescence. The goal of this therapeutic approach would be to alter T- and B-cell repertoire selection or to drive the expansion of regulatory cells and enhance regulation (Daniel and von Boehmer, 2011). Antigen-specific therapies require an understanding of the causative antigen; this remains unknown for most autoimmune diseases. Nevertheless, animal studies suggest that it may be possible to convert a pathogenic T-cell response into a regulatory one, for example, by delivering a strong signal 1 without signal 2 (Crepeau and Ford, 2017), by delivering tolerogenic signals to DCs (Yeste et al., 2016), or by expanding or delivering Tregs (Dawson and Levings, 2017; Dwyer et al., 2016; Song, 2016). Optimizing this type of approach for human use remains a dream for the future (Michels and Eisenbarth, 2011).

Protecting target organs and preventing irreversible tissue damage will require different therapeutic strategies from blocking systemic autoreactivity (Katschke et al., 2007; Sica et al., 2011; Szekanecz et al., 2009). Approaches to treating fibrosis by antagonizing cytokines such as IL-13 and TGF-β will need to take into account the fine balance between antiinflammatory functions and promotion of healing by these cytokines and excessive collagen and matrix deposition (Eming, 2017; Friedman et al., 2013). There is an increasing understanding of the events that lead to maladaptive resolution of inflammation and consequent tissue fibrosis, with the identification of small proresolving lipid mediators that can trigger resolution of inflammatory responses (Dalli and Serhan, 2016; Fredman and Tabas, 2017; Friedman et al., 2013; Serhan, 2017). Other efforts are being directed at blocking or sequestering reactive oxygen species and other toxic metabolites (Telorack et al., 2012), inhibiting transcription pathways that lead to myofibroblast transdifferentiation (Huang et al., 2016; Yu-Wai-Man et al., 2017), decreasing collagen cross-linking, and many others (Friedman et al., 2013). These new therapeutic approaches offer the hope of maintaining immunocompetence while eliminating the consequences of pathogenic autoreactivity.

Finally, the observation that autoimmunity and immunodeficiency can be linked (Grimbacher et al., 2016) suggests that effective treatment of autoimmunity will lead to enhanced immunocompetence, and the reversal of developmental defects in lymphoid cells should reduce autoreactivity. This is the metric against which therapeutic interventions should be judged.

GOALS FOR THE FUTURE

Over the past several years, new technologies have been developed that will substantially increase our understanding of autoimmune disease. High-throughput technologies to examine genetic polymorphisms, epigenetic changes, gene expression, and protein expression and modifications, linked with the collection of well-characterized databases of patients, make it possible to determine the level of expression of a very large number of genes or proteins in defined populations of patients and subpopulations of cells. These data may provide new insights into disease pathogenesis and new ways to phenotype patients with autoimmune disease. These technologies may also provide sets of biomarkers that will help to determine risk for developing a particular disease, characterize the current activity of the disease and disease prognosis, and assess response to therapy at an earlier time point than current clinical endpoints. It is reasonable to predict that patterns of gene and protein expression will reveal differences and similarities among autoimmune diseases.

The development of biomarkers will, undoubtedly, improve the therapy of autoimmune disease. It may be possible to identify early those patients whose disease is likely to be severe and to monitor disease activity without waiting for clinical symptomatology. Furthermore, the recognition, that autoimmunity can be detected before clinical symptomatology and that the likelihood of development of disease in individual patients can be predicted with more certainty, will allow testing of therapies that have the potential to prevent or cure autoimmune disease before tissue damage occurs. Ultimately, it may be possible to customize therapy for each patient, thereby enhancing efficacy and avoiding unnecessary toxicities and expense.

Given that the diagnosis of complex autoimmune diseases may be delayed, preventing and reversing tissue damage once effector cells have arisen is a pressing therapeutic goal for patients with established disease. Approaches to enhance the resolution of inflammation rather than fibrosis in target organs are still mostly in the experimental stage but much progress has been made in understanding this area and two new drugs are now in clinical use (Sathiyamoorthy et al., 2017). Specific targeting of pathogenic lymphocytes is still not possible in humans, although a proof of principle experiment in an animal model with a known autoantigen has recently been successful (Ellebrecht et al., 2016).

CONCLUDING REMARKS

The past several years have witnessed a change in our understanding of autoimmunity and a clear new direction in our approach to the study of autoimmunity. Multiple genetic polymorphisms contribute to autoimmunity risk and more remain to be identified. The complexity of regulation of gene expression suggests several other mechanisms by which gene expression may be aberrantly regulated in autoimmunity. It is clear that the activation of the innate immune system can act as a trigger for the initiation of autoimmunity in susceptible individuals and can amplify tissue damage in target organs. Autoimmunity can result from either a failure in T- and B-cell repertoire selection or a failure in the regulation of activated T and B cells. Autoimmune B and T cells can be identified years before the emergence of clinical disease, suggesting that multiple triggers act sequentially to precipitate disease. It is also clear that autoimmunity needs to be coupled to target-organ vulnerability to immune attack for autoimmune disease to be present and that inflammatory cascades can be interrupted or regulated in the periphery. This understanding suggests new therapeutic targets and new therapeutic strategies.

Multiple new therapies have been developed and tested in clinical trials in the last two decades leading to major advances in treatment for some but not all autoimmune diseases. However, many knowledge gaps remain to be filled, especially in understanding which pathways to target in each disease and in determining which individuals will respond to each therapy. The focus on new technologies to provide biomarkers of immune function represents an exciting opportunity to treat disease prior to tissue damage and to customize therapy for each patient. Furthermore, studies of gene and protein expression will help to elucidate those mechanisms of immune dysfunction that are shared among multiple autoimmune diseases and those that are unique to a particular disease. Thus there are reasons to be optimistic, but acquiring the necessary new knowledge and translating that knowledge to therapy could take some years.

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