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Review

Rethinking mechanisms of autoimmune pathogenesis

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ABSTRACT

Why exactly some individuals develop autoimmune disorders remains unclear. The broadly accepted paradigm is that genetic susceptibility results in some break in immunological tolerance, may enhance the availability of autoantigens, and may enhance inflammatory responses. Some environmental insults that occur on this background of susceptibility may then contribute to autoimmunity. In this review we discuss some aspects related to inhibitory signaling and rare genetic variants, as well as additional factors that might contribute to autoimmunity including the possible role of clonal somatic mutations, the role of epigenetic events and the contribution of the intestinal microbiome. Genetic susceptibility alleles generally contribute to the loss of immunological tolerance, the increased availability of autoantigens, or an increase in inflammation. Apart from common genetic variants, rare loss-of-function genetic variants may also contribute to the pathogenesis of autoimmunity. Studies of an inhibitory signaling pathway in B cells helped identify a negative regulatory enzyme called sialic acid acetyl esterase. The study of rare genetic variants of this enzyme provides an illustrative example showing the importance of detailed functional analyses of variant alleles and the need to exclude functionally normal common or rare genetic variants from analysis. It has also become clear that pathways that are functionally impacted by either common or rare defective variants can also be more significantly compromised by gene expression changes that may result from epigenetic alterations. Another important and evolving area that has been discussed relates to the role of the intestinal microbiome in influencing helper T cell polarization and the development of autoimmunity.

Paul Ehrlich had recognized in the 1890s that the immune system might attack the host it is meant to protect – a phenomenon he called “horror autotoxicus”. No clear mechanisms of relevance to autoimmunity were proposed until the early 1950s well before the function of lymphocytes had been elucidated, Ray Owen, Macfarlane Burnet and Peter Medawar made independent contributions that led to the recognition of the phenomenon of immunological tolerance. In the mid 1940s Owen examined genetically different twin calves, often from two fathers but the same mother, that had shared a circulation in utero. He noted that individual calves were unable to make immune responses after birth to antigens derived from the twin they had shared a circulation with. Burnet and Frank Fenner interpreted these findings to constitute evidence for immunological tolerance in the second edition of their book *The Production of Antibodies* published in 1949 [1].

Medawar had defined the laws of transplantation in studies on rabbits and mice, but had been unable to understand why skin grafts took in non-identical twin calves. He read Burnet and Fenner’s description of Owen’s studies and realized that he had in fact been studying the phenomenon of immunological tolerance. With his colleagues Rupert Billingham and Leslie Brent he experimentally demonstrated the induction of immunological tolerance in inbred mice [2]. Medawar and Burnet shared the Nobel prize in Medicine and Physiology in 1960. Although tremendous advances have been made in lymphocyte biology and genetics since then, our understanding of the underlying basis for autoimmunity remains incomplete.

Why do some individuals develop autoimmunity? Common wisdom holds that some combination of genetic susceptibility and environmental factors contributes to the development of disease. Current paradigms have been developed by looking at common genetic variants and rare genetic variants and attempts are currently being made to explore the role of the microbiome in disease. We will review approaches to genetic susceptibility largely through the prism of trying to connect genetics to a break in tolerance. We will also examine two alternatives possibilities to mechanisms of susceptibility that go beyond the role of inherited genes and the microbiome.

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1. A still evolving story: genetic bases of common autoimmune disorders

It is widely appreciated that twin studies have helped establish that common autoimmune disorders such as rheumatoid arthritis, psoriasis, systemic lupus erythematosus and multiple sclerosis among others must have a genetic basis. Support for a genetic basis for common autoimmune disorders has also been obtained from studies of common genetic variants (polymorphisms) as well as of rare genetic variants. However, although genetic susceptibility is undoubtedly relevant, the degree to which genetic changes can be linked to disease susceptibility is limited. Genome Wide Association Studies have resulted in relatively small Odds Ratios as discussed in more detail below. While rare genetic variants may have stronger effects – validation will require the examination of tens of thousands of subjects in order to achieve statistical significance. This kind of validation has begun to be obtained. There are a few relatively rare "single-gene" autoimmune disorders in which susceptibility alleles are tightly linked to disease.

A large number of human autoimmune disorders involve the production of pathogenic auto-antibodies. Indeed in some autoimmune disorders believed to be primarily linked to defects in immune regulation by T cells, a prominent role for B cells has re-emerged with the advent of therapeutic trials using antibodies to CD20 [3]. Relatively rare autoimmune syndromes have been linked to loss of function mutations in single genes such as AIRE, a regulator of gene expression in thymic medullary epithelial cells, and FoxP3, a transcription factor for T regulatory cells [4–7]. The role of these genes in relatively common autoimmune disorders is unclear. Other single gene diseases include the Autoimmune Lymphoproliferative Syndrome linked to loss of function mutations in Fas or Caspase 10, and Omenn syndrome caused by partial loss of function mutations in RAG1, RAG2, Artemis and other genes involved in V(D)J recombination.

"Common variants", "Rare variants" and autoimmunity. It is widely recognized that most common autoimmune diseases, including systemic disorders such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), represent non-Mendelian polygenic diseases [8–10]. Candidate gene approaches as well as genome wide association studies using SNPs have been generally used to identify susceptibility genes. Some progress has been made in identifying non-HLA genes as susceptibility loci in these non-Mendelian polygenic autoimmune disorders.

A small number of polymorphic variants of candidate genes have been found to confer susceptibility to autoimmune diseases. Some have been identified initially using genetic approaches, whereas others represent candidate genes that have been pursued based on their functional roles in innate or adaptive immunity. Genome wide association studies involving a wide array of SNPs (single nucleotide polymorphisms) have begun to reveal valuable information about "common variants" that are linked to autoimmune disease. Although there has been success in identifying linkage to polymorphic variants in the context of human autoimmune disease, the magnitudes of these associations so far have been relatively weak, with Odds Ratios (ORs) ranging from 1.1 to 2.0.

It has been recognized from a theoretical standpoint [11] for some time that while genome wide association studies are well suited for the identification of "common variants", they would often lack the power to efficiently identify genes in which multiple different allelic variants, so-called "rare variants" may be linked to disease susceptibility. The "rare variant" hypothesis for multigene diseases first found support in a study of multiple allelic variants linked to the predilection for low HDL levels [12]. In the context of autoimmunity, rare variants of the TREX1 exonuclease have been linked to lupus [13]. However the rare variant hypothesis requires deep re-sequencing and has been more labor intensive and expensive to pursue. In addition, the ability to assess the functionality of all rare variants is required in order to permit a proper interpretation of data on these types of variants. The study on variants linked to HDL levels used theoretical predictive approaches to "guess" at the functionality of individual variant alleles [12].

2. Known genetic variants and a break in tolerance at the B or T cell level

Few polymorphic loci so far described in human autoimmunity explicitly affect B cell function, although the Sle1 locus in mice influences receptor editing and susceptibility to lupus in rodents in a yet to be explained way [14]. Not surprisingly some of the genes that have been found to be linked to human autoimmune diseases may represent negative regulators of immune function. The *PTPN22* gene encodes a protein tyrosine phosphatase that regulates the activity of Src family kinases in T cells. The R620W *PTPN22* allele is linked to RA, type 1 diabetes (T1D), and to autoimmune thyroid disease (AITR) with ORs ranging from 1.5 to 2 [15–17]. This R620W PTPN22 variant results in the defective clearance of self reactive B cells and thus contributes to autoimmunity [18]. A polymorphic variant of the *CTLA4* gene, which encodes an inhibitory receptor of the CD28 family, is linked to a similar spectrum of autoimmune diseases with an OR ranging from 1.15 to 1.5 [19,20]. The *PD1* gene encodes yet another inhibitory receptor of the CD28 family, and a polymorphic variant has been reported to be linked to SLE with an OR of 1.6 [21]. Genetic dysregulation of inhibitory signaling represents one mechanism driving autoimmunity (Table 1). This review examines the relevance in human autoimmune disorders of a distinct enzymatic regulator of inhibitory receptors in B cells in some detail as an illustrative example.

3. Inhibitory receptors in B cells linked to autoimmunity: implicating genome and epigenome

Considerable evidence exists to implicate inhibitory receptors in B cells in the regulation of humoral autoimmunity [22–26]. The FcγRIIb1 molecule inhibits B cell signaling relatively late in the antibody response and contributes to a phenomenon known as antibody feedback. Mice engineered to lack the FcγRIIb1 gene develop a lupus like syndrome, presumably because the absence of this inhibitory receptor facilitates the expansion and terminal differentiation of activated self-reactive B cell clones. Lupus prone mice express lower levels of this inhibitory receptor on germinal center B cells and promoter polymorphisms in this gene have been linked to SLE [27–29].

We have been interested in the negative regulation of BCR signaling and its consequences for B cell development [30–33]. BCR signal strength is regulated by a small subset of known proteins including an inhibitory receptor on B cells called CD22 [34–39]. The loss of CD22, like that of the transcription factor Aiolos, leads to a reduction in MZ B cells and the loss of B cells that we now describe as perisinusoidal B cells in the bone marrow [40]. CD22 contains

Table 1
Inhibitory receptor pathway genetic variation and autoimmunity.

Gene	Reference
PTPN22	[15–18,20]
CTLA-4	[19,20]
PD-1	[21]
FcgRIIB	[24]
SIAE	[61,62,65]

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